CAN-ACN

CANADIAN ASSOCIATION FOR NEUROSCIENCE
ASSOCIATION CANADIENNE DES NEUROSCIENCES

Various dates, times and location. Please visit the CAN website for details.

CAN SATELLITE SYMPOSIA

SUNDAY, MAY 17, 2026

5:00 – 7:00 pm
The Neuro, 3801 University St., Montréal, QC

Sponsored by McGill University - Faculty of Science

McGill | Faculty of Science

CAN 2026 PUBLIC LECTURE

Je me souviens – Montréal, the Memory City

Speakers:

Eric Andrew-Gee, author of *The Mind Mappers, Friendship, Betrayal and the Obsessive Quest to Chart the Brain*

Of Two Minds: The Brilliant, Tragic Friendship That Invented Montreal Neuroscience

Mihaela D. Iordanova, Concordia University

Memory Across Eras: From Intervention to Imagination

Blake Richards, McGill University

Why AI needs literal synapses

DAY 1 MONDAY, MAY 18, 2026

05:00 – 05:15 pm
Montreal 1-5

WELCOME AND OPENING REMARKS

Douglas Zochodne, President of the Canadian Association for Neuroscience

05:15 – 06:15 pm
Montreal 1-5

PRESIDENTIAL LECTURE

Clifford J. Woolf, Boston Children's Hospital and Harvard Medical School

Spontaneous Neuropathic Pain

06:15 – 08:00 pm
St-Laurent 1-8

OPENING RECEPTION

Check the back of your badge for your complimentary drink ticket.

Sponsored by CIHR-INMHA

CIHR IRSC | Institute of Neurosciences, Mental Health and Addiction | Institut des neurosciences, de la santé mentale et des toxicomanies

DAY 2 TUESDAY, MAY 19, 2026

8:30 – 10:15 am
Montreal 1-5

PLENARY SYMPOSIUM 1

Single-cell approaches for novel biological insight

Chair: **Shreejoy Tripathy**, Centre for Addiction & Mental Health

Speakers:

Kristen Brennand, Yale School of Medicine
Corina Nagy, McGill University
Shreejoy Tripathy, Centre for Addiction & Mental Health

10:15 – 10:25 am
Montreal 1-5

UPDATE ON BRAIN CANADA INITIATIVES

Viviane Poupon, President and CEO, Brain Canada

10:25 – 10:45 am
St-Laurent 1-8

COFFEE BREAK, POSTERS & EXHIBITS

10:45 – 11:00 am
Montreal 1-5

BRAIN STAR AWARD WINNER TALK

Sangyoon Ko, Korea Advanced Institute of Science and Technology (KAIST)

Sponsored by CIHR-INMHA

CIHR IRSC Institute of Neurosciences, Mental Health and Addiction / Institut des neurosciences, de la santé mentale et des toxicomanies

11:00 am – 12:00 pm
Montreal 1-5

FEATURED PLENARY SPEAKER 1

Keri Martinowich, Lieber Institute

Molecular vulnerability in brain circuits: mechanisms relevant for human brain disorders

12:00 – 1:30 pm
Salon Bonaventure

SCIENCE ADVOCACY SESSION

Advocating together: The importance of partnership and collaboration to support research advocacy

In partnership with the Society for Neuroscience

SfN Society for Neuroscience

pre-registration required

1:30 – 3:00 pm
Montreal 1-2-3

PARALLEL SYMPOSIUM 1

Sleep dynamics in cognition, memory and emotion: a circuit perspective

Co-Chairs: **Bénédicte Amilhon**, Université de Montréal &
Jimmy Fraigne, University of Toronto

Speakers:

Jimmy Fraigne, University of Toronto
REM sleep circuitry and synucleinopathies

Adrien Peyrache, McGill University
An independent thalamic compass in the sleeping brain

Mattia Aime, University of Bern
Hacking emotional memories during sleep

Bénédicte Amilhon, Université de Montréal
Modulation of sleep- and memory-related hippocampus rhythms by raphe glutamatergic inputs

1:30 – 3:00 pm
Montreal 4

PARALLEL SYMPOSIUM 2

Molecular Codes and Trans-Synaptic Architecture of Central Synapses

Co-Chairs: **Derek Bowie**, McGill University & Tabrez Siddiqui, University of Manitoba

Speakers:

Xin-tong Wang, McGill University
Molecular rules governing Ca^{2+} signaling by AMPA receptors at central synapses

Hideto Takahashi, IRCM
A novel α-Neurexin ligand essential for excitatory synapse maintenance in ventral hippocampal circuits

Melina Agosto, Dalhousie University
Role of ELFN1 at photoreceptor synapses

Tabrez Siddiqui, University of Manitoba
Mechanisms governing nanoscale trans-synaptic alignment in the mammalian brain

1:30 – 3:00 pm
Montreal 5

PARALLEL SYMPOSIUM 3

Peripheral Hormones, Central Effects: Mechanisms Linking Metabolism, Motivation, and Mental Health

Symposium chair: **Patricia Pelufo Silveira**, McGill University

Speakers:

Alfonso Abizaid, Carleton University

Ghrelin and the metabolic stress response to social stressors in females

Stephanie Fulton, Université de Montréal

Immunometabolic mechanisms modulating emotional dysregulation and impulsivity

Rodrigo Mansur, University of Toronto

Brain Insulin Resistance in Mood Disorders: Research Developments and Therapeutic Implications

Patricia Pelufo Silveira, McGill University

Neurometabolic Gateways to Resilience: Insulin and Leptin Receptor Pathways Modulating Early-Life Stress Effects on Physical and Mental Health

1:30 – 3:00 pm
Montreal 6-7-8

PARALLEL SYMPOSIUM 4

High-content CRISPR screens to understand and treat genetic disorders of the nervous system

Chair: **Troy McDiarmid**, University of British Columbia

Speakers:

Edward Fon, McGill University

CRISPR-based screening to elucidate the pathogenesis of Parkinson's disease

Maxime Rousseau, University of Ottawa

Probing the synaptome for regulators of alpha-synuclein pathology

Yun Li, University of Toronto

CRISPR screens define regulatory programs and neurodevelopmental disease relevance in human neural stem cell subtypes

Troy McDiarmid, University of British Columbia

Large-scale discovery of neural enhancers for cis-regulation therapies

3:15 – 3:45 pm
Montreal 6-7-8

TRAINEE POWER PITCH SESSION #1

3:45 – 5:15 pm
St-Laurent 1-8

POSTER SESSION 1 & EXHIBITS

5:15 – 5:45 pm
Montreal 1-5

NEW INVESTIGATOR AWARD LECTURE

Maria Ioannou, University of Alberta

Fat Under Fire: How Lipids Drive Neurodegeneration

Sponsored by Brain Canada

Fondation Brain Canada Foundation

5:45 – 6:45 pm
Montreal 1-5

BRAIN PRIZE LECTURE

Michelle Monje-Deissorth, Stanford University

The Neuroscience of Brain Cancers

Sponsored by Lundbeck Foundation

THE BRAIN PRIZE
Lundbeck Foundation

7:30 – 9:30 pm

CAN STUDENT SOCIAL

Sir Winston Churchill Pub
1455 Crescent Rue, Montral QC H3G 2B2
Limited capacity, first come first served.

DAY 3 WEDNESDAY, MAY 20, 2026

8:30 – 10:15 am
Montreal 1-5

PLENARY SYMPOSIUM 2

Computational modeling in theory-driven discovery

Chair: **Paul Masset**, McGill University

Speakers:

Richard Naud, University of Ottawa
Paul Masset, McGill University
Andreea Diaconescu, Centre for Addiction and Mental Health

Sponsored by CIHR-INMHA

CIHR IRSC Institute of Neurosciences, Mental Health and Addiction / Institut des neurosciences, de la santé mentale et des toxicomanies

10:15 – 10:25 am
Montreal 1-5

SOCIETY FOR NEUROSCIENCE UPDATE

Diane Lipscombe, Past President of SfN and current Chair of the SfN Government and Public Affairs Committee

10:25 – 10:45 am
St-Laurent 1-8

COFFEE BREAK, POSTERS & EXHIBITS

10:45 – 11:00 am
Montreal 1-5

BRAIN STAR AWARD WINNER TALK

Akram Hamed, Stanford University

Sponsored by CIHR-INMHA

CIHR IRSC Institute of Neurosciences, Mental Health and Addiction
Institut des neurosciences, de la santé mentale et des toxicomanies

11:00 am – 12:00 pm
Montreal 1-5

FEATURED PLENARY SPEAKER 2

Adam Kepecs, Washington University School of Medicine

Why Bother? Effort, Dopamine, and the Neuroimmune Control of Motivation

12:00 – 1:30 pm
Montreal 6-7-8

CIHR CANADIAN NATIONAL BRAIN BEE SHOWDOWN

limited capacity, first come first served OR Lunch on own

CIHR IRSC Institute of Neurosciences, Mental Health and Addiction
Institut des neurosciences, de la santé mentale et des toxicomanies

1:30 – 3:00 pm
Montreal 1-2-3

PARALLEL SYMPOSIUM 5

Hippocampal circuits in health and disease

Chair: **Justin Botterill**, University of Saskatchewan

Speakers:

Justin James Botterill, University of Saskatchewan

Local and long-range inputs to the hippocampus that influence diverse behaviours and seizures

Jordan Farrrell, Boston Children's Hospital & Harvard Medical School

Corrupted hippocampal computations in hyperexcitability

Lisa Topolnik, Laval University

Neuromodulatory control of Hippocampal CA1 VIP interneurons during novel experience

Esther Krook-Magnuson, University of Minnesota

Inhibitory hippocampal neurons with extended reach

1:30 – 3:00 pm
Montreal 4

SYMPOSIUM 6

Glial-neuron and glial-immune interactions in nervous system development and repair

Chair: **Wendy Xin**, University Health Network

Speakers:

Alana Hoffmann, Keenan Research Centre for Biomedical Science and Barlo MS Centre at St. Michael's Hospital

Myeloid cells regulate myelination in the developing central nervous system

Wendy Xin, University Health Network

Oligodendroglial regulation of cortical maturation and plasticity

Anastassia Voronova, University of Alberta

Chromatin regulator Ankrd11, associated with neurodevelopmental disorders, regulates glial cell development and function

Roberta Piovesana, Université de Montréal

Glial CB1 receptors drive NMJ Plasticity in Injury and ALS

1:30 – 3:00 pm
Montreal 5

SYMPOSIUM 7

Hypothalamic peptides in dual control of homeostasis and behaviour

Chair: **Katrina Choe**, McMaster University

Speakers:

Masha Prager-Khoutorsky, McGill University

Glial cells as regulators of fluid and cardiovascular homeostasis

Melissa Chee, Carleton University

Fructose fuels hunger at the hypothalamus

Valery Grinevich, Heidelberg University

Axonal Oxytocin Signaling in Rat and Human Brain

Katrina Choe, McMaster University

Oxytocin enhances social interaction by rescuing shared social circuit disruptions across two autism-risk genes

1:30 – 3:00 pm
Montreal 6-7-8

PARALLEL SYMPOSIUM 8

Reassessing Structural Plasticity in Depression: Rodent–Human Evidence and Rapid Antidepressant Mechanisms

Chair: **Argel Aguilar Valles**, Carleton University

Speakers:

Giovanni Hernandez, The Douglas Research Centre and McGill University

Infralimbic DCC Receptors Regulate Social Avoidance and Dendritic Architecture in the Cortico-Accumbens Pathway

Omar Ahmed, University of Michigan, Ann Arbor

Rules for psychedelic therapeutic neuroplasticity

Ruth Asch, UT Southwestern Medical Center

Synaptic PET imaging: Closing the bench-to-bedside-and-back loop in psychiatry

Rebecca Price, University of Pittsburgh

Rapid effects of ketamine on plasticity mechanisms across levels of analysis: Findings from clinical trials

3:00 – 3:30 pm
Montreal 6-7-8

TRAINEE POWER PITCH SESSION #2

3:30 – 5:00PM
St-Laurent 1-8

POSTER SESSION 2 & EXHIBITS

5:00 – 6:00 pm
Montreal 1-5

KEYNOTE LECTURE

Catharine Winstanley, University of British Columbia

More than rewarding: how do sound and light cues impact risky decision making?

Sponsored by Brain Canada

Fondation Brain Canada Foundation

6:00 – 7:00 pm
Montreal 6-7-8

EQUITY DIVERSITY AND INCLUSION SESSION

Organized by the CAN EDI Chairs, **Derya Sargin** and **Jenn Murray**
Panelists:

Dr. Tamara Bodnar, Assistant Professor, University of Calgary
Dr. Ibukun Akinrinade, Postdoctoral researcher, University of Calgary
Dr. Catharine Winstanley, Professor, University of British Columbia
Dr. Gareth Rurak, Postdoctoral researcher, Washington University St. Louis

Sponsored by IBRO

7:00 – 8:00 pm
Montreal 6-7-8

NCAMH SPECIAL INTEREST EVENT

Building Capacity and Community in Global Neuroscience

Organized by IBRO

DAY 4 THURSDAY, MAY 21, 2026

8:30 – 10:15 am
Montreal 1-5

PLENARY SYMPOSIUM 3

Neural mechanisms of internal states

Chair: **Rutsuko Ito**, University of Toronto, Scarborough

Speakers:

Jessica Osterhout, University of Utah
Rutsuko Ito, University of Toronto, Scarborough
Adrian Owen, University of Western Ontario

10:15 – 10:25 am
Montreal 1-5

CIHR INSTITUTE OF NEUROSCIENCES, MENTAL HEALTH AND ADDICTION UPDATE

Patricia Conrod, Scientific Director, CIHR INMHA

10:25 – 10:45 am
St-Laurent 1-8

COFFEE BREAK, POSTERS & EXHIBITS

10:45 – 11:00 am
Montreal 1-5

BRAIN STAR AWARD WINNER

Jonathan Michaels, York University

Sponsored by CIHR-INMHA

CIHR IRSC Institute of Neurosciences, Mental Health and Addiction / Institut des neurosciences, de la santé mentale et des toxicomanies

11:00 am – 12:00 pm
Montreal 1-5

FEATURED PLENARY SPEAKER 3

David J. Anderson, Caltech

The Neural Coding of Affective Internal States Underlying Innate Behaviors

12:00 – 1:30 pm

CAN-ACN ANNUAL GENERAL MEETING (AGM) (Montreal 1-5)

Or

CAREER NETWORKING EVENT (Salon Bonaventure)
Limited capacity, pre-registration required

Or

LUNCH ON OWN

1:30 – 2:00 pm
Montreal 6-7-8

TRAINEE POWER PITCH SESSION #3

2:00 – 3:30 pm
St-Laurent 1-8

POSTER SESSION 3 & EXHIBITS

3:30 – 5:00 pm
Montreal 1-2-3

PARALLEL SYMPOSIUM 9

Guiding behavior through reward-predictive cues

Chair: **Matthew Gardner**, Concordia University

Speakers:

Erin Rich, New York University

Attributing value to attributes during value-based decision-making

William Esber, Concordia University

Orbitofrontal neurons encode both the relative and absolute predictive credit of reward cues

Becket Ebitz, Université de Montréal

dACC stimulation suppresses exploration

Paul Cisek, Université de Montréal

Distributed dynamics of decisions about actions

3:30 – 5:00 pm
Montreal 4

PARALLEL SYMPOSIUM 10

RNA Modifications: Implications for Brain Function and Behavior

Chair: **Mathieu Flamand**, Université Laval

Speakers:

Mathieu Flamand, Université Laval
Deciphering the roles of m6A and YTHDF proteins in synaptic function and plasticity

Timothy W. Bredy, University of Queensland
Circular RNA-derived micropeptides at the synapse: a new mechanism of plasticity and memory?

Ina Anreiter, University of Toronto
The role of m6A in behavioural plasticity in Drosophila melanogaster

Yanhong Shi, Beckman Research Institute of City of Hope
RNA modulation in brain disorders

3:30 – 5:00 pm
Montreal 5

PARALLEL SYMPOSIUM 11

Sex and Gender Influences on Stress Disorders and Cognitive Bias

Chair: **Derya Sargin**, University of Calgary

Speakers:

Amanda Namchuk, Centre for Addiction and Mental Health
Characterizing the sex-specific functional networks underlying chronic stress-induced negative cognitive bias

Robert-Paul Juster, Université de Montréal
Beyond the Binary: Unraveling Sexually Polymorphic Cognition Across Biological and Sociocultural Dimensions

Derya Sargin, University of Calgary
Sex differences in long-term stress susceptibility after adolescent stress exposure

Etienne Sibille, Centre for Addiction and Mental Health
Human-mouse translational perspectives on sex differences in depression-related molecular mechanisms

3:30 – 5:00 pm
Osgoode East

PARALLEL SYMPOSIUM 12

The brain vasculature: from imaging to insights into disease.

Chair: **Baptiste Lacoste**, Ottawa Hospital Research Institute

Speakers:

Alexandre Dubrac, Centre de recherche du CHU Sainte-Justine

Neurovascular program dynamics shaping postnatal brain vascularization

Ravi Rungta, Université de Montréal

Modality-specific neurovascular coupling via layer-segregated arteriole networks

Grant R.J. Gordon, Hotchkiss Brain Institute

Astrocyte calcium links norepinephrine dynamics to cerebral blood flow across sleep–wake transitions

Aurelie-Rose de Rus Jacquet, Université Laval

Modeling the neurovascular unit in brain chips: new insights into communication at the blood-brain barrier in neurodegenerative diseases

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PRESIDENTIAL LECTURE

Spontaneous Neuropathic Pain

Clifford J. Woolf, Boston Children's Hospital and Harvard Medical School

Chronic neuropathic pain has two distinct elements, stimulus-evoked pain (allodynia and hyperalgesia) and paroxysmal or continuous spontaneous pain. Almost all pre-clinical investigations of the mechanistic basis of neuropathic pain have focused only on the stimulus-induced pain that manifests soon after nerve injury, even though spontaneous neuropathic pain is more common clinically, and typically persists for decades. Consequently, treatment of spontaneous neuropathic pain is still very limited. By combining a molecular, cellular, and systems-based investigation of both human and rodent persistent painful neuromas, we have identified the mechanistic driver of spontaneous neuropathic pain, a specific genetically-defined subset of injured dorsal root ganglion sensory neurons, and the pathological changes in non-neuronal cells in close proximity to them at the site of the nerve injury, resulting in a pain triggering interactome that leads only after many weeks to an ongoing pathological hyperexcitability driven by changes in ion channel function in a subset of injured axons, opening new therapeutic opportunities to both manage and potentially prevent this major feature of neuropathic pain.

KEYNOTE LECTURE

More than rewarding: how do sound and light cues impact risky decision making?

Catharine Winstanley, University of British Columbia

Risky decision making increases vulnerability for addiction disorders. We have shown that, in both rats and humans, presenting sound and light cues concurrent with reward delivery can increase preference for "high-risk, high-reward" options in laboratory-based gambling tasks. Just like humans, most rats prefer to gamble for cued rather than uncued rewards. It has long been known that audiovisual cues, when paired repeatedly with appetitive outcomes like sugary rewards or liquids, can come to act as reinforcers in their own right due to the attribution of incentive salience. Electronic gambling machines and gaming apps make heavy use of these cues to signal rewarding events during play. However, computational modeling using reinforcement learning algorithms suggest that cue-induced risky choice is not driven by enhanced learning from rewards, as we would expect if the cues were acting as conditioned reinforcers, but instead through impaired learning from penalties. Furthermore, analyses of data from nearly 700 rats suggest that even though the risk-promoting effect of the cues looks superficially similar across sex, cue-induced risky choice may operate via different cognitive processes in females vs males. Data from behavioral pharmacology studies and chemogenetic manipulations suggest reward-concurrent cues alter the recruitment of multiple neurotransmitter systems and brain regions in the decision-making process. Although daunting in its complexity, these studies also suggest a variety of approaches that may neutralize the deleterious effect of such cues on cognition.

FEATURED PLENARY SPEAKER 1

Molecular vulnerability in brain circuits: mechanisms relevant for human brain disorders

Keri Martinowich,Lieber Institute

Understanding how molecular pathology maps onto brain circuits remains a central challenge in neuropsychiatric disease. While single-cell genomic approaches define diverse cell types, they lack the

spatial context needed to resolve how disease-associated processes are organized within intact tissue. Here, I will present work using spatially resolved transcriptomics integrated with single-cell genomics and immunofluorescence-based tissue annotation to map schizophrenia-associated molecular programs in the human dorsolateral prefrontal cortex. By combining spatial gene expression with in situ protein markers, we define molecularly and anatomically distinct tissue microenvironments and localize disease-associated changes within these contexts. We find that transcriptional alterations are not uniformly distributed across cortical layers or cell types, but instead concentrate within specific microenvironments, with prominent enrichment in neuropil and glia-rich domains. Within these regions, synaptic, metabolic, and neuroimmune pathways are coordinately altered, highlighting the neuropil as a key interface for neuron–glia interactions. Integration with genetic risk suggests that neuronal liability converges on circuit-relevant interactions involving non-neuronal cell types. Consistent with this, ligand–receptor analyses identify altered signaling interactions across spatial domains, including trophic and adhesion pathways that may couple neuronal and glial processes. Together, these findings support a model in which molecular vulnerability in schizophrenia is organized across spatially defined microenvironments within cortical circuits, providing a framework for understanding selective vulnerability in human brain disorders.

FEATURED PLENARY SPEAKER 2

Why Bother? Effort, Dopamine, and the Neuroimmune Control of Motivation

Adam Kepecs,Washington University School of Medicine

Apathy and fatigue are common, disabling symptoms of depression, especially prominent in inflammatory states. Rather than viewing these symptoms as nonspecific byproducts of illness, I will argue they are predictable failure modes of adaptive algorithms, computations that determine when effort is worth spending. I will begin by framing psychiatric symptoms as control systems pushed beyond their adaptive range, then turn to a mechanistic account of how immune signals reshape the neural computations that govern motivation. Using mouse models of chronic inflammatory disease, including cancer cachexia and endometriosis, we identified a convergent cytokine-sensing brainstem-to-basal-ganglia circuit that suppresses mesolimbic dopamine and alters effort valuation. I will close by considering how computational phenotyping could guide treatment stratification in inflammation-linked depression.

FEATURED PLENARY SPEAKER 3

The Neural Coding of Affective Internal States Underlying Innate Behaviors

David J. Anderson,Caltech

Innate survival behaviors such as fighting, mating and predator defense are associated with affective or emotion states. Finding neural representations of such states using supervised analyses is challenging due to a lack of direct state measures. To overcome this limitations, we have performed unsupervised modeling of single-trial neural data acquired during naturalistic social behaviors, using recurrent Switching Linear Dynamical Systems (rSLDS). rSLDS learns a dynamics matrix based on latent factor activity in a state-space approximated by a set of linear substates, yielding a probabilistic model of neural dynamics. When used to model single-trial calcium imaging data recorded from hypothalamic “attack” neurons during aggressive encounters, rSLDS discovered an approximate line attractor that represents the intensity and duration of a scalable and persistent state of aggressiveness. I will discuss features of this representation, evidence for its local instantiation in the hypothalamus, mechanistic implementation and generalization to other social behaviors. Together, these results extend the potential role of line attractor dynamics beyond the representation of cognitive variables, to the representation of affective internal states. They also identify a tractable experimental platform to investigate how circuit-level mechanisms give rise to emergent network dynamics at the manifold level in the mammalian brain.

NEW INVESTIGATOR AWARD LECTURE

Fat Under Fire: How Lipids Drive Neurodegeneration

Maria S. Ioannou, University of Alberta

Dysregulation of lipids has emerged as a common feature of neurodegenerative disease. Yet much remains unknown regarding how lipids contribute to disease pathology. Here, I will discuss how neuronal death in Alzheimer's disease is driven by a failure to remove oxidized lipids on ApoE-positive lipoprotein particles. We discovered that the protective ApoE2 and ApoE3-Christchurch isoforms, which reduce the risk of developing Alzheimer's disease, are particularly effective at effluxing oxidized phospholipids from neurons. I will next describe how defects in sphingolipid metabolism promote the propagation of pathology in Parkinson's disease. We discovered that ectosomes, a subtype of extracellular vesicles, form in response to sphingolipid alterations, and transmit misfolded alpha-synuclein between neurons. Collectively, these bodies of work reveal new insights into how lipids contribute to neurodegenerative disease.

BRAIN PRIZE LECTURE

The Neuroscience of Brain Cancers

Michelle Monje, Stanford University

In the central nervous system, neuronal activity is a critical regulator of development and plasticity. Activity-dependent proliferation of healthy glial progenitors, oligodendrocyte precursor cells (OPCs), and the consequent generation of new oligodendrocytes contributes to adaptive myelination. This plasticity of myelin tunes neural circuit function and contributes to healthy cognition, while disruption of myelin plasticity contributes to cognitive impairment in a range of disease states. The robust mitogenic effect of neuronal activity on normal oligodendroglial precursor cells, a putative cellular origin for many forms of glioma, suggests that dysregulated or "hijacked" mechanisms of myelin plasticity might similarly promote malignant cell proliferation in this devastating group of brain cancers. Indeed, the activity of multiple neuron types promotes the growth and invasion of both high-grade and low-grade glioma subtypes in preclinical models. Crucial mechanisms mediating activity-regulated glioma growth include paracrine secretion of tumor-promoting factors and synaptic communication between neurons and glioma cells. Glioma cells integrate into neural circuits synaptically through neuron-to-glioma synapses that exhibit synaptic plasticity, and electrically through potassium-evoked currents that are amplified via gap-junctional coupling between tumor cells. This synaptic and electrical integration of glioma into neural circuits is central to tumor progression in preclinical models and in patients. Thus, neuron-glial interactions not only modulate neural circuit structure and function in the healthy brain, but neuron-glioma interactions also play important roles in the pathogenesis of glial cancers. The mechanistic parallels between normal and malignant neuron-glial interactions underscores the extent to which mechanisms of neurodevelopment and plasticity are subverted by malignant gliomas, and the importance of understanding the neuroscience of cancer.

BRAIN STAR AWARD WINNER TALK 1

Dynamics of Memory Engrams in Health and Disease

Sangyoon Ko, Korea Advanced Institute of Science and Technology (KAIST)

The brain transforms everyday experiences into memories that enable us to recognize and adapt to the world. For decades, the prevailing view has suggested that memories gradually become independent of the hippocampus as they age. However, how memories are dynamically reorganized and persist long-term in the brain remains a fundamental question in neuroscience.

In the hippocampus, engram neurons—neuronal populations activated during learning and reactivated during memory retrieval—provide a cellular framework to address this question. By employing activity-dependent engram tagging and super-resolution confocal imaging, we demonstrate that hippocampal

engram neurons are not static, but instead undergo dynamic structural and functional reorganization during systems memory consolidation. Specifically, newborn neurons generated through adult hippocampal neurogenesis in the dentate gyrus (DG) are progressively integrated into existing DG-to-CA3 engram circuitry, increasing the activity of downstream CA3-to-CA1 engram circuits during exploration in similar environments. This reorganization enables episodic-like memories to generalize across related experiences, supporting the emergence of generalized, memory-guided behavior.

In addition, using mouse models of neurodevelopmental and neurodegenerative disorders, we identify neurobiological evidence that engram formation and reactivation are dysregulated. Together, these findings begin to delineate neural circuit principles underlying hippocampal long-term memory and suggest that targeting engram populations may provide a novel therapeutic avenue for cognitive disorders.

BRAIN STAR AWARD WINNER TALK 2

Gliomagenesis mimics an injury response orchestrated by neural crest-like cells

Akram Hamed, Stanford University

Glioblastoma is an incurable brain malignancy. By the time of clinical diagnosis, these tumours exhibit a degree of genetic and cellular heterogeneity that provides few clues to the mechanisms that initiate and drive gliomagenesis. Here, to explore the early steps in gliomagenesis, we utilized conditional gene deletion and lineage tracing in tumour mouse models, coupled with serial magnetic resonance imaging, to initiate and then closely track tumour formation. We isolated labelled and unlabelled cells at multiple stages—before the first visible abnormality, at the time of the first visible lesion, and then through the stages of tumour growth—and subjected cells of each stage to single-cell profiling. We identify a malignant cell state with a neural crest-like gene expression signature that is highly abundant in the early stages, but relatively diminished in the late stage of tumour growth. Genomic analysis based on the presence of copy number alterations suggests that these neural crest-like states exist as part of a heterogeneous clonal hierarchy that evolves with tumour growth. By exploring the injury response in wounded normal mouse brains, we identify cells with a similar signature that emerge following injury and then disappear over time, suggesting that activation of an injury response program occurs during tumorigenesis. Indeed, our experiments reveal a non-malignant injury-like microenvironment that is initiated in the brain following oncogene activation in cerebral precursor cells. Collectively, our findings provide insight into the early stages of glioblastoma, identifying a unique cell state and an injury response program tied to early tumour formation. These findings have implications for glioblastoma therapies and raise new possibilities for early diagnosis and prevention of disease.

BRAIN STAR AWARD WINNER TALK 3

Sensory expectations shape neural population dynamics in motor circuits

Jonathan Michaels, York University

The neural basis of movement preparation has been extensively studied during self-initiated actions, in which motor cortical activity during preparation shows a lawful relationship to the parameters of the subsequent action. However, movements are regularly triggered or corrected on the basis of sensory inputs caused by disturbances to the body. Since such disturbances are often predictable, and since preparing for disturbances would make movements more prescise, we hypothesized that expectations about sensory inputs also influence preparatory activity in motor circuits. Here we show that when humans or monkeys are probabilistically cued about the direction of future mechanical perturbations, they incorporate sensory expectations into their movement preparation and improve their corrective responses. Using high-density neural recordings, we establish that sensory expectations are widespread across the brain, including the motor cortical areas involved in preparing self-initiated actions. The geometry of these preparatory signals in the neural population state is simple, and scales directly with the probability of each perturbation direction. After perturbation onset, a condition-independent signal shifts the neural state leading to rapid responses

that initially reflect sensory expectations. Using neural networks coupled to a biomechanical model of the arm, we show that this neural geometry emerges only when sensory inputs signal that a perturbation has occurred, before resolving the direction of the perturbation. Thus, just as preparatory activity sets the stage for self-initiated movement, it also configures motor circuits to respond efficiently to sensory inputs.

PLENARY SYMPOSIUM 1

Single-Cell Approaches for Novel Biological Insight

Chair: **Shreejoy Tripathy**, Centre for Addiction & Mental Health

Speakers:

Kristen Brennand, Yale School of Medicine

Gene x Environment Interactions in Brain Disease

Each person's distinct genetics and environment predispose them to some phenotypes and confers resilience to others. We seek to understand the genetic regulation of phenotype, and how it is impacted by developmental, cellular, and environmental contexts. Our functional genomics approach integrates human induced pluripotent stem cell models with CRISPR-based genome engineering to introduce and reverse genetic variation, yielding precision models that can be combined with genetic and pharmacological screens. Given the complex genetic risk architectures associated with psychiatric disorders and neurodegenerative diseases, we ask how diverse risk variants share convergent downstream impacts, and whether when added together, combinatorial perturbations yield outcomes that cannot yet be predicted by individual manipulations alone. Likewise, we ask how stress, inflammation, hormones, and other exposures exacerbate or ameliorate the effect of disease-associated risk factors. We study how genotype-phenotype relationships vary across people and dynamic conditions, within and between the cell types of the brain. Thus, rather than just characterize the impact of trait-associated variants, we seek to uncover modifiers that alter it. Our goal is to decipher the frameworks that buffer genetic risk, in order to confer biological resilience and promote healthy development. Understanding the basic biology governing the complex interplay between genetic variants and the environment will springboard the development of novel, personalized approaches to improve health and prevent brain disease.

Corina Nagy, McGill University

Molecular Architecture of Sex-Specificity in the Brain and Vulnerability to Depression

Major depressive disorder (MDD) exhibits pronounced sex differences in prevalence, symptom profile, and treatment response, yet the underlying molecular basis remains incompletely understood. This work presents an integrative, multiomic framework combining cross-sectional human postmortem analyses with longitudinal studies to define sex-specific brain trajectories in health and disease.

Cross-sectional findings from single-cell and spatial transcriptomic profiling of adult human brains reveal robust, cell-type-specific molecular differences between males and females. These differences reflect distinct patterns of gene expression and regulatory activity within specific neuronal and glial populations. Spatially resolved transcriptomics further implicates glial dysregulation, supporting and extending prior findings in MDD.

Building on these observations, we used longitudinal multiomic analyses to track the evolution of transcriptomic signatures across adolescence in mice. Statistical modeling of temporal gene expression dynamics identified sex-specific trajectories pointing to differential recruitment of biological systems, including stress response, synaptic signaling, and immune-related pathways. Notably, these trajectories reflect both distinct regulatory architectures and in some cases, baseline shifts between sexes.

Together, this work defines a dynamic molecular framework linking sex-specific brain organization to vulnerability for depression and underscores the importance of incorporating sex as a fundamental biological variable in models of brain function and disease.

Shreejoy Tripathy, Centre for Addiction & Mental Health

Resolving cellular pathology in schizophrenia through single-cell and spatial transcriptomic meta-analysis

Schizophrenia is a heterogeneous disorder whose cellular basis in the human cortex remains contested. Decades of work have implicated cortical inhibitory interneurons, but it has been controversial whether these cells are genuinely lost in schizophrenia or instead remain present but functionally altered. Single-cell and spatial transcriptomic technologies, together with increasingly detailed cell type taxonomies of the human neocortex, now offer the resolution needed to address this question directly.

Here, using a meta-analysis approach spanning nine post-mortem brain cohorts profiled by single-nucleus RNA sequencing or spatial transcriptomics, we apply a consistent cell typing framework to identify reproducible cellular changes in schizophrenia. We find that a specific subgroup of somatostatin-expressing (SST) cells is consistently reduced in number across cohorts, technologies, and brain regions. These cells reside in the upper cortical layers, co-express calbindin, and correspond to primate-specific double bouquet neurons that provide vertical inhibition within cortical columns. Moreover, the remaining SST cells show broad cell state changes, including reduced expression of the SST mRNA itself. Together, these findings help reconcile long-standing debates about schizophrenia pathology, showing that both cell loss and altered cell state co-occur within specific interneuron populations, and illustrate how careful integration across datasets can clarify the cellular basis of psychiatric illness.

PLENARY SYMPOSIUM 2

Computational Modeling in Theory-Driven Discovery

Chair: **PaulMasset**, McGill University

Speakers:

Richard Naud, University of Ottawa

Towards a burst coded solution of the credit assignment problem

Pyramidal neurons communicate through a mixture of isolated spikes and high-frequency bursts, and theoretical work has proposed that these two firing patterns can multiplex independent streams of information. In this talk, I will present converging evidence that this burst code allows a sophisticated form of coordination of learning. First I will show theoretical rationale and predictions inspired by a convergence of deep learning techniques and known electrophysiology. Then, I will describe new analyses of juxta-cellular recordings in primary somatosensory cortex during a microstimulation detection task. We found that burst fraction and event rate constitute genuinely independent neural representations with distinct temporal dynamics. The code separates error signals from sensory signals, a central requirement for the credit assignment. I will then extend these findings to publicly available dataset from barrel cortex, demonstrating that the same dissociation between burst fraction and event rate is recoverable at the population level and that there is an encoding of error and sensory information segregated in the burst code. Together, these results argue that burst coding implements a multiplexed signalling, key for online credit assignment in sensory cortex and the hippocampus.

Paul Masset, McGill University

Distributed reinforcement learning in the brain

To thrive in complex environments, animals and artificial agents must learn to act adaptively to maximize fitness and rewards. Such adaptive behaviour can be learned through reinforcement learning, a class of algorithms that has been successful at training artificial agents and at characterizing the firing of dopaminergic neurons in the midbrain. In classical reinforcement learning agents learn a single objective, the value, defined as the exponentially discounted sum of future rewards. This contrasts with the hyperbolic

discounting often observed in humans and animals and the numerous possible definitions of value and rewards. Here, we report that dopaminergic neurons in mice performing two behavioural tasks encode reward prediction error with a diversity of discount time constants. Our model explains the heterogeneity of temporal discounting in both cue-evoked transient responses and slower timescale fluctuations known as dopamine ramps. Crucially, the measured discount factor of individual neurons is correlated across the two tasks, suggesting that it is a cell-specific property and providing a mechanistic basis for the empirical observation that humans and animals use non-exponential discounts in many situations. More generally, our approach provides a new paradigm for understanding functional heterogeneity across dopaminergic neurons and opens new avenues for the design of more-efficient reinforcement learning algorithms.

Andreea Diaconescu,Centre for Addiction and Mental Health

Modelling the Hidden Causes of Mental Illness: Belief Updating, Neural Dynamics, and Clinical Prediction

Computational models offer a principled route from descriptive neuroscience to theory-driven discovery by making latent mechanisms experimentally testable. In this talk, I will present a computational psychiatry framework that links behavioural learning, electrophysiology, neuroimaging, and clinical outcomes through generative models of belief updating and neural dynamics. I will focus on how hierarchical Bayesian and reinforcement-learning models can quantify hidden processes such as uncertainty estimation, precision-weighted prediction errors, social inference, and active-escape biases. Using examples from psychosis-risk and suicidality research, I will show how these latent computations can be mapped onto EEG and neuroimaging measures, including mismatch responses, spectral dynamics, and connectome-constrained models of cortical gain. I will also discuss how gamified behavioural tasks and wearable EEG platforms may support scalable assessment in youth and clinical populations. Across these examples, the central argument is that computational modelling is most powerful when it is used not only for prediction, but also for adjudicating mechanistic theories about how altered learning, inference, and neural circuit dynamics give rise to psychiatric symptoms. This approach aims to identify clinically meaningful biomarkers and intervention targets while preserving a close link between formal theory, brain function, and individual-level clinical heterogeneity.

PLENARY SYMPOSIUM 3

Neural Mechanisms of Internal States

Chair: **Rutsuko Ito**, University of Toronto, Scarborough

Internal states are latent, brain-wide conditions (e.g., fear, hunger, arousal) that are not directly observable but can be inferred from their influence on perception, cognition, and behaviour. They are thought to reflect dynamic and distributed neural configurations that integrate external sensory inputs with prior experience and physiological signals, shaping how organisms respond adaptively to their changing environment. This symposium highlights recent advances in understanding the neural mechanisms of internal states across three domains.

Jessica Osterhout (University of Utah) will discuss the neural correlates of sickness. During infection, animals exhibit stereotyped changes in physiology and behaviour that support immune function and reduce further threat. Recent work has identified neurons critical for key symptoms of sickness and their diverse functions, and yet, their correlated organization points toward a systemic mechanism. Rutsuko Ito (University of Toronto) will discuss the neural circuits and network that mediate a state of approach-avoidance conflict, using cross-species behavioural paradigms combined with chemogenetics, whole-brain cFos mapping, and neuroimaging. These approaches reveal cross-species convergence in identifying the ventral/anterior hippocampus as a hub for conflict detection and resolution. Adrian Owen (University of Western Ontario) will examine how consciousness is defined and measured when overt behaviour is absent. Novel neuroimaging approaches have enabled the documentation of preserved cognitive function, detection of covert

consciousness, and even communication with behaviourally non-responsive patients. These approaches are now improving diagnosis and prognosis in critically brain-injured patients, as well as informing medical ethics and legal discussions around end-of-life decision-making.

Speakers:

Jessica Osterhout, University of Utah

Central control of the sickness state

During infection, animals exhibit a coordinated set of physiological and behavioral responses, collectively termed sickness symptoms, that are orchestrated by the brain to aid the immune response and promote survival. While some neural mechanisms underlying these responses have been identified, others remain poorly understood. Moreover, the organizing principles of circuits that control the sickness state are still unclear. We aim to address these gaps by uncovering the circuit mechanism underlying sickness-induced hyperalgesia, a hallmark of systemic illness that, unlike other symptoms, can persist into the chronic phase. Prevailing models of inflammatory pain largely emphasize peripheral sensory sensitization driven by local immune signals or injury. In contrast, we have identified a specific population of neurons in the brain that specifically increases pain sensitivity during systemic inflammation, with little to no effect on other symptoms of sickness. These results suggest sickness-induced hyperalgesia is controlled systemically by central brain circuits. Using behavioral, functional, and circuit-level analyses, we demonstrate that these neurons modulate mechanical and thermal sensitivity. Integrating circuit dissection, advanced tracing approaches, and single-cell characterization, we define how these neurons engage established pain-modulatory pathways and identify mechanisms of immune-mediated activation. Together, this work reveals a central neural mechanism for generating hyperalgesia during sickness and reveals a divergence in sickness circuit organization, suggesting a mechanism for separating persistent chronic symptoms from acute symptoms. These results have direct implications for treating pain in diseases characterized by dysregulated immune activity.

Rutsuko Ito, University of Toronto, Scarborough

Neural mechanisms of approach-avoidance conflict: circuit- and network-level insights across species

Approach–avoidance conflict arises when competing motivational drives are coactivated, creating a state of ambivalence that demands resolution. This internal conflict, observable as vacillation, prolonged deliberation, and hesitancy, is conserved across species and can be measured through decision times and approach-withdrawal dynamics. Conflict states may also be potentiated in individuals with anxiety, leading to prolonged rumination and maladaptive decision making, highlighting the importance of elucidating the neural substrates of conflict processing. In this talk, I will discuss the neural circuits and large-scale networks that mediate and resolve this conflict state in rodents and humans, using synergistic behavioural paradigms combined with chemogenetic circuit manipulation, whole-brain cFos mapping, and human neuroimaging. These approaches reveal striking cross-species convergence, identifying the ventral/anterior hippocampus as a hub for conflict resolution, with subfield- and circuit-specific control over approach–avoidance decision-making.

Adrian Owen, University of Western Ontario

The Search for Consciousness

What does it mean to be conscious and how does that experience change in sleep, anaesthesia, and coma? Traditionally, consciousness is measured through a recognised behavioural response, which may be as simple as a spoken answer or a non-verbal signal (such as the blink of an eye). But what if the ability to speak, or blink an eye, or move a hand is lost completely, yet conscious awareness remains? In recent years, improvements in our ability to measure the neural mechanisms underlying various states of awareness have started to change the way we think about consciousness and how it should be measured. I will describe

a series of recent studies in which we have used various neurimaging modalities to document preserved cognitive function, detect covert consciousness, and even communicate with behaviourally non-responsive patients. These novel approaches – derived directly from cognitive neuroscience - are now improving diagnosis and prognosis in critically brain-injured patients, as well as informing medical ethics and legal discussions around end-of-life decision-making.

SYMPOSIUM 1:

Sleep dynamics in cognition, memory and emotion: A circuit perspective

S01.1 *REM sleep circuitry and synucleinopathies*

Jimmy Fraigne [1]

[1] *University of Toronto*

Rapid eye movement (REM) sleep is a paradoxical state of consciousness where an active dreaming brain occurs in a paralyzed body. I will discuss the neuronal circuit and neurotransmitter mechanism that generate REM sleep and its characteristics. We found that brainstem glutamate neurons of the sublaterodorsal tegmental nucleus (SLDGLU) are at the center of REM sleep control. Importantly, these cells send descending projections to the ventral medulla (vM) to control the motor atonia of REM sleep. Our work reveals that selective neurodegeneration of this circuit underlies REM sleep behaviour disorder (RBD), in which violent dream enactment can result in serious nocturnal injuries. Importantly, RBD often precedes synucleinopathies (e.g., Parkinson's disease, PD) by years to decades, making it the best-known predictor of these disorders. I will discuss how the same pathological mechanism is at play in both PD and RBD.

S01.2 *An independent thalamic compass in the sleeping brain*

Adrien Peyrache [1]

[1] *McGill University*

The generation of the head-direction (HD) signal, a cornerstone of the brain's navigation system, is classically attributed to the lateral mammillary nucleus (LMN) and associated brainstem structures, where attractor-like dynamics are thought to maintain population coherence. Here, using multi-site recordings and optogenetic perturbations along the mammillary–thalamic–cortical pathway, we demonstrate that HD neurons in the anterodorsal nucleus of the thalamus (ADN) maintain coherent population dynamics even as their LMN inputs fragment into decorrelated, disorganized firing patterns. These findings reveal that thalamic coherence does not strictly depend on structured input from the LMN; instead, it can emerge from local thalamic processes involving shared inhibition and non-linear responses. Together, our findings reveal a previously unrecognized, state-dependent shift in the circuit organizing the HD signal, establishing the thalamus as an active substrate capable of independently sustaining internal representations across brain states.

S01.3 *Hacking emotional memories during sleep*

Mattia Aime [1]

[1] *University of Bern*

The prefrontal cortex (PFC) is essential for encoding emotional information related to environmental danger or safety during both wakefulness and rapid eye movement (REM) sleep. It integrates direct synaptic inputs from the basolateral amygdala (BLA)—a central hub for associative learning and emotional valence encoding—as well as inputs from other cortical and subcortical networks, to exert top-down control over behavioral responses during wakefulness. The heightened activity of both the BLA and PFC during sleep contributes to the encoding and long-term storage of emotional experiences, consistent with dreaming. This process is thought to partly rely on high concentrations of acetylcholine in the cortex during REM sleep; however, the underlying mechanisms remain unclear. Here, I will present my latest data on the synaptic mechanisms of the BLA-PFC pathway during REM sleep, where I identified a segregated pattern of activation in BLA synaptic boutons within the PFC, responsible for the valence discrimination of emotional memories, directly modulated by acetylcholine.

S01.4 *Modulation of sleep- and memory-related hippocampus rhythms by raphe glutamatergic inputs*

Bénédicte Amilhon [1]

[1] *Université de Montréal - Centre de Recherche Azrieli du CHU Sainte-Justine*

During sleep, the hippocampus local field potential displays a diversity of oscillations (or rhythms) that play a critical role in memory consolidation. Those include theta rhythm, a 6-10 Hz oscillation present during active wake and REM sleep, and sharp-wave ripples, brief epochs of high frequency oscillations (50 ms, 150-250 Hz) present during quiet wake and non-REM sleep. Both rhythms have been tightly linked to hippocampus-dependent memory since selective disruption of theta rhythm or sharp-wave ripples impairs learning. We identify raphe glutamatergic neurons as a novel subcortical system that can exert powerful control over learning-related oscillations in the hippocampus. Combining fiber photometry, electrophysiology and optogenetics in freely behaving mice, we show that activity of raphe glutamatergic neurons (expressing the vesicular glutamate transporter VGLUT3) varies across sleep stages and is maximal during theta rhythm epochs. During theta-rich REM sleep, optogenetic activation or inhibition of VGLUT3 neurons disrupted theta rhythm frequency and power. During non-REM sleep, VGLUT3 neurons show bursts of activity tightly anticorrelated with sharp-wave ripples. Short optogenetic activation of VGLUT3 neurons abolishes sharp-wave ripples without affecting sleep, while long optogenetic activation periods tend to promote wake. Taken together, raphe VGLUT3 inputs to the hippocampus are well positioned to profoundly influence sleep-dependent memory consolidation. Considering the dominant role of raphe nuclei in processing aversive information, this raphe-hippocampus pathway is an appealing candidate neural circuit to modulate learning as a function of stress.

SYMPOSIUM 2:

Molecular Codes and Trans-Synaptic Architecture of Central Synapses

S02.1 *Molecular rules governing Ca^{2+} signaling by AMPA receptors at central synapses*

Xin-Tong Wang [1], Derek Bowie [1], Federico Miguez Cabello [1]

[1] *McGill University*

Fast excitatory synaptic transmission in the mammalian brain is mediated by AMPA-type glutamate receptors (AMPARs), whose functional diversity arises from combinatorial assembly of pore-forming subunits and auxiliary proteins. For decades, Ca^{2+} permeability of AMPARs was thought to be dictated almost exclusively by the presence or absence of the GluA2 subunit. Recent work, however, challenges this binary classification and reveals a more nuanced molecular logic governing AMPAR ion permeation. In this talk, I will present findings from two recent studies demonstrating that GluA2-containing AMPARs form a continuum of Ca^{2+}-permeable channels, shaped by both subunit composition and auxiliary protein assembly. Using recombinant receptors with defined stoichiometry, we showed that transmembrane AMPAR regulatory proteins (TARPs) and cornichon homologs (CNIHs) dynamically tune Ca^{2+} permeability by modifying the pore selectivity filter, without necessarily conferring sensitivity to intracellular polyamines. Structural and functional analyses further revealed a Ca^{2+} binding site that forms upon channel opening and works in concert with the Q/R site to regulate divalent ion flux. I will then extend these findings with new, unpublished data from cerebellar synapses, where native GluA2-lacking AMPARs exhibit a striking constraint in their auxiliary subunit usage. Although recombinant GluA2-lacking receptors can associate with multiple auxiliary proteins that differentially regulate polyamine block and permeation, native cerebellar receptors appear to selectively employ only a subset of these auxiliary partners. This selective assembly suggests that neuronal context imposes additional molecular rules that limit receptor diversity in vivo. Together, these results support a model in which AMPAR subunit and auxiliary protein composition acts as a molecular code that specifies Ca^{2+} signaling properties at central synapses. Such coding principles provide a framework for understanding synapse-specific signaling and help explain how disruptions to AMPAR assembly contribute to neurological disease.

S02.2 A novel α-Neurexin ligand essential for excitatory synapse maintenance in ventral hippocampal circuits

Hideto Takahashi [1]

[1] *Institut de recherches cliniques de Montréal (IRCM)*

Neuronal circuits rely on the precise formation and long-term stability of synapses, processes governed partly by synaptic adhesion molecules. The Neurexin (Nrxn) family is a central presynaptic adhesion molecule and is strongly linked to neurodevelopmental disorders. Although many ligands bind both α- and β-isoforms of Nrxns, few selectively engage α-Nrxns, whose large extracellular regions harbor putative functional domains and numerous mutations associated with neurodevelopmental disorders such as autism spectrum disorders and schizophrenia. To identify α-Nrxn-specific interactors, we performed an unbiased proteomic screen and uncovered previously unrecognized immunoglobulin superfamily (IgSF) members as α-Nrxn-selective ligands. These interactions require the SS2 splice insert within the α-Nrxn LNS2 domain, establishing LNS2 as a critical binding hotspot and highlighting SS2 splicing as a key regulatory mechanism. Functionally, the newly identified IgSF protein induces presynaptic assembly through axonal Nrxn2α, yet global deletion of this IgSF gene in mice does not disrupt early glutamatergic synapse formation but rather impairs excitatory synaptic transmission and structural maintenance in the ventral hippocampal CA1 circuits (vCA1). Interestingly, these synaptic deficits are sex-dependent and input-specific, highlighting distinct vCA1 circuit vulnerabilities in male and female mice. Consistent with these synaptic changes, knockout mice exhibit impaired social preference and recognition memory and elevated anxiety-like behavior in a sex-dependent manner. Together, our findings identify a previously uncharacterized α-Nrxn-specific adhesion mechanism that regulates the functional organization and structural stability of glutamatergic synapses in vCA1 circuits, expanding the repertoire of α-Nrxn ligands and revealing a novel molecular pathway contributing to sexually dimorphic social and anxiety-related behaviors.

S02.3 *Role of ELFN1 at photoreceptor synapses*

Melina Agosto [1]

[1] *Dalhousie University*

The cell adhesion molecule ELFN1 interacts trans-synaptically with metabotropic glutamate receptors (mGluRs), modulating synapse formation and function. The ELFN1 extracellular domain can interact with all of the group III mGluRs – mGluR4, mGluR6, mGluR7, and mGluR8. In the retina, information from rod photoreceptors is transmitted to bipolar cells and horizontal cells at glutamatergic synapses in the outer plexiform layer. Expression of ELFN1 in rods is necessary for normal synaptic structure and function, and postsynaptic mGluR6 is required for neurotransmitter reception at bipolar cell dendritic tips. We recently reported that several congenital stationary night blindness mutations in the mGluR6 extracellular domain abolish ELFN1 binding and lead to drastic mislocalization in rod bipolar cells, supporting the conclusion that interaction with ELFN1 is required for mGluR6 synaptic enrichment. Within rod terminals, ELFN1 is located specifically at presynaptic membranes apposed to bipolar cell dendritic tips. However, mechanisms restricting ELFN1 to these sites are unknown. We found that ELFN1 synaptic localization is partially disrupted in mGluR6 null mice, and can be rescued by postnatal expression of mGluR6-EGFP in bipolar cells, suggesting bidirectional stabilization of proteins at this synapse via the ELFN1 extracellular domain. In addition, new results suggest a role for the intracellular C-terminal domain of ELFN1 in localization, pointing to a presynaptic scaffolding mechanism that is specific for sites apposed to bipolar cell dendritic tips.

S02.4 *Mechanisms governing nanoscale trans-synaptic alignment in the mammalian brain*

Tabrez Siddiqui [1]

[1] *University of Manitoba*

Efficient excitatory synaptic transmission in the mammalian brain requires nanoscale trans-synaptic alignment of presynaptic release sites with postsynaptic receptor nanodomains. We demonstrate that this

alignment is governed by defined molecular principles that couple trans-synaptic adhesion complexes with intracellular scaffold interactions to constrain receptor positioning relative to presynaptic release machinery. Building on our identification of molecular principles of synaptic organization, we use targeted genetic perturbations in mice combined with super-resolution imaging to measure nanoscale distributions among synaptic proteins, high-resolution proteomics and advanced biochemical approaches to resolve molecular interaction networks, and extensive electrophysiological and behavioral assays to quantify functional consequences. Together, these findings define mechanistic rules linking nanoscale synaptic architecture to functional output and provide insight into how subtle disruptions in the molecular organization of synaptic proteins contribute to circuit dysfunction in neurodevelopmental disorders.

SYMPOSIUM 3:

Peripheral Hormones, Central Effects: Mechanisms Linking Metabolism, Motivation, and Mental Health

S03.1 *Ghrelin and the metabolic stress response to social stressors in females*

Alfonso Abizaid [1]

[1] *Carleton University*

Ghrelin is an important metabolic hormone that is associated with adaptive responses to chronic social stressors in males. Less is known however about the effects of social stress and metabolism in females and the role of ghrelin on these responses. This is of fundamental importance given the female bias in the development of various pathologies that are exacerbated by stress (e.g., depression, anxiety, and eating disorders) and their co-morbidity with metabolic disorders like type 2 diabetes, cardiovascular disease, and many forms of cancer. In general, female rodents show higher plasma ghrelin concentrations compared to males. However, feeding responses to peripheral ghrelin are attenuated in female mice compared to males and these responses are augmented if female mice are ovariectomized. Together these data suggest that females, like males, respond to repeated stressors by releasing ghrelin, and the secretion of ghrelin in response to social stressors is associated with stressed induced eating. Here we present data that demonstrates that social defeat stress in females also results in increased ghrelin secretion that is associated with increased intake of a high fat diet. This might be mediated by increased entry of ghrelin into midbrain regions like the VTA following social defeat stress.

S03.2 *Immunometabolic mechanisms modulating emotional dysregulation and impulsivity*

Stephanie Fulton [1]

[1] *Université de Montréal*

The incidence of depression and anxiety is amplified by obesity and metabolic dysfunction. Mounting evidence reveals that the inflammatory consequences of poor diet, inactivity, and visceral adipose accumulation are involved. Research advancements on this front will be presented that highlight the contribution of neuroimmune stimulation and microglia reactivity in the nucleus accumbens to anxiodepressive behaviour and impulsive decision-making in mice and the neural circuits involved. These findings bridge metabolic and affective neuroscience by uncovering mechanisms through which peripheral inflammation alters mesolimbic network function and motivational processes. Furthermore, the work underscores how metabolic stress may sensitize reward-related circuits, promoting vulnerability to mood disturbances and maladaptive eating behaviours.

S03.3 *Brain insulin resistance in mood disorders: Research developments and therapeutic implications*

Rodrigo Mansur [1]

[1] *University of Toronto*

Insulin resistance (IR) is a known modifiable risk factor for the onset and progression of mood disorders. Evidence indicates that IR and IR-related conditions (e.g. obesity) are highly prevalent, and are present in approximately 50% of patients. Longitudinal studies have documented that measures of IR predict the development of mood disorders in adults; IR has been associated with a more chronic and complicated course, as well as with a poor response to pharmacological treatments. As a result, metabolic subtypes of mood disorders have been proposed by several authors and insulin sensitizers have been explored as potential treatments. However, results have been mixed, and findings have yet to be translated to clinical practice. Herein, we will discuss the challenges and future perspectives of this line of research. Insulin is a neuropeptide that exerts its effects in the central nervous system via its canonical receptors, which are widely distributed throughout the brain and are known to be involved in both physiological and pathological processes. Imaging and biomarker studies in healthy and clinical populations have implicated brain insulin signaling in disparate mental functions, more notably cognitive and reward processes. We will focus on novel data, including findings from the first study that is directly assessing brain sensitivity to insulin, and its effects on reward behavior, in a population with mood disorders. We will also discuss the therapeutic implications, and review findings from recent studies testing the safety and efficacy of metabolic agents, including glucagon-like peptide-1 receptor agonists (GLP-1RAs).

S03.4 *Neurometabolic gateways to resilience: Insulin and leptin receptor pathways modulating early-life stress effects on physical and mental health*

Bonnie Alberry [1], Randriely Merscher Sobreira De Lima [1], Ameyalli Gomez Ilescas [1], Angela Marcella Jaramillo Ospina [1], Patricia Maidana Miguel [1], Patricia Pelufo Silveira [1]

[1] *McGill University*

Early-life adversity is a major determinant of lifelong vulnerability to both mental and physical health disorders, yet substantial interindividual variability exists in outcomes following similar exposures. This heterogeneity suggests that specific biological systems gate risk versus resilience. Peripheral metabolic hormones such as insulin and leptin, classically viewed as regulators of energy balance, also act on the brain to influence development, emotional regulation, reward processing, and stress responsivity. Disruption of these neurometabolic pathways may therefore represent a key mechanism linking early adversity to long-term disease risk. In this talk, I will present converging translational evidence showing that insulin and leptin receptor pathways function as neurometabolic gateways shaping long-term outcomes following early-life stress. Using rodent models of prenatal adversity, we demonstrate that early metabolic insults program brain insulin signaling across development in a sex- and circuit-specific manner. In the medial prefrontal cortex, altered insulin signaling is associated with long-lasting changes in gene expression linked to stress regulation and emotional behavior. Complementary work in the nucleus accumbens reveals that prenatal adversity reshapes mesolimbic insulin sensitivity, altering dopamine responsivity to palatable food and producing distinct, developmentally dynamic transcriptional responses to insulin. Together, these findings indicate that early adversity reprograms how reward-related circuits respond to peripheral metabolic signals, with implications for motivation, affect, and eating behavior. Extending these mechanistic findings to humans, I will discuss studies using biologically informed expression-based polygenic scores (ePRS) capturing insulin and leptin receptor gene networks in peripheral tissues and brain-relevant pathways. Across multiple longitudinal cohorts, variation in these gene networks moderates the association between early-life adversity and a range of outcomes, including depression, impulsivity, eating behavior, metabolic risk, and adiposity. Notably, these effects are tissue-, sex-, and development-specific, highlighting the importance of context in neurometabolic programming. Together, this body of work supports a framework in which insulin and leptin receptor pathways integrate early environmental signals with brain and peripheral

physiology to shape trajectories of risk and resilience. Identifying these neurometabolic mechanisms may inform early identification of vulnerability and guide the development of targeted, developmentally informed interventions to promote long-term mental and physical health.

SYMPOSIUM 4:

High-Content Crispr Screens to Understand and Treat Genetic Disorders of the Nervous System

S04.1 *CRISPR-based screening to elucidate the pathogenesis of Parkinson's disease*

Nathan Karpilovsky [1], Konstantin Senkevich [1], Ziv Gan-Or [1], Benoit Vanderperre [2], Stephane Angers [3], Thomas Durcan [1], El Bachir Affar [4], Jian Liu [5], Lara Mahal [6]

[1] McGill University, [2] Université de Quebec à Montréal, [3] University of Toronto, [4] University of Montréal, [5] University of North Carolina at Chapel Hill, [6] University of Alberta

One of the major hallmarks of Parkinson's Disease (PD) is the presence of Lewy bodies, which are comprised of protein aggregates including α-synuclein (αSyn). αSyn aggregates have been shown to spread between cells in the brain and are proposed to drive disease progression, which can be modelled in the lab using synthetically generated preformed fibrils (PFF) of αSyn. To elucidate the mechanisms responsible for cell-to-cell spreading of αSyn pathology, we sought to identify genetic modifiers of internalization of αSyn PFFs into cells by carrying out FACS-based genome-wide CRISPR Knockout (CRISPRko) and CRISPR activation (CRISPRa) screens. The CRISPRko (loss-of-function) screen identified C3ORF58 and SLC39A9, two novel modifiers of heparan sulfate proteoglycan (HSPG) biosynthesis, a process which has been described as the main pathway of PFF entry into cells. The CRISPRa (gain-of-function) screen revealed BAP1, a gene linked to PD risk, as a modifier of PFF uptake through its control of the plasma membrane glycoproteome. BAP1 activation reduces HSPGs while increasing O-linked glycosylation, which is inhibitory for PFF internalization. The effects of BAP1 were recapitulated in dopaminergic neurons, but not in microglia, suggesting cell-specific regulation potentially mediated through BAP1's binding partners. Combining our screening approaches, we have unravelled novel mechanisms and risk genes for PD pathogenesis; however, the promise of targeted phenotypic screens using genetically grounded data has yet to be fully realized. To that end, we are developing an arrayed library of the PD genome amenable to high content image-based screening, comprised of genes prioritized from genome-wide association studies (GWAS), familial PD genetics, and literature-based nominations. Targeted phenotypic screening of such understudied PD genes offers significant promise in elucidating novel mechanisms and associating uncharacterized gene functions with PD pathogenesis.

S04.2 *Probing the synaptome for regulators of alpha-synuclein pathology*

Maxime Rousseaux [1]

[1] University of Ottawa

A central feature of Parkinson's disease is Lewy pathology, composed largely of misfolded alpha synuclein (αSyn). αSyn is normally a synaptic protein, but in disease it can misfold, aggregate, and form fibrils. These fibrils act as seeds that recruit additional αSyn, amplifying pathology. Because Lewy pathology appears in a predictable pattern across connected brain regions, αSyn is thought to spread between neurons. The mechanisms driving this process remain unclear. Synaptic dysfunction occurs early in PD, suggesting that key pathogenic events begin at synapses. Given the native synaptic localization of αSyn, we hypothesized that synaptic proteins may regulate αSyn aggregation and propagation. To identify such factors, we incubated mouse cortical synaptosomes with biotinylated αSyn fibrils (PFFs) or monomers, isolated interacting proteins, and analyzed them by mass spectrometry. This approach revealed 67 synaptic proteins that preferentially associate with fibrillar αSyn. Selected candidates were confirmed by co immunoprecipitation and western blotting. In tandem, to test the how synaptic proteins influence pathology, we performed a CRISPR Cas9 loss of function screen in primary cortical neurons. Lentiviral sgRNAs targeting over 600 synaptically-enriched

genes were introduced, followed by PFF treatment to induce αSyn pathology. High content imaging was then used as the primary readout. Automated microscopy enabled unbiased, single cell quantification of αSyn phosphorylation at serine 129 (pS129), neuronal morphology, and cell health across thousands of cells and conditions. Through this workflow, we found synaptic regulators that modulate αSyn aggregation and spread and do so possibly in a direct manner. These findings may uncover novel therapeutic targets and provide insight into early disease mechanisms relevant to PD intervention.

S04.3 *CRISPR screens define regulatory programs and neurodevelopmental disease relevance in human neural stem cell subtypes*

Yun Li [1]

[1] *University of Toronto*

Background and Aim:The expansion of the human cerebral cortex depend on the tightly regulated proliferation and survival of distinct neural progenitor subtypes, including ventricular radial glia and outer radial glia. Disruption of progenitor growth control is a convergent mechanism underlying a broad spectrum of neurodevelopmental disorders, yet the stage-specific genetic dependencies of these human progenitor populations remain incompletely defined. While recent CRISPR-based functional genomics studies have begun to map essential genes in neural cells, few approaches have systematically compared genetically and developmentally distinct human neural stem cell states. Here, we aimed to define shared and subtype-specific regulatory programs governing survival and proliferation of human neural progenitors, and to connect these programs to neurodevelopmental disease risk. Methods:We established scalable 2D human pluripotent stem cell-derived neural progenitor cultures modeling early ventricular radial glia-like and later outer radial glia-like states, validated by transcriptional profiling and marker expression. We performed parallel genome-wide CRISPR-Cas9 knockout screens using a pooled lentiviral library, maintaining high coverage and matched population doublings across developmental stages. Gene essentiality was quantified using established Bayesian classifiers, and proliferation-restricting genes were identified using enrichment-based analyses. Hits were integrated with single-cell transcriptomic datasets of the developing human cortex and cross-referenced with curated neurodevelopmental and neuropsychiatric disease gene lists. Results: Genome-wide screens identified hundreds of essential genes in each progenitor state, including a core set shared across stages as well as distinct stage-specific dependencies. Comparative analyses revealed progenitor-biased expression patterns in fetal cortex datasets and highlighted pathways differentially required in outer radial glia-like cells. In addition to canonical cell cycle and translational regulators, we identified neural progenitor–enriched essential genes not shared with non-neural cell types. We also defined proliferation-restricting genes, including subtype-specific regulators whose disruption selectively enhanced growth in outer radial glia-like cells. Notably, multiple genes emerging from both essentiality and proliferation-restricting analyses overlap with high-confidence autism, microcephaly, and schizophrenia-associated gene sets. Conclusions:These findings provide a systematic functional map of genetic dependencies across human neural progenitor subtypes and reveal stage-specific vulnerabilities linked to neurodevelopmental disease. Our work demonstrates the power of combining stem cell–based models with genome-wide CRISPR screening to uncover regulatory programs that may not be apparent from transcriptomic data alone. By defining shared and subtype-specific growth control mechanisms, this study offers a framework for understanding how disruptions in progenitor biology contribute to human cortical maldevelopment and for prioritizing candidate disease genes for mechanistic investigation.

S04.4 *Large-scale discovery of neural enhancers for cis-regulation therapies*

Troy Mcdiarmid [1]

[1] *University of British Columbia*

CRISPR-based gene activation (CRISPRa) has emerged as a promising therapeutic approach for neurodevelopmental disorders (NDD) caused by haploinsufficiency. However, scaling this cis-regulatory therapy (CRT) paradigm requires pinpointing which candidate cis-regulatory elements (cCREs) are active in human neurons, and which can be targeted with CRISPRa to yield specific and therapeutic levels of target

gene upregulation. Here, we combine Massively Parallel Reporter Assays (MPRAs) and a multiplex single cell CRISPRa screen to discover functional human neural enhancers whose CRISPRa targeting yields specific upregulation of NDD risk genes. First, we tested 5,425 candidate neuronal enhancers with MPRA, identifying 2,422 that are active in human neurons. Selected cCREs also displayed specific, autonomous in vivo activity in the developing mouse central nervous system. Next, we applied multiplex single-cell CRISPRa screening with 15,643 gRNAs to test all MPRA-prioritized cCREs and 761 promoters of NDD genes in their endogenous genomic contexts. We identified hundreds of promoter- and enhancer-targeting CRISPRa gRNAs that upregulated 200 of the 337 NDD genes in human neurons, including 91 novel enhancer-gene pairs. Finally, we confirmed that several of the CRISPRa gRNAs identified here demonstrated selective and therapeutically relevant upregulation of SCN2A, CHD8, CTNND2 and TCF4 when delivered virally to patient cell lines, human cerebral organoids, and a humanized mouse model of hTcf4. Our results provide a comprehensive resource of active, target-linked human neural enhancers for NDD genes and corresponding gRNA reagents for CRT development. More broadly, this work advances understanding of neural gene regulation and establishes a generalizable strategy for discovering CRT gRNA candidates across cell types and haploinsufficient disorders.

SYMPOSIUM 5:

Hippocampal Circuits In Health and Disease

S05.1 *Local and long-range inputs to the hippocampus that influence diverse behaviours and seizures*

Justin Botterill [1]

[1] *University of Saskatchewan*

The hippocampus is critical for spatial navigation, learning, and episodic memory, whereas hippocampal dysfunction is often associated with psychiatric and neurological disorders. In this talk, I will focus on local and long-range circuits that influence hippocampal function in physiological and pathophysiological states. In the first part of the talk, I will discuss research on a relatively understudied hippocampal cell type known as mossy cells, which reside in the hilus (polymorphic) layer of the dentate gyrus. Mossy cells feature complex local and long-range axonal projections that span the septotemporal axis of the hippocampus to regulate excitation-inhibition balance. I will present data on how mossy cells influence dentate granule cell activity in physiological and pathological states such as epilepsy. I will also show data on the role of mossy cells in cognitive and affective behaviours. In the second part of the talk, I will present unpublished data on the supramammillary nucleus of the hypothalamus (SuM), which sends projections to the dentate gyrus and area CA2 to influence hippocampal activity and support diverse behaviours. Interestingly, the SuM has been minimally investigated in pathophysiological states, and I will present how the SuM and its projections to the dentate gyrus and CA2 contribute to seizures and epilepsy. In vitro slice electrophysiology optogenetics data will show that activating SuM-hippocampal projections can drive epileptiform-like activity, whereas inhibiting this pathway is anti-epileptic. I will also present in vivo data using modern tools (e.g., chemogenetics, optogenetics, dual-color multi-site fiber photometry, and 24/7 electroencephalography recordings) that demonstrates the SuM contributes to acute and chronic seizures . Taken together, this data will demonstrate how local and external inputs to the hippocampus influence its function.

S05.2 *Corrupted hippocampal computations in hyperexcitability*

Jordan Farrell [1]

[1] *Boston Children›s Hospital, Harvard Medical School*

Synchronous population events support memory computations under physiological conditions but may become a substrate for epileptiform activity under conditions of hyperexcitability. We previously found the dentate spike, an understudied local field potential signature recorded in the dentate gyrus, is associated with profound brain-wide spiking activity beyond any known physiological event. Beyond their physiological role in supporting memory, here we show that dentate spikes are distinctly prone to pathological corruption

across a range of mouse models associated with hyperexcitability and epileptiform activity. We also demonstrate that we can leverage this tight association of dentate spikes and epileptiform activity with closed-loop optogenetics to predict the occurence of epileptiform activity and silence it before it has a chance to develop. This work suggests that dentate spikes are a point of convergence for the emergence pathological activity under varied disease conditions, which may inspire generally applicable treatment approaches that maintain precision.

S05.3 *Neuromodulatory control of Hippocampal CA1 VIP interneurons during novel experience*

Xiao Luo [1], Dimitri Topolnik [2], Vandana Dulam [2], Aurélie Bergeron [2], Louis-David Coulombe [2], Megan Besner [2], Justine Fortin-Houde [3], Judy Davies [2], Félix Michaud [1], Risna Kanjirassery Radhakrishnan [1], Bénédicte Amilhon [4], Lisa Topolnik [2]

[1] Université Laval, [2] Laval University, [3] Université de Montréal, [4] Université de Montréal - Centre de Recherche Azrieli du CHU Sainte-Justine

How hippocampal circuits adapt to novel experience depends critically on disinhibitory circuits formed by VIP interneurons, which transiently relieve inhibition to reconfigure network processing, yet the neuromodulatory mechanisms that recruit these cells remain poorly understood. Here, we show that input from the median raphe nucleus dynamically gates the engagement of CA1 VIP interneurons during novelty through complementary glutamatergic and serotonergic signaling. This work identifies a brainstem-driven mechanism for flexibly tuning hippocampal disinhibition and highlights neuromodulation as a key regulator of VIP interneuron recruitment during experience-dependent circuit states.

S05.4 *Inhibitory hippocampal neurons with extended reach*

Esther Krook-Magnuson [1]

[1] University of Minnesota

The hippocampus -- a brain region important for learning and memory -- is enriched with a diversity of neuronal cell-types, including a large variety of inhibitory neurons. While “interneuron” and “inhibitory neurons” are often used interchangeably when discussing the hippocampus, hippocampal inhibitory neurons can also be projection neurons, with an extensive and extended reach. While less numerous than other types of hippocampal inhibitory neurons, hippocampal inhibitory projection neurons are found broadly within the hippocampus, originating from a variety of hippocampal regions, including the dentate, CA3, CA2, and CA1, and along the entire anterior-posterior axis of the hippocampus. In addition to originating from a range of hippocampal regions, hippocampal inhibitory projection neurons can target a large diversity of downstream targets. Long-range inhibitory nNOS-expressing cells (LINCs) alone project to a range of brain regions, including the tenia tecta and the supramammillary region (SuM), illustrating the breadth of influence even one type of hippocampal inhibitory projection neuron can have. We find that LINCs are not the only hippocampal long-range inhibitory neuron type to project to the SuM, with a population of M2R-negative, somatostatin-positive, inhibitory neurons also providing key inputs to the SuM. Inhibitory hippocampal projections to the SuM preferentially target SuM neurons that themselves project to the hippocampus. Inhibitory neurons appear to be the sole connection from the hippocampus proper to the SuM, further highlighting the importance of inhibitory hippocampal projections in interregional communication. Hippocampal GABAergic projection neurons can influence oscillations and coordinate activity within and across brain regions, and ultimately help shape cognition.

SYMPOSIUM 6:

Glial-Neuron and Glial-Immune Interactions in Nervous System Development and Repair

S06.1 *Myeloid cells regulate myelination in the developing central nervous system*

Alana Hoffmann [1], Rebecca Holloway [1], Annette J. Haughian [1], Gessica Goncalves [2], Justyna Cholewa-Waclaw [3], Anna Raper [3], Katherine R. Long [2], Veronique Miron [1]

[1] Unity Health Toronto, [2] King›s College London, [3] The University of Edinburgh

Myelin is the insulating membrane surrounding central nervous system (CNS) axons and is required for their health and function. It is formed by oligodendrocytes in a process called myelination and starts in the developmental period. Despite the known importance for myelin in sensory, motor and cognitive function, there is still a lack of understanding of the fundamental mechanisms regulating developmental myelination. Though CNS myeloid cells as a whole have been implicated in myelination, the role of individual subsets is still unknown. CNS myeloid cells encompass several populations including microglia in the parenchyma, border-associated macrophages (BAMs) at border regions, and infiltrating monocytes. Surprisingly, our recent work used a mouse model specifically lacking microglia to uncover that microglia alone are not required for myelination. To study the roles of the other myeloid cell populations in regulating myelination, we developed transgenic models specifically depleting BAMs or monocytes. We found that BAMs in white matter regions emerge during myelination initiation in mouse and human brain, and consist of two subpopulations known to derive from yolk sac progenitors (LYVE1+ or CD38+) or infiltrating monocytes (MHCII+). Lineage tracing revealed that depletion of BAMs led to replacement by monocytes, increasing the MHCII+ subpopulation, which was associated with increased myelination. In addition, inhibition of monocyte infiltration alone (in the presence of BAMs) reduced myelination. Overall, we reveal distinct roles of myeloid cell populations in developing white matter, and uncover that monocyte-derived cells promote myelination either directly or by compensating for the loss of brain macrophages. These findings have important implications for understanding how myelination is affected following CNS injury - where BAMs are known to be depleted and monocytes are increased – now identifying a novel cellular target to sustain myelin health.

S06.2 *Oligodendroglial regulation of cortical maturation and plasticity*

Wendy Xin [1]

[1] University Health Network

The generation of oligodendrocytes and myelin is extremely protracted relative to other neurodevelopmental processes, spanning the first few decades of human life. Perhaps as a result, myelin deficits are a common pathological hallmark across many neurodevelopmental and psychiatric disorders, including autism spectrum disorders, schizophrenia, and mood disorders. To determine how developmental oligodendrogenesis and myelination influence neuronal circuit maturation and function, we genetically blocked oligodendrogenesis by deleting the transcription factor Myrf specifically from oligodendrocyte precursor cells in juvenile mice. We then assessed neuronal function and plasticity in the adult visual cortex using a combination of in vivo functional/structural imaging and ex vivo slice electrophysiology. In adult mice lacking developmental oligodendrogenesis (Myrf cKO), synaptic connectivity was significantly impaired, with inhibitory synaptic inputs being markedly reduced relative to excitatory inputs. Furthermore, synaptic turnover was enhanced in Myrf cKO mice, with a pronounced increase in the rate of synapse elimination. Functionally, sensory-evoked neuronal activity was dampened in adult Myrf cKO mice relative to control mice, and altering sensory input led to a form of experience-dependent neuronal plasticity normally restricted to juvenile mice. These results demonstrate a crucial role for oligodendrocytes and myelin in cortical circuit maturation and support the concept of therapeutically targeting oligodendrocyte lineage cells in neurodevelopmental disorders that present with dysmyelination.

S06.3 *Chromatin regulator Ankrd11, associated with neurodevelopmental disorders, regulates glial cell development and function*

Anastassia Voronova [1]

[1] University of Alberta

While neurons are the main signalling cell types in the brain, recent work has emphasized the role of glia (non-neuronal cells) in orchestrating brain development and function. Glia include neural stem cell (NSC) derived cells, such as ependymal cells, which line the brain lateral ventricles and circulate the cerebrospinal fluid, and oligodendrocytes, which myelinate axons for proper signal propagation. These cells interact with yolk-sac derived microglia (brain macrophages). Chromatin regulation controls the spatiotemporal formation and/or function of several glial cell types. ANKRD11 (Ankyrin Repeat Domain 11) regulates global gene expression via interactions with histone (de)acetylases and is one of the most frequently de novo mutated gene in monogenic neurodevelopmental disorders. We have previously shown Ankrd11 regulates formation of neurons. However, the role of Ankrd11 in glia is unknown. To address this gap, we conditionally knocked out Ankrd11 in murine NSCs via the tamoxifen inducible Cre/Lox system at embryonic day 14, prior to the start of gliogenesis, but after the majority of neurons is formed (Ankrd11fl/fl;NestinCreERT2 or Ankrd11nscKO). By postnatal day (P) 7-10, Ankrd11nscKO brains displayed hydrocephalus. This was accompanied by aberrant formation of ependymal cells and increased numbers of microglia. Single nucleus RNA sequencing (snRNA-seq) of P15 lateral dorsal ventricle wall and corpus callosum (myelin tracts) showed transcriptionally divergent subsets of oligodendroglia, suggesting aberrant function of Ankrd11-deficient oligodendrocytes. Transmission electron microscopy confirmed aberrant myelin formation by the Ankrd11nscKO oligodendrocytes. Moreover, snRNAseq showed a shift from homeostatic to a disease associated microglia in the Ankrd11nscKO brain, suggesting an aberrant communication of Ankrd11-deficient NSCs with yolk-sac derived microglia. In agreement, co-cultures of wild-type microglia with Ankrd11nscKO NSCs showed an increase in microglia proliferation and reactivity, when compared to control NSCs. Thus, Ankrd11 is a critical regulator of glial differentiation of NSCs, as well as their communication with microglia. These results could shed light on the mechanism of common brain phenotypes in patients harbouring ANKRD11 variants.

S06.4 *Glial CB1 receptors drive NMJ plasticity in injury and ALS*

Roberta Piovesana [1], Sophie Charron [1], Danielle Arbour [1], Luigi Bellocchio [2], Giovanni Marsicano [2], Richard Robitaille [1]

[1] Université de Montréal, [2] INSERM

Neuromuscular junction (NMJ) maturation and repair require coordinated neuron–glia interactions, yet the molecular mechanisms by which perisynaptic Schwann cells, the glial cells at the NMJ, regulate motor synapse stability remain incompletely defined. Although the endocannabinoid system is a major modulator of neural plasticity, its role in peripheral synapse development and degeneration is unknown. Here, we demonstrate that glial cannabinoid type-1 receptors (CB1Rs) are essential regulators of NMJ maturation, reinnervation, and stability across development, injury, and amyotrophic lateral sclerosis (ALS). Genetic or pharmacological inhibition of CB1R signaling delayed postnatal synapse maturation and impaired reinnervation following nerve injury. Conversely, premature CB1R activation accelerated morphological maturation but disrupted coordinated innervation, indicating that temporally balanced CB1R signaling is required for proper synaptic assembly. In SOD1G37R ALS mice, CB1R expression declined early at vulnerable NMJs and reached minimal levels at symptomatic stages. Functionally, CB1R blockade exacerbated denervation and accelerated motor decline, whereas systemic CB1R activation preserved NMJ integrity and improved motor performance. Together, these findings identify glial CB1R signaling as a key determinant of motor synapse plasticity and reveal a therapeutically targetable pathway for ALS.

SYMPOSIUM 7:

Hypothalamic Peptides in Dual Control of Homeostasis and Behaviour

S07.1 *Glial cells as regulators of fluid and cardiovascular homeostasis*

Masha Prager-Khoutorsky [1]

[1] *McGill University*

The brain continuously monitors and fine-tunes internal physiological states to maintain fluid balance and blood pressure. The contribution of hypothalamic neuronal populations to these homeostatic regulations through the coordination of neuroendocrine, cardiovascular, and fluid balance systems has been well established. However, the role of glia in these processes remains less clear. Our recent studies suggest that diverse hypothalamic glia populations, including tanycytes, astrocytes, and microglia, play key roles in regulating neuronal activity, brain-body communication, thereby contributing to fluid balance and cardiovascular regulation in healthy states and conditions associated with fluid imbalances. These glial cells perform multiple functions, including sensing and responding to circulating molecules, gating their access to the brain, generating new neurons and glia, and modulating synaptic communication and neuronal activity to regulate physiology (e.g. hydration & blood pressure) and behavior (e.g. thirst). These findings highlight the critical role of glia in governing homeostatic regulation in health and disease.

S07.2 *Fructose fuels hunger at the hypothalamus*

Mikayla Payant [1], Persephone Miller [1], Aditi Sankhe [1], Jenny Phy-Lim [1], Yasmina Dumiaty [2], Sarah Vieira [1], Melissa Chee [1]

[1] *Carleton University,* [2] *McGill University*

Fructose is commonly added to processed foods and baked goods as a sweetener to increase food palatability, but the rise in fructose intake is a major driver of obesity. In the brain, specialized neurons in the arcuate nucleus that produce Neuropeptide Y and agouti-related peptide (NPY/AgRP) are powerful stimulators of food intake and weight gain, and fructose intake can increase Npy mRNA expression. However, it is not known if fructose intake impacts the function of NPY/AgRP neurons. We confirmed that both male and female mice fed a 60% high fructose diet ate more calories and gained more body fat than mice fed standard chow or an isocaloric high dextrose diet. To elucidate the mechanisms underlying fructose-mediated obesity, we performed ex vivo patch-clamp recordings from NPY/AgRP neurons. While fructose feeding did not alter the excitability of NPY/AgRP neurons, it markedly increased and sustained synaptic excitation by promoting glutamatergic afferent input to NPY/AgRP neurons. This synaptic profile at NPY/AgRP neurons following fructose feeding mimicked that during hunger and may occur independently of any metabolic effects from fructose. Importantly, these findings implicated glutamatergic, fructose-sensitive candidates that innervate NPY/AgRP neurons and that may be fructose-sensitive. These neural maladaptations represent novel avenues to intercept the obesogenic actions of dietary fructose on the brain.

S07.3 *Axonal Oxytocin signaling in rat and human brain*

Valery Grinevich [1]

[1] *Heidelberg University*

Over the past decade, major advances have deepened our understanding of the oxytocin (OT) system, yet a central question remains: how can a single neuropeptide mediate such diverse actions in the brain? I propose that this diversity arises from distinct types of OT neurons, their widespread axonal projections, and the variety of OT-responsive cell populations across brain regions. In this talk, I will focus on axonal OT projections to the medial prefrontal cortex in rats, demonstrating OT action on local interneurons and its profound facilitation of social interactions. I will also present complementary findings from human stem cell-derived OT neurons, which extend axons toward cortical assembloids and, when integrated into the rat hypothalamus, form functional connections with multiple brain regions and the pituitary. Together, these results reveal conserved principles of axonal OT signaling across species, shedding light on the mechanisms underlying the peptide's diverse functions in the mammalian brain.

S07.4 *Oxytocin enhances social interaction by rescuing shared social circuit disruptions across two autism-risk genes*

Aishwarya Patwardhan [1], Emily Tse [1], Atyan Moslemian [1], Katrina Choe [1]

[1] *McMaster University*

Autism spectrum disorder (ASD) has a strong genetic basis, but the mechanistic link between ASD-risk gene mutations and social phenotypes remains unclear. Mice with loss-of-function mutations in ASD-risk genes Cntnap2 and Fmr1 exhibit lower sociability, allowing dissection of how distinct molecular perturbations converge on similar behavioral outcomes. We and others have reported that both mutations disrupt hypothalamic OXT neurons (Kadoba et al., 2014, Peñagarikano etc al., 2015, Patwardhan & Li et al., 2025). Given the central role of these neurons in social processing through OXT release and modulation of downstream social circuits, we hypothesized that disrupted OXT signaling in key social regions is a common circuit-level mechanism underlying low sociability in Cntnap2- and Fmr1-KO mice. To test this, we examined social investigation-associated neuronal activity in the nucleus accumbens shell (NAcSh) and central lateral amygdala (CeAL), two regions that play critical roles in social reward and salience, in adult (10-13 weeks old) Cntnap2- and Fmr1-KO mice and their wildtype (WT) littermates. Fiber photometry recordings of population-level neuronal activity (using Ca^{2+} signals as a proxy) revealed distinct sex differences in social investigation-associated neuronal activity phenotypes in both regions. NAcSh D1-MSN activity increased during social investigation in WT males, but decreased in KO males. CeAL neurons revealed increased activity during social investigation in WT females, but decreased activity in KO females. No genotype differences were observed when we compared NAcSh activity in females and in CeAL activity in males. To examine whether these altered NAcSh/CeA activity dynamics during social investigation are associated with aberrant local OXT release patterns, we recorded its release dynamics with the GRAB-OT sensor (Qian et al., 2023). We found NAcSh OXT levels increased during social investigation in WT males, but not in Cntnap2-KO males. Data collection is ongoing to examine social investigation-associated OXT release in both NAcSh and CeAL in our other experimental groups. Finally, we tested whether restoring OXT release could rescue these NAcSh/CeAL activity phenotypes. Optogenetic stimulation of PVN-OXT fiber terminals, targeted specifically to the NAcSh in males, or the CeAL in females, reinstated WT-like activity dynamics and significantly increased social interaction durations in both KO models. Together, these data reveal convergent effects of two ASD-risk gene mutations on OXT modulation of social circuits in a sex-divergent manner. Moreover, normalizing activity within these circuits through evoked OXT release rescues both circuit and behavioral phenotypes in a sex-specific fashion, highlighting shared circuit dysfunction across ASD-risk gene KO models and identifying sex-informed targets for OXT-based intervention.

SYMPOSIUM 8:

Reassessing Structural Plasticity in Depression: Rodent–Human Evidence and Rapid Antidepressant Mechanisms

S08.1 *Infralimbic DCC receptors regulate social avoidance and dendritic architecture in the cortico-accumbens pathway*

Ashraf Mahmud [1], Radu Gabriel Avramescu [2], Fatme Abboud [2], Daniela Gaytan Zamudio [2], Angela Ferreiro Osorio [2], Cecilia Flores [1]

[1] *McGill University,* [2] *Douglas Research Center*

Major depressive disorder is characterized by impaired neuroplasticity and structural atrophy within the prefrontal cortex (PFC). While the guidance cue receptor DCC (Deleted in Colorectal Cancer) is primarily known for organizing neural connections during development , it remains expressed in the adult brain where it regulates synaptic reorganization and stress susceptibility. Our research investigates how social stress in adulthood utilizes distinct axon guidance systems to remodel PFC-to-nucleus accumbens (NAc) circuitry in a sex-specific manner. Using a chronic social defeat stress (CSDS) paradigm, we demonstrate that adult

male and female mice exhibit divergent molecular responses within the PFC. In males, stress susceptibility is driven by the upregulation of Dcc mRN. Specifically, CSDS induces a significant loss of mature mushroom spines on the apical dendrites of infralimbic (IL) PFC neurons projecting to the NAc shell. This structural atrophy correlates highly with social avoidance, and targeted downregulation of Dcc within this IL-NAc shell pathway appears sufficient to confer behavioral resilience. In contrast, adult female mice subjected to CSDS do not seem to show a large dysregulation of the Netrin-1/DCC system in the PFC. Instead, their response is characterized by the engagement of the Slit/Roundabout (Robo) guidance cue system. Defeated females show elevated Slit2 and Robo1 mRNA. These findings identify DCC as a key molecular trigger of stress-induced PFC structural plasticity and suggest that the Slit/Robo system may serve a parallel role in females, remodeling motivation-relevant circuitry. This highlights the necessity for sex-specific therapeutic strategies that target guidance cue processes in depression.

S08.2 *Rules for psychedelic therapeutic neuroplasticity*

Tyler Ekins [1], Chloe Rybicki-Kler [1], Tao Deng [1], Izabela Jedrasiak-Cape [1], Isla Brooks [1], Omar Ahmed [1]

[1] University of Michigan

Classical psychedelic drugs show promise as a treatment for major depressive disorder and related psychiatric conditions. This therapeutic efficacy stems from long-lasting psychedelic-induced neuroplasticity onto prefrontal cortical neurons and is thought to require the postsynaptic expression of serotonin 2A receptors (5-HT2AR). However, other cortical regions such as the granular retrosplenial cortex (RSG) – important for memory, spatial orientation, fear extinction, and imagining oneself in the future, but also impaired in depression and Alzheimer's disease – lack 5-HT2AR and are thus considered unlikely to benefit from psychedelic therapy. Here, we show that RSG pyramidal cells lacking postsynaptic 5-HT2A receptors still undergo long-lasting psychedelic-induced synaptic enhancement. A suite of newly engineered mouse lines reveals specific receptor-based rules for this plasticity. Experiments in preclinical neuropsychiatric mouse models show that impaired cell-type-specific synaptic activity can be rescued by psychedelic treatment, even at advanced stages of disease progression. These results suggest a broader psychedelic therapeutic utility than currently appreciated, and highlight the potential for psychedelic neuroplasticity even in brain regions that lack of 5-HT2A receptors.

S08.3 *Synaptic PET imaging: Closing the bench-to-bedside-and-back loop in psychiatry*

Ruth Asch [1], Irina Esterlis [2]

[1] UT Southwestern Medical Center, [2] Yale School of Medicine

Recent advances in positron emission tomography (PET) using radioligands targeting synaptic vesicle protein 2A (SV2A), such as [18F]SynVesT-1, now permit quantification of synaptic density in the living brain, offering a powerful translational bridge between mechanistic preclinical research and studies in human clinical populations. Here, we integrate evidence from rodent and human SV2A PET studies to examine how stress- and symptom-related synaptic alterations map onto behavior, molecular processes, and affective symptom dimensions. For preclinical experiments, male and female rats exposed to chronic unpredictable stress exhibited significant reductions in synaptic density measured with SV2A PET in prefrontal cortex and hippocampus relative to controls. Observed synaptic deficits were associated with anhedonia-like behavior and cognitive impairment. Proteomic analyses were performed to link in vivo imaging with molecular measures additional molecular measures. Findings revealed significant relationships between the SV2A PET outcome measure and the abundance of proteins implicated in synaptogenesis and neurodegeneration. Extending to humans, SV2A PET was used to measure synaptic density in a transdiagnostic sample of middle- to older-aged adults. Greater depressive symptom severity was associated with lower synaptic density across functional brain networks. Further analysis revealed synaptic density within specific circuits differentially contributed to depressive symptoms, with notable sex differences: in males, executive control network was most strongly associated with depressive symptoms, with salience network predominating in females. Together, these findings provide convergent preclinical and clinical evidence that stress-related affective and cognitive symptoms are associated with synaptic deficits in corticolimbic brain networks that

we demonstrate can be measured in vivo using SV2A PET. Critically, these studies provide a novel framework that capitalizes on the translational potential of SV2A PET, laying the groundwork for translational research that can identify and evaluate novel mechanisms subserving synaptic alterations and subsequent symptom expression in psychiatric disorders.

S08.4 *Rapid effects of ketamine on plasticity mechanisms across levels of analysis: Findings from clinical trials*

Rebecca Price [1]

[1] *University of Pittsburgh School of Medicine*

Ketamine is known for its rapid antidepressant effect, which is hypothesized to be rooted in rapid enhancement of neuroplasticity mechanisms. However, ketamine's impact across a range of putative 'plasticity' markers in human patients remains relatively unexplored. These potential markers are measurable across multiple levels of analysis, and include: affective information processing patterns (e.g., attentional bias towards sad content); cognitive flexibility in goal-directed decision making (e.g., 'model-based' planning); psychological/conscious experiences (e.g., experiences of awe, vastness, connectedness, etc.); and neuroimaging markers of functional and structural connectivity. In a series of studies using both randomized (RCT) and open-label designs in depressed patients, we harnessed a single dose of ketamine (0.5mg/kg over 40min) to assess mechanistic shifts in a range of integrative 'plasticity' markers and their relation to antidepressant efficacy. Rapid antidepressant effects of ketamine were evident in clinical outcomes across all datasets. Patients exhibited a robust reduction in attentional bias toward sad film content—a marker of plasticity at the level of affective information processing—from pre- to 24-hrs post-ketamine infusion, and changes in attentional bias were correlated with improved symptoms from pre- to post-infusion. Patients also reported robust, ketamine-specific acute infusion day experiences of 'awe,' a marker of subjective cognitive mindset, which strongly mediated both rapid and more enduring antidepressant effects of ketamine. Patients exhibited rapid, ketamine-specific shifts in both structural and functional neuroimaging markers of neuroplasticity within prefrontal and affective circuits, which were tied to the degree of depression improvement across individuals. In contrast, no evidence emerged across several datasets for a rapid effect of ketamine on behavioral indices derived from the 'two-step task,' a performance-based index of cognitive flexibility and goal-directed behavior. Findings across multiple levels of analysis indicate that ketamine reliably and rapidly impacts several specific markers of cognitive, behavioral, and neural plasticity, including attentional bias, structural and functional connectivity, and induces an acute cognitive shift towards self-reported 'awe-like' experiences; and yet, does not impact 'model-based planning,' a specific form of cognitive flexibility that has been previously associated with clinical phenotypes (most notably, compulsivity). Findings offer novel translational insights into the precise mechanisms involved in ketamine's rapid antidepressant action among human patients, informing an integrative model of ketamine's rapid, plasticity-enhancing effects.

SYMPOSIUM 9:

Guiding Behavior Through Reward-Predictive Cues

S09.1 *Attributing value to attributes during value-based decision-making*

Erin Rich [1], **Aster Perkins** [1]

[1] *New York University*

The orbitofrontal cortex (OFC) is known to be important for evaluation, choice, and motivated behavior, but theories on its precise role have continually evolved. In this talk, I will discuss new perspectives on OFC function in light of work from our lab and others. I will focus on our recent finding that information encoded by OFC neurons is dynamically modulated by visual attention and argue that these dynamics also reflect evolving computations that underlie the decision process. Specifically, we find that activity in OFC reflects a sequential process of evaluating individual attributes of multi-attribute options and comparing them

against the similar attribute of the other option, with shifts in attribute comparison occurring with shifts of gaze. I will conclude by suggesting that a useful framework to understand these data comes from theories of embodied decision-making, in which moment-by-moment processing is determined by ongoing interactions between the individual and their environment.

S09.2 *dACC stimulation suppresses exploration*

Becket Ebitz [1], Rishabh Singhal [1]

[1] Université de Montréal

Neurons in the dorsal anterior cingulate cortex (dACC) are correlated with many task-relevant variables, including errors, value, and exploratory decisions. However, the causal role of dACC in these processes remains unclear. To address this question, we used electrical microstimulation to perturb dACC activity in a non-human primate performing a sequential decision-making task. Although dACC neurons were correlated with errors and performance, stimulation had a highly selective behavioral effect: it transiently suppressed the initiation of exploratory decision-making. Stimulation after exploration began had no effect, stimulating nearby regions had no effect, and a control experiment confirmed that dACC stimulation did not function as a supplementary reward. To understand the mechanism by which dACC stimulation supressed exploration, we recorded from populations of dlPFC neurons during a subset of stimulation sessions. We recovered dlPFC spiking activity during and after dACC stimulation trains through a processing pipeline that orthogonalized the raw signal from the stimulation artifact. The immediate neural response to stimulation weakly the predicted magnitude of the behavioral effect, but the best predictor was the extent to which stimulation shifted neural activity along an explore-exploit axis during a pre-choice epoch. Together, these results suggest that dACC stimulation is sufficient to deepen exploitative states and shift the dlPFC population's position with respect to the explore-exploit decision boundary.

S09.3 *Orbitofrontal neurons encode both the relative and absolute predictive credit of reward cues*

William Esber[1]

[1] Concordia University

Behavior is guided by cues that predict important outcomes, yet how cues acquire predictive credit remains unclear. Although classical theories propose that credit depends on a cue's relative validity compared with other predictors, growing evidence shows that cue-evoked behavior can also reflect absolute validity. Individual differences in how people and animals assign credit suggest that relative and absolute modes lie on a continuum. We examined the role of the lateral orbitofrontal cortex (lOFC) in this continuum. Using a task in which relative and absolute credit assignment generate opposite response patterns to two target cues, we recorded single-unit activity in rats characterized behaviorally as relative or absolute learners. Distinct lOFC neuronal subpopulations tracked either relative or absolute cue validity, independent of behavioral phenotype, but the proportions of these subpopulations predicted each animal's profile. Moreover, opto- and chemogenetic inhibition of lOFC facilitated relative credit assignment. These results reveal parallel lOFC representations of relative and absolute predictive validity.

S09.4 *Distributed dynamics of decisions about actions*

Paul Cisek [1], Ayuno Nakahashi [2]

[1] Université de Montréal, [2] German Primate Center

Many previous studies have shown that neural activity in prefrontal areas reflects information pertinent to ongoing decisions, suggesting that decision-making is part of the frontal lobe's executive functions. However, decision-related neural modulation is also observed in sensorimotor areas. Does this imply that these areas are also causally involved in the decision process? Or are they instead merely recipients of the final decision, which is made in the prefrontal cortex on the basis of a unified, integrated estimate of utility? Here, we investigated neural activity in the dorsal premotor (PMd) cortex and the parietal reach region (PRR), while

rhesus monkeys performed a multi-attribute value-based decision task. In the task, subjects are presented with reach targets whose reward value is indicated by two attributes - its brightness (”bottom-up” feature) and its orientation (“top-down” feature). Importantly, in some cases (“conflict trials”) the two attributes differ but the total value for each target is nonetheless equal. We predicted that the latency of choice-predictive activities in PMd and PRR would reflect their causal role, especially when the attributes are in conflict. A population analysis of early-tuned cells showed that both PMd and PRR predicted choices before action execution, with PMd often preceding PRR. Furthermore, conflict resolution was biased by baseline activity in PMd, but not PRR. However, a neural space analysis on the entire population showed that neural state trajectories of bottom-up choices reflected the monkey’s choice earlier in PRR than in PMd, whereas the opposite was true for top-down choices. This is not consistent with the hypothesis that a unified decision command is sent to these regions from other brain areas, such as prefrontal cortex. It instead supports models where, at least in the case of choosing between concrete reach actions, value-based decisions are made at the individual attribute levels in a distributed decision network that also includes PMd and PRR.

SYMPOSIUM 10:

Rna Modifications: Implications for Brain Function and Behavior

S10.1 *Deciphering the roles of m6A and YTHDF proteins in synaptic function and plasticity*

Mathieu Flamand [1]

[1] *Université Laval*

RNA modifications have emerged as a pervasive feature of cellular mRNAs with diverse impacts on gene expression. N6-methyladenosine (m6A), the most abundant internal mRNA modification, is involved in the control of mRNA processing, stability, and translation and has important roles within the nervous system. Studies in animal models have revealed severe neurodevelopmental and cognitive deficits linked to disruptions in mRNA modification machinery. However, the specific molecular mechanisms through which m6A mediates these effects remain poorly defined. We previously found that m6A contributes to the localization of select mRNAs to dendrites and axons in mouse hippocampal neurons. We propose that m6A readers interact with distinct proteins in both the soma and synapses, thereby locally regulating gene networks crucial for synaptic plasticity. We hypothesize that disruption in these networks cause defects in synaptic function and contribute to the progression of neurodegenerative disorders associated with cognitive impairment. Advancements in this line of research critically rely on a better understanding of the local interactions and functions of RBPs in the brain. However, the tools to identify interactions in neurites harboring functional synapses are lacking. To overcome this obstacle, we are developing proximity labeling methods to map protein-protein and protein-RNA interactions in neuronal projections in vitro and at synapses in vivo. By integrating biochemical assays, transcriptomic analyses, and advanced imaging techniques, we aim to elucidate the complex roles of m6A readers at synapses and understand how their functions are altered during neurodegeneration.

S10.2 *Circular RNA-derived micropeptides at the synapse: a new mechanism of plasticity and memory?*

Timothy Bredy [1]

[1] *Queensland Brain Institute*

Circular RNAs (circRNAs) are enriched in synapses and implicated in cognitive processes, and recent studies have shown that circRNAs can encode micropeptides, which suggests that there may be novel synaptic proteoforms in the brain that await discovery. Here we report the discovery of a synapse-enriched micropeptide (P1) that is derived from a single exon circRNA, the mRNA host of which encodes an E3 ubiquitin ligase associated with protein turnover and repair. Although P1 is only a third of the size of the full-length protein, it is locally expressed, enzymatically active, and interacts with plasticity-related proteins,

including CaMKIIα. In addition to direct effects on synaptic activity, targeted P1 knockdown impairs whereas its overexpression enhances fear extinction memory. These findings shed new light on the 'dark' proteome in the brain and reveal circRNA translation as a novel mechanism of plasticity and memory.

S10.3 *The role of m6A in behavioural plasticity in Drosophila melanogaster*

Ina Anreiter [1]

[1] *University of Toronto*

RNA modifications have emerged as key regulators of gene expression, affecting translation, RNA stability and subcellular localization. In recent years, one of the most common RNA modifications, N6-methyladenosine (m6A), has been shown to influence brain development, cognitive functions, and behavior. We will discuss work using Drosophila as a model organism to explore the role of m6A in regulating behavioural plasticity including feeding behaviour and neuroinflammation. Using a CRISPR-Cas9 knockout of Mettl3, the methyltransferase that deposits m6A on mRNA, we show that knockout animals have reduced lifespans, while partial rescue extends lifespan. We show that this phenotype is linked to altered feeding behaviour and energy homeostasis, key regulators of lifespan, and deficient stress response in the brain with links to neurodegeneration.

S10.4 *RNA modulation in brain disorders*

Yanhong Shi [1]

[1] *Beckman Research Institute of City of Hope*

RNA modifications occur in all classes of cellular RNAs and play important roles in important biological processes and pathological events. Increasing studies demonstrate that RNA modifications could have key regulatory roles parallel to those of DNA and protein modifications. The biological relevance of RNA modifications in development and human diseases has been explored extensively in recent years. Our study aims to decipher the functional roles and underlying mechanisms of RNA modification in brain disorders. We will explore how RNA modification impacts the nervous system and dysregulated RNA modification links to brain disorders.

SYMPOSIUM 11:

Sex and Gender Influences on Stress Disorders and Cognitive Bias

S11.1 *Characterizing the sex-specific functional networks underlying chronic stress-induced negative cognitive bias*

Amanda Namchuk [1], Yagoda Oleksak [2], Kanak Gupta [3], Sandra Ledesma-Corvi [4], Andrew J. McGovern [4], Samantha Blankers [1], Liisa Galea [4]

[1] *Centre for Addiction and Mental Health,* [2] *University of Toronto,* [3] *University of Toronto, CAMH,* [4] *Centre for Addiction & Mental Health*

Major depressive disorder (MDD) is a debilitating illness affecting 2x more females than males. Negative cognitive bias (NCB), or the interpretation of ambiguous stimuli as negative, is a treatment-resistant cognitive symptom of MDD. Disrupted functional connectivity between limbic and reward regions is a hallmark of MDD, but little is known about the functional connectivity underpinning NCB. We used 21 days of chronic unpredictable stress (CUS) to induce depressive-like endophenotypes in male and female rats and administered a fear conditioning-based cognitive bias task. Following 16 days of training in negative (shock-paired) and neutral (no shock) contexts, freezing was assessed in an ambiguous context with a mix of cues from the negative and neutral contexts. We stained resulting brain tissue for the immediate early gene cFos, and used graph theory to construct functional connectivity networks. We found that CUS increased freezing in the ambiguous context, suggesting increased NCB in both sexes, but through sex-specific mechanisms. CUS disrupted the functional networks recruited in response to ambiguity, shifting the regional activation that

best predicted NCB from the infralimbic cortex and nucleus accumbens to the amygdala and subiculum in males, and from the dorsal hippocampus and retrosplenial cortex to the amygdala and nucleus accumbens in females. Next, to characterize what types of neurons were activated in response to the ambiguous context, we used multiplex in situ hybridization to visualize Fos and cell type markers such as transporters and neuropeptides in the hippocampus and amygdala. Females exposed to CUS exhibited a higher ratio of inhibitory to excitatory activity in the basolateral amygdala compared to all other groups. Together, these data suggest that a CUS-induced increase in interneuron activity within amygdala microcircuitry may drive increased NCB in females, but not in males. Advancing our understanding of the sex-specific mechanisms driving NCB could help improve treatment options for MDD.

S11.2 *Beyond the Binary: Unraveling Sexually Polymorphic Cognition Across Biological and Sociocultural Dimensions*

Robert-Paul Juster [1]

[1]*University of Montreal*

Background: Sexually polymorphic cognition (SPC)—the variability in cognitive abilities influenced by sex- and gender-related factors—has long been oversimplified by binary frameworks. The SEXCOG study aimed to integrate biological (birth-assigned sex, sex hormones) and socio-cultural (gender identity, gender roles, sexual orientation) dimensions to better characterize SPC in cisgender, transgender, and nonbinary adults.

Methods: Across four complementary analyses involving 222–488 participants, adults completed an extensive 150-minute cognitive battery covering spatial, verbal, memory, and fine motor tasks. Participants provided saliva samples for hormone assays (testosterone, estradiol, progesterone, DHEA, cortisol) and completed psychosocial measures. Experimental conditions manipulated gender stereotype exposure to assess its impact on cognition.

Results: Biological and psychosocial factors jointly shaped SPC. Sex hormones better predicted performance on male-typed spatial tasks, whereas gendered variables (gender roles, sexual orientation) better explained variance in female-typed verbal tasks. Sexual orientation modulated both cognitive performance and DHEA levels, particularly among women. Gender diverse participants showed hybrid or enhanced cognitive profiles, performing similarly to cis men on spatial tasks, to cis women on fine motor tasks, and superiorly on verbal learning. Explicit gender stereotype priming did not directly alter performance but interacted subtly with group differences.

Conclusion: SPC emerges from dynamic intersections between biology and culture rather than binary sex categories. Integrating hormonal, gender identity, and psychosocial indices clarifies why prior “sex difference” findings have been inconsistent and underscores the importance of inclusivity in.

S11.3 *Sex differences in long-term stress susceptibility after adolescent stress exposure*

Derya Sargin [1]

[1] *University of Calgary*

Adolescence is a sensitive period of brain maturation characterized by heightened plasticity and increased vulnerability to stress. Chronic stress during this adolescence increases the risk for emotional dysregulation and neuropsychiatric disorders later in life, yet the neural mechanisms underlying these outcomes, particularly in a sex-specific manner, remain poorly understood. We examined how chronic unpredictable stress (CUS) during adolescence alters socioemotional behavior, stress susceptibility and brain-wide functional connectivity in adulthood across sexes. Male and female C56BL/6 mice were exposed to a CUS paradigm from postnatal day (PND) 28-40. Anxiety-like, social, cognitive and stress coping behaviors were assessed immediately following stress. Adolescent CUS selectively increased social interaction time in females, with no significant effects in other behaviors. In adulthood (>PND 70), mice with or without prior CUS exposure were subjected to an acute footshock stressor followed by behavioral testing to assess stress susceptibility. Both male and female mice with an adolescent CUS history exhibited reduced social preference following acute stress and increased center time in open field, suggesting impaired social

behavior and enhanced risk-taking. Brain-wide functional connectivity associated with acute stress revealed baseline sex differences and an overall reduction in significant network connections in CUS-exposed mice, greater in females. Together, these findings demonstrate that adolescent stress produces long-lasting, sex-dependent alterations in socioemotional behavior and stress-related neural circuitry, providing mechanistic insight into sex-specific vulnerability to stress-related neuropsychiatric disorders.

S11.4 *Human-mouse translational perspectives on sex differences in depression-related molecular mechanisms*

Etienne Sibille [1]

[1] University of Toronto & CAMH

Sex differences in major depressive disorder (MDD) implicate cell type–specific molecular mechanisms involving neurotrophic and inhibitory systems. Postmortem analyses of the amygdala and cingulate cortex revealed region- and sex-dependent molecular profiles converging on downregulated BDNF signaling and somatostatin (SST)-expressing GABA interneuron, suggesting cell-dependent vulnerability of SST interneurons. Parallel findings in BDNF-deficient mouse models recapitulated this transcriptional profile, linking reduced constitutive and activity-dependent BDNF signaling to interneuron dysfunction in depression. Using the Four Core Genotypes mouse model, we demonstrated that sex chromosome complement independently regulates frontal cortex expression of GABA-, serotonin-, and dopamine-related genes under chronic stress, with XY mice exhibiting consistently lower GABA-related gene expression and heightened anxiety-like behaviors relative to XX mice. These effects were partially opposed by circulating testosterone, revealing a dynamic interaction between genetic sex and hormones in affect regulation. This presentation will then summarize how this data was used to develop novel compounds that rescue the deficient SST-cell/dendritic inhibition pathway and its on-going translation to male and female human patients. Complementing these findings, a novel polygenic risk score indexing SST-related gene regulation (SST-PRS) predicted reduced SST+ interneuron proportions in the dorsolateral prefrontal cortex and was associated with greater depressive symptom severity and cognitive deficits, particularly in males with late-life depression. Together, these cross-species results identify distinct yet converging sex-dependent mechanisms involving BDNF signaling, SST+ interneuron integrity, and sex chromosome effects that differentially shape vulnerability, symptom expression, and circuit-level dysfunction. Funding: NIH, CIHR, Campbell Institute, Weston Brain Institute.

SYMPOSIUM 12:

The Brain Vasculature: From Imaging to Insights Into Disease.

S12.1 *Neurovascular program dynamics shaping postnatal brain vascularization*

Mathilde Bizou [1], Élise Drapé [2], Gael Cagnone [3], Joel Howard [4], Frans Irgolitsch [5], Severine Leclerc [4], Mei Xi Chen [4], Blanche Boisseau [4], Isabelle Robillard [6], Matthieu Ruiz [7], Frédéric Lesage [8], Jean-Sébastien Joyal [3], Gregor Andelfinger [4], Alexandre

[1] UDEM, [2] CHU Sainte-Justine, [3] University of Montreal, [4] Centre de Recherche, [5] Laboratoire d›Imagerie optique et Moléculaire, Polytechnique Montréal, [6] Montréal Heart Institute, [7] Institut de Cardiologie de Montréal, [8] Polytechnique de Montréal

The cerebral vasculature undergoes extensive growth, specialization, and maturation after birth to meet the evolving metabolic and functional demands of developing neural circuits. While neurovascular interactions are increasingly recognized as key regulators of adult brain homeostasis and disease, the developmental principles governing postnatal brain vascularization and their contribution to pediatric neurological vulnerability remain poorly understood. In particular, when region-specific neurovascular programs emerge, and how their disruption creates selective susceptibility to neurovascular pathology, remain unclear. Here, I will present our recent work defining how neurovascular unit (NVU) communication regulates vascular development across brain regions during postnatal maturation. Using spatial transcriptomics

and region-resolved endothelial single-cell RNA sequencing in the postnatal mouse brain, we map the spatiotemporal dynamics of cortical and thalamic NVU signaling during vascular maturation. We identify marked regional divergence in endothelial developmental trajectories and show that neuronal and glial maturation parallels distinct angiogenic programs across brain regions. These findings support a model in which dynamic, region-specific neurovascular programs govern postnatal brain vascularization and establish vascular specialization during critical developmental windows. Defining these mechanisms provides a framework for understanding how early-life neurovascular perturbations may contribute to pediatric neurological disorders and regional susceptibility to neurovascular disease.

S12.2 *Modality-specific neurovascular coupling via layer-segregated arteriole networks*

Ravi Rungta [1], Antoine Malescot [1], Milene R. Malheiros-Lima [1], Laurianne Zana [2], Michael Bennett [1], Eric Martineau [2], Franca Shmid [3]

[1] Université de Montréal, [2] University of Montréal, [3] ARTORG Center for Biomedical Engineering Research

Neurovascular coupling links neuronal activity to changes in cerebral blood flow and underlies widely used brain imaging signals such as fMRI. While neurovascular coupling is often assumed to be relatively stable within a given brain region, it remains unclear whether it is conserved across different forms of neural input. Here, using multiscale optical imaging, we examined how cortical vascular responses relate to neuronal activity across distinct input conditions, including tactile stimulation, nociceptive activation, motor-sensory feedback, and spontaneous activity. We find that vascular responses can differ in their spatial and laminar organization despite broadly comparable levels of neuronal activation. Notably, for touch and nociceptive stimulation, similar levels of neuronal activity in L2/3 were associated with markedly different blood flow responses, with changes differing by more than 50%. These differences are associated with the recruitment of distinct classes of penetrating arterioles and their downstream vascular territories, with superficial and deeper networks contributing differentially depending on the input pattern. The role for vascular architecture in shaping these laminar blood flow patterns, was further supported by computational modeling. Together, these findings suggest that neurovascular coupling reflects an interaction between the structure of the vascular network and the spatiotemporal features of neuronal activity, with important implications for the interpretation of hemodynamic signals across modalities.

S12.3 *Astrocyte calcium links norepinephrine dynamics to cerebral blood flow across sleep–wake transitions*

Grant Gordon [1]

[1] University of Calgary

Astrocyte calcium signals regulate local cerebral blood flow (CBF), but their contribution to hemodynamic changes across natural sleep–wake transitions remains unclear. We used in vivo two-photon imaging in head-fixed, unanesthetized mice to monitor astrocyte calcium activity and penetrating arteriole diameter in retrosplenial or barrel cortex during spontaneous transitions between wakefulness, NREM sleep, and REM sleep. During quiet wakefulness, astrocyte endfoot calcium and arteriole diameter were only weakly correlated. In contrast, sleep-to-wake transitions produced coordinated increases in astrocyte calcium and CBF. Astrocyte-specific IP3R2 knockdown reduced both the calcium and vascular responses during these transitions. Using GRAB-NE, we further found that norepinephrine transients coincided with many astrocyte calcium events and that tonic norepinephrine levels varied across sleep–wake states. Together, these findings suggest that norepinephrine-dependent astrocyte calcium signaling contributes to state-dependent regulation of cerebral blood flow.

S12.4 *Modeling the neurovascular unit in brain chips: new insights into communication at the blood-brain barrier in neurodegenerative diseases*

Aurelie De Rus Jacquet [1]

[1] Centre de recherche du CHU de Québec - Université Laval

The blood-brain barrier (BBB) has historically been difficult to model in vitro due to its complex multicellular architecture and the requirement for fluid flow to recapitulate physiological shear stress. Recent advances in microfluidic technologies now enable the generation of patient-specific neurovascular cells, reconstruction of the neurovascular unit on a chip (organ-on-chip), and application of controlled shear stress to better mimic the BBB microenvironment. The neurovascular unit is a highly specialized interface composed of endothelial cells, pericytes, astrocytes, and an extracellular matrix-rich basal lamina. Astrocytes secrete critical matrix components, including nidogen-2, a basal lamina protein that crosslinks extracellular matrix networks, as well as matrix metalloproteinases (MMPs) that regulate vascular remodeling. While Parkinson's disease (PD) is classically defined by progressive dopaminergic neuron loss in the substantia nigra, we and others have documented concomitant BBB dysfunction. We previously demonstrated that astrocytes harboring the PD-associated LRRK2 G2019S mutation impair BBB integrity, implicating astrocytes in PD-related vascular pathology. Our recent findings indicate that altered basal lamina composition — particularly reduced astrocyte-derived nidogen-2— contributes to BBB dysfunction in PD. Using a novel human induced pluripotent stem cell (iPSC)-derived microfluidic BBB-on-chip model, we show that LRRK2 G2019S astrocytes exhibit decreased nidogen-2 expression and reduced secretion via extracellular vesicles. Importantly, supplementation with recombinant nidogen-2 or pharmacological inhibition of MMP activity restores BBB intgrity in our microfluidic system. Collectively, these results identify basal lamina remodeling as a key feature of PD-associated vascular pathology and support a model in which astrocyte-driven alterations in extracellular matrix composition contribute to BBB breakdown in PD.

POSTER SESSION 1

Poster #	Abstract Title	Presenter
P1-A-1	*A clinical trial to evaluate the feasibility, safety, and tolerability of fecal microbiota transplantation (FMT) in adolescents with attention deficit hyperactivity disorder (ADHD)*	Cleo Hendrickson
P1-A-2	*A hyperexcitable ensemble in CA2 deep layer encodes social recognition memory during early development*	Xiaoxuan Han
P1-A-3	*A Live ER-Stress-Enabled System to Study Developmental Dysregulation in Dual-Isoform CRB1-Deficient Retinal Organoids*	Ali Zahedi Amiri
P1-A-4	*Studying the impact of maternal stress on fetal brain development during pregnancy*	Kodee Bao
P1-A-5	*High frequency oscillation morphology changes in healthy children throughout development*	Tatsuya Hansen
P1-A-6	*Advancing Neural Developmental Research Through Stem Cell–Derived Systems*	Afrida Rahman-Enyart
P1-A-7	*Adverse Childhood Experiences Alter Adolescent Social Behaviour and Neuroplasticity in a Mouse Model of Abusive Head Trauma and Neglect*	Sydney Harris
P1-A-8	*Age- and Formulation-Dependent Effects of Combined Oral Contraceptive Exposure on Depression- and Anxiety-Like Behavior in CD-1 Mice*	Sarah Kheloui
P1-A-9	*Altered Cerebellar Serotonin Dynamics Underlie Anxiety and Spatial Memory Deficits in Engrailed-2 Knockout Mice*	Hoda Ranjbar
P1-A-10	*Astroglial VEGF regulates postnatal cerebrovascular development in mice*	Moises Freitas-Andrade
P1-A-11	*Brain Metabolite Profiles in Youth: Associations with Mental Health, Behavior, and Development Across Stress-Sensitive Regions*	Marie-Ange Barthel
P1-A-12	*Characterizing cell-type-specific contributions of a high-penetrance gene for autism spectrum disorder: Implications for brain and behavioral development*	Indra Bishnoi
P1-A-13	*Characterizing the Role of ShcD in Adult Neurogenesis and Neurobehavioral Function*	Hyeyun Yang
P1-A-14	*Decoding Temporal RNA Regulation in Brain Development*	Yu-Yun Gao
P1-A-15	*Exposure to early-life adversity heightens rats' stress sensitivity and impacts oxytocin expression in the paraventricular nucleus of the hypothalamus in a stress-sensitization model.*	Megan Babcock
P1-A-16	*Differential expression of neurotransmitter synthesis genes in aminergic neurons is associated with social roles in ants*	Carlos Zavaleta Zamora
P1-A-17	*Early-life adversity during infantile amnesia alters anxiety-like behaviour in mice*	Neilan Tan

Poster #	Abstract Title	Presenter
P1-A-18	*Early-Stage Disruption of Network Memory Capacity and Spatiotemporal Sequences in SHANK2 and MECP2 Mutant Human iPSC-Derived Neural Networks*	Marjan Mahmoudi
P1-A-19	*Effect of Prenatal, Gestational, and Postnatal Vitamin D Deficiency on mTOR Expression and Physical and Behavioural Development in a Wistar Rat Model*	Georgia Heilman
P1-A-20	*Studying the impact of maternal sleep disruptions on neurodevelopment and offspring behaviour*	Krystyna Macrae
P1-A-21	*Enduring Sex-Dependent Effects of Pubertal Chronic Unpredictable Stress on Anxiety-Like Behaviour and Neuroinflammation, and the Modulatory Role of Probiotics in CD-1 Mice*	Michaela Dworsky-Fried
P1-A-22	*Evaluating Tylenol vs maternal illness during pregnancy for autism risk; a registered report*	Shrabontee Deepanwita
P1-A-23	*Examining the Effects of a Double-Hit Model of Early-Life Stress on the Behavioural and Physical Development of Wistar Rat Pups*	Yolanda Plaza
P1-A-24	*Exploring PTEN-mediated γ-clustered protocadherin trafficking*	Pristine Rey Garay
P1-A-25	*Exploring the impact of maternal sleep disruption on fetal neurodevelopment*	Jolie Wanlin Wu
P1-B-26	*High-throughput mapping reveals distinct excitatory wiring rules in V1 and M1*	Shawniya Alageswaran
P1-B-27	*"Hydrid" dendrimer modulates IL-33 interaction at RAGE in human microglia*	Issan Zhang
P1-B-28	*A critical window for axonal function during myelination*	Bruna De Souza
P1-B-29	*Activation of the OVLT enhances astrocytic calcium signaling in the supraoptic nucleus*	Karoline Martins Dos Santos
P1-B-30	*Acute effects of Omega-3 polyunsaturated fatty acids on Kv1.2 channels and potential utility to KCNA2-related neurological diseases*	Tian Kong
P1-B-31	*Age-Induced Structural and Functional Impairments in Parvalbumin Interneurons.*	Kabirat Adigun
P1-B-32	*All-Optical Mapping of GABA Driving Force Reveals Cell-Type-Specific BDNF Sensitivity in the Hippocampus*	Ariel Kraitzick
P1-B-33	*Antihistamines Alter Sleep-Like Brain States Under Urethane Anesthesia*	Abigail Riesen
P1-B-34	*Astrocyte Contributions to Sensory Circuit Development and Stability*	Justin Kim
P1-B-35	*Astrocyte IP3R2 mediates "wake-up" blood flow increases in neocortex*	Fangying Wang
P1-B-36	*Astrocyte Nanoarchitecture and Organelle Complexity Across Brain Regions and Species Revealed by Deep Learning Segmentation with Curvature Consistency*	Albert Fok
P1-B-37	*Astrocytes Gate Layer-5 Pyramidal Cell Timing-Dependent LTD in Visual Cortex*	Airi Watanabe
P1-B-38	*Astrocytes in Fish: An Underexplored Glial Population with Implications for Brain Plasticity and Regeneration*	Mitra Tabatabaee

Poster #	Abstract Title	Presenter
P1-B-39	*ATGL-Mediated Lipid Droplet Breakdown in Microglia Reduces Neuroinflammation and Regulates Glucose Homeostasis*	Frederick Boisjoly
P1-B-40	*Autism-associated CHD8 controls reactive gliosis and neuroinflammation via remodeling chromatin in astrocytes.*	Platon Megagiannis
P1-B-41	*BDNF-induced enhancement of excitatory synaptic transmission in layer III of the rat entorhinal cortex.*	Kiera Tordon
P1-B-42	*CASK is presynaptic in rod photoreceptors*	Faiyaz Abid
P1-B-43	*CD51 expression delineates functionally distinct astrocyte subpopulations in neural circuits*	Michael Williamson
P1-B-44	*Characterizing Differential Purinergic Trafficking in Sympathetic Nerves*	Joshua Ham
P1-B-45	*Frequency of firing modulates synaptic facilitation in electrically coupled neuroendocrine cells*	Hayley Albert
P1-B-46	*Characterizing the interaction between ORL-1 and Cav1.2*	Aiden Shaver
P1-B-47	*Cholinergic regulation of synaptic inputs to the parasubiculum*	Emily Kacur
P1-B-48	*Cilia beating of ependymal cells regulates adult neural stem cell quiescence via mechanical forces mediated by PKD1/2-TRPM3*	Raquel Rodriguez Aller
P1-B-49	*Cocaine-induced disruption of endosomal recycling: a novel mechanism in psychostimulant addiction*	Sara-Maude Bélanger
P1-B-50	*Cofilin Inactivation Impacts Electrocorticographic Activity during Sleep/Wake States in Mice*	Scanny Chancelle Nzie
P1-B-51	*Comparative Evaluation of the Performance of Neuron Maturation Media in Generating Functional hPSC-Derived Forebrain Neurons*	James Vinnai
P1-B-52	*Contextual gating of circuit-specific stress responses by astrocytes*	Marie-Josette De Medeiros
P1-B-53	*Coordinated Epigenetic Regulation Supports Second-Order Threat Learning*	Tian Qin
P1-B-54	*Coordination of Post-Transcriptional Regulation Shapes AMPA Receptor Function During CNS Neurodevelopment*	Xin-Tong Wang
P1-B-55	*Co-transmitter interactions shape short term plasticity in the medial habenula-interpeduncular nucleus circuit*	Claire Richter Gorey
P1-B-56	*Oligodendroglial UNC5B regulates the organization of paranodal junctions and modification of myelin during aging*	Nonthué Uccelli
P1-B-57	*Delineating the regulation of cerebellar Purkinje cell excitability and synaptic inputs by the gamma protocadherins*	James Li
P1-B-58	*Dendritic Nanostructures Suppress Inflammation in a Model of Ischemic Stroke*	Roberto Charles
P1-B-59	*DEVELOPING AN ANTIBODY PANEL FOR CELL SURFACE RECEPTORS AT THE SYNAPTIC CLEFT*	Travis Riedel
P1-B-60	*Disrupted Microglial–TGF β1 Signaling as a potential Mechanistic Basis for Cerebellar Underdevelopment*	Ariane Delisle
P1-B-61	*Distinct subtypes of astrocytes selectively regulate specific inhibitory synapses*	Darren Clarke

Poster #	Abstract Title	Presenter
P1-B-62	*Diurnal molecular characterization of aged WT and Per1 KO rat hippocampus*	Shinwon Kang
P1-B-63	*DNA Methylation in Astrocyte Maturation*	Naama Brezner
P1-B-64	*The expression of core clock gene Bmal1 is minimal or absent in human and mouse cerebral microglial cells*	Reza Rahimian
P1-B-65	*Early functional immaturity of the reinnervated neuromuscular junction*	Simon Alvado
P1-B-66	*Early seizure drives hippocampal circuit rewiring through target-specific disinhibition*	Ting Ting Wang
P1-B-67	*Effects of blocking endocannabinoid degradation on spreading depolarization*	Adam Institoris
P1-B-68	*Effects of Physical Activity on Hippocampal Cells in an Animal Model of Alzheimer's Disease*	Jessica Avila Lopez
P1-B-69	*Elucidating roles for the postsynaptic GABAergic synapse organizer IgSF21 in synaptic plasticity in mouse hippocampus*	Jie Jiang
P1-B-70	*Elucidating the impact of interneuron subtypes on neurovascular coupling during sensory processing*	Laurianne Zana
P1-B-71	*Estradiol Rapidly Reduces Synaptic Inhibition in Layer V of the Prelimbic Cortex*	Nima Rahaei
P1-B-72	*Examining Fragile X Syndrome across the lifespan: a focus on purinergic signaling.*	Mavis Chinn
P1-B-73	*Examining the Impact of Early Life Adversity on Cerebellar Perineuronal Nets in Adult Mice and Human*	Refilwe Mpai
P1-B-74	*Examining the molecular mechanism through which the cell-surface receptor Neogenin modulates inhibitory synaptic function*	Lina Champain
P1-B-75	*Exploring the physiological function of GPR139 in dorsal root ganglia*	Mengyi Xu
P1-B-76	*Feedforward inhibition of dorsal horn inhibitory neurons that gate mechanical allodynia after nerve injury*	Haoyi Qiu
P1-B-77	*Targeting TRPM2 as a novel therapeutic intervention for Alzheimer's Disease*	Parisa Tabeshmehr
P1-B-78	*Molecular characterization of a L-type calcium channel from molluscan neuroendocrine cells*	Faith Bawden
P1-C-79	*5kEEG: Probing the Diversity of Brain Dynamics in Genetic and Neurodevelopmental Disorders*	Adrien Dubois
P1-C-80	*A Novel Brain-Penetrant Apelin Receptor Probe for Targeted Glioblastoma Radiotherapy*	Émile Breault
P1-C-81	*A novel Cannabinoid Receptor 1 (CB1) PAM-antagonist dampens amphetamine-induced dopamine levels; evidence of CB1-mediated indirect modulation of high DA states.*	Catharine Mielnik
P1-C-82	*A Role of Neurodevelopmental Disorder-associated Gene Arid1b in Purkinje Cell Development and Cerebellar Function in Mice*	Xinzhu Tan
P1-C-83	*A transcriptional timeline of Alzheimer's disease related damage in neurons*	Ryan Ripsman

Poster #	Abstract Title	Presenter
P1-C-84	*A unifying neuropathological spectrum underlies medial temporal lobe epilepsy*	Larissa Kraus
P1-C-85	*Activating Systemic Inflammation with LPS Drives Microglia-Mediated Degradation of Perineuronal Nets after Cervical Spinal Cord Injury in Female Lewis Rats*	Jaison Cucarian
P1-C-86	*Acute intermittent hypoxia improves blood-brain and blood-spinal cord barrier integrity in the experimental autoimmune encephalomyelitis model of multiple sclerosis*	Nataliya Tokarska
P1-C-87	*Acute Intermittent Hypoxia Mobilizes trkA NGF Receptors to the Plasma Membrane of Sensory Neurons*	Maya Wilson
P1-C-88	*Adenosine restoration improves pericyte-regulated retinal blood flow in glaucoma*	Camila Figueiredo
P1-C-89	*Age- and idiopathic Parkinson disease-associated mitochondrial impairment in induced neurons*	Emilie Legault
P1-C-91	*Alterations in motor cortical circuit recruitment and dorsal striatal glutamate signaling during a motor task in a mouse model of Huntington's disease*	Daniel Ramandi
P1-C-92	*Altered BDNF and TrkB levels in cerebellar Purkinje cells may contribute to ataxia in a Christianson syndrome mouse model*	Julia Tourbina-Kolomiets
P1-C-93	*Applying Machine Learning with Neuroimaging Biomarkers to Detect Parkinson's Disease and Cognitive Impairment*	Anthaea-Grace Patricia Dennis
P1-C-94	*ARB2A-loss of function as a putative cause of Amyotrophic lateral sclerosis (ALS) in mice*	Narjiss Messy
P1-C-95	*Assessing the Neuroprotective Effects of Dutasteride in an α-Synucleinopathy Mouse Model of Parkinson's Disease*	Marie Rieux
P1-C-96	*Astrocytic adaptations foster stress resilience by regulating BBB function*	Luisa Bandeira Binder
P1-C-97	*Asymmetric Parietal Cortical Atrophy in a Patient with RAB39B-Associated Parkinsonism: A Novel Truncating Variant*	Emna Benmansour
P1-C-98	*Autologous T cells form significant ICAM-1-mediated contacts with primary CNS myeloid cells in neuroinflammation*	Jennifer Auvergnon
P1-C-99	*Axonal Propagation Failure and Axon Initial Segment Disorganization in the Purkinje cells of a Mouse Model of ARSACS*	Amy Smith-Dijak
P1-C-100	*Baseline Microstructural Integrity of Nigrostriatal and Mesolimbic Pathways Predicts Freezing of Gait Conversion in Parkinson's Disease*	Mojtaba Sharafkhah
P1-C-101	*Behavioral and Multi-Omic Analysis of Neurodevelopmental Disorder-Linked Neurexin 2α Knockout Mice*	Manni Wang
P1-C-102	*Beta-Parvin and Its Role in Vascular Remodeling and Blood Flow Regulation Following Ischemic Stroke*	Tanaka Maravanyika
P1-C-103	*Brain-wide activity-dependent hemodynamic changes accompanying persistent cortical tactile sensory adaptation and its impairment in a mouse model of Rett syndrome*	University of Victoria
P1-C-104	*Brain-Wide c-Fos Signatures Underlying Individual Differences in Chronic Pain*	Damien Boorman

Poster #	Abstract Title	Presenter
P1-C-105	*BTK inhibition prevents microglia-mediated demyelination induced by multiple sclerosis patient antibodies*	Lindsay Osso
P1-C-106	*Calcium Permeability of NMDARs in GRIN1-related Neurodevelopmental Disorders*	Liam Clancy
P1-C-107	*Cannabidiol reduces the accumulation of amyloid beta plaques via cannabinoid receptor 2 and peroxisome proliferator activated receptor γ*	Sarah Ng
P1-C-108	*CB1 Receptor Modulation Alters Dentate Gyrus Network Activity in Animal Model of Temporal Lobe Epilepsy*	Alina Trofimova
P1-C-109	*Cerebellar modulation of anxiety linked behaviours in neurotypical and autism spectrum mice*	Jason Arsenault
P1-C-110	*Changes in Alzheimer's disease-associated biomarkers in post-COVID-19 patients with cognitive deficits*	Fernanda G. Q. Barros-Aragao
P1-C-111	*Characterizing chronic hippocampal injections of recombinant 2N4R human tau in a wild-type mouse model*	Daniel Lamontagne-Kam
P1-C-112	*Characterizing novel C. elegans models of Huntington's disease expressing the caspase-6 cleavage fragment of mutant huntingtin*	Jiaxi Guan
P1-C-113	*Characterizing potassium chloride co-transporter 2 (KCC2) protein interactions in Huntington's Disease*	Lilliana Pavicic
P1-C-114	*CLCN3 Regulates Lysosomal Homeostasis and α-Synuclein Accumulation in Parkinson's Disease*	Donovan Worrall
P1-C-115	*CNS Myeloid Cell Activation in Chronic MS and EAE Is Sustained by ICAM-1 Mediated Interactions with T Cells*	Haritha Desu
P1-C-116	*Combined effects of activity-based therapy and transcutaneous spinal cord stimulation on sub-acute spinal cord injury individuals for upper limb rehabilitation: a pilot study*	Sujata Sinha
P1-C-117	*Comparative Analysis of Amyloid Beta Deposition in Two Different Alzheimer's Disease Mouse Models Using Whole-Brain Two-Photon Microscopy*	Mojtaba Nazari
P1-C-118	*Connectome-Wide Mega-Analysis Identifies a Reproducible Functional Network Signature of Temporal Lobe Epilepsy*	Ke Xie
P1-C-119	*Cortical Morphological Correlates of Apolipoprotein E4 in Parkinson's Disease: Structural MRI Evidence With Exploratory CSF Analyses From the PPMI Cohort*	Angenelle Eve Rosal
P1-C-120	*Cortical rescue of neuronal Neuroligin-2 mitigates sleep and behavioral impairments in adult knockout mice*	Tanya Leduc
P1-C-121	*Could postpartum behavioral disturbances resulting from postnatal stress be related to inflammatory changes in the gut-brain axis?*	Victoria Mordvinova
P1-C-122	*CSF oligoclonal band frequency in a Cuban cohort of patients with multiple sclerosis. Comparison with Latin American countries and association with latitude*	Marisol Peña Sanchez
P1-C-123	*Curcumin-Mediated Modulation of Thermometabolic Dysregulation in Neonatal Hypoxic–Ischemic Brain Injury*	Xianxuan Wang
P1-C-124	*Defining the role of GBA in C. elegans models of Parkinson's disease*	Maisha Maliha Promi

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P1-C-125	*Depressive-like Behaviour In A Humanized Knock-in Mouse Model Of APOE, Amyloid, And Tau Is Sex- & APOE Allele-specific*	Cadence Opoka
P1-C-126	*Determining whether PD-associated lysosomal genes influence lysosomal homeostasis and stress phenotypes*	Isabella Pietrantonio
P1-C-127	*Development of a novel anti-amyloid therapeutic: an orally administrable anti-abeta-oligomer compound*	Hedi Zhou
P1-C-128	*Developmental Alterations in A Mouse Model of Spinocerebellar Ataxia Type 6*	Elyse Zadigue-Dube
P1-C-129	*Developmental disruption of ventral hippocampal inhibitory neurons drives hippocampal–prefrontal network dysfunction and cognitive deficits in mice*	Jennifer Robinson
P1-C-130	*Discovery of novel hyperphosphorylation sites of neurofilaments in amyotrophic lateral sclerosis mice correlating with the efficacy of novel Borsantrazole (TM)*	Nitesh Sanghai
P1-C-131	*Disrupted Spatiotemporal Noradrenaline Dynamics in Motor Cortex Underlie Delayed Motor Learning in an ASD Mouse Model*	Xuming Yin
P1-C-132	*Drug repurposing screening for spinocerebellar ataxia treatment in a C. elegans model*	Taylor Shirtliff-Hinds
P1-C-133	*SeizureBiomeDB: A unified database of gut microbiome alterations in pediatric and adult epilepsy*	Chunlong Mu
P1-C-134	*Dysregulated dopaminergic signaling in the dorsal striatum: a novel approach to compulsivity in anorexia nervosa*	Héloïse Hamelin
P1-C-135	*Dysregulation of RNA metabolism contributes to neurodegeneration and synapse pathology in multiple sclerosis*	Miranda Messmer
P1-C-136	*Early Fatigue Symptom Detection of MS in a String Pulling EAE Mouse Model*	Jordan Caetana Dudley
P1-C-137	*Early hypothalamic dysfunction in Alzheimer's disease: evidence for vascular and tanycyte involvement*	Pablo Valderrama-Carmona
P1-C-138	*Early structural neuroimaging and multiple sclerosis polygenic risk*	Mavi Sorella
P1-C-139	*Early synaptic degeneration and oxidative stress precede retinal ganglion cell loss in optineurin mutant mice*	Barbara J Morquette
P1-C-140	*Ectosomes carrying tau are released by Parkinson's disease neurons*	Kennedi Chik
P1-C-141	*Effects of a Lipid Metabolism-Targeting Treatment on Recovery Sleep Following Sleep Deprivation in the 3xTg Mouse Model of Alzheimer's Disease*	Salma Attebaa
P1-C-142	*Efficacy and Safety From a Phase 1/2 Open-label Trial of GTX-102, an Investigational Antisense Oligonucleotide for the Treatment of Patients with Angelman Syndrome*	Kenneth Myers
P1-C-143	*Reduced cerebrovascular reactivity in youth with congenital heart disease: links with cognition*	Zacharie Potvin-Jutras
P1-C-144	*Elucidating the Physiological Role of Amyloid Precursor Protein through multi-omics*	Marina Ruelas Hernandez

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P1-C-145	*Neuronal Growth Regulator 1 as a potential target for gene expression modulation in human pluripotent stem cell models of Alzheimer's Disease*	Pablo Leal Cardozo
P1-D-146	*Steady-State Visual Evoked Potentials Reveal Visual Symmetry Processing in the Common Marmoset*	Amirhossein Asadian
P1-D-147	*A Drosophila model of Diabetic Neuropathy*	Gwen Haslam
P1-D-148	*Acoustic Transparency Enables Transcranial Functional Ultrasound Imaging in Nonhuman Primates Without Craniotomy*	Hamidreza Ramezanpour
P1-D-149	*Action Intention Modulates Functional Connectivity: an fMRI Study*	Gaelle Luabeya
P1-D-150	*Age- and Sex-Dependent Modulation of Descending Pain Control : Effects of Physical Activity in Mice.*	Hania Oukil
P1-D-151	*Altered post-incision pain and subsequent disturbance of gut homeostasis in aging mice*	Yu Guo
P1-D-152	*An ascending pathway for the relay of warm and cool sensation*	Xinying Zhang
P1-D-153	*An ethogram-based approach reveals the widescale behavioral impact of vision loss and provides a sensitive benchmark for assessing vision restoration*	Mingyu Wan
P1-D-154	*Analgesic effects of 3,4-methylenedioxymethamphetamine in the acetic acid and formalin mouse pain assays*	Alameen Alajeely
P1-D-155	*Assessing Local and Global Stereopsis Using Tasks of Depth Detection and Discrimination*	Tara Nichols
P1-D-156	*ASSESSING THE IMPACT OF ELECTRODE PLACEMENT ON AUDITORY BRAINSTEM RESPONSE WAVEFORMS*	Charlotte Kruger
P1-D-157	*At First Sight: Cortical Processing of Restored Vision Following an Extended Period of Vision Loss*	Erica Cianfarano
P1-D-158	*Auditory and vestibular neurotoxicity of agricultural chemicals: A global mapping of the current research*	Alex Bégin
P1-D-159	*Auditory Context Modulates Attentional Gating during Sensorimotor Performance*	Jessica Vander Vaart
P1-D-160	*Behaviour-Dependent Immediate Early Gene Activation in the Mouse Cerebellum*	Megan Sholomiski
P1-D-161	*Benchmarking human dorsal root ganglion organoids with cultured primary human tissue models*	Andrew Mocle
P1-D-162	*Central Integration of Proprioception in Controlling Homolateral Leg Movements*	Mohammad Amin Dolatkhah
P1-D-163	*Cerebellar Rhomboid-3 Modulates Motor Coordination Through Membrane Signaling Pathways in Aging*	Yujia Li
P1-D-164	*Coherence dynamics and neural reorganization during motor sequence learning and at rest*	Jhelum Paul
P1-D-165	*Combined cortical and peripheral stimulation alleviates locomotor deficits in a feline model of incomplete spinal cord injury*	Ali Gharbienne
P1-D-166	*Cortical Beta-Band Dynamics During Motor Control in Tourette Syndrome*	Lyna Hanafi

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P1-D-167	*Cortical specificity matters: Targeted hindlimb cortical stimulation enhances locomotor recovery after spinal cord injury*	Anne-Catherine Chouinard
P1-D-168	*Cortical states modulation of cortical activity and connectivity in congenital blind mice.*	Véronique Chouinard
P1-D-169	*D2 receptor-expressing neurons in the gigantocellular reticular nucleus modulate locomotion and orienting movements in mice.*	Jacinthlyn Sylvia Suresh
P1-D-170	*Decreased phase-dependant modulation in corticospinal excitability during walking in human individuals with Spinal Cord Injury.*	Heloise Bourgeois
P1-D-171	*Developing Human Spinal Cord Methodology to Study Pain circuits*	Lois Miraucourt
P1-D-172	*Differential Cerebellar Modulation of PA- and AP-Sensitive Sensorimotor Circuits*	Michael Perrier
P1-D-173	*Differential roles of muscle and cutaneous afferents in motor recovery after spinal cord injury in adult mice*	Reese Letawsky
P1-D-174	*Dimensionality of neural manifolds during adaptive motor behaviors*	Maria Pescaru
P1-D-175	*Disruption of Glomerular Map Formation in the Accessory Olfactory System Impairs Chemosensory Processing and Social Behavior*	Sydney Fearnley
P1-D-176	*Distinguishing modality-specific and shared cognitive networks in a low-dimensional neural space*	Hadi Choubdar Parvin
P1-D-177	*Diverse Neuronal Responses to Visual Precision in Cat Cortical Area 21a: Unraveling the Complexity of Orientation Processing*	Lamyae Ikan
P1-D-178	*Do blind mice recover better from a stroke than healthy mice ?*	Behiye Sanliturk
P1-D-179	*Dorsomedial higher visual cortex is a locus for visual attention in mice*	Julia Forestell
P1-D-180	*Dynamic Coupling Between the Action-Mode Network and Sensorimotor Cortex During Human Motor Learning*	Maryam Ansari Esfeh
P1-D-181	*Dynamic Intra-Hemispheric Premotor–Motor Functional Connectivity During Precision Grasp in Macaques*	Soraya Rahimi
P1-D-182	*Effect of norepinephrine release in movement refinement during directional reaching*	Camille Balazuc
P1-D-183	*Effects of early blindness on odor discrimination and cortical activity in mice*	Vanessa Bordonaro
P1-D-184	*Electrophysiological Biomarkers of Thermal Pain in the Insula Revealed by Stereo-electroencephalography*	Marc-Antoine Gobeil
P1-D-185	*Electrophysiological differences in auditory processing in the inferior colliculus of Cntnap2 knockout rats*	Cassandra Lemarquand
P1-D-186	*Elucidating mechanisms of cell-type–specific noradrenergic modulation in motor cortex circuits of 16p11.2 deletion mice to rescue delayed motor learning*	Nathaniel Jones
P1-D-187	*Estrous cycle modulates cortical auditory responses across species*	Maria Isabel Carreno Munoz
P1-E-188	*Role of basolateral amygdala neurons activated by sleep deprivation on risk- and mood-related behaviours*	Nikita Koziel Ly
P1-E-189	*Agouti integrates environmental cues to regulate paternal behaviour*	Forrest Rogers
P1-E-190	*Brain-wide Klb expression in a novel Klb-cre mouse line*	Bianca Bono

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P1-E-191	*Cannabidiol regulates EGFR and GPER levels in a Glioblastoma model in vitro*	Diana Ramirez Martinez
P1-E-192	*Developing behavioural paradigm to study state-dependent stress sensitivity in awake head-fixed mice.*	Aashi Panchal
P1-E-193	*Differential calbindin and calretinin expression in subfornical organ neurons of rats and mice*	Begum Saka
P1-E-194	*Effects of an Oxytocin Receptor Antagonist (OTRA) on Estrogens' Facilitative Effects on Social Recognition (SR) in the medial Prefrontal cortex (mPFC) of Female Mice*	Milad Akbarzadehmoallemkolaei
P1-E-195	*Effects of vaporized Δ9-tetrahydrocannabinol exposure on the behavioral and neuroendocrine consequences of acute stress*	Mijail Rojas-Carvajal
P1-F-196	*ATP Administration Enhances Sensitivity to Outcome Devaluation in the Dorsomedial but not Dorsolateral Striatum in Rats*	Madison Fedele
P1-F-197	*A comparison of canonical and informed basis set modelling of the haemodynamic response during N-back cognitive testing*	Kj Woudsma
P1-F-198	*A Mechanical Analogy for the Observed Oscillations in Choice Behavior of a Population Facing a Time-Varying Reward*	Nasim Nozarnejad
P1-F-199	*A MRI Study of Metabolic and Cerebrovascular Health*	Shilan Heshmati
P1-F-200	*Acute and delayed effects of psilocybin on prefrontal cortical neuronal activity*	Serena Wu
P1-F-201	*Acute psilocin alters aversive memory retention and extinction learning in Drosophila melanogaster*	Maximiliano Elgueta Reyes
P1-F-202	*Adolescent N-Acetylcysteine Intervention Attenuates Neurobehavioral Deficits Following Prenatal THC Exposure*	Nicholas Hamati
P1-F-203	*Age-Related Differences in Learning Rate Across Memory Tasks*	Basem Abu Shamleh
P1-F-204	*Aging Reduces Scale-Free Temporal Persistence of Resting BOLD Signals Independent of Cerebral Blood Flow: Evidence from 550 Adults in HCP-A*	Shima Yaghoubian
P1-F-205	*Altered Neuronal Lactate Dehydrogenase A Expression in Mice Results in Age-Dependent Changes to Spatial Memory and Region-Specific Changes to the Lipid Profile*	Marc Courchesne
P1-F-206	*An intrinsic evolving hippocampal scaffold guides the encoding of novel spatial memories*	Javad Karimi Abadchi
P1-F-207	*Anatomical and functional investigation of VGLUT3-positive projections from the median raphe nucleus to the lateral septum in anxiety modulation*	Elsa Lalot
P1-F-208	*Artificial Reactivation of a Cocaine-Associated Engram in the Dorsal Dentate Gyrus Attenuates Cocaine Prime-Induced Reinstatement of Drug-Seeking*	Morgan Brody
P1-F-209	*Assessing Probabilistic Reward Sensitivity in an Early-Life Stress Rodent Model*	Tara Laverty
P1-F-210	*Astrocytes integrate noradrenaline inputs to modulate fear memory specificity*	Mathias Guayasamin Alfaro
P1-F-211	*Basolateral Amygdala Astrocytes Encode Anxiety States*	Ossama Ghenissa

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P1-F-212	*Behavioural Ratings of Appetitive Conditioning in Adolescent Anorexia Nervosa: Interim Analysis*	Hayah Siddiqui
P1-F-213	*CA1 time cell dynamics during interval timing in a mouse model of schizophrenia*	Maya Viegas
P1-F-214	*Can imaging biomarkers reliably predict persistent post-concussion symptoms following mild traumatic brain injury? A pilot study*	Erin Ford
P1-F-215	*Cannabinoid type 1 receptor (CB1R) blockade in adolescence alleviates the effects of adolescent social instability stress (SS) on social interaction and social reward motivation in female rats.*	Amanda Leonetti
P1-F-216	*Characterizing Ventral Hippocampal Neural Dynamics During Heroin and Cocaine Self-Administration and Drug-Seeking Using Fiber Photometry*	Paul Jung
P1-F-217	*Chronic Adolescent Stress Reprograms Stress-Responsive Connectivity and Socioemotional Behaviors throughout the Lifespan*	Olivia O'neill
P1-F-218	*Chronic Modulation of Sdk1+ Prefrontal Neurons Alters Reward Learning Strategies*	Peter Vitaro
P1-F-219	*CHRONIC VOLUNTARY CONSUMPTION OF CANNABINOIDS IN C57BL/6 MICE*	Alayna Jones
P1-F-220	*Circuit-specific noradrenergic dynamics are associated with stress susceptibility in a learned helplessness model*	Maryia Bairachnaya
P1-F-221	*Claustro-cortical communication is disrupted by increased kappa opioid signaling in chronic pain*	Christian Faig
P1-F-222	*Closing in on the quarry of a 72-year search: the cellular origins of MFB reward signals*	Jacques Voisard
P1-F-223	*Comparative evaluation of the degree of transparency of AI-based transcription tools.*	Sarah Haloui
P1-F-224	*Cortical switching dynamics shape delta activity under propofol anesthesia*	Clara Pic Roca
P1-F-225	*Vocal Development in a Social Context in Common Marmosets*	Constance Dollet
P1-F-226	*Cross-linguistic Comparison of Brain Response to Speech Predictability in English, Mandarin Chinese, and French Narratives*	Yanan Liu
P1-F-227	*Cross-Species Sensitivity to Reward Schedules: Ratio and Delay Variability in Reward Seeking*	Madison Gal
P1-F-228	*Deficits in Contextual Remapping Underlie the Tendency to Generalize Fear: Implications for Post-Traumatic Stress Disorder*	Aasrita Tulluri
P1-F-229	*Differential Activation of Lateral Septum Subregions During Social and Nonsocial Novelty Detection*	Nastasia Mitrikeski
P1-F-230	*Differential Limbic System Activation During Passive Processing of Emotional and Non-Emotional Music and Smells: An ALE Meta-Analysis*	Federico Andreoni
P1-F-231	*Discovering translational behavioral strategies of reward processing across species*	Zahra Rostami
P1-F-232	*Dissociable roles of DG and CA1 engram ensembles in context-specific rule retrieval in mice*	Mohammed Sarikahya

Poster #	Abstract Title	Presenter
P1-F-233	*Distinct neural dynamics during encoding differentiate fast and slow episodic retrieval*	Moh Ishraq
P1-F-234	*Distinct roles of Vglut2+ and Vglut2- VTA dopamine neurons during social Interactions*	Cameron Oram
P1-F-235	*Dopamine D1 receptor activation is necessary for object memory destabilization in female mice.*	Matthew Rumas
P1-F-236	*Dopamine dynamics in nucleus accumbens core during the odour span task in rats*	Aiden Glass
P1-F-237	*Dopamine Pathways in Temporal Task Acquisition: Evidence from Chronic and Acute Disruptions*	Sergey Grigorovich
P1-F-238	*Dopaminergic Control of Predictive Memory in the Subiculum*	Pola Tuduri
P1-F-239	*Monkeys choose to make mistakes.*	Meriam Zid
P1-F-240	*Dynamic Regulation of Foraging Behavior by the Habenulo-Raphe Pathway*	Amarpreet Dheer
P1-F-241	*Dynamics of catecholamine release in the pre-frontal cortex of adult mice during associative learning*	Mariama Aboudou
P1-F-242	*Early life adversity induces changes in palatable food-seeking behaviors and the mesolimbic system in a sex-dependent manner*	Tamara Trowsse
P1-F-243	*Effect of Exercise on Sleep Microarchitecture, netwrok dynamic, connectivity and dendritic spine morphology in the case of sleep restriction: a translational approach*	Francois Pointeau
P1-F-244	*Emotion aware generative AI for simulating cognitive behavioral therapy dialogue and affective regulation*	Christian Dominique
P1-F-245	*Effects of Sustained Cannabis Abstinence on Depressive Symptoms: Preliminary Analyses*	Lyne Baaj
P1-G-246	*A direct comparison of EEG/EMG and EEG/Accelerometer approaches for mice sleep staging*	Dawson Green
P1-G-247	*3D Spatial Analysis of Purkinje Cell Distributions in the Macaque Cerebellum*	Mathieu Johnson
P1-G-248	*A brain–spine interface for state-dependent stabilization of blood pressure after spinal cord injury*	Wenbin Yang
P1-G-249	*A Canadian guidance framework for integrating social determinants of health in aging and Alzheimer's disease research*	Stefanie Tremblay
P1-G-250	*A Computational Pipeline for Identifiability and Parameter Recoverability in Cognitive Models*	Aziz Ktari
P1-G-251	*A neuronal waveform classification assay to characterize inhibitory and excitatory bursting characteristics in MEA data: Erinacine A as a model drug*	Evan Spangenberg
P1-G-252	*A Novel Non-Obese Mouse Model of Obstructive Sleep Apnea with Transient Inspiratory Flow Limitation*	Natalia Zubieta - De Urioste
P1-G-253	*A Systematic Comparison of MPRAGE and BRAVO T1-Weighted MRI Pulse Sequences*	Mahmoud Elsayed
P1-G-254	*Addgene Data Hub: a platform for sharing AAV and antibody experimental data*	Ashley Waldron

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P1-G-255	*An Atlas of Parvalbumin Interneuron Diversity in Mouse Visual and Somatosensory Cortex*	Maheshwar Panday
P1-G-256	*An Open-Source Closed-Loop Behavioural Control System for the Raspberry Pi*	Jamie Sanson
P1-G-257	*An optogenetic and imaging approach to study noradrenergic modulation of neuro-vascular coupling*	Francis Bernard
P1-G-258	*Bio-imaging strategy to follow the infectious pathway of adeno-associated viruses in neurons*	Laurence Paquet
P1-G-259	*Brain dynamics associated with noxious stimulation under general anesthesia are characterized by changes in redundancy and synergy measured using EEG*	Joaquim Streicher
P1-G-260	*Correction of the APP London (V717I) mutation using an optimized prime editing system*	Sina Ramezani
P1-G-261	*Cerebral Vein Segmentation in Quantitative Susceptibility Maps using Physics Constrained Deep Learning*	Yousif Al-Khoury
P1-G-262	*Characterization of Neuronal Subpopulation and Network Activity in the External Globus Pallidus*	Gabriela Paskevicius
P1-G-263	*Connectivity, Complexity, and Chaos in the Ageing Brain: Synthesis of the Literature*	Zahra Khalilzad
P1-H-264	*Augmented Reality for Teaching Neuronal Signaling in Undergraduate Psychology*	Nina Di Pietro
P1-H-265	*Characterizing prognostication practices after drug toxicity-related post-cardiac arrest brain injury*	Harjeev Sudan
P1-H-266	*Convergence: Transforming Knowledge Translation through Transdisciplinary Art-Science Collaboration to Foster Critical Thinking and Cognitive Connection with Brain Research.*	Nour Chahine
P1-D-267	*Large Glutamatergic Neurons in the Lateral Cerebellar Nuclei Are Essential for Motor Coordination and Cognitive Function in Mice*	Azam Asemi Rad
P1-B-268	*Astrocyte-specific eIF2 alpha-dependent mRNA translation regulation of hippocampal synaptic plasticity and memory in Alzheimer's disease*	Vijendra Sharma

POSTER SESSION 2

Poster #	Abstract Title	Presenter
P2-A-269	*Developmental axonal swellings formation depends on extracellular calcium signalling*	Bruna De Souza
P2-A-270	*Fate-restricted embryonic precursors define gray and white matter astrocyte specification in the spinal cord*	Caterina Sister
P2-A-271	*Fetal microglia show sex-specific neurodevelopmental responses to maternal stress during pregnancy*	Alexandra Lawson
P2-A-272	*Floor plate derived netrin-1 is an instructive long-range guidance cue for commissural axons in the embryonic spinal cord*	Melissa Pestemalciyan
P2-A-273	*Free fatty acid receptor GPR120 regulates dopamine neuronal development and social behavior*	Shingo Nakajima

Poster #	Abstract Title	Presenter
P2-A-274	*From brain age deviations to developmental trajectories in adolescence*	Anthony Gagnon
P2-A-275	*Guidance cue integration by growth cones: spatial regulation of microRNAs*	Alicia Piazza
P2-A-276	*Gut–brain axis dysregulation produced by adolescent edible Δ 9 tetrahydrocannabinol (THC) exposure*	Marieka Devuono
P2-A-277	*Transcriptomic and Protein Expression Analyses of Early Differentiating Neurons in the Developing Mouse Cerebellar Nuclei*	Farshid Ghiyamihoor
P2-A-278	*How do substantia nigra dopamine neurons grow such a complex axonal arbor? An in vitro exploration.*	Raphaëlle Denis
P2-A-279	*Identification of a novel mirror movement causing gene: A recurrent MCF2 variant which disrupts DCC binding and subcellular relocalization leads to congenital mirror movements*	Dennis Drewnik
P2-A-280	*Ikaros family members network drives neuronal diversification in the mouse developing retina*	Pedro Franca
P2-A-281	*In Vivo Measurement of Glutamate and GABA in the Pediatric Anterior Cingulate Cortex: Feasibility and Preliminary Findings*	Marie-Ange Barthel
P2-A-282	*Inflammation profiles induced by mechanical ventilation in the developing brain*	Roqaya Imane
P2-A-283	*Investigating Associations Between Maternal Prenatal Nutrition and Neurocognitive Development in Early Childhood*	Stefanie Perrier
P2-A-284	*Investigation of Endothelial Deficits in Models of SYNGAP1 Haploinsufficiency*	Leya Aubert-Tandon
P2-A-285	*It's all in the vessels: the neonatal brain vasculature provides a unique combination of molecular cues to neural stem cells that alters with age*	Marissa Lithopoulos
P2-A-286	*Longitudinal Study of Neurovascular and Cognitive Health in Aging Mice*	Alexandre Cléroux Cuillerier
P2-A-287	*Metal co-exposure alters sensory and social behaviors in C. elegans with a loss-of-function mutation in neurexin.*	Victor Anadu
P2-A-288	*Microglial/Macrophage Androgen Receptor Knockout Produces ADHD-Like Phenotype in Male Mice*	Kerri Sparkes
P2-A-289	*Mlp60a and Sallimus are required to restrict branching of developing dendritic arbors.*	Alex Hanadel
P2-A-290	*Modeling Early-life Adversity in Wistar Rats: Effects of Maternal Dietary Fiber During Lactation on Offspring Development*	Fabi Funes
P2-A-291	*Morphological evidence suggestive of a hierarchical mode of glial cell diversification and intrinsic developmental plasticity within the murine enteric nervous system*	Marie Lefèvre
P2-A-292	*Integration of human and mouse single-cell transcriptomes of the developing cerebellum nominates cells-of-origin for Group 3 and 4 medulloblastoma*	Shraddha Pai
P2-B-293	*Characterizing the effects of diazepam on tau hyperphosphorylation and spatial memory in a mouse model*	Daniel Lamontagne-Kam

Poster #	Abstract Title	Presenter
P2-B-294	*Functional characterization of CG17698, a novel memory suppressor gene*	Illia Pimenov
P2-B-295	*GATOR1-dependent mTORC1 hyperactivity Drives the Development of Neuronal Communication*	Maéline Muller
P2-B-296	*GATOR1-dependent signaling in astrocyte metabolic reprogramming and neurotransmitter recycling: phenotypic insights and mTOR-targeting therapy*	Imane Hadj-Aissa
P2-B-297	*GDNF-induced neuroregeneration in Hirschsprung mice occurs through non-canonical signaling in diverse enteric neural progenitor subtypes*	Alassane Gary
P2-B-298	*Glial coverage of neuromuscular junction predicts motor performance in Humans*	Danielle Arbour
P2-B-299	*Glial-Specific Glutamate Transporters Required for Sleep Regulation in Drosophila.*	Jishang Jiang
P2-B-300	*GluA2-lacking AMPA receptor-Auxiliary complexes offer a diversity of polyamine block sensitivity*	Xin-Tong Wang
P2-B-301	*Glutamate-releasing immature inhibitory terminals in the auditory brainstem contain distinct excitatory and inhibitory synaptic vesicles*	Andrei Alexe
P2-B-302	*Heterochronic myeloid cell replacement reveals the local brain environment as a key driver of microglia aging*	Claire Gizowski
P2-B-303	*High-Throughput Optogenetic Mapping of Prefrontal Layer 2/3 Microcircuits*	Elia Painchaud-Lakatos
P2-B-304	*Hippocampal Place Cell Remapping During Spatial Reward Learning*	Elizabeth Leggett
P2-B-305	*Hormetic thermal stress confers benefit and promotes adaptive resilience in C. elegans*	David Oyeniran
P2-B-306	*Identifying GluN1 subunit N1-cassette residues controlling N1-cassette regulated function*	Homa Farahani
P2-B-307	*Identifying the MHCI interactome during typical synapse development and following immune stimulation*	Scott Cameron
P2-B-308	*Impact of MDGA2 Haploinsufficiency on Dendritic Spine Architecture in the Dentate Gyrus*	Demetra Economopoulos
P2-B-309	*Impact of the CA1-Specific Deletion of Sigma-1 Receptor on Neuronal Activity and Behavior*	Mathieu Lapalme
P2-B-310	*Inflammation during development alters axonal morphology and microglial engulfment activity in D. rerio.*	Anna Kim
P2-B-311	*Investigating a role for netrin-1/DCC signaling in excitatory homeostatic synaptic upscaling*	Kira Feighan
P2-B-312	*Dysfunctional somatodendritic AMPA receptor signaling in Fragile X Syndrome Cerebellum*	Zhe Zhao
P2-B-313	*Investigating the effect of behavioral context on time cell dynamics and formation.*	Jacob Duda
P2-B-314	*Investigating the effects of probiotics on corticospinal excitability*	Malaikah Ahmad
P2-B-315	*Investigating the role of adaptor protein ShcD in oligodendrocyte development and myelination*	Alice Nielissen

Poster #	Abstract Title	Presenter
P2-B-316	*Investigation of Transcriptomic Changes in the Anterior Cingulate Cortex in a Mouse Model of Chronic Neuropathic Pain*	Ana Leticia Simal Dourado
P2-B-317	*Long-range amygdala-prefrontal engram projection supports remote fear retrieval*	Ashutosh Patel
P2-B-318	*Mapping CCK-Projections From The Edinger-Westphal (EW) And Their Function*	Maryam Fazili
P2-B-319	*Mechanisms of Laminar Organization of Hippocampal Excitatory Synapses*	Mohammed Abrar Basha
P2-B-320	*Mechanistic insight into mild traumatic brain injury induced circadian and sleep abnormalities in mice*	Anzala Murtaz
P2-B-321	*Mef2 transcription factors enable microglial support of brain vasculature functions*	Lyanne Begin
P2-B-322	*Microglial TNF signaling is required for behavioral and cognitive deficits in a rodent model of post-traumatic stress disorder*	Houaria Adaïdi
P2-B-323	*Microglial trogocytosis in activity-dependent axonal pruning in the visual system during development*	William Nguyen
P2-B-324	*Miglustat protects against demyelination of smaller diameter axons and promotes myelin formation*	Jean-David Gothié
P2-B-325	*Mitochondrial Calcium & Hydrogen Peroxide Interact to Control Nonselective Cation Channels in Aplysia Neuroendocrine Cells*	Elijah Rajsky
P2-B-326	*Modality-specific neurovascular coupling via layer-segregated arteriole networks*	Antoine Malescot
P2-B-327	*Modulation of interneuronal functioning and perineuronal nets by microglia in female ovariectomized mice*	Antonia Landwehr
P2-B-328	*Neocortical Microcircuit Changes Associated with Fragile X Syndrome*	Meghan Appleby
P2-B-329	*NeuroD1-AAV9 Astrocyte-to-Neuron Reprogramming Improves Motor Function and Neuron-to-Glia Balance Following Ischemic Stroke in Non-Human Primates*	Golnar Taheri
P2-B-330	*Neurophysiological Properties of Subthalamic Nucleus Neurons expressing Corticotropin-Releasing Hormone*	Anusha Kamesh
P2-B-331	*Neuroplastic mechanisms underlying the antidepressant effects of psychedelics*	Kathleen Ngo
P2-B-332	*New tools to promote release of endogenous serotonin in the prefrontal cortex*	Haushe Suganthan
P2-B-333	*NMDA Receptor Signaling Is Not Monolithic: Location Determines Plasticity Function*	Sabine Rannio
P2-B-334	*Not only Neurons; Dopamine Receptor Signaling in Microglial Cells Drive Behaviour and Neuroinflammatory State*	Ghazal Fakhfouri
P2-B-335	*Opioid-induced hyperalgesia develops in the periphery and in the absence of proinflammatory microglia*	Julia Nickols
P2-B-336	*Pannexin1 homolog regulates plasticity required for adaptive learning in larval zebrafish*	Fatema Nakhuda
P2-B-337	*Panx1 channel mediates TNFα-induced endothelial barrier permeability in human brain microvasculature*	Stefany Órdenes

Poster #	Abstract Title	Presenter
P2-B-338	*Pharmacological rescue of GABAergic synapse strengthening in a mouse model of Fragile X Syndrome*	Xinyuan (Cecilia) Chen
P2-B-339	*Silent Synapse Recruitment Drives GABAergic Potentiation in the Cerebellar Stellate Cells.*	Siqi Wang
P2-B-340	*Phasic axonal dopamine release appears to involve mechanisms beyond synaptotagmin-1*	Soraya Paquereau--Gaboreau
P2-B-341	*Physiological properties of VGLUT1 mediated glutamatergic neurotransmission in the Substantia Nigra*	Adeeb Akhavan
P2-B-342	*Pregnancy-induced microglia activation promotes Neural Stem Cells niche remodelling and maternal neurogenesis*	Sareen Warsi
P2-B-343	*Presynaptic intracellular calcium stores modulate acetylcholine release and α4β2 nicotinic responses in layer 1 prefrontal cortical neurons*	Raad Nashmi
P2-B-344	*Unsilencing the silent synapse: Evaluating mechanisms of glutamatergic synapse maturation in the retinotectal circuit of Xenopus laevis*	Natasha Szulist
P2-C-345	*Enhancing Neuronal Glucose Uptake via GLUT3 Protects Retinal Ganglion Cells and Visual Function in Glaucoma*	Vu Thao Hien Pham
P2-C-346	*Evaluation of the implication of Parkin, microglia and CD8+ T cells in the vulnerability of dopamine neurons*	Amandine Even
P2-C-347	*Exploring Brain Asymmetry in Depression: Molecular Insights from a Single-Cell Study*	Kayleigh Casmey
P2-C-348	*Exploring kefir as a therapeutic approach for Alzheimer's disease using an in vitro β-amyloid aggregation model*	Fernanda Mascarenhas
P2-C-349	*Exploring neurophysiological mechanisms and risk factors behind the development of chronic postsurgical pain after thoracic surgery using electroencephalography*	Mustaali Hussain
P2-C-350	*Fish oil supplementation prevents memory loss in experimental chronic liver disease*	Alexandre Bourgeois
P2-C-351	*Fluoxetine enhances TrkB expression and function to rescue motor coordination deficits in a mouse model of spinocerebellar ataxia type 6*	Rana Abdelhalim
P2-C-352	*From synaptic instability to serum biomarkers: NMJ-derived protein change in ALS*	Maïka Doré
P2-C-353	*Functional contributions of afferent and corticocortical projections to human motor control*	Kylee Graham
P2-C-354	*Gene Polymorphisms and Metabolomics Alterations in Mouse Models of Sporadic Alzheimer's Disease*	Behroo Mirza Agha
P2-C-355	*Genetic insights into neural mechanisms underlying sensorimotor dysfunction in familial restless legs syndrome: A whole-genome study in French-Canadian families*	Andrew Roth
P2-C-356	*Genome Wide CRISPR Activation Screen Unveils BAP1 as a Modulator of a-Synuclein Fibril Internalization*	Nathan Karpilovsky

Poster #	Abstract Title	Presenter
P2-C-357	*Hemodynamic and electrophysiological progression of the Rose Bengal photothrombotic stroke model in mice*	Patrick Chary
P2-C-358	*High-Resolution Spatial Transcriptomics of the Maternal Brain in a Rodent Model of Postpartum Depression*	Maria Eleni Fafouti
P2-C-359	*High-throughput screening using ratiometric fluorescent-based GCase substrate to identify activity modulators of lysosomal GCase, as Parkinson's disease-associated genetic risk factor*	Faezeh Jame-Chenarboo
P2-C-360	*Hippocampal interneuron dysfunction during working memory in a mouse model of schizophrenia*	Mark Gerlai
P2-C-361	*Hippocampal short-term potentiation deficits occur in a mouse model of late-onset Alzheimer's disease*	Rachael Ingram
P2-C-362	*Hypertension in Huntington's Disease: The Effect of Propranolol Treatment on Symptom Onset*	Aimee Dawe
P2-C-363	*Identification of pathogenic variants in the BORCS5 and BORCS8 genes associated with neurodevelopmental disorders*	Adeline Paimboeuf
P2-C-364	*Identifying Naturalistic Behavioural Signatures of Chronic Pain using Keypoint-Moseq*	Andrew Boyce
P2-C-365	*Illness Duration-dependent Subcortical Iron Accumulation in Schizophrenia: Findings from a Quantitative Susceptibility Mapping Study*	George Nader
P2-C-366	*Impact of Beta-Amyloid Oligomers on Hippocampal Network Activity and Neurotransmission*	Vincent Hervé
P2-C-367	*Impact of chronic stress on blood-brain barrier and stress responses in adolescence*	Béatrice Daigle
P2-C-368	*Impact of Exercise-based Interventions for Individuals with Essential Tremor: A Scoping Review*	Geneviève Marcotte
P2-C-369	*Impact of Hexavalent Chromium on White Matter Integrity and Cognitive Function in a Model of Multiple Sclerosis-Like Demyelination*	Elyse Wiebe
P2-C-370	*In vivo effects of hippocampal tau pathology on brain oscillations, neurotransmission, and memory*	Rime Balafrej
P2-C-371	*Inhibiting stearoyl-coA desaturase modulates hippocampal fatty acid composition, increases dendritic spine density and normalizes interneuron and astrocytic gene expression in the amyloidogenic 5xFAD model of Alzheimer's disease*	Marta Turri
P2-C-372	*Integrating Serum Biomarkers with Diffusion MRI Identifies History of Concussion Signatures*	Taylor Snowden
P2-C-374	*Investigating a Novel Intravenous Antisense Oligonucleotide (ASO) Therapy in a Mouse Model of Dravet Syndrome*	Lakshmini Balachandar
P2-C-375	*Investigating eIF2α-Mediated Translational Control in Taste Memory Formation*	Josh Miller
P2-C-376	*Investigating the impact of elevated blood pressure on cerebrovascular alterations in Huntington's disease*	Alivia Moneypenny
P2-C-377	*Investigating the Molecular Function of THAP12*	Bryce Rampal

Poster #	Abstract Title	Presenter
P2-C-378	*Investigating the presence of complement factor C6 in periventricular white matter lesions in multiple sclerosis disease progression*	Sara Chafik
P2-C-379	*Investigation of Gene–Environment Interactions in the Progression of Parkinson's Disease (PD) and Multiple System Atrophy (MSA)*	Divya Shiroor
P2-C-380	*Investigation of the long-term effects of COVID-19 on the autonomic nervous system based on neurophysiological and neuroimaging measures*	Oren Gurevitch
P2-C-381	*Isoform-Specific Roles of ZDHHC8 in Neurodevelopment and Disease*	Emma Breyak
P2-C-382	*Ketogenic diets partially restore bioenergetic pathways in the hippocampus of an Alzheimer's disease mouse model*	Isaura Suárez-Uribe
P2-C-383	*Ketone-driven modulation of mitochondrial function in FUS-ALS models*	Antoine Desmeules
P2-C-384	*Lipid alterations promote non-vesicular secretion of tau by hippocampal neurons.*	Ju-Young Bae
P2-C-385	*Longitudinal Characterization of Alpha-Synuclein on Brain Connectivity, Cognitive, and Behavioral Symptoms in Marmosets' Model of Parkinson's disease*	Jiayue Yang
P2-C-386	*Loss of Calcium-Binding Protein Frequenin Results in Nociceptive Hypersensitivity Through Changes in Nociceptive Circuit Excitability*	Alexandria St. Louis
P2-C-387	*Machine Learning-Based Prediction of Pain Recurrence Following Trigeminal Neuralgia Surgery*	Jana Mahmoud
P2-C-388	*MALDI-TOF imaging mass spectrometry demonstrates sex- and age-dependent spatial changes in brain energy metabolism in response to amyloid stress using a mouse model of Alzheimer's Disease*	Sandra Grahovac-Nemeth
P2-C-389	*Metabolic Dysfunctions May Be Causing Selective Anterior Purkinje Cell Loss in the Cerebellum of a Christianson Syndrome Mouse Model.*	Atchaya Kanagasabai
P2-C-390	*Metformin as a therapeutic intervention for Phelan-McDermid syndrome*	Laura Marsal-García
P2-C-391	*Mild Mitochondrial Uncoupling Restores Neuronal Resilience and Preserves Vision in Glaucoma*	Heberto Quintero
P2-C-392	*Mistrafficking of KCC2 in Endolysosomal system in the hippocampus of Christianson Syndrome mouse model*	Jamie Mustian
P2-C-393	*A role for injury-associated microglia in neural responses to cortical white matter and parenchymal damage*	Ashleigh Willis
P2-C-394	*Modelling Individual Differences in Chronic Pain-Related Social Behaviours*	Farhada Khaled
P2-C-395	*Molecular mechanisms underlying local inhibitory control over cortico-accumbal and tegmental pathways in stressed male and female mice*	Arturo Marroquin Rivera
P2-C-396	*Molecular Pathogenesis of Juvenile ALS: Dissecting the Impact of the E102Q SIGMAR1 Variant on Cellular Homeostasis and Autophagy*	Vina Banouvong
P2-C-397	*Mouse models of BCOR-associated inherited retinal degenerations uncover potential pathogenic mechanisms*	Camille Michaud
P2-C-398	*mTOR-dependent regulation of synaptic FUS translation in ALS*	Bastien Glasson

Poster #	Abstract Title	Presenter
P2-C-399	*Multimodal differentiation of MRI phenotypes in left and right temporal lobe epilepsy*	Benjamin Lévesque Kinder
P2-C-400	*Multimodal sensory training as a leverage to improve motor function in individuals with spinal cord injury.*	Lucie Chesné*
P2-C-401	*Multiple-Sclerosis-Relevant Stressors Converge on RBP Mislocalization and Neurite Degeneration in Primary Mouse Neurons*	Jay Gabriel Larga
P2-C-402	*Mutant huntingtin reshapes mitochondrial protein interactions in Huntington's disease*	Aya El Haqaoui
P2-C-403	*Neural Markers of Social Interaction Deficits in Neurodevelopmental Disorders: A Normative Modelling Approach*	Annemarie Wolff
P2-C-404	*Neuronal SorCS1 Promotes Synaptic Resilience and Selectively Restores Working Memory in Alzheimer's Disease*	Nayoung Yi
P2-C-405	*Neuron-specific knockout of GIGYF2 in mice results in autism-related behaviour and learning and memory impairments.*	Carlota Navas Via-Dufresne
P2-C-406	*Neuroprotective Effects of Pyrroloquinoline Quinone in Folate Deficiency–Induced Blood–Brain Barrier Disruption*	Sara Aboulhassane
P2-C-407	*Neuroprotective Effects of Remote Ischemic Conditioning in a Mouse Model of Repetitive Mild Traumatic Brain Injury*	Aly Muhammad Salim
P2-C-408	*NMJ proteomic signatures underlying resistance and vulnerability in ALS progression*	Roberta Piovesana
P2-C-409	*No evidence for genetic role of the tumor necrosis factor pathway in Parkinson's disease*	Morvarid Ghamgosar Shahkhali
P2-C-410	*Essential Tremor and BACE2: a role for oligodendrocyte-specific Aβ metabolism in disease etiology*	Matthew Pelletier
P2-C-411	*Contrasting Oculomotor Abnormalities in Right- and Left-Sided Parkinson's Disease Using Eye-Tracking*	Daria Hinton
P2-D-412	*Evolutionarily conserved neural dynamics across mice, monkeys, and humans*	Margaux Asclipe
P2-D-413	*Posterior-Anterior Propagation of Beta Bursts During Motor Control*	Siyu Long
P2-D-414	*Exploring Homeostatic Plasticity as a Mechanism Underpinning Prolpnged Pain*	Noran Almomen
P2-D-415	*Eye vs. hand effector-specificity in human parietal and frontal cortices*	Kiana Masoudi
P2-D-416	*Factorial Analysis of Ensemble Representation of Attention and Decision-making in Prefrontal Cortex of Macaque Monkeys*	Wanyi Lyu
P2-D-417	*Feedback gains reflect unfolding decisions during ongoing actions*	Cesar Canaveral
P2-D-418	*Foraging plasticity in Caenorhabditis elegans or how developmental stress leads to cautious foragers in rich environments*	Jorge Luna Herrera
P2-D-419	*Frequency-specific modulation of beta-band dynamics by transcranial alternating current stimulation in younger and older adults*	Guofeng Ye
P2-D-420	*Functional brain mapping of stroke-induced cortical blindness in mice using neurophotonics*	Catherine Albert
P2-D-421	*Functional connectivity of reticulospinal neurons within the medullary reticular formation*	Yasmine Zmantar

Poster #	Abstract Title	Presenter
P2-D-422	*Functional contribution of glutamatergic neurons of Mesencephalic Locomotor Region nuclei to locomotion.*	Kayvan Combadiere
P2-D-423	*Impact d'une perturbation transitoire des voies corticales sur les relations fonctionnelles entre le cortex visuel primaire et le pulvinar chez la souris*	David Vasii
P2-D-424	*In vivo characterization of strainspecific entourage effects in Psilocybe mushrooms in a rat model of autism spectrum disorder*	Stefan Salo
P2-D-425	*Investigating how an immune challenge impacts the trajectory of chemotherapy-induced peripheral neuropathy*	Arina Pang
P2-D-426	*Investigating the Circuit Mechanism of Steering in Isothermal Tracking of Caenorhabditis elegans (C. elegans)*	Yue Wang
P2-D-427	*Investigating the effects of lorazepam and baclofen on TMS evoked transcallosal inhibition.*	Faith Adams
P2-D-428	*Kinematic analysis of motor responses evoked by circumferential stimulation of the lumbar spinal cord in cats*	Oriane Herviault
P2-D-429	*Lateral entorhinal–piriform projections in context-dependent odor processing*	Carla Concilio
P2-D-430	*Lateral Hypothalamic Pathways Drive Locomotor Control and Recovery after Spinal Cord Injury*	Abderraouf Redjem
P2-D-431	*Localized Reorganization of Brain Structure Following Early Auditory Deprivation*	Danial Ghiaseddin
P2-D-432	*Mechanisms of activity-dependent cortical sensory adaptation in the rodent hindlimb somatosensory circuitry*	Vasil Kecheliev
P2-D-433	*Mechanisms of decision-making during natural interactive behaviour*	Tyler Peel
P2-D-434	*Mechanisms responsible for increasing repiratory activity during locomotion*	Jessica Zevounou
P2-D-435	*Microstimulation of V4 domains modulates visual perception in non-human primates*	Younes Valibeigi
P2-D-436	*Milliseconds that matter: how temporal fine structure shapes sensory detection and discrimination.*	Isabelle Mackrous
P2-D-437	*Müller Glia-Mediated Light Transmission as a Potential Trigger for Cone Planar Cell Polarity in Mice*	Melissa Villarreal Morales
P2-D-438	*Natural self-motion is actively recoded in vestibular cortex*	Jerome Carriot
P2-D-439	*Neural and Behavioural Correlates of Audiovisual Gaze-Orienting in Common Marmosets*	Tyler Cook
P2-D-440	*Neural Markers of Interocular Grouping during Binocular Rivalry with MEG*	Janine Mendola
P2-D-441	*Neuroanatomical organisation of glutamatergic reticulospinal neurons*	Marc-Antoine Bouchard
P2-D-442	*Quantitative Study of Perineuronal Net Plasticity in the Mouse Visual Cortex Following Retinal Injury and Cholinergic Potentiation*	Odile Desaulniers
P2-D-443	*Neurovascular and corticospinal dynamics of intermittent theta burst stimulation*	Willy Nguyen

Poster #	Abstract Title	Presenter
P2-D-444	*Noradrenaline shapes top-down inhibition of the cortex by NDNF+ neurons in reinforcement and behaviour*	Emmeraude Tanguay
P2-D-445	*Oculomotor behaviour during free viewing of dynamic video in non-human primates: translating to human clinical application.*	Tyonna Ashby
P2-D-446	*Oculomotor dance learning task: Implications for audio-visual cued spatial learning*	Michael Petrovski
P2-D-447	*OPIOIDS DO NOT INHIBIT SPINAL OXYGEN SENSORS DURING HYPOXIA*	Jessica Dickenson
P2-D-448	*Opposite effects of CB2 receptor activation on visual cortical dynamics*	Capucine Mandel
P2-D-449	*Perineuronal nets in a vocal motor nucleus regulate vocal development*	Xinghaoyun Wan
P2-D-450	*Pose-estimation reveals behavioral signatures of social recognition and neuromodulation in sensory circuitry*	Daria-Salina Storch
P2-D-451	*Prefrontal and Parietal Local Field Potentials Employ Different Visuospatial Codes for Reach: A Complex-Valued Network Classification Approach*	Ashkan Karimi
P2-D-452	*Protocadherin-gamma (Pcdh-γ) impacts axon-keratinocyte interactions – A coculture model approach*	Honyi Ong
P2-D-453	*Pulvinar-Inspired Skip Connectivity Regulates Gain and Decision Criterion in Hierarchical Vision Networks*	Narmin Zarinabadi
P2-E-454	*Endothelial calcium signalling regulates capillary blood flow dynamics and vessel tone in the cerebral microvasculature*	Sam Paton
P2-E-455	*Fructose-mediated glutamatergic but not GABAergic maladaptations at NPY/AgRP neurons*	Persephone Miller
P2-E-456	*Functional and morphological adaptations of hypothalamic tanycytes to caloric restriction*	Zachary Silver
P2-E-457	*Gustatory Influences on the Metabolic Fate of Sugar: When Taste Tricks the Body*	Golnaz Arjmand
P2-E-458	*How ghrelin and its actions on the GHSR interact with chronic social stress effects in female mice.*	Brenna Macaulay
P2-E-459	*Hypothalamic satiety neurons are inhibited by α2-adrenoceptor activation through direct and indirect mechanisms*	Olivier Lavoie
P2-E-460	*Investigating the Role of Endothelial Calcium Transients in Cerebral Capillary Stall Recanalization*	Andrew Hubbard
P2-E-461	*Mechanisms Underlying Estrogens' Rapid Facilitative Effects on Social Recognition in the Medial Amygdala of Female Mice*	Charlotte La Rochelle-Compton
P2-E-462	*Vesicular transporters VNUT and VMAT1 anti-colocalize in ATP and norepinephrine 'co-releasing' PC12 cells*	Layla Sadafi
P2-F-463	*Effect of Number of Training Trials on Olfactory Learning and Memory in a Pavlovian Conditioned Odour Preference Task*	Mohammed Ali Ahmed
P2-F-464	*Enhancement of cocaine-primed reinstatement by 17ß-estradiol in ovariectomized rats is concomitant with increased activation mesolimbic brain regions*	Davin Peart

Poster #	Abstract Title	Presenter
P2-F-465	*Examining Network Gain dynamics in the Subiculum during Reorientation*	Apoorv Sharma
P2-F-466	*Examining the contribution of serotonin dynamics within the mesolimbic dopamine system to motivation*	Mya Chronopoulos
P2-F-467	*Experience-Dependent Specialization of VIP Interneurons and CA1 Circuit Dynamics during Contextual Memory*	Suhel Tamboli
P2-F-468	*Exploration drives reward-dependent long-term memory*	Gabrielle Dufresne
P2-F-469	*Exploring Sec5/EXOC2 as a Conserved Regulator of Sociability*	Jack Rosenbaum
P2-F-470	*Exploring sex differences in inhibition of prefrontal cortical dopamine during a novel context threat discrimination task*	Liv Engel
P2-F-471	*Flavour-nutrient and flavour caffeine conditioning*	Yasmina Dumiaty
P2-F-472	*From hardware to science communication: How Yutu became a virtual influencer*	Zahrat-El-Nor Maynard
P2-F-473	*From Prediction to Action: Habenular Control of Ventral Tegmental Area Circuits in Defensive Behaviors*	Marina Ihidoype
P2-F-474	*Fronto-parietal activation supports narrative reintegration following distraction during movie-watching*	Samuel Ketcheson
P2-F-475	*Functional heterogeneity of hippocampal CA1 VIP interneurons in novelty-driven memory processing*	Risna Kanjirassery Radhakrishnan
P2-F-476	*Given the choice: Individual differences in concurrent intravenous cocaine and fentanyl self-administration in male and female rats*	Adiia Stone
P2-F-477	*Granularity in configural learning of abstract 2D space*	Nuria Larochelle
P2-F-478	*Humanized mice learn by seeking information*	Chiara Bramati
P2-F-479	*Impacts of Chronic Stress on Cortico-Accumbal and Cortico-Tegmental Activity in Goal-Directed Behaviours and Motivation*	Sara-Maude Leclerc
P2-F-480	*Influence of Intertrial Interval (ITI) Duration on Learning Acquisition of Elemental and Configural Discrimination Tasks*	Toni Kach
P2-F-481	*Inhibition of Microglia in the DMS Impacts Goal-Directed Behaviors in a Rat Model of Diet-Induced Obesity*	Elif Sari
P2-F-482	*Integrating Internal and External Signals to Optimize Food Decision Making*	Yige Sun
P2-F-483	*Integration of appetitive features in the orbitofrontal cortex during food-based choices*	Elizabeth Rye
P2-F-484	*Intraoperative functional mapping of white matter tracts: a scoping review and meta-analysis*	Yousra Lecheheb
P2-F-485	*Inverse effects of diet and adiposity on nucleus accumbens volume in humans.*	Justin Sung
P2-F-486	*Investigating decision making in the hippocampus using open-source touchscreen chambers*	Matthew Cooke
P2-F-487	*Investigating how pre-existing anxiety levels modulate adolescent nicotine vapor-induced behavioural and neural changes*	Marwa Idrissi

Poster #	Abstract Title	Presenter
P2-F-488	*Investigating the Contributions of Chromosomal and Gonadal Sex on the Gut Microbiome and Stress Resiliency through Cecal Transfer in a Mouse Model of Chronic Stress*	Meagan Hinks
P2-F-489	*Investigating the discriminative stimulus properties of the mu opioid receptor antagonist, naloxone, through Pavlovian associative learning*	Ella Claridge
P2-F-490	*Investigating the Effects of Exercise on Attentional Correlates in Long-Term Concussion*	Caelan Fernando
P2-F-491	*Investigating the role of actin dynamics in the perirhinal cortex for object memory destabilization in a rodent model*	Jiayu Zheng
P2-F-492	*Investigating the role of nucleus accumbens D1 receptor neuronal outputs to ventral midbrain in anxiodepressive behaviour elicited by diet-induced obesity*	Solal Aubailly
P2-F-493	*Investigation into the activity of claustrum interneurons across different states*	Alison Do
P2-F-494	*Laminar Organization of Medial Frontal β-Bursts During a Stop Signal Task*	Pranavan Thirunavukkarasu
P2-F-495	*Lateral hypothalamic input engages a disinhibitory microcircuit in the dorsal raphe to promote behavioral activation*	Renata Sadretdinova
P2-F-496	*Learning constrains the generative capacity of the hippocampus*	Zeeshan Haqqee
P2-F-497	*Levonorgestrel reduces sex differences in tests of anxiety-like behaviour in Long-Evans rats.*	Alison Randell
P2-F-498	*Activity of prefrontal Sidekick1-expressing neurons regulates behavioral adaptation to chronic stress*	Vedrana Cvetkovska
P2-F-499	*Male and female rats trained on appetitive and inhibitory learning contingencies generalize the stimulus effects of morphine to other opioids*	Jessica Karlovcec
P2-F-500	*Maturational trajectory of hippocampal networks revealed by longitudinal calcium imaging in vivo*	Adam Ramsaran
P2-F-501	*Median Raphe Glutamatergic and Serotonergic Inputs Support Recruitment of Hippocampal CA1 VIP Interneurons During Novel Experience*	Lisa Topolnik
P2-F-502	*Median raphe VGLUT3+ neurons modulate hippocampal theta rhythm and sharp-wave ripples*	Justine Fortin-Houde
P2-F-503	*Microglia regulate memory consolidation by modulating engram neuron activity*	Xiaoyu Chen
P2-F-504	*Modelling population dynamics in cortical–basal ganglia circuits for decision-making*	Haoyang Li
P2-F-505	*Multiplicity of Error Centers in the Cerebral Cortex*	Benjamin Corrigan
P2-F-506	*Multi-scale organization of hippocampal activity across CA1 and subiculum during structured locomotion*	Regan Campbell
P2-F-507	*Multivariate Behavioural and Psychological Profiles Predict Adherence to a Physical Activity Intervention in Adults at Risk for Alzheimer's Disease*	Sathurthika Selvanayagam

Poster #	Abstract Title	Presenter
P2-F-508	*Multi-voxel pattern analysis for characterizing functional connectivity underlying grit in cognitively unimpaired older adults at-risk for Alzheimer's disease*	Vasvi Dhir
P2-F-509	*Network Gain Regulates Stability and Flexibility in a Ring Attractor Network*	Harshith Nagaraj
P2-F-510	*NEURAL CIRCUIT AND BEHAVIORAL SIGNATURES OF STRESS RESILIENCE IN CAENORHABDITIS ELEGANS*	Felix Akoyo
P2-F-511	*Neuronal network linking the olfactory bulb to the prefrontal cortex regulates familiarity-induced affective state transfer*	Marie Fénéry
P2-F-512	*Offspring fear conditioning and latent inhibition following cannabis smoke exposure before and during pregnancy in mice.*	Kaylen Young
P2-G-513	*Can We Capture Resting State Functional Connectivity in a Shorter Time? A Systematic Comparison between the Hyperband- and Conventional fMRI*	Mahmoud Elsayed
P2-G-514	*Development of a head fixation protocol for awake repeated live two-photon imaging in the adult zebrafish telencephalon*	Christine D'souza
P2-G-515	*Development of Reflectin as a Phase-Contrast Marker for Digital Holographic Microscopy — A Future Approach for Live Subcellular Imaging in Neuroscience*	Jean Honoré Laurent
P2-G-516	*DROSOPHILA MELANOGASTER AS A NOVEL MODEL ORGANISM TO STUDY STRESS AND ANTIDEPRESSANT DRUGS*	Fabiola Eckert
P2-G-517	*Electrochemical biosensor for mitochondrial DNA integrity assessment as a biomarker of major depression*	Pedro Guedes
P2-G-518	*Evaluating the Repeatability of fNIRS for Assessing Cerebrovascular Function*	Erin Mazerolle
P2-G-519	*Expanding AAV Diversity: An AI Guided Unbiased Exploration of Exotic Viromes*	Chloé Guillemette
P2-G-520	*Fast AAV validation pipeline in rats for translational primate studies*	Zhihao Zheng
P2-G-521	*Feasibility of Accelerated Intermittent Theta Burst Stimulation Combined with Balance Training in Alzheimer's Disease and Related Dementias*	Karishma Ramdeo
P2-G-522	*From Temporal Precision to Delusion Formation: Gamma Synchrony and Perceptual Deficits in Schizophrenia*	Andrew Sedrak
P2-G-523	*Frontal Alpha Asymmetry Across Graded Sensory Challenge: Investigating Regulatory Demands During Standing Balance*	Rachel Cluett
P2-G-524	*Guided Topic Modeling of Single-Cell Human Prefrontal Cortex Methylome for Cell-Type Deconvolution and Epigenetic Trajectory Analysis in Major Depressive Disorder*	Neda Esfehani
P2-G-525	*HeteroRC: Decoding latent information from dynamic neural responses with interpretable heterogeneous reservoir computing*	Runhao Lu
P2-G-526	*High SNR Outperforms High Diffusion Weighting for OGSE-TDS Axon Diameter Mapping Precision*	Madison Chisholm
P2-G-527	*Hippocampal-claustrum coupling during sleep*	Brian Marriott

Poster #	Abstract Title	Presenter
P2-G-528	*Improved Sleep Spindle Detection Using the BOSC Method: A Comparison with Traditional Approaches*	Cameron Turnbull
P2-G-529	*Increasing Corticospinal excitability using personalized Brain Stimulation: A Feasibility Study*	Amandeep Atwal
P2-G-530	*Information-geometric classification of EEG signals with motor imagery tasks*	Eric Albers
P2-H-531	*Improving Brain Health Literacy Among Adolescents: The Maintain Your Brain Game*	Lydia Shaw-Peters
P2-H-532	*Making the brain visible: EEG-based brain–computer interfaces for education and social impact in corporate wellness*	Sujata Sinha
P2-H-533	*RetINaBox: A hands-on learning tool for experimental neuroscience*	Flavia Arias Armas
P2-B-534	*Changes in Excitation/Inhibition Balance Following Developmental Ethanol Exposure*	Roaa Abu Zeid
P2-B-535	*Profiling LTP Decay by Distinguishing the Synaptic Differences Between De Novo and Rescued Memories*	Matthew Mollicola
P2-G-536	*Molecular signatures from neuronal and oligodendrocytic extracellular vesicles isolated from blood samples in patients with ALS undergoing focused ultrasound and IVIg treatments*	Matheus Uba Chupel

POSTER SESSION 3

Poster #	Abstract Title	Presenter
P3-A-537	*N-acetylcysteine mitigates behavioral impairments and neuronal dysregulation caused by adolescent nicotine exposure in rats*	Leandro Val Sayson
P3-A-538	*Parental Origin Modulates Testosterone Genetic Effects on the Tangential Growth of the Cerebral Cortex*	Hubert Fiset-Renaud
P3-A-539	*Perinatal Delta-9-tetrahydrocannabinol alters development of sleep and hypoxic ventilatory reflex in newborn rats*	Vivian Biancardi
P3-A-540	*Post-Natal Disruption Of The Blood-Brain Barrier And Abnormal Brain Development In An Autism Model*	Celeste Laporte
P3-A-541	*Probing parallel changes in the synaptic proteome and transcription regulation in the MDGA2 deficient autism model mouse*	Kyle Patel
P3-A-542	*Regulation of inhibitory interneuron survival by the clustered Protocadherins and PTEN/PI3K signaling*	Mercedesz Praszner
P3-A-543	*Selective neurotoxic effects of prenatal cannabis exposure on white matter*	Mayuura Rajendram
P3-A-544	*Sex Shapes the Development of Neuroinfectious Virus Receptors Across the Human Lifespan*	Nadine Barone
P3-A-545	*Sex-dependent modulation of lateral hypothalamic–dorsal raphe and infralimbic circuits following acute stress*	Nahid Rouhi
P3-A-546	*Sex-specific offspring neurodevelopmental outcomes in a rodent model of postpartum depression*	Kristen Montgomery

Poster #	Abstract Title	Presenter
P3-A-547	*Single-cell multiomics define a gradual, spatially-regulated epigenetic and transcriptional transition from embryonic to adult neural stem cells*	Beatrix Wang
P3-A-548	*Spatiotemporal development of sparse excitatory neuronal types within the deep mouse cortex*	Shalini Iyer
P3-A-549	*Striatal dopamine release is region-, sex-, and age-dependent in young mice*	Sean Coady
P3-A-550	*Elucidating the Neurodevelopment of Multisensory Integration in the Common Marmoset*	James Wang
P3-A-551	*A molecular basis of somatotopic map formation*	Kevin Sangster
P3-A-552	*The cholesteryl ester transfer protein impacts HDL quantity and quality disrupting neurovascular integrity*	Jose Antonio Vazquez Coba
P3-A-553	*The Effects of Pubertal Lipopolysaccharide and Chronic Fluoxetine Treatments on Anxiety-Like Behavior in Adult Male and Female Mice*	Abigale Hinterberger
P3-A-554	*The Role of Ago1 and Ago2 in Neurodevelopment*	Aimee Xinxo
P3-A-555	*The role of Kirrel3 in mitral cell dendrite morphogenesis during olfactory system development and its impact on odour processing in mice*	Mary-Elizabeth Allen
P3-A-556	*Timing-specific effects of maternal separation stress on development in protein-restricted neonatal Wistar rats*	Amber Jurke
P3-A-557	*Transcriptional and Splicing Dysregulation in CHARGE Syndrome Mouse Models Explains the Cerebellar Developmental Defects*	Sanaa Tork
P3-A-558	*Abnormal MYCBP2-EPHB2 signaling interplay causes neurodevelopmental defects*	Sara Banerjee
P3-A-559	*Vasopressin Dysregulation Following Transient Neonatal Hyperoxia in Rats*	Roqaya Imane
P3-A-560	*β-Neurexin-1a knockout impairs zebrafish visual function in prey capture under low-light conditions.*	Fannie Yang
P3-B-561	*Properties and activation mechanisms of membrane localized, chloride permeable Pannexin 2 channels.*	Christian Humphreys
P3-B-562	*PVN astrocytes regulate corticosterone secretion and stress responses*	Manon Duquenne
P3-B-563	*Radial astrocytes modulate the encoding of visual signals and plasticity in the developing Xenopus laevis optic tectum.*	David Foubert
P3-B-564	*Region-specific synaptic adaptations in a mouse model of spinocerebellar ataxia type 6*	Ben Rogers
P3-B-565	*Rescue of Dopaminergic Network Stability During Metabolic Stress by Pharmacological and Genetic Targeting of Panx1a*	Georg Zoidl
P3-B-566	*Rescuing the Cellular and Metabolic Alterations Underlying Chemotherapy-Induced Cognitive Impairment and Fatigue*	Jared Vanderzwaag
P3-B-567	*Restoring astrocytic metabolism potentiates cortical reorganization after stroke*	Andrea Trevisiol
P3-B-568	*Rethinking memory consolidation: protein synthesis inhibition mimics neural shutdown*	Saja Al-Smadi

Poster #	Abstract Title	Presenter
P3-B-569	*Role of Astrocytes in Regulation of CRH Neurons and the HPA Axis.*	Clara Ireland
P3-B-570	*Role of astrocytic N-methyl-D-aspartate (NMDA) receptors in regulating cortical neuronal function via purinergic signalling*	Meher Kantroo
P3-B-571	*Role of Elfn1 in Mossy Fibre to Stratum Lucidum Interneuron Information transfer*	Niko Merlak Radojcic
P3-B-572	*Role of TrkCPTPσ–regulated Shank3 phosphorylation in synapse development and plasticity*	Mai Inagaki
P3-B-573	*Amyloid Beta protein increases dendritic spine density in stellate, but not pyramidal neurons, and causes cell type specific alterations in spine morphology in the rat medial entorhinal cortex*	Marcus Suvanto
P3-B-574	*Serotonin modulation of behavioral time scale plasticity in mouse prefrontal cortex*	Baoqing Lu
P3-B-575	*Sex Differences in Endocannabinoid System Gene Expression in the Anterior Cingulate Cortex and Basolateral Amygdala following Inflammatory and Neuropathic Pain*	Haley Vecchiarelli
P3-B-576	*Sex Differences in Microglial Responses to Cerebral Microbleeds: Influence of Estrogen*	Dhwani Sura
P3-B-577	*Shaping Synapses During Development and Aging: Netrin-1 Regulation of Hippocampal Dendritic Spines*	Jiaqi Xu
P3-B-578	*Pharmacological study of cannabichromene and cannabigerol at the serotonin 1A receptor (5-HT1A)*	Riley Brown
P3-B-579	*Slice preparation matters: protective solutions shape synaptic plasticity in ex vivo brain slices*	Priscilla Welter
P3-B-580	*Spacing theta burst episodes improves plasticity in prefrontal cortex of socially isolated mice*	Angela Zolis
P3-B-581	*Spatial learning promotes phosphorylation of CRMP2 in the hippocampus.*	Harshit Thakare
P3-B-582	*Spatiotemporal Dynamics of Microglia in Response to Recurrent Capillary Injury In Vivo*	Frances Armas
P3-B-583	*Spatiotemporal maturation of astrocyte calcium dynamics during hippocampal development*	Gareth Rurak
P3-B-584	*Spontaneous and miniature excitatory postsynaptic currents in medium spiny neurons of the dorsomedial striatum in Bmal1 knock-out mice.*	Mahgol Darvishmolla
P3-B-585	*Sublayer-specific inhibitory and disinhibitory control of hippocampal CA1 pyramidal cells by VIP interneurons*	Jordan Grenier
P3-B-586	*Synaptic Transmission Onto Somatostatin Interneurons is Enhanced Under Acidic Conditions in an Elfn1-dependant Manner*	Mark Bobbitt
P3-B-587	*Synthetic Synapses: Testing Biomimetic Electrode Coatings for Enhanced Neural Integration*	Teddy Fisher
P3-B-588	*Frequency-dependent regulation of serotonin signaling in prefrontal cortex is expanded by chronic SSRI treatment*	Saige Power
P3-B-589	*The Brain on Cannabis: How THC affects brain rhythms during sleep-like states*	Lexi Stein

Poster #	Abstract Title	Presenter
P3-B-590	*The Effect of High Salt Intake on RhoA–mDia1 Signaling and the Cytoskeleton in Vasopressin Neurons*	Banruo Li
P3-B-591	*The Effect of Serotonin Modulation on Lateral Parabrachial Nucleus Inputs in Pain Conditions*	Shirin Sadighparvar
P3-B-592	*The Effect of Systemic Injections of CBD on Sleep-like Brain State Alternation During Urethane Anesthesia*	Layan Fayad
P3-B-593	*Investigating the Cellular Functions of Rhomboid-Related Protease 3*	Megan Verma
P3-B-594	*The mechanistic role of extracellular matrix proteins, growth factors, and peptide hormones in synapse formation and function*	Olivia Hawco
P3-B-595	*The Role of Glial Ferritin and Transferrin 1 in regulating Drosophila Motor Behavior*	Megan Corsini
P3-B-596	*The Role of Neuronal Primary Cilia in Regulating Dendritic Spines*	Lizheng Wang
P3-B-597	*The Role of Non-Ionotropic NMDA Receptor Signaling in Synaptic Depotentiation in the Hippocampus*	Rachel Ha
P3-B-598	*The role of oligodendrocyte precursor cells (OPCs) in memory consolidation*	Sakthivel Srinivasan
P3-B-599	*The Role of Oxysterol-Binding Protein in Synaptic Vesicle Cycling and Development*	Niha Sohail
P3-B-600	*The Role of RIM1/2 Proteins in Dopamine Release*	Madeleine Morris
P3-B-601	*The sigma-1 receptor: a molecular hub for psychostimulant drugs in the nucleus accumbens*	Nora Chagar
P3-B-602	*Theta burst calcium signals to optimize synaptic plasticity in mouse prefrontal cortex*	Hsin-Yun Hsieh
P3-B-603	*Time course development of synaptic plasticity deficits following adolescent repetitive mild traumatic brain injuries.*	Eric Eyolfson
P3-B-604	*TNFa Role in Homeostatic Synaptic Plasticity in HD*	Talia Segal
P3-B-605	*Top-down modulation of the dorsal peduncular cortex in anxiety-like and fear behaviour*	Anna Canella
P3-B-606	*Transsynaptic Organization Underlying a Cerebellar Gateway*	Mohd Sarim Siddiqui
P3-B-607	*TRPA1 channels drive pericyte dysfunction during oxidative stress*	Chris Groten
P3-B-608	*Tyrosine kinase inhibition gates a non-selective cation channel in Aplysia bag cell neurons*	Emily Robichaud
P3-B-609	*Unlocking the regenerative potential of the mammalian retina*	Ajay David
P3-B-610	*Unveiling Glial Contributions to Parkinson's Pathology by Mitochondrial NDUFA13 Knockout in Dopaminergic Neurons*	Skylar Donovan
P3-B-611	*Value coding features of serotonin neurons*	Emerson Harkin
P3-B-612	*Viral silencing of glutamatergic PreBötzinger Complex neurons induces apneas in mice*	Gabriele Matteoli
P3-C-613	*Non-invasive Profiling Reveals Heterogenous Mitochondrial Respiration Profiles in Autism and ADHD Without Clear Genomic Stratification*	Tina Ram
P3-C-614	*Novel mTOR-independent mechanisms underlying GABAergic synapse dysfunction in epilepsy*	Vranda Garg

Poster #	Abstract Title	Presenter
P3-C-615	*Optic Nerve Blood Barrier Disruption Precedes Axon Loss and is Restored Through Tight-Junction Gene Therapy*	Isaac Vidal Paredes
P3-C-616	*Oxytocin modulates social salience network connectivity in ASD, scaling with social trait expression*	Jacco Renstroem
P3-C-617	*Parkinson's disease pathogenesis influences human microglia transcriptional identity and contributes to inflammatory responses in microglia containing midbrain organoids*	Ghislaine Deyab
P3-C-618	*Personalized Biomarkers of Multiscale Functional Alterations in Temporal Lobe Epilepsy*	Ke Xie
P3-C-619	*Pharmacological study of allosteric mechanisms at the type 1 cannabinoid receptor and their application in a mouse model of acute pain*	Theodor Zaharia
P3-C-620	*Pleiotrophin induces changes in the gene expression of mice cerebral cortices following ischemic strokes*	Ron Miguel Bertenshaw
P3-C-621	*Proprioceptive Impairment Mediates the Relationship Between White Matter Disconnection and Motor Impairment After Stroke*	Mika Kaeja
P3-C-622	*Valproic Acid Modulates Seizure-Like Network Dynamics in Neonatal Hippocampal Slices Recorded on 3D Microelectrode Arrays*	Umar Zaidi
P3-C-623	*Purinergic receptor P2Y2 regulates neurogenesis and functional recovery following spinal cord injury in zebrafish*	Isaac Sullivan
P3-C-624	*Recovery of Cortical and Subcortical Signatures of Pain in Trigeminal Neuralgia Following Surgical Pain Relief*	Jerry Li
P3-C-625	*Re-discovering a reaching task for mice: assessing recovery in a mouse model of intracerebral hemorrhage (ICH) using the tray reaching task*	Sierra Hedges
P3-C-626	*Electrophysiological Mapping of the Subthalamic Nucleus in Parkinson's disease: Towards Improved Functional Characterization for Deep Brain Stimulation*	Marc-Antoine Gobeil
P3-C-627	*Reduced Presence of Spinal Inhibitory Neurons in a Mouse Model of Fragile X Syndrome*	Ann Derham
P3-C-628	*Age- and Sex-dependent effects of immune challenges on motor function in mice*	Charles Veilleux
P3-C-629	*Regional and temporal dynamics of early amyloid pathology and lysosomal co-localization in 5XFAD mice*	Thomas Van Der Sloot
P3-C-630	*Region-Specific Deletion of STEP in the hippocampal region CA2: Consequences for Social and Spatial Memory*	Laurie Bonenfant
P3-C-631	*Regulation of the intracellular accumulation of Tau by Numb and its role in tauopathies*	Sarah Hales
P3-C-632	*Regulatory Roles of Parkinson's Disease-Associated MicroRNAs in Alpha-Synuclein Expression*	William Gauthier-Naud
P3-C-633	*Reinstating GDNF-RET response to achieve dopaminergic cell rescue in a rat model of alpha-synuclein pathology*	Elin Arvidsson
P3-C-634	*Repeated Injury Impacts Immune and Neural Stem Cell-Mediated Repair in the Zebrafish Forebrain*	Sanjana Grover

Poster #	Abstract Title	Presenter
P3-C-635	*Repetitive transcranial magnetic stimulation paired with augmented reality to alter post-concussion dizziness*	Daniel Soppitt
P3-C-636	*Resolving Variants of Uncertain Significance in ALS through Integrated In Silico and Functional Approaches*	Minhal Ahmed
P3-C-637	*Role of A2A purinergic receptor in glial bridge formation and cellular and functional recovery following spinal cord injury in Danio rerio*	Ashley Chen
P3-C-638	*Role of mitochondrial dynamics in C. elegans models of Alzheimer's disease*	Grant Booth
P3-C-640	*Seizure-Sensitive Neurons Gate Memory Specificity After Early life seizures*	Yajing Guan
P3-C-641	*Selective Resistance and Vulnerability of Extra-Motor Circuits in ALS Revealed by Eye Tracking*	Emmaley Hunter
P3-C-642	*Selective seeding of human abnormal tau proteins in subiculum projecting entorhinal cells impairs temporal association memory in a mouse model of early Alzheimer's disease*	James Carmichael
P3-C-643	*Sensory dysregulation affects brain development and behavior in a mouse model of KBG syndrome*	Yana Kibalnyk
P3-C-644	*Purinergic Dysregulation in the Developing Fragile X Hippocampus*	Matthew Napier
P3-C-645	*Sex differences in a stress induced depressive phenotype: a time course of behavioural and central effects*	Maja Ramljak
P3-C-646	*Sex-Dependent Neurovascular and Network Disruption Following Diffuse Microvascular Occlusion*	Jessika Royea
P3-C-647	*Sex-specific behavioural, regional and synaptic landmarks of tauopathy revealed by PET imaging and EEG*	Christopher Morrone
P3-C-648	*Sex-specific transcriptional reorganization of dopaminergic projections following chronic social stress*	André Moreira Pessoni
P3-C-649	*Shared vulnerability of SST neuron subtypes in Schizophrenia and Alzheimer's Disease*	Nicole Endresz
P3-C-650	*Single-axon tracing of the subthalamic nucleus afferent projections arising from the external pallidum in cynomolgus monkeys*	Talha Khan
P3-C-651	*Single-molecule fluorescence in situ hybridization analysis of immature granule neurons in the depressed human dentate gyrus*	Sophie Simard
P3-C-652	*Sleep and Non-Motor Health Over Six Years of Community Dance in Parkinson's Disease*	Simran Rooprai
P3-C-653	*Spatially resolved molecular-cellular dysregulation in the subiculum of young 5xFAD mice*	Margarita Kapustina
P3-C-654	*SRSF3 regulates microglia immune response in Alzheimer's disease models with Abeta and Tau-mediated pathology*	Victor Coelho
P3-C-655	*Stress, seizures, and hyperactivity: Machine-learning-based behavioural analysis in a GRIN1 disorder mouse model*	Daria Nazarkina
P3-C-656	*Subanesthetic Ketamine Disrupts Predictive Signaling in the Prefrontal Cortex*	Benjamin Corrigan
P3-C-657	*Sublethal and lethal toxicity of amyloid-beta 1-42 oligomers in human iPSC-derived neurons*	Milton Guilherme Fernandes

Poster #	Abstract Title	Presenter
P3-C-658	*Suicide in youth: is local microglial gene regulation implicated?*	Elisa Gonçalves De Andrade
P3-C-659	*SUMO2-BASED INTERVENTIONS REDUCE SYNUCLEIN PATHOLOGY*	Sofi Aubert-Tandon
P3-C-660	*Synaptopodin: A novel therapeutic target for treatment of Autism Spectrum Disorders*	Loc Dang
P3-C-661	*Targeted Probiotic Intervention Remodels the Hippocampal Proteome and Confers Seizure Protection in a Neonatal Rat Model of Infantile Epileptic Spasms Syndrome*	Valeriya Dontsova
P3-C-662	*Targeting the Parkinson's Disease-associated protein alpha-synuclein using microRNAs*	Andrew Park
P3-C-663	*Testicular dysfunction in a murine model of Parkinson's disease*	Margaux Cavaliere
P3-C-664	*The Effect of Cannabinoid Receptor 2 on Blood-Brain Barrier Dysfunction in Epilepsy*	Hannah Reid
P3-C-665	*The fate of serotonin neurons in Parkinson's disease*	Laurie-Shan Verville
P3-C-666	*The Hypothalamic Supramammillary Nucleus Contributes to Seizures in Mouse Models of Temporal Lobe Epilepsy*	Mckenna Bolger
P3-C-667	*The Importance of Cleaning Up: Preliminary insights into the impact of AIH and nerve injury on the phagocytic properties of macrophages*	Miles Magno
P3-C-668	*The integrated stress response pathway in depression*	David Ho-Tieng
P3-C-669	*The PD-associated LRRK2 G2019S mutation alters antigen presentation in human iPSC-derived macrophages*	Zaya Haj Mohamad
P3-C-670	*The role of m6A-mediated chaperone expression in Drosophila brain*	Ryan Yip
P3-C-671	*The Roles of Astrocytic GR and ESR1 in the Regulation of Chronic Stress-Induced Emotive Behaviour*	Alexander Abou-Falah
P3-C-672	*Therapeutic Effects of Zuranolone in a Murine Model of Parkinson's Disease.*	Morgane André
P3-C-673	*Transcriptional and activity-dependent regulation of social dominance by prefrontal inhibitory interneurons*	Minza Haque
P3-C-674	*Understanding Sensory Dysfunction in Christianson Syndrome*	Circe La Mache
P3-C-675	*Understanding the role of rfc1 loss of function in the context of CANVAS pathogenicity using the zebrafish model*	Fanny Nobilleau
P3-C-676	*Using living human brain tissue to model and causally interpret Alzheimer's disease*	Julia Groening
P3-C-677	*Voluntary exercise rescues motor coordination deficits in a mouse model of ARSACS*	Alyssa Abou-Chakra
P3-C-678	*Human mutations in EPHB2 uncover its novel role in callosal axon growth*	Sung Soon Park
P3-C-679	*Cell-type-specific mechanisms implicated in mRNA translation and memory in Aging and Alzheimer's disease*	Rogers Koboji
P3-D-680	*Neuronal dynamics in the cortex of a mouse engaged in a virtual reality environment*	Ayman Driouich
P3-D-681	*Regeneration of descending brainstem locomotor pathways after complete spinal cord injury in salamanders.*	Jordan Swiegers

Poster #	Abstract Title	Presenter
P3-D-682	*Reinstatement of default mode network manifold structure underlies motor memory retrieval*	Ali Rezaei
P3-D-683	*Relationship between corticospinal excitability and inhibition and fractionated reaction time of the first dorsal interosseous muscle*	Kim Uyeno
P3-D-684	*Reorganisation of Dopaminergic Innervation to the Motor Cortex Following Cortical Lesion*	Deepshikha Sen
P3-D-685	*Role of large somatosensory afferents in speed modulation during treadmill locomotion following pyridoxine intoxication in cats.*	Stéphanie Gabriella Tonleu Dongmo
P3-D-686	*Role of NCK in the development of locomotor circuit*	Lïa Mayet
P3-D-687	*Role of the potassium channel TREK1 in mechanotransduction in peripheral sensory neurons.*	Hugo Alendouro
P3-D-688	*Roles of the Subthalamic Nucleus and Zona Incerta in Locomotion before and after Spinal Cord Injury*	Baptiste Hardoin
P3-D-689	*Sex-dependent analgesic effects of MDMA in mouse models of acute, inflammatory and neuropathic pain*	Yik Lok Wong
P3-D-690	*Sex-Specific Development of Plasticity Mechanisms in the Human Visual Cortex*	Leanne Monteiro
P3-D-691	*Shared and separate cortical manifold structure supports error- and reinforcement-based learning*	Keanna Rowchan
P3-D-692	*Single-cell transcriptomic diversity of projection neurons of the spinal cord dorsal horn*	Robert Brian Roome
P3-D-693	*A Bipartite Analysis of the Drosophila Synapse-level Connectome Uncovers Organizational Principles in the Visual System*	Aarushi Vardhan
P3-D-694	*Structural Changes in the Lateral Geniculate Nucleus Following Perinatal Auditory Deprivation*	Nicholas Murphy
P3-D-695	*STUDYING THE FUNCTION OF LONG-RANGE PROJECTING VIP-EXPRESSING NEURONS IN THE FACIAL MOTOR NUCLEUS*	Nima Raman
P3-D-696	*Sub-anesthetic ketamine impairs auditory deviance detection across cellular, population, and mesoscale levels*	Alessandra Ciancone Chama
P3-D-697	*Subcellular synaptic connectivity patterns and motor control in C. elegans*	Hannah Owens
P3-D-698	*Task-dependent modulation of hindlimb cutaneous reflexes during forward and backward walking before and after cervical spinal cord injury in cats*	Rasha Al Arab
P3-D-699	*Thalamic integration of basal ganglia and cerebellar circuits during motor learning*	Richard Roth
P3-D-700	*Thalamocortical-like circuits hierarchically process sensory information in topographically organized regions in the zebrafish forebrain.*	Anh-Tuan Trinh
P3-D-701	*The Drosophila central complex and navigation in three dimensions*	Peter Mussells Pires
P3-D-702	*The effects of cervical spinal cord injury on cutaneous reflexes from forelimb afferents to muscles of all four limbs during locomotion in adult cats*	Sirine Yassine

Poster #	Abstract Title	Presenter
P3-D-703	*The role of claustro-cortical projections in sleep-mediated motor learning consolidation*	Xiaonan Li
P3-D-704	*The Role of MicroRNAs in Drosophila Nociception*	Cara Scholey
P3-D-705	*The role of the lumbar spinal network in hindlimb locomotor recovery after incomplete spinal cord injury depends on lesion level in adult cats*	Johannie Audet
P3-D-706	*The role of V3 spinal interneurons in the vestibular control of posture in mice*	Abigail Strayer
P3-D-707	*The Structure-Function Relationship of the Oscillatory Pacemaker Nucleus Network in Weakly Electric Fish*	Abigail Kos
P3-D-708	*Theta-specific dual-brain stimulation of the right temporo-parietal junction modulates the sense of joint agency during alternating tapping*	Yuto Kurihara
P3-D-709	*Timing-related activity in the supplementary eye field of macaques*	Amirhossein Asadian
P3-D-710	*TMS Reveals Causal Contributions of Egocentric and Allocentric Functional Connectivity Hubs to Reach Behaviour*	Lina Musa
P3-D-711	*Too Much of a Good Thing: How the Spinal Cord Responds to Oxygen Excess*	Marina Rincon Sartori
P3-D-712	*Transformation of vestibular signals in the interposed versus rostral fastigial nuclei of the cerebellum*	Félix Buron
P3-D-713	*Ultrasonic Noise in the Housing Colony Affects Behaviour and Physiology of Adult Rats*	Paul Bernard
P3-D-714	*Uncovering distinct NPAS4-expressing SST-IN ensembles during the acquisition of different motor movements*	Jan Raineir Sidiangco
P3-D-715	*Uncovering the role of Podxl in photoreceptor cell polarity and function*	Samantha Boudreau
P3-D-716	*Unraveling the Impact of Aging on Neural Barrier Integrity in Mice*	Hongqian Wang
P3-D-717	*Using combined TMS-EEG to investigate cortical changes in response to acute muscle pain*	Thu Pham
P3-D-718	*Vision Loss Triggers Transient Changes in Motor-Related Cortical States in the Adult Mouse Visual Cortex.*	Ismaël Djerourou
P3-D-719	*Visual Attention in Peripersonal Space: Hand Vision and Proprioception Differentially Modulate V2 Feature Selectivity*	Hamid Ramezanpour
P3-D-720	*Visuospatial context and task performance are encoded in Ventrolateral Prefrontal Cortex LFP activity during a head-unrestrained, memory-guided reach task*	Jennifer Lin
P3-D-721	*Acute Effect of VTA Stimulation on M1 Neuronal Activity*	Aoxue Miao
P3-D-722	*Examining the Relationship of Interocular Delays, Depth Perception, and Suppression in Amblyopia*	Brooke Lim
P3-E-723	*mTBI Suppresses Water Intake Without Impairing the Thirst Circuit in Mice*	Zoe Krisko
P3-E-724	*Neurometabolic remodelling in hypothalamic appetite neurons in high-fat diet induced obesity*	Daemon Cline

Poster #	Abstract Title	Presenter
P3-E-725	*Persistent Sensitization of osmoresponsiveness by chronic Salt Loading: a potential Role for NaX Channels as mediators of homeostatic Memory in rat vasopressin neurons*	Sandra Salgado Mozo
P3-E-726	*Regulation of Vasopressin Neuron Activity and Fluid Balance in Pregnancy*	Olena Makashova
P3-E-727	*Absence of TNF-α Exacerbates Hedonic Feeding, Weight Gain, and Behavioral Alterations during Chronic High-fat High-sugar Diet Exposure*	Adora Wang
P3-E-728	*Tanycytes in the Central Regulation of Cardiovascular and Hydromineral Homeostasis*	Chris Chen
P3-E-729	*The effects of oxytocin signalling on anxiety-like behaviour and TNF expression in a mouse model of PTSD*	Maria Petryk
P3-E-730	*Traumatic brain injury activates vasopressin and oxytocin neurons of the supraoptic nucleus, causing hyponatremia*	Julie O'reilly
P3-E-731	*Mechanistic Insights into Neurotensin-Mediated Control of Body Temperature and Hypotension*	Frédérique Lussier
P3-F-732	*Opioid receptor distribution in the claustrum-dorsal endopiriform complex*	Matthew Bolger
P3-F-733	*Pannexin-2 Modulates Glutamatergic-Dependent Habituation Memory and Cellular Stress Responses*	Riya Shanbhag
P3-F-734	*Passive versus active waiting paradigms differentially affect trial-to-trial dependencies impacting impulsive action*	Sophia Robinson
P3-F-735	*Planning Mechanisms Assessed with Sequence Unblocking*	Thomas Leir
P3-F-736	*Population structure of reward-induced remapping in the hippocampal CA1*	Chen Jiang
P3-F-737	*Predicting learning outcomes by manipulating mushroom body neurophysiology in Drosophila melanogaster*	Haining Liang
P3-F-738	*Prenatal alcohol exposure alters social reward behaviour and dopamine receptor expression in male and female rats*	Andrew Sheehan
P3-F-739	*Psilocybin Enhances Reward-Based Learning by Reshaping Attractor Dynamics in Decision Making*	Veronica Chelu
P3-F-740	*Region-Specific Constraints on Neuronal Allocation During Visual Fear Memory Encoding*	Joseph Lee
P3-F-741	*Resilience as a Moderator of Discrimination-Related Cortical Thinning: A Neuroimaging Investigation of Social Determinants of Health*	Rachel Cluett
P3-F-742	*Resolving deliberation under threat: implications for anxiety*	Chelsey Damphousse
P3-F-743	*Rôle du pulvinar dans les réponses défensives et la réaction à la nouveauté sociale chez la souris*	Amirah Boulianne
P3-F-744	*Role of Cajal-Retzius neuron-derived PD-L1 in hippocampal-dependent behavior*	Karla Manzanet Freyre
P3-F-745	*Role of hypocretin/orexin neurons in social behavior and social stress*	Matthew Dawson
P3-F-746	*Role of the lateral periaqueductal grey in flexible defensive strategies*	Megan Lozzi

Poster #	Abstract Title	Presenter
P3-F-747	*Septal Interneuron Inhibition Reveals Time-course of Spatial Memory Consolidation into Hippocampus-Independent Form*	Zahra Alizadeh
P3-F-748	*Serotonergic modulation of identified ventral hippocampus output pathways in anxiety*	Lucia Pizzoccaro
P3-F-749	*Sex dependent effects of dopaminergic and endocannabinoid tone on fear expression in DAT heterozygous mice*	Stefan Vislavski
P3-F-750	*Sex-specific cortico-accumbal transcriptional remodeling links fetal growth restriction to attention-deficit/hyperactivity disorder (ADHD)-like behaviors*	Patricia Miguel
P3-F-751	*Sex-Specific Effects of Oral Lactate on Hippocampal Neurogenesis and Memory in Young Mice*	Jennifer Hanna Al-Shaikh
P3-F-752	*Shared and Individualized Representations in Vision and Mental Imagery*	Laurence Lessard
P3-F-753	*Sigma-1 Receptor Signaling in D1 Neurons Shapes Cocaine-Induced Plasticity of Intrinsic Excitability and Cocaine-Seeking Behavior*	Kiarash Eskandari
P3-F-754	*Sport-Related Concussion History Is Associated With Persistent Neural Noise and Altered Attentional Context Processing*	Zaidullah Raheen
P3-F-755	*Structural and Functional Plasticity Across Changing Social Environments*	Daniel Gale
P3-F-756	*Structuring the world drives the developmental self-organization of behavioral and neural niches*	Jorge Ramírez-Ruiz
P3-F-757	*Telling Friends from Foes: Contributions of the Medial Amygdala to Social Memory*	Sofiya Zbaranska
P3-F-758	*Retrosplenial Cortex encodes peer direction and coordinates social approach behavior in mice*	Donovan Ashby
P3-F-759	*The basal ganglia as a distributed reinforcement learning system computing general values*	Zijing Wu
P3-F-760	*The effect of chronic Δ9-THC consumption on flexible decision making*	Catherine Orr
P3-F-761	*The effects of chemogenetic activation of the anterior paraventricular nucleus of the thalamus to ventral subiculum pathway on cue-induced heroin seeking following chronic food restriction in abstinent rats*	Emily Ah-Yen
P3-F-762	*The impairing effect of electroconvulsive shocks on retrograde memory processing, neural ensemble retention, and engram reactivation*	Peiying Wen
P3-F-763	*The Lateral Entorhinal Cortex Supports Adaptive Switching between Memory Encoding and Retrieval*	Zihe Chen
P3-F-764	*The mediating role of alcohol demand in pathways from drinking motives to hazardous drinking*	Lauren Winfield-Ward
P3-F-765	*The Role of Basolateral Amygdala Neuronal Ensembles in Fear Discrimination*	Sepideh Hosseini
P3-F-767	*The role of microglial GPR120 in anxiodepressive behavior, energy metabolism and microglia reactivity in response to chronic unpredictable stress*	Samar Naili-Douaouda

Poster #	Abstract Title	Presenter
P3-F-768	*The role of the orbitofrontal cortex in integral learning of a two-dimensional auditory task*	Ruthie Poizner
P3-F-769	*Time Cells in the Human Brain Support Working Memory Maintenance*	Xiaoxuan Xiao
P3-F-770	*Transcranial Magnetic Stimulation over the Cerebellum Promotes Attentional Performance in ADHD*	Simran Mughal
P3-F-771	*TRAPing neurons involved in contextual fear learning and memory*	Katherine Chang
P3-F-772	*Ultrasonic Vocalizations as Markers of Anxiety and Depression in Rats After Spinal Cord Injury*	Kale Scatterty
P3-F-773	*Understanding the mechanisms of psilocybin-enhanced fear extinction in the lateral amygdala*	Katarina Krunic
P3-F-774	*Unravelling Non-Canonical Subicular Circuits: Projecting Somatostatin Cells Anatomy and Function in Memory*	Eve Honore
P3-F-775	*Unreinforced spatial learning and memory using massed and spaced training in juvenile and adult rats*	Klara Doelle
P3-F-776	*Using Naturalistic Stimuli and EEG-fMRI to Uncover the Neural Activity Associated with Emotion*	Jessica Din
P3-F-777	*Using Overexpectation and Pavlovian Instrumental Transfer (PIT) to understand the mechanisms of behavioural change*	Bhoomi Sati
P3-F-778	*Valence encoding in molecularly and spatially defined cell types of the nucleus accumbens*	Heike Schuler
P3-F-779	*VIP Interneuronal Dynamics in Memory-Encoding Hippocampal Spiking Sequences*	Tianwei Liu
P3-F-780	*Viral tools to alter Blood-brain barrier gene expression and decipher its role in memory and cognition*	Alice Cadoret
P3-F-781	*Creation of a Normative Database of Younger Adult Data for Telephone-Based Neuropsychological Assessment*	Alexis Hubbard
P3-F-782	*Win-stay and win-shift rule-coding in rat medial frontal cortex*	Ryley Nathaniel
P3-G-783	*Intermittent synchronization between arousal and spontaneous brain activity*	Jeremie Guilbert
P3-G-784	*Investigating multizonal convergence in the cerebellar nuclei through input-specific viral labelling*	Amna Saleem
P3-G-785	*Investigating the transcriptomic profile of cells encapsulated by perineuronal nets in the human brain: establishment of a novel protocol*	Júlia Alcaide i Pozo
P3-G-786	*Mesoscale reconstruction of 3D microstructure and fibre orientation in whole brains with automated serial tilted polarization sensitive optical coherence tomography*	Mathieu Johnson
P3-G-788	*New in vitro and ex vivo methods for studying human dorsal root ganglia*	Celia Cuculiere
P3-G-790	*Paired Neuroimaging and Transcriptomics in the Same Individuals Reveal Region-Specific Molecular Correlates of Brain Structure*	Thomas Delong
P3-G-791	*Reconstruction of the corpus callosum fibers of the rat with tilt-angle polarization-sensitive optical coherence tomography*	Mario Gomez Martinez

Poster #	Abstract Title	Presenter
P3-G-792	*Spatial tuning reflects linear perceptual versus nonlinear memory encoding in hippocampus*	Maxime Daigle
P3-G-793	*STUAART: Real-time assessment of mouse health and behaviour through its weight*	Valérie Pineau Noël
P3-G-794	*Targeted Gene Delivery to Astrocytes Using Intelligent Phagemid-Assembled Gene Expression (iPhAGE) Technology for Neuronal Regeneration*	Anna Ffrench
P3-G-795	*TEMPO: 4D Motion Distillation for Unsupervised Monocular 3D Pose Estimation*	Amirhossein Mohammadi
P3-G-796	*Testing the Efficacy of qEEG-guided TMS for the Treatment of Persistent Post-Concussion Symptoms (PCS)*	Eline Poinsignon-Clavel
P3-G-797	*The creation of a psychedelic platform technology for future drug screening and cognitive discovery*	Kaleb Edwards
P3-G-798	*TRACR: A novel transsynaptic tracer toolkit for in vivo visualization of mammalian circuit connectivity*	Sofia Eiras
P3-G-799	*Using multi-omics knowledge graphs to discover novel neurodevelopmental disorders mechanisms*	Arnaud Maupas
P3-G-800	*Using Self-Supervised Foundation Model for Confocal Microscopy for Microglia Segmentation*	William Saxon
P3-G-801	*Visualizing Melanin Granules in Parkin-Expressing Neural Cells Using Transmission Electron Microscopy*	Nazia Hassan
P3-H-802	*Teaching Neuropsychology Through Simple and Cost-Effective Activities: Paper Cortex and Case Study Escape Room*	Nicole Vittoz
P3-H-803	*The Efficacy and Shortcomings of Spinal Surgery Referral Systems across Canada: A Systematic Review*	Tharushi Perera

POSTER SESSION 1

A - DEVELOPMENT

P1-A-1 *A clinical trial to evaluate the feasibility, safety, and tolerability of fecal microbiota transplantation (FMT) in adolescents with attention deficit hyperactivity disorder (ADHD)*

Cleo Hendrickson [1], Illiana Ortega [1], Keith Sharkey [1], Deborah Kurrasch [1], Valerie Taylor [1]

[1] *University of Calgary*

Background: Attention Deficit Hyperactivity Disorder (ADHD) is a common neurodevelopmental disorder and leaves many experiencing limited symptom relief, despite being on first-line pharmacotherapy. The gut–brain axis is increasingly implicated in ADHD, with evidence suggesting a distinct, potentially dysbiotic microbiome profile. A technique called Fecal Microbiota Transplantation (FMT) shows benefit in preclinical models, but clinical data in ADHD is limited. Objectives: To evaluate the feasibility, safety, and tolerability of FMT in adolescents with ADHD and explore links between microbiome changes and clinical outcomes. Methods: We will conduct a phase 2, placebo-controlled feasibility trial in 64 adolescents (13–17 y/o) with ADHD on first-line approved medication. Participants will be randomized (n=16/group) in a 2×2 factorial design to active vs placebo FMT and active vs placebo antibiotics. Stool, blood, and saliva will be collected at six timepoints over 24 weeks for microbiome profiling (next generation sequencing), metabolomics (H-NMR), inflammatory marker analyses, and the measurement of stimulant metabolism. All results will be linked to clinical outcomes including ADHD symptom severity, functional impairment, and safety and tolerability measures. Conclusion: This study will generate feasibility, safety, and tolerability data for FMT-based interventions in an adolescent population with ADHD and will clarify the relative contribution of FMT versus preparatory elements, informing future trials and microbiome-targeted strategies for neurodevelopmental disorders.

P1-A-2 *A hyperexcitable ensemble in CA2 deep layer encodes social recognition memory during early development*

Xiaoxuan Han [1], Yajing Guan [1], Tingting Wang [1], HONGYU SUN [1]

[1] *Carleton University*

Social recognition memory emerges early in postnatal development and critically depends on the hippocampal CA2 region. However, whether a selective subpopulation of CA2 neurons is preferentially recruited to encode social recognition memory in the immature brain remains unknown. Using a c-Fos–based activity-dependent tagging and manipulation approach in mice, we examined ensemble recruitment across CA2 sublayers in P9-11mice following interaction with their caregiving dam. We found that significantly more neurons in the CA2 deep layer were recruited into the social memory ensemble compared to the superficial layer. Deep-layer CA2 neurons exhibited a significantly higher excitation/inhibition balance, driven by reduced GABAA receptor–mediated inhibitory charge transfer compared to CA2 superficial layer neurons. Minimally evoked single fiber stimulation of entorhinal cortex inputs revealed larger AMPAR-mediated EPSC amplitudes in CA2 deep-layer neurons, indicating greater response potency. Furthermore, social recognition memory ensemble itself displayed heightened excitability, evidenced by an increased AMPAR-mediated sEPSC frequency. Importantly, selective chemogenetic silencing of these ensemble neurons impaired social recognition behavior, supporting their functional necessity. Together, our findings identify and characterize a selective, hyperexcitable social recognition memory ensemble in the CA2 deep-layer that is necessary for social recognition memory during early development.

P1-A-3 *A live ER-stress-enabled system to study developmental dysregulation in dual-isoform CRB1-deficient retinal organoids*

Ali Zahedi Amiri [1], Jessica Wang [1], Cassandra D'amata [2], Brian Ballios [1]

[1] University of Toronto, [2] Donald K. Johnson Eye Institute, Krembil Research Institute, University Health Network

Mutations in CRB1 cause inherited retinal dystrophies with a strong developmental component, including disrupted retinal organization and altered neurogenesis. Patient-derived retinal organoids (ROs) mimic early retinal development but are limited by genetic background variation and lack dynamic access to intracellular processes, such as endoplasmic reticulum (ER)-stress signaling, that influence progenitor competence and fate decisions. To address these limitations, we developed a RO system combining isogenic CRB1 disruption with live ER-stress reporting. Human induced pluripotent stem cells (iPSCs) from a CRB1 patient and a healthy donor were differentiated into ROs and analyzed across weeks 8-32 of development. CRB1 patient-derived ROs exhibited early developmental abnormalities, including ectopic basal localization of proliferating progenitors and a shift toward early-born retinal fates, with increased retinal ganglion cells and cones and reduced late-born rods and Müller glia, despite comparable proliferation and minimal cell death. Transcriptional profiling revealed early, transient attenuation of NOTCH signaling followed by progressive Hippo/YAP activation, indicating a temporal shift in progenitor signaling. In parallel, a fluorescent ER-stress reporter combined with dual-guide RNA CRISPR/Cas9 targeting of retinal CRB1 isoforms (A, B) established an isogenic background for longitudinal ER-stress monitoring across control, CRB1-deficient, and patient-derived ROs, enabling temporally resolved analysis of stress-development interactions in CRB1-associated disease.

P1-A-4 *Studying the impact of maternal stress on fetal brain development during pregnancy*

Kodee Bao [1], Matthew Rosin [2], Jessica Rosin [2]

[1] The University of British Columbia, [2] University of British Columbia

The prevalence of neurodevelopmental disorders (NDDs) is on the rise, with emerging evidence implicating the intrauterine environment. Maternal stress is a key risk factor and immune dysregulation is common in NDDs, suggesting a role for fetal microglia in altered brain development. Accordingly, we aimed to examine how maternal stress disrupts microglia–neural stem cell (NSC) signalling to reshape fetal neurodevelopment. Hypothalamic neurosphere assays showed that neurons derived from both male and female NSCs exhibited longer axons following maternal stress exposure. However, only males showed a significant increase in TUJ1+ neurons in response to maternal stress, whereas only stressed females displayed enhanced dendritic arborization. To explore the molecular basis of these changes, we performed single-cell RNA sequencing on fetal hypothalamic NSCs. Differential gene analysis uncovered distinct transcriptional signatures between control male and female NSCs and showed that maternal stress shifted female NSCs toward a more male-like transcriptional profile. In females only, maternal stress upregulated pathways related to neuronal growth, GABAergic neuron differentiation, and neuron projection morphogenesis. Cell–cell interaction analysis further suggested that maternal stress primarily alters NSC–NSC signalling, with males and females showing changes in opposing directions. These findings demonstrate sex-specific effects of maternal stress on fetal neurodevelopment and identify distinct cellular pathways that may contribute to sex differences in NDD presentation and risk.

P1-A-5 *High frequency oscillation morphology changes in healthy children throughout development*

Tatsuya Hansen [1], Daniel Lachner Piza [2], Riddhi Chabrotra [1], Margarita Maltseva [2], Julia Jacobs [2]

[1] University of Calgary, [2] Alberta Children›s Hospital Research Institute

Epileptic high frequency oscillations (HFOs) have been identified as a promising biomarker for epilepsy. Conversely, physiological HFOs in healthy individuals play an important role in memory consolidation and cognition. Despite their significance, distinguishing between healthy versus pathological HFOs remain a

challenge. This study seeks to examine age and sex related differences in healthy HFO morphology.244 scalp EEGs from healthy participants between 1 month and 17 years old were analyzed. Nonparametric tests were performed to investigate sex differences and differences between age groups for the following HFO characteristics: amplitude measures, frequency content, and duration. The analysis revealed significant differences between sexes in the following HFO characteristics. Females recorded higher amplitude measures and duration, but lower frequency content compared to males ($p<.001$ for all tests). There were also significant differences between age groups. 11-13 year olds exhibited the lowest amplitudes measures, while the 3-5 year olds exhibited the lowest frequency content. Both amplitude and frequency characteristics followed a U-shaped trend, first decreasing but then increasing in older age groups. Currently, no research has been done to show how HFO morphology changes throughout childhood development. This research will provide an atlas of normative values for HFO morphology across ages in children and may help to separate healthy vs. epileptic HFOs leading to more accurate clinical tools using HFOs. This project is funded by NSERC.

P1-A-6 *Advancing neural developmental research through stem cell–derived systems*

Jamuna Karanankattil Sukumaran [1], Sreethu Sankar [1], Timothy Sontag [1], Deepa Shankar [1]

[1] *Proteintech Group*

Stem cells possess the unique ability to differentiate into any specialized cell type, making them an invaluable resource in both basic research and regenerative medicine. Differentiated stem cell models enable the investigation of proteins involved in developmental and disease processes—many of which are otherwise inaccessible due to the rarity or ethical inaccessibility of certain human tissues. Embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs), when directed along specific lineages, offer robust systems for studying cell-type–specific proteins and functions. For example, three-dimensional midbrain organoids derived from human pluripotent stem cells (hPSCs) have emerged as physiologically relevant models to explore human neurodevelopment and neurodegenerative diseases such as Parkinson's disease. In this study, we utilized defined combinations of human cell expressed growth factors demonstrating superior bioactivity and stability to drive hPSC differentiation toward regionally specified neural lineages. Differentiation efficiency and cell-type specification were monitored using a panel of well-validated antibodies targeting key developmental and neuronal markers. Our workflow highlights the critical role of precisely timed signaling cues and the use of high-quality reagents in achieving consistent and efficient neural differentiation. This strategy enables reliable characterization of stem cell–derived neural models and broadens their applicability across developmental studies, disease modeling, and therapeutic discovery.

P1-A-7 *Adverse childhood experiences alter adolescent social behaviour and neuroplasticity in a mouse model of abusive head trauma and neglect*

Sydney Harris [1], Hiruni Ratnayaka [1], Marissa Sgro [1], Richelle Mychasiuk [2]

[1] *Monash University,* [2] *University of Sydney*

Adverse childhood experiences (ACEs) are negative events occurring before age 18, including physical abuse and neglect. Exposure to ACEs increases the likelihood of chronic health disorders, with cumulative exposure further potentiating this risk. Many ACE-related deficits emerge during adolescence, a period marked by heightened neuroplasticity, particularly in brain regions involved in social behaviour. This study investigated the effects of two neonatally-experienced ACEs: maternal neglect [RM1] and abusive head trauma (AHT), on adolescent social behaviour and neuroplasticity. Briefly, mice underwent maternal separation (MS) for 4 hours daily from postnatal day (P) 2–12 to model maternal neglect. On each day, between P8-12 mice were also subjected to an AHT. During adolescence, mice were assessed in a social interaction task using age- and sex-matched stimulus mice. Brains were collected, and the medial prefrontal and orbitofrontal cortices were immunostained for perineuronal nets (PNNs) and parvalbumin-expressing (PV) interneurons, as markers of neuroplasticity. The results of the 3-way ANOVA (sex x AHT x MS) indicated that MS reduced social interactions, regardless of AHT ($F(1,110) = 5.13$, $p = 0.03$). While neither of the ACEs altered overall PNN or PV cell counts, AHT was associated with a significant reduction in PNN complexity ($F(1, 46) = 5.290$, $p = 0.026$).

These findings suggest that neglect and AHT may not produce cumulative effects but instead exert distinct influences on adolescent social behaviour and cortical neuroplasticity.

P1-A-8 *Age- and formulation-dependent effects of combined oral contraceptive exposure on depression- and anxiety-like behavior in CD-1 mice*

Sarah Kheloui [1], Heba Shaji [2], Luna Cappelletti [2], Lisa Brighenti [2], Francesca Carraro [2], Shelina Azad Kassim [2], Freya Anderson [2], Jacky Liang [2], Nafissa Ismail [3]

[1] University of Ottawa, [2] Neuroimmunology, Stress, and Endocrinology (NISE) Laboratory, School of Psychology, [3] University of Ottawa; LIFE Research Institute

Puberty is a critical period of development during which combined oral contraceptives (COCs) exposure might increase vulnerability to mental illness. This study examined whether COC formulation and age of COC onset increase depression-like and anxiety-like behaviours and alter brain related markers (5-HT and GABA). Beginning at 5 (pubertal groups) or 10 (adult groups) weeks of age, mice received 250µL of either EE/LNG, EE/DRSP or a vehicle via oral gavage daily for a duration of 5 weeks. They were then exposed to a battery of behavior tests to examine depression-like and anxiety-like behaviors such as the Tail suspension, Open field, Elevated Plus Maze, and Forced swim tests. Contrary to our hypotheses, we found that both pubertal COCs groups and males showed reduced immobility (i.e. increased active coping) during the Forced swim test. EE/LNG adult females spent more time in the center of the Open Field. Moreover, EE/DRSP-treated adult females displayed increased GABA expression in the CA2 and CA1, whereas EE/LNG-treated adult females displayed lower GABA expression in the CA3 region. Our results indicate that the effects of COC on the brain and behaviour are formulation- and age-dependent, and they also vary across tests. These findings suggest heterogeneity in the impact of COC on mood disorders, suggesting that risk may differ across formulations and developmental stages.

P1-A-9 *Altered cerebellar serotonin dynamics underlie anxiety and spatial memory deficits in engrailed-2 knockout mice*

Hoda Ranjbar [1], Shi Chen Xu [1], Derya Sargin [1]

[1] University of Calgary

Objective: Autism spectrum disorder (ASD) is characterized by social, cognitive, and motor impairments, with growing evidence implicating cerebellar dysfunction in its pathophysiology. The cerebellum receives serotonergic innervation, and serotonin plays a critical role in modulating Purkinje cell (PC) activity and cerebellar output. However, how cerebellar serotonin signaling is disrupted in ASD remains poorly understood. We hypothesized that altered serotonin-mediated modulation of cerebellar circuits contributes to behavioural dysfunction in ASD. Method: Using Engrailed-2 knockout (En-2 KO) mice, a genetic model associated with ASD, we assessed anxiety-like behaviour, spatial recognition memory, cerebellar serotonin dynamics, and PC responsiveness to serotonin in both sexes. Results: Behavioural analysis revealed that female and male En-2 KO mice exhibit increased anxiety-like behaviour in open field, and impaired spatial recognition memory, as measured in the Y-maze. Photometry recordings of cerebellar serotonin release demonstrated altered serotonergic dynamics in En-2 KO mice during both open-field exploration and Y-maze testing. At the cellular level, patch recording of PCs in En-2 KO mice displayed disrupted responses to serotonin, indicating impaired neuromodulatory control of cerebellar output. Conclusions: Collectively, these findings implicate cerebellar serotonin dysregulation and impaired PC responsiveness as contributors to behavioural deficits in En-2 KO mice. Our results highlight a critical role for cerebellar serotonergic signaling in ASD-related behaviours and suggest that targeting cerebellar neuromodulation may offer a promising therapeutic possibility.

P1-A-10 *Astroglial VEGF regulates postnatal cerebrovascular development in mice*

Moises Freitas-Andrade [1], Peter Van Dyken [2], Paniz Akbari [3], Sara Kawtharani [3], Baptiste Lacoste [1]

[1] Ottawa Hospital Research Institute, [2] University of Ottawa, [3] Translational and molecular medicine, University of Ottawa

To identify mechanisms underlying gliovascular growth during postnatal brain development, we assessed gene expression changes in astrocytes between postnatal day (P)0 and P14. We found that Vegfa expression by astrocytes increases after birth and peaks at P7. We performed conditional, astrocyte-specific ablation of Vegfa starting at P0, in Aldh1l1-CreERT2;Vegf flox/flox (Aldh1l1-Vegf DAstro) mice, to test whether VEGF is critical for gliovascular development. Preliminary data showed that Aldh1l1-Vegf DAstro mice exhibited a significant reduction in VEGF protein levels and reduced levels of blood-brain barrier markers such as beta-catenin and occludin at P7, compared to control littermates. Aldh1l1-Vegf DAstro mice exhibited a 2-fold reduction in vascular area in the cerebral cortex as well as aberrant cortical distribution of Connexin43 gap junction protein. Aldh1l1-Vegf DAstro mice did not survive past P7, due to loss of VEGF in Aldh1L1+ VEGF-expressing hepatocytes. To investigate astrocyte-specific ablation of Vegfa, without affecting VEGF levels in other organ systems, we generated Glast-CreERT2;Vegf flox/flox (Glast-Vegf DAstro) mice, where CreERT2 is under the control of the glial high affinity glutamate transporter (GLAST) promoter. Glast-Vegf DAstro mice exhibited robust CreERT2 activation, in astrocytes, and VEGF levels were not affected in liver. This study suggests that astrocyte-derived VEGF is critical for postnatal vascular development in the brain. Moreover, caution should be applied when using the Aldh1l1-CreERT2 mouse line for brain-specific studies.

P1-A-11 *Brain metabolite profiles in youth: Associations with mental health, behavior, and development across stress-sensitive regions*

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Background: Early-life stress is associated with altered neurodevelopment and increased risk for mental health problems, yet underlying neurochemical mechanisms remain poorly understood. While neuroimaging studies have shown stress-related brain differences, less is known about in vivo neurochemistry. Using Magnetic Resonance Spectroscopy (MRS), this study examined metabolite levels in stress-sensitive regions (ACC, RPFC, LBG) and their associations with mental health symptoms. Methods: MRS data were acquired in thirty-seven youth (8–16 years) on a 3T scanner using Point-RESolved Spectroscopy (PRESS), with voxels placed in the ACC, RPFC, and LBG. Glutamate and glutamine were quantified using Osprey and LCModel and expressed relative to water. Parents completed the Child Behavior Checklist (CBCL). Correlations and group comparisons were conducted in SPSS with correction for multiple testing. Results: No sex differences were observed in metabolite concentrations. CBCL total problems, internalizing, externalizing, and attention scores were not associated with metabolite levels in any region (all $p > .05$). Cross-region analyses revealed a significant positive correlation between NAA in the ACC and LBG ($r = .412$, $p = .017$). No other significant cross-region correlations were found. Conclusions: Coordinated NAA levels between the ACC and LBG suggest inter-regional neurochemical integrity in youth, even in the absence of behavioral associations. Larger, longitudinal studies are needed to clarify how early adversity influences neurochemical development.

P1-A-12 *Characterizing cell-type-specific contributions of a high-penetrance gene for autism spectrum disorder: Implications for brain and behavioral development*

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The global prevalence of autism spectrum disorder (ASD) has risen by ~240% since 2000. ASD is characterized by changes in social, communication, and perseverative behaviors. About 85% of children with chromodomain-helicase-DNA-binding protein 8 (CHD8; Chd8 in non-primates) haploinsufficiency present with ASD, macrocephaly, and gastrointestinal disruptions. Pancellular Chd8 knockout models recapitulate these phenotypes but lack the cellular resolution to pinpoint cell-type-specific contributions to CHD8-associated ASD. We hypothesized that neuronal Chd8 conditional knockout (cKO) drives ASD-like

behavioral, brain volumetric, and gut alterations. To test this, we generated and validated novel mouse lines targeting Chd8 in neurons, oligodendrocytes, microglia, and astrocytes. Male and female mice underwent neonatal (communication, coordination) and adolescent (social, perseverative, cognitive, and anxiety-like) behavioral assays. Thus far, neuronal Chd8 cKO altered coordination and communication in neonatal males. In adolescence, neuronal Chd8 cKO heightened anxiety-like behavior in females and altered cognitive and perseverative behaviors in males. Microglial Chd8 cKO impaired cognition in both sexes. Volumetric (14T MRI and histology) and gut microbiome analyses are ongoing. By targeting Chd8 in specific cell types, this work aims to reveal the drivers of CHD8-associated phenotypes. These findings will guide molecular, functional, and human neuroimaging studies to ultimately support therapeutic strategies for CHD8-linked ASD and conditions with converging neurobiology.

P1-A-13 *Characterizing the role of ShcD in adult neurogenesis and neurobehavioral function*

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Olfactory dysfunction is increasingly recognized as a feature of neuropsychiatric disorders, including depression and anxiety, where alterations in sensory processing and neuroplasticity are observed. The olfactory system is uniquely positioned at the intersection of sensory function and adult neurogenesis, as it remains one of the few brain niches to undergo continuous neuronal renewal. Newly generated neurons from the subventricular zone migrate to the olfactory bulb and integrate into existing circuits that influence odor discrimination. Disruption to this tightly regulated process has been implicated in mood-related phenotypes. Our protein of interest, ShcD is the least characterized member of the Shc family that is involved in the signaling cascade of pathways downstream of receptor tyrosine kinases. ShcD knockout mice exhibited altered olfactory bulb morphology and impaired olfaction. Given the anatomical and functional connections between the olfactory system and limbic structures, perturbations in olfactory neurogenesis may represent a critical but underexplored mechanism contributing to affective dysfunction. Based on its putative involvement in neuronal development, ShcD is hypothesized to influence adult neurogenesis within the olfactory system, thereby contributing to alterations in olfactory function and anxiety/depression-like behaviours. By integrating behavioral, cellular, and molecular approaches, this work aims to investigate how disruptions in adult neurogenesis influence olfactory function and neurobehavioral outcomes relevant to anxiety and depression.

P1-A-14 *Decoding temporal RNA regulation in brain development*

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Mammalian brain development is precisely regulated by gene expression coordinated across multiple levels, including the translation of mRNA into proteins. Mutations in RNA-binding proteins (RBPs) that control target-specific mRNA regulation are increasingly recognized as a major cause of neurodevelopmental disorders (NDD), exemplified by our recent identification of a novel NDD associated with the RBP CELF2. While we now know that its mutations alter mRNA function in neural stem cells during neurogenesis, its persistent expression throughout development suggests CELF2 likely affects other aspects of neural stem cell development relevant to the clinical phenotypes. However, further investigation is hindered by a lack of methods for analyzing RBP targets in rapidly dividing stem cells within complex, heterogeneous tissues. To address this challenge, we developed SaRTI-seq (Spatially assisted RNA-binding protein Target Identification sequencing), a novel approach that enables selective bioorthogonal labeling of RBPs in stem cells to analyze their temporal regulation of RNA targets. We applied SaRTI-seq to investigate CELF2 binding of target mRNA at different timepoints during the development of the mouse cerebral cortex. Notably, we found that CELF2 undergoes temporal switches in its target binding in neural stem cells, including those that regulate neurogenesis, gliogenesis, and stem cell quiescence, and those relevant to clinical symptoms of the affected individuals. Thus, our new SaRTI-seq strategy expands the toolkit for studying RBP biology in neurodevelopment and reveals dynamic mRNA regulation critical for normal brain development and disease.

P1-A-15 *Exposure to early-life adversity heightens rats' stress sensitivity and impacts oxytocin expression in the paraventricular nucleus of the hypothalamus in a stress-sensitization model*

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Early-life adversity (ELA), such as neglect or maltreatment, increases the risk of later psychopathology, yet is often not necessary or sufficient to cause psychopathology alone. One framework proposes that ELA sensitizes stress response systems, heightening vulnerability to later stress. The impact of ELA on sensitivity to subthreshold stressors remains largely unexplored. This study tested whether neonatal ELA sensitizes the stress response enough that subthreshold stress becomes sufficient to produce depression-like behaviour. Long-Evans dams and their litters experienced either standard housing conditions (neonatal control; nCON) or limited bedding and nesting stress (LBN) from postnatal day (PD) 2-10. During adolescence (PD48-60), offspring were assigned to either a no-stress adolescent control (aCON) or 12-day subthreshold chronic mild stress (CMS) group. In adulthood, LBN-CMS offspring exhibited greater depression-like responding in the forced-swim test and reduced sucrose preference compared to all three other groups, as well as greater aggression in a social play test. The three remaining groups (nCON-aCON, nCON-CMS, and LBN-aCON) did not differ from each other. Offspring exposed to LBN also had fewer oxytocin-immunoreactive cells in the paraventricular nucleus than offspring without a history of LBN. These results suggest that ELA, via LBN, sensitized offspring to subthreshold stress, rendering mild adolescent stress sufficient to elicit adult depression-like behaviour. Altered oxytocin signaling may be one mechanism underlying this heightened vulnerability.

P1-A-16 *Differential expression of neurotransmitter synthesis genes in aminergic neurons is associated with social roles in ants*

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IntroductionAnts exhibit age-related task specialization, or temporal polyethism: young workers are prone to nurse inside the nest, while matures forage outside. Biogenic amines, particularly dopamine and octopamine, modulate neural circuits that underlie this behavioral transition. However, the anatomical distribution of aminergic neurons and the expression patterns of their biosynthetic genes remain poorly characterized. Methods We used RNA fluorescent in situ hybridization to locate the dopaminergic and octopaminergic neurons in the brain, by labeling the transcripts for synthesis enzymes tyrosine hydroxylase and tyramine beta hydroxylase, respectively. Then, we quantified fluorescence intensity, and performed qPCR to compare these genes' expression between young (eclosion to 3 weeks) and mature (>1 month old) workers. Results Both dopaminergic and octopaminergic neurons were present in the protocerebrum and subesophageal zone. Dopaminergic cells were also found in the optic lobes, whereas octopaminergic neurons were detected in the antennal lobes. Fluorescence intensity analysis revealed lower expression of both genes in mature workers. In contrast, qPCR showed significant age-related differences only in tyrosine hydroxylase expression. Discussion Aminergic neurons are distributed in regions associated with sensory processing, integration, and social behavior. Octopamine-related transcripts might be transported from the soma to the neurites in mature subjects. Dopaminergic mRNA levels are elevated in young workers, which mainly perform tasks inside the nest.

P1-A-17 *Early-life adversity during infantile amnesia alters anxiety-like behaviour in mice*

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Infantile amnesia, a phenomenon present in both humans and mice alike, refers to the inability to consciously recall experiences from early infancy. Prior research in the field has clarified that these early-life experiences aren't erased but instead persist in a dormant state, requiring artificial activation of the relevant

memory engram cells for recall. While these silent memories are present in the brain, it remains unclear whether these early-life memories manifest behaviourally. Particularly, whether stressors experienced during infancy can exert long-lasting effects on behaviour is poorly understood. Here, we investigated the behavioural consequences of early-life adversities during periods of infantile amnesia in mice. Male and female mice were exposed to established early-life adversity paradigms during early postnatal development, including scarcity bedding and contextual fear conditioning. These stressors were administered prior to P19, a period where explicit memories are not retained into adulthood. In adulthood, the mice were assessed using a battery of anxiety-related behavioural assays, including the novelty suppressed feeding test (NSF), to evaluate persistent alterations in behaviour. Despite the absence of explicit memory for early-life stressors, preliminary analyses suggest a differential trend for anxiety-related behaviour during NSF between male and female mice across groups. These findings indicate a potential for distinct early-life stressors experienced during infantile amnesia to have long-lasting effects in anxiety-related behaviour in adulthood.

P1-A-18 *Early-stage disruption of network memory capacity and spatiotemporal sequences in SHANK2 and MECP2 mutant human iPSC-derived neural networks*

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The ability to store long-term memories depends on connection patterns within neuronal networks. When and how human networks develop this memory capacity, however, remains an open question, and the factors that disrupt this process are not yet sufficiently studied. In this study, we utilized human stem cell-derived excitatory neurons and the Ngn2 protocol to investigate the origins of memory at the cellular level. Using high-density multielectrode arrays (MEAs), we observed that neuronal firing typically progresses from Poisson-like activity to organized network bursts by days 24–27. To understand how specific genetic factors disrupt this memory formation, we compared networks with mutations in the SHANK2 or MECP2 genes against isogenic controls (CTRL). Although these mutations result in overlapping clinical features, they demonstrated opposite activity profiles in our system. Both mutant networks exhibited slower initial development and fewer spiking neurons compared to controls. By day 26, however, a divergence occurred: SHANK2 networks exceeded controls in spiking activity with higher synchrony, while MECP2 networks remained suppressed with lower synchrony. Our research identifies that network bursts exhibit repetitive patterns we refer to as a “spatiotemporal engram”. This serves as a form of network memory that resembles the neural sequences observed in the hippocampus during memory tasks. We found that while control networks maintain consistent spatiotemporal patterns, mutations in SHANK2 and MECP2 disrupt the capacity to form these engrams from the earliest stages of development. These findings provide a necessary framework for understanding the early-stage disruption of memory and the breakdown of hippocampal-like network activity.

P1-A-19 *Effect of prenatal, gestational, and postnatal vitamin D deficiency on mTOR expression and physical and behavioural development in a wistar rat model*

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Developmental vitamin D deficiency (VDD) through the prenatal, gestational, and postnatal periods is a concern due to its sustained impact on offspring. The hippocampus is particularly susceptible to environmental influence and can be altered by vitamin D fluctuation. Vitamin D also influences the mechanistic target of rapamycin (mTOR) pathway, which is critical for growth and neurodevelopment. This study explored the effect of developmental VDD on hippocampal mTOR expression and physical and behavioural development. Wistar rat dams were assigned to a vitamin D deficient or control diet from six-weeks preconception until sacrifice on postnatal day 21. Hippocampal mTOR was quantified by ELISA. Physical and behavioural development were assessed through the righting reflex, negative geotaxis, grip strength, open field testing, and developmental milestones of fur development, ear and eye opening, and incisor eruption. Significant differences were observed in body weight, incisor eruption, and mTOR

concentration. VDD pups had lower body weight potentially resulting from reduced muscle mass and impaired bone development. Control pups achieved incisor eruption earlier than VDD pups and had differing exploration patterns during open field testing. VDD pups had elevated hippocampal mTOR protein concentrations. These findings reinforce the role of vitamin D on development and its influence on mTOR signaling. Future work will examine complex-specific mTOR expression and mTOR pathway signaling molecules.

P1-A-20 *Studying the impact of maternal sleep disruptions on neurodevelopment and offspring behaviour*

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Rates of neurodevelopmental disorders (NDDs) are on the rise and while NDD risk has been linked to prenatal stressors, the impact of maternal sleep disruptions on neurodevelopment remains less understood. Modern lifestyle factors, including shift work, artificial lighting, and chronic stress, can destabilize the light–dark cycle, potentially altering glial cell composition, fertility, and offspring behaviour. To explore how maternal sleep disruptions affect neurodevelopment and offspring behaviours, we established a sleep disruption paradigm whereby pregnant mice are exposed to 24 hours of constant light or dark between embryonic day 12 (E12) and E16—a critical period of hypothalamic neurodevelopment—or a 6-hour shift in the light cycle every four days from E5 onwards. Assessment of glial cell composition in the postnatal day 70 (P70) suprachiasmatic nucleus (SCN), including microglia, astrocyte, and oligodendrocyte numbers and localization, revealed a significant alteration in astrocyte distribution within the male SCN. To evaluate fertility, vaginal cytology was performed on female offspring between P50–63, revealing significant disruptions to estrous cycling. In parallel, sexual preference was assessed using scent preference testing between P57–63 with male urine, which showed significant alterations across all stages of the estrous cycle. Together, these findings suggest that maternal sleep disruptions influence fetal brain development, fertility, and offspring behaviour, providing insight that may inform interventions and policies aimed at reducing NDD risk.

P1-A-21 *Enduring sex-dependent effects of pubertal chronic unpredictable stress on anxiety-like behaviour and neuroinflammation, and the modulatory role of probiotics in CD-1 mice*

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Pubertal stress alters gut microbiome composition, resulting in gut dysbiosis and neuroinflammation in stress-sensitive brain regions, increasing the risk of stress-related disorders like anxiety. This study explored the effects of chronic unpredictable stress (CUS) during puberty on anxiety-like behaviour and neuroinflammatory gene expression in the prefrontal cortex (PFC), hippocampus, and amygdala in male and female CD-1 mice. It also assessed whether the probiotic formulation Cerebiome® could mitigate these effects. One hundred twenty CD-1 mice (60 males, 60 females) were given water or water supplemented with Cerebiome® (10^9 CFU/day; L. helveticus R0052 and B. longum R0175) starting at three weeks of age. At four weeks, mice were assigned to either the control or the 28-day CUS condition. Anxiety-like behaviour was assessed using the elevated plus maze, open field test, and light/dark box, while NLRP3, CASP1, NFκB1, and NFκB2 mRNA expression were quantified using RT-qPCR. Results showed that CUS decreased the time spent in the center of the open field, indicating increased anxiety-like behaviour. In the hippocampus, CUS elevated NLRP3 expression in water-treated males, which probiotics mitigated. The PFC exhibited sex- and treatment-specific changes in NFκB signalling. In the amygdala, probiotic treatment reduced NLRP3 levels in males and increased NFκB2 levels in females. Overall, pubertal CUS activated neuroinflammatory pathways in a region, sex, and treatment-dependent manner, underscoring the role of neuroinflammation in adolescent stress and anxiety vulnerability, and highlighting neuroinflammation as a potential mechanistic link between adolescent stress, gut-brain interactions, and vulnerability to anxiety-related outcomes.

P1-A-22 *Evaluating Tylenol vs maternal illness during pregnancy for autism risk; a registered report*

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Epidemiological associations between prenatal Tylenol (acetaminophen) exposure and autism spectrum disorders have generated public discussion. Conversely, illness during pregnancy is a well-established risk factor for developmental disorders. Since Tylenol is commonly taken for illness during pregnancy, the link with autism may reflect the effects of maternal illness rather than Tylenol. In this study, we will directly test the impact of Tylenol and illness on autism using the Maternal Immune Activation (MIA) mouse model. MIA simulates a viral infection by injecting a synthetic RNA into pregnant mice. Along with MIA or control treatment at embryonic day 12.5, Tylenol or control will be administered via drinking water. Food intake and activity will be recorded. Offspring will be evaluated across development for prenatal placental blood flow, neonatal vocalizations, sociability in the three-chamber social interaction test, and repetitive-like behavior using the marble burying assay. In addition, neuroimmune outcomes will be assessed in serum and cortical tissue via multiplex cytokine analysis. We hypothesize that MIA will adversely affect prenatal health and autism-relevant behavioral phenotypes. We further predict that at recommended doses, Tylenol will attenuate these MIA-induced deficits without producing independent adverse effects. By disentangling the effects of maternal illness from Tylenol exposure, this study aims to clarify the biological mechanisms underlying epidemiological associations and inform evidence-based guidance regarding Tylenol use during pregnancy.

P1-A-23 *Examining the effects of a double-hit model of early-life stress on the behavioural and physical development of wistar rat pups*

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Early-life stress (ELS) and malnutrition contribute to many neurodevelopmental and physiological disorders. However, it remains unknown whether these factors combined work in an additive or synergistic manner. This study explored the effects of ELS and malnutrition on the physical, behavioural and molecular development of a Wistar rat model. Rat pups (N=24 litters) were separated into four groups: control, maternal separation (MS), protein restriction (PR), and MS+PR. Physical development was measured using body weight, eye and ear opening and fur development, as well as reflexive tests including righting reflex, negative geotaxis and grip strength. Behavioural development was measured using ultrasonic vocalizations (USVs). Results demonstrate that PR pups weigh significantly less than control pups, while MS pups show significantly delayed ear opening, lower performance on grip strength and emitted less USVs than control pups. The MS+PR pups had differentially delayed ear opening. However, the results did not suggest additive or synergistic effects with combined exposure in a single test. Bulk RNA sequencing examined differential gene expression within hypothalamic tissue at postnatal day 21. Ingenuity Pathway Analysis associated with the interaction of MS+PR revealed changes in the regulation of gene transcription related to head development and cellular growth. Together, MS and PR produce independent effects on physical and behavioural development, while combined exposure is associated with alterations in hypothalamic gene expression related to growth and development.

P1-A-24 *Exploring PTEN-mediated γ-clustered protocadherin trafficking*

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Vertebrate retinal development requires coordinated refinement of neuronal populations to assemble functional visual circuits. Clustered protocadherins (cPcdhs) comprise a large family of cell adhesion molecules (CAMs) that regulate dendritic arborization, self-avoidance, and neuronal survival. The cPcdhs encode 58 genes, which are organized in three linked gene clusters: Pcdhα, -β, and -γ. Within the Pcdhγ

cluster, isoform-specific functions have been identified: PcdhγC3 promotes dendritic arborization, whereas PcdhγC4 supports survival of inhibitory interneurons, though molecular mechanisms remain unknown. Our lab identified Phosphatase and Tensin Homolog (PTEN), a negative regulator of the PI3K/Akt pathway, as a modulator of Pcdhγ function in the mouse retina. Using Gad2-Cre conditional knockouts in inhibitory interneurons, PTEN deletion increased interneuron numbers, while Pcdhγ deletion caused interneuron loss. Double Pcdhγ;PTEN mutants did not rescue the Pcdhγ phenotype, suggesting PTEN regulates Pcdhγ-mediated survival. Given PTEN's role in CAM trafficking, I hypothesize that PTEN modulates Pcdhγ cell-surface availability, underlying their distinct functions. In transfected Neuro2a cells expressing tagged constructs, PcdhγC3 localized to the cell surface and colocalized with early endosomal/lysosomal markers, indicating endocytic-lysosomal trafficking. In contrast, PcdhγC4 showed minimal membrane and endosomal colocalization, suggesting intracellular retention outside endocytic pathways. Future studies will examine PTEN's role in regulating these trafficking patterns. Given PTEN's association with neurodevelopmental disorders, this work links retinal development to broader NDD pathways.

P1-A-25 *Exploring the impact of maternal sleep disruption on fetal neurodevelopment*

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Recent scientific literature suggests a strong link between prenatal environmental perturbations and neurodevelopmental disorders (NDDs), highlighting the sensitivity of the intrauterine environment to early life exposures. Preliminary findings from our lab suggest that exposure to various forms of maternal sleep disruption in mice (i.e., exposure to continuous light or dark from embryonic day 12 (E12) to E16 or a 6-hour shift in the light cycle every 4 days from E5 onwards) significantly increases the number of arginine vasopressin neurons in the fetal suprachiasmatic nucleus—the master regulator of circadian rhythms, and alters sleep patterns in offspring postnatally. Accordingly, the objective of my project is to examine how maternal sleep disruptions impact neural stem cell (NSC) proliferation and differentiation programs in the fetal hypothalamus. I hypothesize that maternal sleep disruptions will alter NSC transcriptional signatures, shifting NSC programs away from proliferation to result in precocious differentiation. To characterize changes in fetal hypothalamic NSC transcriptomic signatures in response to maternal sleep disruption, I will perform single-cell RNA sequencing on NSCs collected from the fetal hypothalamus. I will validate any changes that exist (DEGs) by performing fluorescence in situ hybridization and immunofluorescence staining on embryonic hypothalamic cryosections. Together, this research will improve our understanding of how maternal sleep disruptions alter NSC programs in the fetal brain to result in adverse impacts on offspring sleep circuits.

B - NEURAL EXCITABILITY, SYNAPSES, AND GLIA: CELLULAR MECHANISMS

P1-B-26 *High-throughput mapping reveals distinct excitatory wiring rules in V1 and M1*

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Circuit structure determines circuit function. Mapping synaptic connectivity, therefore, helps clarify how circuits work. However, traditional mapping methods, such as multiple patch-clamp recordings, are challenging and low-throughput for large-scale circuit mapping. To address this, we developed optomapping, a high-throughput circuit mapping method that combines two-photon optogenetics with patch-clamp electrophysiology. Here, we used optomapping to investigate how microcircuits differ across two key cortical input and output areas: the primary visual cortex (V1) and primary motor cortex (M1). To enable optogenetic activation of neocortical pyramidal cells (PCs), we infected neonatal Emx1-Cre mice with the soma-targeted ChroME opsin. In acute slices from postnatal days 18-26 mice, we evoked spikes in ChroME-expressing PCs using 1040-nm Ti:Sa laser spiral scans. We patched PCs, basket cells (BCs), and Martinotti cells (MCs) in V1 and M1 while sequentially activating surrounding PCs to map excitatory inputs across all neocortical layers. We confirmed layer boundaries post hoc with fluorescent in situ hybridization. In both V1 and M1, the L5 PC to L5 BC pathway was the strongest. V1 L2/3 PCs received the densest excitation from L4 ($p<0.001$), whereas

in M1 the dominant source was L2/3 ($p<0.001$). Excitatory input strengths onto PCs, BCs, and MCs were log-normally distributed in both V1 and M1. Thus, while microcircuits were broadly conserved across V1 and M1, these areas exhibited distinct laminar rules of excitation that may support the specific functions of each region.

P1-B-27 *"Hydrid" dendrimer modulates IL-33 interaction at RAGE in human microglia*

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IL-33 is a dual-function nuclear protein that becomes an alarmin when released extracellularly. IL-33 binds the receptor ST2 and contributes to inflammatory processes. In the central nervous system, glial cells release alarmins in response to injuries such as infectious diseases, neurodegenerative diseases and stroke. Recently, IL-33 was shown to crosstalk with the alarmin high mobility group box 1 (HMGB1) at the receptor for advanced glycation end-products (RAGE) in lung epithelial cells. Our previous studies showed that heparan sulfate-inspired dendrimers can bind HMGB1, thereby inhibiting its role in inflammatory functions. Given the important role of RAGE in neuroinflammation and the aging brain, we aimed to determine if IL-33 interacts with RAGE in human microglia, and to modulate its interactions using charged dendrimers. We used dendritic polyglycerol nanostructures with negatively-charged (sulfated, dPGS), positively-charged (aminated, dPGA) and combined positively- and negatively-charged (dPGSA) terminal groups to modulate IL-33 interactions at ST2 and RAGE. Structural modelling revealed protein interfaces and electrostatic forces participating in ligand-receptor and nanostructure-protein interactions. Biological experiments using proximity ligation assays showed that IL-33 binds ST2 and RAGE in lipopolysaccharide-activated microglia. Mixed-charged dendrimer dPGSA inhibited IL-33 interactions at both ST2 and RAGE, without causing cytotoxic effects. Our study gives insights into the crosstalk and modulation of IL-33 in human microglia.

P1-B-28 *A critical window for axonal function during myelination*

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Myelination is an important process during neuronal development, enabling the high-fidelity saltatory conduction of action potentials in axons. We have previously demonstrated that Purkinje cell axons display axonal swellings transiently during postnatal development in mice which improve the fidelity of action potential propagation in axons. Since myelination occurs concurrent with the transient appearance of axonal swellings along Purkinje cell axons, we wondered whether there was a functional relationship between them. We tested this by depleting oligodendrocytes precursor cells (OPCs) with injections of 5-azacytidine (5mg/g) between P6 and P15. Although the number of immature oligodendrocytes was reduced at P11, the density of axonal swellings was not affected. However, extending the treatment to P15, an age at which the axonal swellings density normally decreases, we observed a higher density of axonal swellings and a reduction of myelin on Purkinje cell axons. When we ablated premyelinating oligodendrocytes genetically (Mobp-KD), we observed a similar trend. These results demonstrate that oligodendrocytes that are myelinating Purkinje cell axons are not required for axonal swelling formation but are necessary for their removal. These findings argue that the window during which myelination occurs is a critical time during which axonal function is especially vulnerable, requiring axons to temporarily compensate for impairments by forming axonal swellings.

P1-B-29 *Activation of the OVLT enhances astrocytic calcium signaling in the supraoptic nucleus*

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Extracellular osmolality is tightly regulated to maintain cellular and physiological homeostasis. In the central nervous system, osmoreception is detected by circumventricular organs, particularly the organum vasculosum of the lamina terminalis (OVLT), which conveys this information to hypothalamic nuclei such as the supraoptic nucleus (SON), thereby regulating the vasopressin and oxytocin release. While SON magnocellular neurons are well characterized in osmoregulatory control, the role of astrocytes in OVLT–SON circuit remains poorly understood. Given the involvement of astrocytes in tripartite synapse signaling, we hypothesized that astrocytes are actively recruited during OVLT-SON pathway activation. To test this, we electrically stimulated the OVLT to mimic osmostimulation while monitoring astrocytic calcium activity in the SON using GCaMP-based imaging. Adult male C57BL/6 mice (8 weeks old) received an astrocyte-specific GCaMP viral vector into the SON. After 3-4 weeks, astrocytic activity was recorded before, during (5 min, 5 Hz), and after OVLT stimulation. OVLT stimulation significantly increased astrocytic calcium transients during stimulation, as evidenced by increases in peak $\Delta F/F_0$, half-width and event frequency. Because many OVLT inputs to the SON are glutamatergic, we next examined whether this response was glutamate-dependent. Pharmacological antagonism of glutamate receptors avoided the OVLT-evoked response in all paramenters. These findings demonstrate that OVLT stimulation robustly increases astrocytic activity in the SON via a glutamate-dependent mechanism, supporting a role for astrocytes in OVLT–SON osmoregulatory circuitry.

P1-B-30 *Acute effects of Omega-3 polyunsaturated fatty acids on Kv1.2 channels and potential utility to KCNA2-related neurological diseases*

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Kv1.2 (encoded by KCNA2) loss- and gain-of-function (LOF and GOF) mutations have been linked to autism spectrum disorder, epilepsy and ataxia, but few therapeutics are available. We explored the effects on Kv1.2 of Omega-3 Polyunsaturated Fatty Acids (n-3 PUFAs) which are essential fatty acids with long-chain amphipathic molecules including a hydrophilic carboxyl head, a long hydrophobic tail of carbons, and the first double bond at the third carbon from the methyl end. In voltage clamp recordings of stable Kv1.2-GFP CHO cells, DHA in low micromolar concentrations shifts activation threshold left, accelerates activation and decelerates deactivation, acting as a potent PAM for Kv1.2 channel with the highest potency and efficacy among n-3 PUFAs, e.g. alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and DHA, . When concentration is elevated by an order of magnitude, DHA introduces a distinct and opposite effect on Kv1.2 current. Using a combination of in silico simulation and site-directed mutagenesis, we showed that DHA exerts its PAM effect by directly binding to a cavity near the voltage sensor (S4) of Kv1.2 and blocking effect by interaction with a site within the pore. This study defines multifaced roles of PUFAs in regulating Kv1.2 channels, exemplifying mechanistic complexity of these essential fatty acids with potential utility at different dosing to treat neurodevelopmental disorders with both KCNA2 LOF and GOF mutations. By resolving bona fide binding sites for PUFAs to exert two opposite effects, we unravel 3D structural templates on the Kv1.2 channel (and potentially other Kvs) as druggable sites for developing new generation of pharmacological therapeutics.

P1-B-31 *Age-induced structural and functional impairments in parvalbumin interneurons*

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Parvalbumin (PV) interneuron loss in the retrosplenial cortex (RSC) is linked to the hyperexcitability that is seen in the brain at the onset of Alzheimer's disease (AD). In the early stages of AD, the RSC shows hypometabolism and altered connectivity, contributing to cognitive impairment. This loss of PV interneurons in the RSC is sex-dependent, with females exhibiting more pronounced alterations in parvalbumin earlier

than males. Since aging is the most significant risk factor for AD, we examined the effects of aging itself on PV interneurons and PV-related alterations that occur in the RSC in females. Using young adult (2 months) and aged (20 months) C57BL/6 female mice we examined neuronal excitability by immunohistochemistry staining for cFos. Immunohistochemistry was also performed to determine changes in parvalbumin, including parvalbumin interneuron density, perineuronal net density and colocalization, and synaptotagmin-2 density. We also performed Xemium-5x spatial transcriptomics to determine the variations in gene expression between young and old female mice. Older mice exhibited loss of PV interneurons, perineuronal nets, and a reduction in the broad density of synaptotagmin-2 in the RSC, accompanied by an increase in synaptotagmin-2 boutons on PV neurons. The transcriptomics analysis showed a decrease in inhibitory-related genes when compared with the 2-month-old mice. The downregulation of inhibitory-related genes, coupled with cellular and synaptic loss, suggests a pathway for the increase in susceptibility to AD through aging in females.

P1-B-32 *All-optical mapping of GABA driving force reveals cell-type-specific BDNF sensitivity in the hippocampus*

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GABAergic driving force (DFGABAA), the difference between the membrane potential and the GABAA receptor reversal potential, determines the nature of fast inhibition. In epilepsy, inhibition is often compromised due to reduced function of the chloride extruder KCC2. Brain-derived neurotrophic factor (BDNF), which is consistently upregulated in epilepsy and known to downregulate KCC2, may therefore contribute to weakened inhibition by depolarizing DFGABAA. However, whether this effect is uniform across neuronal cell types remains unclear. To address this, we employed ORCHID, an all-optical approach enabling high-throughput measurement of DFGABAA by combining optogenetic activation of an anion-conducting channelrhodopsin with fluorescent voltage imaging. Using organotypic mouse hippocampal slice cultures, we measured DFGABAA in dentate granule cells, pyramidal neurons, and interneurons under control and BDNF-treated conditions. At baseline, DFGABAA exhibited marked cellular heterogeneity, being depolarizing in dentate granule cells but hyperpolarizing in pyramidal neurons and interneurons. In BDNF-treated slices, DFGABAA was significantly more depolarized in dentate granule cells (+2 mV) and pyramidal neurons (+5 mV), whereas interneurons showed no change. These findings indicate that BDNF preferentially weakens GABAergic inhibitory efficacy in excitatory neurons while sparing interneurons. This cell-type-specific effect supports the idea that BDNF upregulation in epilepsy may contribute to network hyperexcitability through differential disruption of chloride homeostasis.

P1-B-33 *Antihistamines alter sleep-like brain states under urethane anesthesia*

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The purpose of sleep and its related patterns of brain activity remain a physiological enigma. A major issue with studying sleep is its natural fragility, which creates methodological challenges necessitating a more tractable model. Our lab has shown urethane anesthesia to be an unparalleled model of sleep in the rat, as it produces spontaneous, rhythmic alternations between REM- and nREM-like states. Extensive central and peripheral measures exist to suggest that these alternations appear nearly identical to those in natural sleep. Both sleep, and the sleep cycle, are known to be affected by centrally acting drugs. The most common over-the-counter sleep aid is the antihistamine diphenhydramine (DIP). This drug promotes drowsiness and tends to bias brain states during sleep into NREM-like activity patterns. Here we evaluated a number of antihistamines, including DIP, on the states produced during urethane anesthesia. To do so, bipolar electrodes are used to collect LFP recordings from the cortex and hippocampus of urethane anesthetized rats before and after I.V. administration of DIP, loratadine (peripheral control), or PBS (vehicle control). Results thus far have indicated that DIP produces a shift into a transitional state between activated and deactivated patterns, with broad increases in slower power in cortex and a combination of slow and spindle

frequencies in hippocampus. These results suggest that DIP promotes NREM-like patterns but not deep slow-wave activity states in the urethane model.

P1-B-34 *Astrocyte contributions to sensory circuit development and stability*

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Astrocytes undergo extensive morphological and functional maturation during early postnatal development, yet how this process contributes to the long-term stability of cortical circuits remains unclear. While studies of circuit development have focused largely on neurons, astrocytes elaborate fine processes that closely associate with synapses and position them to regulate neurotransmitter dynamics and network activity. Here we investigate a developmental astrocytic mechanism that links astrocyte morphology to sensory circuit function. We find that disruption of a transient astrocytic molecular program during early development leads to persistent alterations in astrocyte structure in the adult somatosensory cortex, characterized by hypertrophy of primary branches and loss of fine, synapse-associated processes. In vivo two-photon imaging reveals that these morphological changes are accompanied by compartment-specific alterations in astrocytic calcium signaling and disrupted astrocyte–neuron coupling. Simultaneous calcium imaging in awake animals shows increased neuronal excitability and reduced trial-by-trial reliability of sensory-evoked responses. Ultrastructural and molecular analyses suggest impaired astrocyte engagement with presynaptic domains and altered regulation of glutamatergic signaling. Importantly, selective restoration of astrocytic gene expression during early postnatal development, but not in adulthood, rescues astrocyte morphology, astrocytic signaling, and circuit reliability. These findings identify astrocyte morphological maturation as a critical determinant of functional circuit stability and highlight a developmental window during which astrocytes actively shape enduring properties of sensory processing.

P1-B-35 *Astrocyte IP3R2 mediates "wake-up" blood flow increases in neocortex*

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Changes to astrocyte free calcium regulates local cerebral blood flow. Astrocyte calcium activity also changes during different awake and sleep states. Yet, whether astrocytes help regulate cerebral blood flow during awake, non-REM and REM sleep states, remains unclear. Using in vivo two-photon fluorescence imaging in head-fixed, unanesthetized mice (10-12 weeks old), we monitored astrocyte calcium activity using GCaMP8m and diameter changes of penetrating arterioles in the retrosplenial or the barrel cortex. To determine the physiological state, we continuously measured the size of the pupil and the movement of whisker during two-photon imaging. We found arteriole diameter and astrocytes calcium activity concomitantly increased during wake up events, in both male and female mice. We also observed dramatically enhanced arteriole diameter during REM sleep, with simultaneous decreases in astrocyte end feet calcium. Astrocyte specific IP3R2 knockdown using shRNA delivered by AAV, reduce the endfoot Ca2+ signal and the magnitude of vasodilation seen during sleep to awake transitions. Using the GRAB-NE sensor expressed on astrocytes, we found that noradrenaline largely tracked astrocyte calcium changes: going up when the mouse wakes up, and going down when the mouse falls asleep, suggesting noradrenaline instructs astrocyte control of arterioles. Taken together, our data demonstrate cerebral blood flow regulation during sleep to awake cycles is functionally linked with astrocytic IP3R2 signaling that I likely driven by noradrenaline input.

P1-B-36 *Astrocyte nanoarchitecture and organelle complexity across brain regions and species revealed by deep learning segmentation with curvature consistency*

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Cellular function depends on the precise deployment and distribution of nanoscale structures, but these features remain difficult to measure and compare between cells, across cell types, and among species. While volume electron microscopy (vEM) is the gold standard for nanostructure characterization, the segmentation and analysis of the regions of interest requires immense manual labour (i.e., several years). This challenge is pronounced for astrocytes, whose intricate three-dimensional nanostructures interface with neurons, glia, and vasculature, to control brain development, synaptic development and plasticity, homeostasis, and responses to injury. To overcome these challenges, we developed deep learning approaches with curvature regularization for automated astrocyte segmentation across heterogeneous vEM datasets, reducing ultrastructure reconstruction time by twelve-fold and enabling interrogation of astrocytic architecture across brain regions and species. This approach uncovered conserved organizational principles and motifs alongside notable ultrastructural divergence between mouse and marmoset astrocytes. While both species exhibit a similarly wide but shallow core–expansion–constriction topological network, primate astrocytes display increased process thickness, density and enhanced branching complexity. We further identified abundant extrasynaptic neuronal engulfment and a robust astrocytic endosomal system, with substantial variation in their prevalence across species and brain regions. Together, these findings demonstrate a conserved structural basis of astrocyte-neuron communication across species, which involves neuronal spinule formation, astrocytic endocytosis, and the potential release of endosomal vesicles.

P1-B-37 *Astrocytes gate layer-5 pyramidal cell timing-dependent LTD in visual cortex*

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Spike timing-dependent plasticity (STDP) is widely viewed as a cellular mechanism for learning and circuit refinement. In primary visual cortex (V1), timing-dependent long-term depression (tLTD) at synapses between layer-5 (L5) pyramidal cells (PC→PC) has classically been modeled as a neuron-intrinsic process involving presynaptic NMDA receptors and retrograde endocannabinoid signaling. However, astrocytes also express endocannabinoid receptors (CB1Rs) and have been shown to influence long-term plasticity through Ca2+-dependent signaling in other brain regions. Here, we tested whether astrocytes are required for V1 L5 PC→PC tLTD in acute slices from juvenile mice. Using quadruple whole-cell recordings, we found that pre-incubation with sodium fluoroacetate abolished tLTD without acutely altering baseline synaptic transmission (EPSP change after/before induction = 103 ± 7% in treatment vs 74 ± 6% in control, $p < 0.01$). To more specifically disrupt astrocyte signaling, we expressed the Ca2+-extruding pump CalEx in astrocytes, which prevented tLTD induction (109 ± 4% CalEx vs 104 ± 6% in control, $p = 0.54$). Complementarily, loading local astrocyte networks with BAPTA blocked optogenetically evoked PC→PC tLTD. Moreover, activating astrocytic Gq signaling during induction interfered with LTD expression. Finally, pharmacological and genetic manipulations implicated astrocytic CB1 receptors in this form of plasticity, including loss of tLTD following astrocyte-specific CB1 receptor deletion (114 ± 7% in CB1 homozygous deletion vs 59 ± 14% in CB1 heterozygous deletion, $p < 0.01$). Together, these results indicate that astrocyte Ca2+ signaling and astrocytic CB1 receptors are required for neocortical L5 PC→PC tLTD, revising prior working models that this plasticity is purely neuronal.

P1-B-38 *Astrocytes in fish: An underexplored glial population with implications for brain plasticity and regeneration*

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Astrocytes are crucial for neural circuit development, synaptic function, and behavior in mammalian brains, yet they have been largely overlooked in fish. This neglect stems from the belief that teleost brains lack "true" astrocytes, as radial glial cells dominate their glial populations. However, recent research, especially in zebrafish, has identified astrocyte-like cells with similarities to mammalian counterparts. Teleosts, known for their neural plasticity and regenerative abilities, may utilize astrocytes differently than mammals, possibly supporting lifelong neurogenesis and aiding recovery from CNS injuries without forming inhibitory glial scars. Our research seeks to clarify these mechanisms and establish a framework for identifying conserved and divergent astrocyte functions related to brain repair. We are trying to identify and isolate astrocyte-like cells in Rainbow Trout brain cell cultures using molecular markers GFAP, GLAST, S100B, and glutamine synthetase. Microscopic observations show astrocyte-like structures alongside radial glial and other parenchymal cells. RT brain astrocytes initially grow more slowly than other brain cells in vitro but eventually dominate cultures over a month, likely due to their resilience to environmental changes comparable with mammalian astrocytes or potential differentiation from RGCs in vitro. Future studies will focus on these factors and the calcium signaling capabilities of fish brain astrocytes. Fish models uniquely allow whole-brain analysis of astrocyte development and function at the cellular level, unmatched by other vertebrates.

P1-B-39 *ATGL-mediated lipid droplet breakdown in microglia reduces neuroinflammation and regulates glucose homeostasis*

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Lipid droplets (LD) are organelles that store neutral lipids such as triglycerides (TG). While LD are well known as a source of fatty acids (FA) acting as energy substrates, they also play a key role in inflammation by sequestering or releasing FA that serve as precursors of pro-inflammatory lipid mediators, in macrophages and microglia, the brain's resident immune cells. Our recent study showed that inhibition or loss of microglial adipose triglyceride lipase (ATGL), the enzyme catalyzing the first step of LD lipolysis, reduces neuroinflammation in response to LPS, a phenotype associated with a decreased availability of pro-inflammatory lipid mediators derived from LD, such as PGE_2. However, the role of microglial ATGL in the development of diet-induced obesity and associated neuroinflammation and metabolic alterations remains unknown. To address this, we investigated energy and glucose homeostasis in male and female mice with ATGL loss-of-function in microglia (Cx3CR1-CreER) under chow-fed and high-fat-fed conditions. Loss of microglial ATGL did not affect susceptibility to high-fat-diet-induced obesity but altered glucose tolerance and insulin secretion in both dietary conditions and in both sexes. To further determine whether these alterations involve changes in neuronal activity linked to metabolic control, we are assessing the role of hypothalamic Proopiomelanocortin (POMC) neurons, a population of neurons known to play a crucial role in glucose homeostasis. Consistent with this hypothesis, we showed that PGE_2 modulates POMC neuronal activity, supporting a functional link between microglial lipid signaling and neuronal regulation of glucose metabolism.

P1-B-40 *Autism-associated CHD8 controls reactive gliosis and neuroinflammation via remodeling chromatin in astrocytes*

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Neuroinflammation plays a central role in the progression of various neurodegenerative disorders such as in neurodegeneration. Glial cells, particularly astrocytes and microglia, are major mediators of neuroinflammation, responding to inflammatory stimuli in a process termed reactive gliosis. Contemporary

research has highlighted reactive gliosis as a potential therapeutic target for neurodegenerative diseases. Understanding the molecular and cellular mechanisms underlying neuroinflammation is critical for developing strategies to modulate gliosis and improve disease outcomes. In this study, we demonstrate that the ASD-associated chromatin remodeler CHD8 regulates the brain's inflammatory response through its activity in astrocytes. We show that global deletion of the Chd8 gene in adult mice impairs reactive gliosis. Conditional Chd8 deletion specifically in astrocytes—rather than in microglia—suppresses reactive gliosis by inhibiting astrocyte proliferation and morphological changes in a stab-wound injury model. Furthermore, astrocyte-specific Chd8 ablation reduces LPS-induced neuroinflammation, conferring protective effects in mice. Gene expression profiling and ATAC sequencing reveal that Chd8 loss in astrocytes attenuates neuroinflammation by disrupting astrocyte-microglia interactions and altering metabolic and lipid-related pathways, with these changes reflecting an epigenetic reprogramming of astrocyte function. These findings uncover a novel role of CHD8 in regulating neuroinflammation through astrocytes in the adult brain. Our work suggests a therapeutic potential via targeting CHD8 to mitigate harmful neuroinflammation in neurodegenerative conditions. Currently, we are probing the functions of CHD8 in diverse astrocytic populations and their relevance in neurodegenerative conditions.

P1-B-41 *BDNF-induced enhancement of excitatory synaptic transmission in layer III of the rat entorhinal cortex*

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Brain-derived neurotrophic factor (BDNF) supports excitatory synaptic transmission through multiple pathways and may contribute to cognitive processes in the entorhinal cortex. In addition to structural modification of synapses, the binding of BDNF to its receptor (TrkB) can lead to the release of internal calcium stores and the phosphorylation of NMDA receptors, indicating that BDNF can enhance excitatory synaptic transmission on a shorter timescale than that required for structure-mediated enhancements. Here, we compared excitatory transmission in the rat entorhinal cortex from groups of slices incubated for at least 1 hour in either a BDNF-containing solution (50 ng/ml) or a control solution. Field excitatory post-synaptic potentials were recorded simultaneously from layers I and III of the entorhinal cortex in response to pairs of stimulation pulses (30 ms interval) of increasing duration delivered to layer I. Results indicate that BDNF incubation enhances excitatory transmission in layer III, since response amplitudes were significantly increased in slices from the BDNF group as compared to the control group at pulse durations of 0.15 ms or greater. There was no significant difference in paired-pulse ratios between the two groups, suggesting that the increase in synaptic responses observed in the BDNF-treated group was due to post-synaptic factors. Intracellular recording studies are now investigating the effects of BDNF incubation and focal application on cell excitability and firing rates.

P1-B-42 *CASK is presynaptic in rod photoreceptors*

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In the retinal outer plexiform layer (OPL), rod photoreceptors (PRs) form tripartite synapses with bipolar and horizontal cells. The mechanisms responsible for organizing rod presynaptic proteins specifically at sites apposed to BC dendrites are poorly understood. Previous immunostaining results in mouse retina revealed CASK (calcium/calmodulin-dependent serine protein kinase), a MAGUK family scaffolding protein, colocalized with BC synapses in the OPL. However, CASK is expressed ubiquitously, and it was unknown whether the OPL protein is presynaptic or postsynaptic. To determine whether CASK is presynaptic in the OPL, we performed somatic CRISPR knockout specifically in PRs by in vivo electroporation of sgRNA along with Cas9 under control of a PR-specific promoter. We observed that in rods positive for transfection marker EGFP, CASK immunostaining at synaptic puncta was absent, while EGFP negative spherules in the same fields had robust CASK signal. In retinas electroporated with a control construct expressing Cas9 but no sgRNA, there was no difference between EGFP positive and negative cells. These results demonstrate that OPL CASK is expressed

only in the presynaptic rods, and also serve as validation for the specificity of CASK antibody labeling in the OPL. A small but significant decrease in enrichment of the postsynaptic transduction channel TRPM1 was also observed in the CASK knockout rods, suggesting a role in organizing other synaptic proteins. Future studies will focus on identifying CASK interaction partners and functional roles at rod presynapses.

P1-B-43 *CD51 expression delineates functionally distinct astrocyte subpopulations in neural circuits*

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Astrocytes execute a diverse range of tasks that facilitate brain physiology, raising the possibility that these diverse astrocytic roles are enabled by functionally distinct subtypes. Recent studies identified molecular diversity amongst astrocytes, however whether this molecular heterogeneity reflects specialized astrocyte subpopulations with distinct functions remains unknown. Leveraging prior molecular and functional studies, we generated a CD51-FLP mouse line that enables the direct comparison of functional properties between CD51+ and CD51- astrocyte subpopulations in neural circuits in vivo. Here we show that CD51+ and CD51- astrocytes are endowed with unique morphological, physiological, and developmental properties in both the cortex and hippocampus. Functional studies demonstrate that CD51+ astrocytes selectively promote synapse formation in the developing cortex and circuit plasticity in the hippocampus. Mechanistically, we found that CD51+ astrocytes function through glypican 6 to promote synapse formation in the cortex, while CD51 itself drives circuit plasticity in the hippocampus. Applying these findings to brain injury, we found that exploiting the unique properties of CD51+ astrocytes promotes functional recovery after stroke through enhanced synaptic remodeling. Taken together, our studies identify specialized astrocyte subpopulations that exhibit distinct functional properties in the developing, mature, and injured brain.

P1-B-44 *Characterizing differential purinergic trafficking in sympathetic nerves*

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Adenosine Triphosphate (ATP) regulates vasomotor tone in the peripheral nervous system. The Vesicular Nucleotide Transporter (VNUT) loads vesicles with ATP, mediating purinergic neurotransmission, but little is known about the molecular basis for differential trafficking, release, and recycling of purinergic versus adrenergic vesicles in sympathetic neurons. Based on our previous work, we hypothesize that VNUT localizes to a non-releasable, intermediate sorting compartment in rat tail artery sympathetic nerves, and that generation of purinergic vesicles requires ADP-ribosylation factor guanine nucleotide exchange factors (ArfGEFs) GBF1, ArfGEF1 and or 2. Field-stimulated purinergic neurotransmission depletes more rapidly than adrenergic, so we further tested if purinergic signalling relies on canonical clathrin-mediated vesicle recycling. Brefeldin-A, but not golgicide A, selectively attenuated purinergic neurotransmission, showing a role for ArfGEFs 1 and 2 but not GBF1. Dynamin inhibition with dynasore accelerated depletion of purinergic signalling, suggesting clathrin-mediated vesicle recycling may play a role, but does not fully explain the rapid depletion of purinergic vesicle release by persistent stimulation. We do not find functional sex or age-dependent differences. Immunostaining confirms that VNUT localizes to perivascular nerves but does not colocalize with canonical vesicle markers. These findings are a first step to understanding the molecular underpinnings behind differential ATP and NE vesicle release, consistent with the co-transmission model.

P1-B-45 *Frequency of firing modulates synaptic facilitation in electrically coupled neuroendocrine cells*

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Gap junctions are intercellular channels that pass ions from pre- to postsynaptic neurons at electrical synapses. In the snail, Aplysia, reproduction is controlled by two clusters of electrically coupled neuroendocrine cells called bag cell neurons. Following synaptic input, bag cell neurons depolarize from an ~-60 mV resting potential to fire an ~30-min afterdischarge of synchronous action potentials at ~-40 mV. The afterdischarge presents at ~1 Hz, with an irregular pattern, and is associated protein kinase C (PKC) activation. Here, dual whole-cell recording of coupled, cultured bag cell neurons was used to examine the effect of initial membrane potential and spike timing in control vs kinase-activated conditions. Stimulating presynaptic action potentials with a 1-Hz, 100-ms depolarizing current train caused facilitation of the postsynaptic electrotonic potential at -40, but not -60 mV. Delivering 1-Hz, 30-sec stimulus-trains of presynaptic action potential-like waveforms in voltage-clamp, while recording the postsynaptic response in current clamp at -40 mV, using a uniform or non-uniform pattern, the latter derived from bona fide afterdischarges, resulted in feedforward excitation, which was enhanced by PKC. Remarkably, the extent of facilitation or feedforward excitation did not differ between uniform vs non-uniform stimulus-trains. Thus for bag cell neurons, starting voltage strongly influences transmission, but changes in input pattern are opposed. This may reflect the need for maximal signalling efficiency at electrical synapses during reproductive hormone release.

P1-B-46 *Characterizing the interaction between ORL-1 and Cav1.2*

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Cav1.2 is an L-type voltage-gated Ca2+ channel (VGCC) that opens in response to membrane depolarization and allows Ca2+ influx into the cell, where it acts as a secondary messenger to activate intracellular signaling cascades. Ca2+ entering via Cav1.2 alters gene expression and has been implicated in synaptic plasticity. VGCCs are regulated by various mechanisms, including interactions with other membrane proteins, such as G-protein-coupled receptors (GPCRs). ORL-1 is a Gi/o coupled GPCR expressed in the central nervous system, particularly in the spinal cord. Previous research on ORL-1 regulation of L-type calcium channels, such as Cav1.2, showed conflicting results: some studies show that ORL-1 activation produces modest inhibition, while others find no effect. Preliminary data from the Zamponi lab revealed a physical interaction between ORL-1 and the pore-forming α1c subunit of Cav1.2. To characterize this interaction, Cav1.2 (α1c, α2δ-1, β1) was expressed with ORL-1 in TsA-201 cells, followed by biochemical and electrophysiological analysis. ORL-1 co-immunoprecipitated with α1c, and its co-expression reduced Cav1.2 peak current density and caused a depolarizing shift in half activation potential. In contrast, calcium-dependent inactivation was not altered, and acute perfusion with the ORL-1 receptor agonist nociceptin (1μM) did not affect current density. Overall, our results demonstrate a clear physical interaction but mixed effects on Cav1.2 biophysical properties. Experiments testing the effect of the ORL-1 on Cav1.2 trafficking are ongoing.

P1-B-47 *Cholinergic regulation of synaptic inputs to the parasubiculum*

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The parasubiculum (PaS) is a retrohippocampal region that has been implicated in spatial navigation, but its role remains unclear. PaS activation can modulate synaptic responses in the superficial layers of the medial entorhinal cortex (EC), which is a critical navigation hub that contains grid cells and forms the origin of the perforant and temporoammonic pathways. Recent work has suggested that the PaS is innervated by brain regions that show head direction-sensitive firing, suggesting that the PaS may serve as an integrative hub within spatial navigational circuitry. The excitability of PaS neurons is regulated by acetylcholine, which has

been linked to calcium-dependent plateau potentials and persistent firing in other hippocampal regions. This form of activity has been proposed to serve as the cellular mechanism underlying spatial working memory. However, how the cholinergic system modulates PaS activity remains poorly understood. We show that the PaS receives dense cholinergic input from the medial septum/vertical limb of the diagonal band of Broca. Further, muscarinic receptor activation using carbachol (10 µM) triggers persistent firing in ~85% of PaS neurons. Using a combination of retro- and anterograde viral tracing in adult mice, we show that the PaS receives inputs from regions involved in spatial navigation such as the CA1 region of the hippocampus, the anterior dorsal thalamus (ADT), and the retrosplenial cortex (RSC); while sending major outputs to the contralateral PaS and EC. Moreover, we show that optogenetic activation of fibers from the ADT or RSC expressing channelrhodopsin-2 elicits excitatory postsynaptic potentials in PaS neurons. These studies show that excitatory synaptic drive from brain regions involved in head direction converge on the PaS, and that these inputs are regulated by cholinergic receptor activation.

P1-B-48 *Cilia beating of ependymal cells regulates adult neural stem cell quiescence via mechanical forces mediated by PKD1/2-TRPM3*

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In many tissues stem cells are located lining a fluid-filled volume and their neighboring niche cells include cells with beating cilia. The role of mechanical forces created by cilia beating on stem cells remains elusive. However, we have developed an approach to transiently inhibit cilia beating of ependymal cells (EC) lining the forebrain ventricle by injecting magnetic beads-coupled antibodies specifically targeting EC cilia and applying a magnetic field. We show that EC cilia beating enforces neural stem cells (NSCs) quiescence through mechano-sensitive PKD1/2 and TRPM3-mediated Ca2+ transients, and only few hours of EC cilia beating inhibition triggered NSCs activation in vivo. CRISPR-Cas9-mediated deletion of TRPM3 or PKD1/2 in NSCs phenocopied the effect of EC cilia beating inhibition, while TRPM3 pharmacological activation rescued NSC quiescence in the absence of cilia beating. Our data demonstrate a novel regulator of stem cells exposed to fluids via the mechanical forces mediated by cilia beating.

P1-B-49 *Cocaine-induced disruption of endosomal recycling: a novel mechanism in psychostimulant addiction*

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We previously identified Kv1.2 and Sigma-1R (S1R) protein as critical players in dopamine-independent cocaine-induced neuronal hypoactivity in the nucleus accumbens shell—an adaptation that enhances cocaine reward. Understanding the mechanism underlying this adaptation is of clinical importance. Our research demonstrates that S1R interacts with Kv1.2 and that cocaine activation of S1R enhances this interaction and Kv1.2 expression at the plasma membrane (PM). Using a transient expression system in cell culture models, we performed transcriptional and translational chase assays, revealing that S1R enhances Kv1.2 translation and stability. Cell-based ELISA assays confirmed that cocaine exposure increases Kv1.2 PM expression when S1R and Kv1.2 are co-expressed. Furthermore, using GST-Pull down analyses, we validate S1R-Kv1.2 interaction. Next, we demonstrate that S1R regulates Kv1.2 cell surface expression by enhancing both ER-to-Golgi trafficking and endosomal recycling pathways. Given the role of small Rab GTPases in these pathways, we examined Rab11, a key regulator of slow endosomal recycling. We found that S1R colocalizes with both Kv1.2 and Rab11. Notably, a Rab11-dominant negative mutant significantly reduces cocaine-induced Kv1.2 expression at the PM. Significantly, our preliminary data reveal that methamphetamine—one of the most devastating drugs globally—induces S1R-dependent behavioral, electrophysiological, and cellular adaptations similar to those observed with cocaine. This suggests that the newly identified mechanism may

serve as a fundamental process underlying stimulant addiction. Since dysregulation of Rab pathways is implicated in several brain disorders, our findings provide new insights into how cocaine—and potentially other psychostimulants—disrupts endosomal trafficking and its role in addiction neurobiology.

P1-B-50 *Cofilin inactivation impacts electrocorticographic activity during sleep/wake states in mice*

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Cofilin, a regulator of actin dynamics, shapes dendritic spine and influences synaptic plasticity, and responds to sleep deprivation (SD). Given the bidirectional links between plasticity and the sleep-wake cycle, we hypothesized that cofilin shapes cortical synchronization and hence electrocorticographic (ECoG) activity. Accordingly, we aimed to determine the involvement of cofilin in the regulation of ECoG activity in mice of the two biological sexes. To test this, male and female C57BL/6J mice received adeno-associated virus expressing inactive cofilin (AAV9-CaMKIIα-cofilinS3D-HA) or a control virus (AAV9-CaMKIIα-eGFP) in motor and visual cortices. ECoG electrodes were implanted concurrently. Recordings included a 24-hour baseline, a 6-hour SD, and 18 hours of recovery. Our results indicate that cofilin inactivation did not change time spent awake and asleep during baseline or after SD in either sex. For the motor cortex, absolute spectral power did not significantly differ between cofilin-S3D and GFP groups at baseline or after SD in males and females. For the visual cortex, cofilin-S3D mice exhibited higher absolute spectral power than GFP controls at baseline across all vigilance states in both sexes. During SD and recovery, this pattern persisted for wake, SWS and paradoxical sleep. These findings show that cortical cofilin inactivation increases ECoG power specifically for the visual cortex without altering sleep architecture, suggesting a region-dependent impact of actin stabilization on general cortical synchrony captured by ECoG.

P1-B-51 *Comparative evaluation of the performance of neuron maturation media in generating functional HPSC-derived forebrain neurons*

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The composition of neuron maturation media is critical for reliably generating mature, functional neurons across human pluripotent stem cell (hPSC) lines. Here, we compare the performance of BrainPhys™ Neuronal Medium (BP) to another common commercial maturation medium (CM) using forebrain neuronal precursors derived from 3 hPSC lines. To assess cell type composition, we quantified HuC/D (neurons), GFAP (glia), and SOX2 (progenitor cells) by immunocytochemistry after 14 days in maturation media. To assess function, neuronal activity was measured using SCTi003-A-derived neurons on microelectrode array over 7 weeks. Notably, BP generated higher purity neuron cultures in 2 of 3 cell lines with 82% and 62% less GFAP+ astrocytes than CM. In addition, BP supported higher firing rates (FRs) over time, increasing from 0.74 ± 0.14 Hz at week 4 to 2.67 ± 0.44 Hz at week 6. In contrast, FRs in CM were 0.08 ± 0.03 Hz and 0.23 ± 0.08 Hz at the same timepoints (mean ± SEM, 64 electrodes; n = 1). To compare the effect of basal media, CM basal medium was replaced with BP basal on day 28, without altering the supplements. In BP basal, FRs increased from 0.05 ± 0.02 Hz to 1.22 ± 0.32 Hz within 2 hours. This increase was sustained over 7 days and declined when the basal medium was switched back to CM. These results demonstrate that medium formulation strongly influences neuronal maturation, cell type composition, and electrophysiological function, with BrainPhys™ consistently supporting robust neuronal activity.

P1-B-52 *Contextual gating of circuit-specific stress responses by astrocytes*

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Our previous work demonstrated a critical role of glucocorticoids, acting on astrocytes, in mediating the effects of early-life stress on cellular and behavioral scales (Depaauw-Holt et al. 2025). The effects we described were most prominent in the lateral hypothalamus (LH), where excessive glucocorticoid activity resulted in maladaptive changes in astrocyte structure and function, orexin neuron output, and behavioral activity levels in a sex-specific manner. Despite this, we still know little regarding the physiological role of astrocytes in this brain region and whether they can drive adaptive stress responses. Here we set out to investigate the physiological role of astrocyte glucocorticoid receptors (GR), in stress adaptation using LH-specific GR knockout mice. We show that deleting astrocytic GR alters the baseline activity of orexin neurons. These cellular changes are mirrored by a disrupted endocrine response to stress in knockout mice. Interestingly we reveal that LH astrocytes appear to be tuned to context, with LH astrocyte GR deletion impairing responses to stressors that specifically engage the LH, compared to stressors that recruit parallel circuits. Overall, these data suggest that astrocytes act as contextual gates, showing that astrocytic GR signaling is a key part of the circuit-specific regulation of stress adaptation.

P1-B-53 *Coordinated epigenetic regulation supports second-order threat learning*

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Second-order threat conditioning allows neutral cues to acquire aversive value through indirect associations and contributes to fear generalization in anxiety and trauma-related disorders. Although this process engages distributed brain circuits, the molecular mechanisms coordinating these regions remain unclear. We investigated the epigenetic organization supporting olfactory second-order conditioning in rats, focusing on interactions between the basolateral amygdala (BLA) and posterior piriform cortex (pPC). Using behavioral assays, region-specific pharmacology, immunohistochemistry, and single-nucleus ATAC- and RNA-sequencing in rats, we show that both acquisition and expression of second-order threat memories require epigenetic regulation. Inhibition of DNA methylation or histone acetylation in either the BLA or pPC impaired learning and recall. Acquisition was associated with coordinated epigenetic signaling between the BLA and pPC, whereas retrieval engaged broader cross-regional coordination involving hippocampal and auditory cortical areas. Despite region-specific gene expression programs, chromatin accessibility and transcriptome-wide expression magnitude were highly correlated across regions during both learning and recall. Enrichment of AP-1 family transcription factor motifs supports activity-dependent regulation within a shared permissive chromatin landscape. These findings support a hierarchical model in which higher-order threat memories emerge from coordinated epigenetic states that enable region-specific transcription across distributed circuits.

P1-B-54 *Coordination of post-transcriptional regulation shapes AMPA receptor function during CNS neurodevelopment*

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[1] McGill University

AMPA receptors (AMPARs) mediate fast excitatory neurotransmission in the mammalian brain and are essential for circuit formation, synaptic plasticity, and cognitive function. During development, AMPAR properties diversify through coordinated changes in subunit composition, RNA editing, alternative splicing, and association with auxiliary proteins such as TARPs and GSG1L. Although each of these regulatory mechanisms has been studied individually, their developmental timing and integration remain poorly understood. Here, we propose a unifying framework in which post-transcriptional modifications of AMPARs progressively accumulate during brain maturation, establishing a molecular context that permits TARPs to exert their full modulatory influence. We further show that RNA editing and alternative splicing interact

functionally, enabling fine-grained and combinatorial control of receptor properties. Together, these findings define a temporally regulated genetic program that shapes excitatory synapse maturation and highlight post-transcriptional AMPAR regulation as a potential point of vulnerability during neurodevelopment. Disruption of this program may help explain how relatively subtle alterations in RNA processing can produce disproportionate effects on synaptic signaling in certain neurodevelopmental conditions and suggests new avenues for developmentally targeted therapeutic intervention.

P1-B-55 *Co-transmitter interactions shape short term plasticity in the medial habenula-interpeduncular nucleus circuit*

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The interpeduncular nucleus (IPN) is a key regulator of aversive states. It is innervated by a combined cholinergic-glutamatergic input from the medial habenula (MHb). Most research has examined cholinergic or glutamatergic signalling in pharmacological isolation, leaving unresolved how these co-transmitters interact during physiological MHb activity. We hypothesize that both acetylcholine and glutamate are physiologically relevant in the functioning of this aversive circuit and play key roles in its plasticity. To probe endogenous cholinergic-glutamatergic co-transmission in the MHb-IPN circuit, we use angled brain slices from transgenic mice expressing channelrhodopsin in cholinergic neurons. We record from rostral IPN neurons and activate their MHb afferents optogenetically. We detect clear opto-evoked excitatory postsynaptic currents (EPSCs) in a portion of IPN neurons, but many cells do not initially show this response to 10 Hz or 20 Hz opto-stimulation. Upon repeated stimulation, however, we observe robust potentiation of this postsynaptic response. This plasticity of excitatory signalling is strong, repeatable, and exquisitely sensitive to cholinergic modulation. In ongoing experiments, we are further interrogating the timing and the molecular mechanisms of induction and expression. This work reframes cholinergic-glutamatergic signaling in the IPN, providing new insight into how this circuit reacts to repeated bursts of habenular activity. The circuitry appears wired for a rapid escalation of aversive responses under certain patterns of habenular activity.

P1-B-56 *Oligodendroglial UNC5B regulates the organization of paranodal junctions and modification of myelin during aging*

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Netrin-1 is expressed by neurons and oligodendrocytes in the mature CNS and is required to maintain the stability of axo-oligodendroglial paranodal junctions. The netrin receptor UNC5B is highly expressed by mature oligodendrocytes and enriched at paranodes; however, its function in mature myelin remains unknown. To investigate the contribution of oligodendroglial UNC5B to the maintenance of myelin structure and function we generated Olig2cre/Unc5bflox/flox mice. Examining internode and paranode ultrastructure in the optic nerve of 9-month-old wild-type (WT) and UNC5B conditional knockout (cKO) mice we observed intact compact myelin and found that the expression of compact myelin proteins MBP and PLP were unchanged. In contrast, paranodal junctions were disorganized, with glial loops everted away from the axon, and gaps detected at interfaces between paranodal loops. Confocal immunofluorescence analyses revealed disruption of the segregation of axonal domains around nodes of Ranvier. Behavioural monitoring of the optokinetic response provided evidence for reduced visual acuity in mice lacking oligodendroglial expression of UNC5B. Our findings indicate that Unc5b expression by oligodendrocytes is required to maintain the ultrastructural organization of paranodal junctions, properly segregate functional axonal domains associated with nodes of Ranvier, and support normal visuomotor function.

P1-B-57 *Delineating the regulation of cerebellar Purkinje cell excitability and synaptic inputs by the gamma protocadherins*

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The gamma protocadherins (γ-Pcdhs) are adhesion molecules widely expressed in the brain. They facilitate multiple aspects of morphological development; however, how they affect neuronal firing is poorly defined. We aim to address this gap by studying their contribution to cerebellar Purkinje cell (PC) electrophysiology, using mice with γ-Pcdh deletions (cKO). The field positions γ-Pcdhs as synaptic regulators; however, our early results showed altered intrinsic (synapse-independent) firing in cKO PCs. Therefore, we ask: do γ-Pcdhs affect PC firing by regulating synapses, or instead by a novel role in tuning intrinsic neuronal excitability? In patch-clamp recordings, cKO PCs displayed depressed intrinsic firing and excitability. Additionally, cKO PCs had upregulated K+ currents apparently from Kv3.3, voltage-gated K+ channels that enable high frequency firing. We followed up by expressing Kv3.3 in CHO cells, and found that co-expressing γ-Pcdhs inhibits Kv3.3 currents. I will present ongoing work into whether γ-Pcdhs modulate Kv3.3 channel gating or trafficking. Meanwhile, we labelled synaptic terminals of PC inputs. Climbing fibre terminal distribution was altered in cKO pups, but not adults, suggesting altered developmental progression. In contrast, parallel fibre terminals were morphologically intact. Future work will measure synaptic transmission. In summary, we find evidence that γ-Pcdh deletion affects both PC intrinsic excitability and synapses. We will next aim to uncover the common or independent mechanism(s) by which γ-Pcdhs tune these properties.

P1-B-58 *Dendritic nanostructures suppress inflammation in a model of ischemic stroke*

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Stroke is the second leading cause of death globally, with ischemic events comprising ~60%. They occur when arterial occlusion deprives the brain of oxygen and glucose, causing extensive cell damage and death. The only approved treatment, tissue plasminogen activator, dissolves blood clots but does not address the neuroinflammation that worsens the injury. To address this, we investigated a nanostructure with demonstrated potent anti-inflammatory properties, dendritic polyglycerol sulfate (dPGS). We hypothesize that dPGS promotes an anti-inflammatory environment in a stroke model in our mouse organotypic hippocampal slices, a brain region crucial for cognition and highly vulnerable to ischemic injury. These slices were first treated with dPGS, then ischemia-like conditions were induced through an oxygen-glucose deprivation (OGD) treatment. Microglial uptake, morphology, and the dendritic spine structure of pyramidal cells were assessed by immunohistochemistry, while cytokine release was quantified using ELISA. We find that microglia internalized dPGS and that both OGD treatment and dPGS altered microglial morphology. Additionally, dPGS increased the levels of cytokines linked with anti-inflammatory signaling (IL-10 and IL-33) and mitigated the dematuration of dendritic spines observed in OGD-treated slices. Together, these findings suggest that dPGS modulates microglial responses, promotes a protective anti-inflammatory environment, and preserves dendritic spine integrity under OGD, highlighting its potential as a complementary ischemic stroke therapy.

P1-B-59 *Developing an antibody panel for cell surface receptors at the synaptic cleft*

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The Institute for Protein Innovation (IPI) is a non-profit research organization dedicated to advancing protein science. The Institute is currently developing recombinant antibody panels targeting the human and mouse neuronal cell surfaceome. More specifically, IPI is building antibody collections that target cell surface receptors and ligands involved in synaptic cleft signaling, axon guidance and glial cell phenotyping. Our strategy is to target entire receptor-ligand families, in part to eliminate cross-family interactions and ensure antibody selectivity. Each IPI antibody is evaluated for binding kinetics, potency, specificity and aggregation,

and formulated as a chimeric human/rabbit antibody. IPI antibodies are validated both internally and through a unique community crowdsourced model. Overall, IPI is addressing unmet needs in the molecular neuroscience domain by generating a reliable set of protein binding reagents to support studies in synaptic transmission, axon guidance, neuronal migration and the molecular characterization of synapse types.

P1-B-60 *Disrupted microglial–TGF β1 signaling as a potential mechanistic basis for cerebellar underdevelopment*

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Background: Each year, about 2% of newborns are very preterm, and nearly half develop long-term neurodevelopmental delays. Among the affected brain structures, the cerebellum—crucial for motor and cognitive functions—shows impaired growth, yet the cellular and molecular mechanisms remain unclear, limiting targeted therapies. Hypothesis and Methods: We hypothesize that altered microglial responses, including impaired TGF-β1 signaling, key pathway in brain tissue repair, drive cerebellar underdevelopment and later functional deficits. Using a mouse model combining cerebellar hemorrhage and systemic inflammation at postnatal day 2 (P2), we reproduce key clinical features including microgliosis, cerebellar atrophy and persistent socio-cognitive deficits. Results: Cerebellar microglia were analyzed from P3-P15 by flow cytometry and profiled at P15 using single-cell RNA sequencing. Combined insults decreased homeostatic microglia and increased activated inflammatory cells. These changes coincided with downregulation of reparative pathways (TGF-β, IL-6/JAK2/STAT3, mTORC1). Expression of TGF-β receptors type 1 and 2, key regulators of tissue repair, axonal growth and neuronal migration, was significantly reduced. These findings are leading us to investigate if impaired microglial TGF-β signaling contributes to cerebellar atrophy and behavioral deficits. Conclusions: Our transcriptomic data indicate that TGF-β–mediated repair mechanisms are key to microglial responses during cerebellar development. Future work will assess how their disruption affects cerebellar structure and function.

P1-B-61 *Distinct subtypes of astrocytes selectively regulate specific inhibitory synapses*

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Astrocyte functional heterogeneity within a given neuronal circuit remains largely undetermined, particularly their role at tripartite synapses. Here, we examine multiple functional characteristics of astrocytes distinguished by their specific spatial relation to inhibitory synapses made on distinct hippocampal CA1 pyramidal cell domains: astrocytes covering the peri-somatic area in stratum pyramidale (SP) receiving input from Parvalbumin interneurons, or the apical dendritic area in stratum radiatum (SR) innervated by inhibitory inputs from Somatostatin interneurons. SP and SR astrocytes exhibit differences in morphological polarization, syncytial architecture and input resistance. The two populations of astrocytes display physiologically different intrinsic Ca2+ signaling properties and transcriptional signatures, notably for regulation of cell growth and morphology, synaptic function and signaling. Additionally, SP astrocytes have greater level of connexin 43 protein. SP and SR astrocytes regulate inhibitory synapses exclusively in their own syncytial territory, and selectively mediate long-term depression at the respective inhibitory synapses through Ca2+- dependent modulation of post-synaptic targets. Overall, our findings reveal a functional specialization of astrocyte subtypes in the hippocampus with discrete regulatory domains for inhibitory synapses in hippocampal networks.

P1-B-62 *Diurnal molecular characterization of aged WT and Per1 KO rat hippocampus*

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Circadian rhythms are fundamental to learning and memory and are accompanied by diurnal variation in synaptic signalling – processes that are often disrupted with ageing. Period circadian regulator 1 (PER1) is a core molecular clock component that coordinates rhythmic gene expression. However, its contribution to synaptic receptor and enzyme signalling in the aged hippocampus remains unclear. Here, we investigated how time-of-day and PER1 influence synaptic and plasticity-related protein expression and phosphorylation in hippocampal slices from aged (17-25 month) male wildtype (WT) and Per1 knockout (KO) rats during the light (ZT6) and dark (ZT18) phases. Samples were processed as total homogenates or synaptically-enriched (SNP) fractions and were analyzed by immunoblotting. Strikingly, we observed an increase in GluA1 Ser845 phosphorylation during the dark phase in total homogenates and SNP fractions, while GluA1 levels were unchanged, in both WT and Per1 KO rats. Furthermore, key NMDA receptor phosphorylation sites, as well as NMDA and other AMPA receptor subunit expression, did not differ between phases or genotypes. We also found that phosphorylation of GSK-3α at Ser21, but not GSK-3β at Ser9, was increased in total homogenates from both genotypes in the dark phase. Collectively, these results demonstrate that pGluA1 Ser845 and pGSK-3α Ser21 are under circadian control in the aged hippocampus and are undergo diurnal regulation in a PER1-independent manner.

P1-B-63 *DNA methylation in astrocyte maturation*

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[1] McGill University

Epigenetic regulation, such as DNA methylation, is well studied in gene regulation and early astrocyte specification, but its role in astrocyte maturation remains unclear. During maturation, astrocytes undergo molecular, structural, and functional changes required for supporting adult brain physiology. A recent study found that chromatin remodeling occurs during astrocyte maturation, raising the question of whether DNA methylation is involved. Since a higher ratio of 5-hydroxymethylcytosine (5-hmC) to 5-methylcytosine (5-mC) in the brain is associated with increased gene expression, I investigated the potential shift in the balance of these epigenetic marks as astrocytes mature. Using immunolabelling, I compared 5-hmC/5-mC ratios in immature astrocytes at P14 and P21, and mature astrocytes, across brain regions in mice. I found region-specific DNA methylation dynamics: astrocytes in somatosensory cortex maintained stable 5-hmC/5-mC ratios throughout development, whereas astrocytes in striatum exhibited a progressive decrease, and astrocytes in visual cortex exhibited an increase. These findings suggest region-specific changes in methylation states during astrocyte maturation, suggesting an epigenetic basis for their maturation and heterogeneity. Ongoing work will map these methylation changes to specific genes using sequencing approaches and test causality by knocking down DNA methyltransferases (DNMTs). I hypothesize that DNMT-mediated DNA methylation drives gene expression changes required for astrocytic maturation, which is essential for brain development and function.

P1-B-64 *The expression of core clock gene Bmal1 is minimal or absent in human and mouse cerebral microglial cells*

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Microglia orchestrate immunological responses in the brain and play an important role in maintaining homeostatic brain functions. Several studies have reported clock gene expression in microglia and the circadian rhythm they drive has been linked to the modulation of immune responses and neuronal functions. In the current study, complementary approaches, including immunofluorescence, multiplexed fluorescence in situ hybridization, and liquid chromatography-mass spectrometry proteomics of isolated CD11b+ microglia, were combined with publicly available transcriptomic and epigenomic datasets to investigate the expression

of the core clock gene BMAL1 in human post-mortem cortical and limbic areas as well as mouse brain. Most BMAL1-expressing cells were found to be neurons, with microglia representing a negligeable proportion. We also identified significantly lower chromatin accessibility or “openness” for BMAL1 gene regulatory regions (such as promoters and enhancers) in microglia compared to neurons. These regulatory regions in microglia were enriched for ETS domain transcription factor (TF) binding sites. Together, this suggests a strong role of chromatin remodeling factors in suppressing BMAL1 gene expression in microglia. Finally, while we observed a very low expression, BMAL1 TF motifs were accessible in open chromatin landscape of microglia, which may lead to downstream gene-regulatory effects upon binding, even if BMAL1 expression is constitutively low. Overall, our results reveal low or absent expression of BMAL1 in microglia and point towards potential epigenetic mechanisms regulating its expression in these cells.

P1-B-65 *Early functional immaturity of the reinnervated neuromuscular junction*

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While neuromuscular junction (NMJ) is a stable and robust synapse, it can also undergo efficient reinnervation owing to reliable repair mechanisms. This repair appears deficient in Amyotrophic lateral sclerosis (ALS) where NMJs exhibit abnormal denervation-reinnervation cycles. However, the rapid response leading to functional repair remains unexplored, limiting our understanding of the ALS NMJ instability. We posit that an inadequate functional reinnervation contributes to the instability of NMJs in ALS. We developed the Single Axon In-vivo Injury (SAIVI), a method that allows us to damage few axons and denervate 50µm downstream NMJs to precisely monitor in time and space the reinnervation. After a recovery time (3-28 days), muscles and nerves were dissected, and synaptic electrophysiological recordings were performed on reinnervated NMJs and non-injured control nearby NMJs. Confocal imaging assessed structural NMJ innervation. We observed in WT mice that all NMJs were reinnervated at 5 days postinjury (DPI). However, we noticed a maintained synaptic immaturity until 11 DPI while NMJ structure was restored and robust. We interpret this delay of the function gain over the NMJ morphology as a consolidation period. Surprisingly, it was shorter in females. Furthermore, in our ALS mouse model, this period became critical with a worsening of the synaptic function from 5 to 11 DPI. Hence, while morphological NMJ reinnervation is efficient, it depends on a slower process of functional stabilisation that encompasses a critical period, before reaching functional maturity.

P1-B-66 *Early seizure drives hippocampal circuit rewiring through target-specific disinhibition*

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Early-life seizure (ELS) is frequently refractory to anticonvulsant treatments and is associated with epilepsy and long-term cognitive deficits, yet the underlying cellular and molecular alterations remain poorly understood. Although hippocampal neurons are highly heterogeneous, this diversity is often overlooked in epilepsy research, leaving the contribution of distinct neuronal populations to ELS undefined. Using a c-Fos–based, activity-dependent labeling and manipulation approach, we identified a selective population of deep-layer hippocampal CA1 neurons preferentially activated by ELS at P10. Simultaneous dual whole-cell patch-clamp recordings from CA1 parvalbumin (PV) interneurons and ELS-activated or non-activated pyramidal neurons revealed that ELS acutely and selectively disrupts PV-mediated perisomatic inhibition exclusively onto ELS-activated pyramidal neurons, driven by reduced presynaptic release probability and increased synaptic failures. Notably, this inhibitory deficit persists into adulthood and contributes to lasting cognitive impairments. Importantly, targeted chemogenetic suppression of only the ELS-activated neurons restores PV-mediated inhibition and excitation–inhibition (E/I) balance and rescues long-term cognitive deficits. Together, these findings demonstrate for the first time that ELS induces highly target-specific disinhibition within the developing hippocampal circuits, linking maladaptive circuit reorganization to enduring cognitive dysfunction.

P1-B-67 *Effects of blocking endocannabinoid degradation on spreading depolarization*

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Spreading depolarization (SD) is a slow wave of electrical potential shift that disrupts ion balance and silences neuronal activity, requiring significant energy to restore. Clinically, SD underlies migraine aura and, when coupled with arteriole constriction, can exacerbate brain damage during stroke, traumatic brain injury, and subarachnoid hemorrhage. Endocannabinoids (eCBs) are released from depolarized cells and regulate neural communication, excitability, ion distribution, and local cerebral blood flow. The eCB system has shown neuroprotective properties in SD-related pathologies, yet its role in SD remains unexplored. This study investigated sex-specific differences in cerebrovascular responses to SD and evaluated the effects of acutely elevated eCB levels via pharmacological inhibition of monoacylglycerol lipase (MAGL) and fatty acid amide hydrolase (FAAH). Using two-photon microscopy in acute mouse brain slices, changes in SD-related neuronal and glial Ca2+ responses, and arteriole diameter changes were visualized with a fluorescent Ca2+ indicator and an intravascular dye, respectively. We observed that female mice exhibited delayed vasodilation following SD, which was attenuated by MAGL and FAAH inhibition. Conversely, males showed enhanced early vasoconstriction in response to acutely elevated eCB levels. These effects occurred independently of changes in neural Ca2+ dynamics. Further experiments in males revealed that inhibiting eCB-substrate-specific cyclooxygenase-2 (COX-2) inhibition attenuated the enhanced vasoconstriction caused by MAGL and FAAH inhibition, suggesting a COX-2-dependent mechanism for eCB-mediated vascular effects during SD. These findings suggest that modulating eCB and COX-2 pathways could potentially attenuate vasoconstriction during SD, offering a novel avenue for limiting secondary injury in acute SD-related brain disorders.

P1-B-68 *Effects of physical activity on hippocampal cells in an animal model of Alzheimer's disease*

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Alzheimer's disease (AD) is characterized by progressive hippocampal degeneration, which impairs learning and memory. Despite extensive research, there are no disease-modifying treatments. Evidence suggests that modifiable lifestyle factors, such as physical activity (PA), may reduce AD risk. However, the cellular mechanisms behind this protective effect remain unclear. This study aims to investigate whether PA exerts protective effects on hippocampal cell populations in AD, specifically in the context of the transgenic 5xFAD mouse model. To investigate the effects of physical activity (PA) on hippocampal cell populations in Alzheimer's disease (AD), 2.5-month wild-type and 5xFAD transgenic mice were used. Mice were assigned to either a voluntary running (RUN) or sedentary (LD) group. The RUN group had access to running wheels for 14 days, a period known to promote hippocampal neurogenesis. Hippocampi from female mice (N=3) were collected for single-nucleus RNA sequencing (snRNA-seq).snRNA-seq analysis yielded 89,353 high-quality nuclei, representing several major hippocampal cell types: excitatory neurons, astrocytes, inhibitory neurons, oligodendrocytes, oligodendrocyte precursor cells and vascular cells. Gene Set Enrichment Analysis (GSEA) identified AD-related transcriptional alterations across these cell types. PA reversed several of these changes, with OPCs showing the greatest response: 21% of altered pathways were corrected by PA, including 60 uniquely corrected pathways. Downregulated pathways were mainly related to cell cycle processes, while upregulated ones involved synaptic function. These findings demonstrate that PA modulates hippocampal gene expression in a cell-type-specific manner in AD, highlighting candidate pathways through which exercise may confer neuroprotection.

P1-B-69 *Elucidating roles for the postsynaptic GABAergic synapse organizer IgSF21 in synaptic plasticity in mouse hippocampus*

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Synapse organizing proteins serve as molecular codes that coordinate synapse specification and function throughout the brain. The importance of these organizers is demonstrated by gene linkage and loss-of-function studies which consistently link synapse organizer impairments to neurodevelopmental and neuropsychiatric disorders. Immunoglobulin superfamily member 21 (IgSF21) is a novel GABAergic synapse organizer which interacts with presynaptic neurexin2α to selectively regulate inhibitory inputs. Accordingly, Igsf21-/- mice exhibit impaired GABA-mediated synaptic transmission in hippocampal CA1 pyramidal neurons, providing a unique model for exploring how loss of GABAergic synapse development impacts neural circuit properties. Accordingly, we sought to determine if IgSF21 deficiency affects synaptic plasticity in Igsf21-/- mice. Combining our transgenic model with ex vivo slice electrophysiology, we examined how IgSF21 deficiency alters long-term potentiation (LTP), a leading cellular model for learning and memory, in mouse hippocampus slices. We hypothesize that compromised GABAergic synapse development in Igsf21-/- mice will impair theta-burst stimulation (TBS)-induced LTP due to increased pyramidal neuron disinhibition. Through probing the role of IgSF21 in synaptic plasticity, this study aims to gain insights into how loss of inhibitory synapse regulation compromises hippocampal microcircuits and contributes to neural pathologies underlying neurodevelopmental and neuropsychiatric disorders.

P1-B-70 *Elucidating the impact of interneuron subtypes on neurovascular coupling during sensory processing*

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Background: Vascular-based imaging techniques such as fMRI are used as surrogate measures of neuronal activity, yet how the hemodynamic response reflects the activity patterns of different neuronal populations remain ill-defined. Mounting evidence suggests the involvement of various interneuron subtypes in neurovascular coupling (NVC), with optogenetic activation capable of evoking large increases in blood volume. Yet, the relative importance of inhibitory vs. excitatory activity on NVC during physiological stimulation remains undetermined. Aims: 1) Correlate the activity of different interneuron subpopulations with hemodynamic changes across space, 2) Determine to what extent inhibitory neurons directly vs. indirectly modulate neurovascular coupling during sensory processing. Methods and results: Using the well-defined columnar organization of the barrel cortex, we first performed wide-field calcium imaging in combination with intrinsic measurements of hemoglobin to examine the spatial relationship between calcium elevations in parvalbumin (PV) and somatostatin (SOM) interneurons and blood volume increases during short whisker stimulation. We found that calcium signals from all three cell types (excitatory and both PV and SOM inhibitory neurons) were highly correlated with increases in blood volume across space. While silencing of inhibitory neurons lead to highly variable changes in the hemodynamic response across mice, which could be well predicted by changes in excitation, overall, the relationship between excitatory activity and blood volume was largely preserved at the mesoscale. Conclusions: These results suggest that during brief sensory stimulation, inhibitory cells exert a greater impact on NVC via their effects on overall circuit activity, rather than through direct signaling to the vasculature.

P1-B-71 *Estradiol rapidly reduces synaptic inhibition in layer V of the prelimbic cortex*

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Estradiol regulates cognition in humans and animals and can modulate neural activity within minutes in the medial prefrontal cortex (mPFC) via membrane-associated receptors. Elevated estradiol levels are associated with increased ventral mPFC activation during fear extinction learning and recall, and local estradiol infusion

in the mPFC can rapidly alter the choice of cognitive strategies in female rats. Estradiol also enhances cocaine-related behaviors, potentially by disinhibiting the excitatory outputs of the mPFC. Despite this, the synaptic mechanisms underlying the rapid effects of estradiol in the mPFC remain unclear. We examined the effects of estradiol on evoked field excitatory postsynaptic potentials in superficial and deep layers of the prelimbic mPFC in female rats. Application of estradiol for 20 minutes did not affect synaptic responses evoked in either layer I or V following stimulation of layer I, but facilitated synaptic responses evoked in layer V by layer V stimulation. In whole-cell patch-clamp recordings of pharmacologically isolated inhibitory synaptic responses, estradiol caused a strong reduction in the amplitude of evoked inhibitory postsynaptic currents in layer V neurons. Results suggest that estradiol enhances neuronal excitability in the deep layers of the prelimbic cortex by rapidly reducing the strength of GABA-mediated inhibitory synaptic transmission. Ongoing studies are identifying the receptors and intracellular signaling mechanisms that mediate this rapid effect of estradiol.

P1-B-72 *Examining fragile x syndrome across the lifespan: A focus on purinergic signaling*

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Fragile X Syndrome (FXS) is the leading heritable cause of intellectual disability and autism in children. Individuals with FXS live a relatively normal lifespan, however, they exhibit premature age-related cognitive and motor deficits. This is consistent with impaired cortical excitatory neuronal activity in aged Fmr1 knockout (KO) mice, the model of FXS. This project aims to uncover the cellular and molecular mechanisms underlying these alterations throughout the lifespan. Neuronal activity is regulated by glial cells such as astrocytes. Indeed, astrocyte-mediated signaling via purinergic compounds is highly dysregulated in FXS and manipulation of purinergic receptors prevents FXS-dependent network hyperactivity during development. One such receptor, the adenosine A2A receptor, appears to be involved in neuron and astrocyte dysregulation in FXS and during the aging process. Hence, we hypothesize that the A2A receptor is elevated in Fmr1 KO cortex and that it mediates cellular hyperactivity throughout the lifespan of Fmr1 KO mice. Wildtype (WT) and Fmr1 KO neuronal activity was measured both in vitro using primary neuron-astrocyte co-cultures on microelectrode array plates and in vivo with neuron-specific calcium imaging via miniature microscopy in adult WT and Fmr1 KO mice. We also characterized A2A receptor expression and distribution in whole cortical tissue and in primary astrocyte and neuron cultures via Western blot and immunofluorescence. This work will contribute to the understanding of neurobiological changes in FXS across the lifespan and will provide meaningful insight for therapeutic avenues.

P1-B-73 *Examining the impact of early life adversity on cerebellar perineuronal nets in adult mice and human*

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Early life adversity (ELA) impacts brain development and increases the risk for mental illness. Our group reported an association between a history of severe child abuse (CA) and increased density and maturity of perineuronal nets (PNNs) in human ventromedial prefrontal cortex. PNNs are condensed extracellular matrix structures that surround the soma and proximal dendrites of certain neurons. Their maturation during development coincides with the closure of critical periods of cortical plasticity. Little is known about the impact of ELA on cerebellar PNNs, which we recently characterized in humans, macaques, and mice (Mpai et al., 2025, Cerebellum 24(6):168). In the current study, we used immunofluorescence (IF) to label PNNs and fluorescence in situ hybridization to label GABAergic, glutamatergic, and parvalbumin-positive cells to examine PNN density in the dentate nucleus of adult depressed suicides with, and without, a history of severe CA (n=15/group;12M, and 13M, respectively) compared to matched psychiatric controls (n=15; 13M). In parallel, we used a similar approach in a limited bedding and nesting model of ELA in C57BL/6 mice (n=8; 4M) to compare PNN densities in the deep cerebellar nuclei with standard-reared mice (n=9; 4M). PNN

densities did not differ between ELA and control mice (fastigial, p > 0.999; interposed, p = 0.888; dentate, p = 0.481). These results will be presented alongside near-complete analyses of human samples to assess the vulnerability of cerebellar PNNs to ELA across species.

P1-B-74 *Examining the molecular mechanism through which the cell-surface receptor Neogenin modulates inhibitory synaptic function*

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Synaptic function in the brain is crucial for neuronal communication and depends on precise protein–protein interactions that regulate neuronal signaling. Disruptions in these interactions can lead to neurological disorders such as Autism Spectrum Disorder (ASD), epilepsy, and schizophrenia. Neogenin (Neo1) is a transmembrane receptor known to interact with multiple ligands, including the synaptic protein Cerebellin4 (Cbln4). Studies in our lab have shown that Neo1 localizes to inhibitory synapses and that its selective ablation in GABAergic inhibitory neurons increases inhibitory synaptic transmission in cortical pyramidal neurons, suggesting a role in maintaining proper excitation-inhibition balance in these neurons. Loss of Neo1 also results in reduced synaptic levels of Cbln4, a secreted protein shown to modulate inhibitory synaptic transmission by binding to Glutamate Receptor Delta-1 (GluD1/Grid1) expressed on the postsynaptic terminal of pyramidal cortical neurons. We hypothesize that Neo1 modulates inhibitory synaptic transmission by stabilizing Cbln4 localization at the synapse through the formation of a trans-synaptic Neo1-Cbln4-GluD1 tripartite complex. We have investigated this model using an in vitro cell aggregation assay to probe Neo1-Cbln4-GluD1 interactions and are employing complementary biochemical and proteomic approaches to characterize Neo1-dependent changes in inhibitory synaptic protein composition.

P1-B-75 *Exploring the physiological function of GPR139 in dorsal root ganglia*

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Itch and pain are both unpleasant sensations that, when chronic, can profoundly affect quality of life. This sensation can be transmitted from the skin to the central nervous system (CNS) by G protein-coupled receptors (GPCRs) in pruriceptors (sensory neurons activated by itch-causing compounds) from dorsal root ganglion (DRG). GPR139 is a GPCR whose transcripts can be detected in somatostatin-positive (Sst+) pruriceptors. However, its function in these neurons remains unknown. In this project, I propose to validate the expression pattern of GPR139 in mouse DRG, examine its function in vitro with heterologous cell lines and primary DRG neurons, and finally, reveal the role of peripheral GPR139 in somatosensation with in vivo models. In my preliminary data, RNAscope in situ hybridization in mouse DRG demonstrated that Gpr139 is mainly expressed in somatostatin-positive neurons. GPR139 can couple to both Gi/o and Gq/11 in an overexpression system using HEK293 cell line. Activation of GPR139 by a selective agonist triggers a rise of [Ca2+]i in HEK293 cells and F11 overexpressing GPR139 and cultured DRG neurons endogenous expressing GPR139. In vivo behavior experiments reveal that subcutaneous injection of the GPR139 agonist leads to cold hypersensitivity in naïve mice. Taken together, these preliminary results indicate that GPR139 is expressed in small diameter neurons of the mouse DRG and enriched in Sst+ pruriceptors and activation of GPR139 peripherally causes cold allodynia. This project focuses on investigating the physiological functions of GPR139 in DRG, which may facilitate a more comprehensive understanding of somatosensation.

P1-B-76 *Feedforward inhibition of dorsal horn inhibitory neurons that gate mechanical allodynia after nerve injury*

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The dorsal horn of the spinal cord contains highly organized circuits that process somatosensory information, including touch and pain. Inhibitory interneurons play a key role in gating these inputs, and loss of inhibition is a hallmark of neuropathic pain, leading to mechanical allodynia—where innocuous touch is perceived as painful. A well-characterized circuit implicated in this process involves parvalbumin-expressing inhibitory interneurons (PVNs), which normally suppress polysynaptic nociceptive pathways activated by Aβ mechanoreceptors. Following peripheral nerve injury, PVN output is reduced, resulting in disinhibition of these touch-evoked pain circuits. This reduction is partly due to a decrease in Ab input onto PVNs, as well as an increased failure rate of these PVNs to generate action potentials. Interestingly, our results demonstrate that after nerve injury, PVNs will not only receive less Ab inputs, but they also receive more inhibitory input from a yet-to-be identified subset of inhibitory neurons. We have identified a disynaptic feedforward inhibitory circuit in which Aβ fibers activate both PVNs and a subset of inhibitory interneurons that in turn inhibit PVNs. Using pseudo-typed rabies tracing, we aim to characterize this novel inhibitory population. We hypothesize that silencing these interneurons will restore PVN activity and re-establish inhibitory tone in the dorsal horn, thereby reducing mechanical allodynia after nerve injury.

P1-B-77 *Targeting TRPM2 as a novel therapeutic intervention for Alzheimer's Disease*

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Introduction: Cognitive decline in Alzheimer's Disease(AD) is caused by accumulation of Aβ oligomers(AβOs), consequent synapse failure and microglia-mediated neuroinflammation. TRPM2, a Ca2+ permeable channel, drives AβO-induced synaptotoxic cascades, including those contributed by microglia, and might be a potential target for AD therapeutic interventions. We previously demonstrated that TRPM2 knockout in an AD mouse model is associated with attenuated cognitive decline. Here, we assessed whether JNJ-28583113(JNJ), a potent and selective TRPM2 blocker, can prevent AβO-induced synaptotoxicity and neuroinflammation. Methods: We tested the mechanism of TRPM2 inhibition by JNJ and its ability to block: 1)TRPM2 currents in TRPM2-expressing HEK293 cells, 2)AβO-induced synaptotoxicity in hippocampal slices, during fEPSP recordings, 3)AβO-stimulated GSK3β activity(pGSK3βSer9/total) in hippocampal slices, 4)AβO-stimulated nitric oxide(NO) production from cultured microglia. We also examined the differential vulnerability of apical and basal synapses to AβOs. Results: JNJ completely inhibits TRPM2 currents. Our preliminary data suggest that this inhibition is in a Ca2+-dependent manner. When applied to hippocampal slices, JNJ prevents the synaptotoxic effects of AβOs on LTP, while having no effect on basal synaptic transmission or LTP when applied to healthy control slices. Interestingly, although apical synapses in the stratum radiatum are vulnerable to the AβOs, basal synapses in the stratum oriens are resistant to their disruptive effects. In cultured microglia, JNJ prevents AβO-induced NO release, providing a candidate mechanism underlying the synaptoprotective properties of JNJ. Conclusion: TRPM2 channels are important players in AβO-synaptotoxicity and neuroinflammation and JNJ, pharmacological TRPM2 inhibitor, attenuates microglial responses and synaptic failure.

P1-B-78 *Molecular characterization of a L-type calcium channel from molluscan neuroendocrine cells*

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Intracellular Ca2+ is an essential second messenger that regulates multiple neuronal processes, including excitability and secretion. In the neuroendocrine bag cell neurons, from the sea snail Aplysia, L-type Ca2+ channels mediate the Ca2+ influx necessary for both the regulation of other ion channels as well as

the secretion of reproductive hormone. The native Ca2+ current has been studied extensively; however, the complete molecular identification remains unknown. In the present study, we used in silico cDNA sequences from the Aplysia transcriptome to design primers to clone a full length Aplysia CaV1 channel from cDNA reverse transcribed from bag cell neuron tRNA. Based on homology with mammalian CaV1 Ca2+ channel α1 subunits, this gene appeared to code for a complete channel that included 4 domains, each with 6 transmembrane segments, 4 pore-loops presenting the critical glutamate residue for Ca2+ selection, segment 4 of each domain containing negatively charged residues as voltage sensors, and an IQ motif near the C-terminus for calmodulin binding. The identity, at the amino acid level, between Aplysia CaV1 and human CaV1.1, 1.2, 1.3, and 1.4, was 48, 50, 49, and 47%, respectively. Future characterization in an heterologous expression system is predicted to result in currents similar to that of native bag cell neurons, ie, relatively long lasting voltage-dependent currents which undergo use- and Ca2+-dependent inactivation. This molecular foothold will facilitate the understanding of how hormone release is triggered via Ca2+ influx in neuroendocrine systems.

P1-B-268 *Astrocyte-specific eIF2 alpha-dependent mRNA translation regulation of hippocampal synaptic plasticity and memory in Alzheimer's disease*

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Alzheimer's disease (AD) is a neurodegenerative disorder characterized by the loss of memory and cognitive function. The key pathological features of AD include the accumulation of neurotoxic amyloid-β peptides and the formation of neurofibrillary tangles composed of hyperphosphorylated tau proteins. These protein aggregates induce oxidative stress and activate the integrated stress response (ISR) pathway. This pathway facilitates the translation of stress response genes, thereby alleviating cellular stress and promoting cell survival. Astrocytes, the most abundant glial cells in the brain, form functional synaptic connections with neurons and play a crucial role in memory formation. We have shown that reducing p-eIF2α levels in the hippocampal astrocytes increases protein synthesis and enhances fear memory in mice. During AD, astrocytes become reactive in response to amyloid-β deposition and undergo morphological and functional remodelling. We observed higher levels of p-eIF2α in the CA1 of the dorsal hippocampus astrocytes from AD patients and a mouse model with AD-related pathologies (5xFAD). Genetic reduction of p-eIF2α in hippocampal astrocytes of the 5xFAD lowers the threshold for the induction of the late phase of long-term potentiation (L-LTP) and enhances hippocampus-dependent LTM. These findings validate that the eIF2α pathway in astrocytes plays a critical role in strengthening synaptic plasticity and is a promising strategy for improving memory in conditions associated with memory impairment, such as aging and AD-related memory deficits.

C - DISORDERS OF THE NERVOUS SYSTEM

P1-C-79 *5KEEG: Probing the diversity of brain dynamics in genetic and neurodevelopmental disorders*

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Neurodevelopmental disorders (NDDs) affecting youth mental health present a variety of symptoms and etiologies. This poses challenges for accurate diagnosis and personalized treatment. Although electrophysiology has demonstrated potential to reveal the neural basis of NDDs, inconsistent findings and methodological heterogeneity have impeded its practical applications. Moreover, genetics has highlighted correlations between genetic variants and NDDs, but predictive power is limited by the complex nature of the brain. We hypothesize that an enhanced approach, integrating electrophysiology and genetics, can identify reliable biomarkers of NDDs, enhance biological interpretability, and advance the development of actionable biomarkers and a better understanding of biological mechanisms. We established standardized

growth charts of electrophysiological biomarkers using normative modeling on a large-scale dataset (N=4547) obtained from diverse international cohorts. This approach accounts for nonlinear age-related effects on EEG measures, as well as variations in gender, sex, and differences across cohorts, thereby enabling rigorous statistical analyses of large-scale, multi-site data. Thereafter, a deviation score, representing the difference from normative values, can be calculated for each individual based on their electrophysiological measurements. Moreover, we analyze how these measurements correlate with the influence of genetic variants. We found significant EEG deviations in NDDs. Spectral, connectivity and entropy components show convergent deviations among NDDs. Additionally, genetic analysis revealed a mirror effect where deletions and duplications correlate differently with NDDs.

P1-C-80 *A novel brain-penetrant apelin receptor probe for targeted glioblastoma radiotherapy*

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Glioblastoma (GBM) is the most aggressive primary brain tumor and remains associated with a poor prognosis, with a 5-year survival rate of approximately 4%. We recently identified the apelin receptor (APJ), a class A G protein-coupled receptor, as a promising therapeutic target for GBM. Bioinformatic analyses of The Cancer Genome Atlas (TCGA) revealed significant overexpression of APJ in GBM relative to healthy brain tissue. Building on these findings, we developed a theranostic strategy based on a radiolabeled APJ ligand that enables PET-based target validation and imaging, followed by radionuclide therapy using the same molecular scaffold. To this end, a 64Cu-labeled-APJ ligand was rationally designed by conjugating an apelin-13 derivative to the blood-brain-barrier shuttle peptide Angiopep-2. The resulting radioligand exhibited nanomolar affinity for APJ and demonstrated full agonist activity for B-arrestin-2 recruitment at APJ, accompanied by robust receptor internalization and trafficking to early endosomes. In vivo stability and whole-body biodistribution studies in CD-1 mice revealed favorable pharmacokinetic properties, including moderate plasma protein binding (15–38%) and low accumulation in critical organs. Finally, using an orthotopic U87-MG GBM model and monitoring tumor progression by MRI and secreted Gaussia luciferase, we demonstrated that APJ expression significantly contributes to tumor aggressiveness. Altogether, these findings support APJ-targeted theranostics as a novel and promising precision oncology strategy for glioblastoma.

P1-C-81 *A novel cannabinoid receptor 1 (CB1) PAM-antagonist dampens amphetamine-induced dopamine levels; Evidence of CB1-mediated indirect modulation of high DA states*

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The endocannabinoid system (ECS) is a homeostatic filter that integrates signaling pathways, including dopamine (DA). Within the context of psychiatry, and based on previous pitfalls of targeting DA directly, indirectly targeting dysregulated DA signaling may be therapeutically advantageous. Targets such as cannabinoid receptor 1 (CB1) offer this indirect modality. We show proof-of-principle via novel class of drug-like allosteric modulators for CB1; positive allosteric modulator (PAM)-antagonists. CB1 PAM-antagonists increase agonist affinity, block signalling, and are highly effective in models of hyperDA. High DA is likely exacerbated by positive feedback between high DA and high 2-arachidonoylglycerol (2-AG), most abundant EC in the brain. Overactive 2-AG signaling is found in some psychiatric conditions, where high 2-AG and CB1 signalling drive the pathology. Here, we look to directly measure DA levels in vivo to establish a mechanism of action for our novel CB1 PAM-antagonists and their indirect modulation of DA signaling levels via CB1. Pre-treatment with ABM300 dampened AMPH-induced DA release, decreasing area under the curve (AUC) in time-course of DA signal; DLS (AUC: p=0.016) and NAc (AUC: p=0.0676). DA transient peak width/prominence were unchanged in DLS and NAc. We see influences of sex on DA signal decrease magnitude. DA dynamics mirrored the behavioural effects previously published, correlating between simultaneous open-field

and fiber photometry recordings; ABM300 dampened AMPH-induced psychomotor activity. We provide substantiative evidence for a novel therapeutic strategy in treatment of hyperDA psychiatric pathologies: indirect modulation of DA via CB1.

P1-C-82 *A role of neurodevelopmental disorder-associated gene Arid1b in purkinje cell development and cerebellar function in mice*

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The cerebellum is a brain structure important to motor function. Pathological changes of cerebellum, including reduction of Purkinje cell (PC) density, cerebellar vermis underdevelopment, reduced connectivity have been frequently reported in patients with neurodevelopmental disorders (NDD). ARID1B is a high confident risk gene of NDD. It has been shown to play roles in proliferation, dendritic innervation, and synapse formation of neurons. A subset of patients with ARID1B-related disorders exhibits cerebellar malformation. ARID1B is enriched in cerebellar neurons, but very little is known about its function in the cerebellum. Here, we report that in vivo ablation of ARID1B in PCs suppresses dendritic arborization. The ARID1B-absent PCs exhibit altered electrophysiological properties. Through cerebellar transcriptomic analysis, we show that conditional knock out (cKO) of Arid1b in PCs influence the transcriptional programs involved in cell development, structural organization and neuronal excitability. Moreover, mice with PC-specific Arid1b cKO exhibit altered motor learning. These findings uncover the molecular and cellular role of ARID1B in PC development, cerebellar function and animal behavior.

P1-C-83 *A transcriptional timeline of Alzheimer's disease related damage in neurons*

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Background: Alzheimer's disease (AD) is the most common cause of dementia worldwide. AD is characterized by a progressive loss of synapses culminating in neuronal death. While numerous studies have identified markers of transcriptomic dysregulation in AD, a comprehensive timeline of the transcriptomic changes neurons undergo over the course of the disease has not yet been established. Methods: We examined changes in the transcriptional program of neurons in the entorhinal cortex and hippocampus using data from the ROSMAP study. We used MEGENA, a gene co-expression analysis technique, to find gene modules that are perturbed during different stages of AD progression. Results: We found three different AD-associated modules that are conserved across different types of neurons. These modules were expressed at different stages of the disease, indicating that neurons may continuously change their transcriptional program as the amount of cellular damage increases. Despite previous studies showing that only certain types of neurons are vulnerable to AD pathology we found evidence of these AD related transcriptomic changes across all the classes of neurons we examined. Conclusion: A better understanding of how AD pathology damages neurons could allow for the development of novel treatments to prevent or ameliorate neuronal damage for patients with AD.

P1-C-84 *A unifying neuropathological spectrum underlies medial temporal lobe epilepsy*

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Medial temporal lobe epilepsy (mTLE), characterized by seizures arising from the hippocampus, is the most common form of focal epilepsy, with up to 70% of patients failing to respond to medication. Regional patterns of neuronal loss in the hippocampus have been used to classify mTLE into discrete histopathological subtypes. Here, using single-cell spatial transcriptomics, we examine molecular-cellular alterations in mTLE and reassess this discrete-subtype framework. We collected single-cell spatial transcriptomic data (Xenium, 10x Genomics) from the hippocampus of 18 individuals, including epilepsy samples with varying degrees of hippocampal sclerosis, and postmortem non-epileptic controls, using a

366-gene panel. Our gene panel included marker genes for major hippocampal cell types, such as excitatory and inhibitory neurons and multiple glial populations, as well as genes reported to be affected in epilepsy. Our data reveal previously unresolved signatures of molecular-cellular vulnerability in mTLE, including neuronal degeneration, glial remodeling, and region-specific susceptibility across individuals. At the level of molecules, cells, and regions, we identify a singular pathological spectrum across histopathological subtypes. This unified axis captures major patterns of molecular variation in mTLE and highlights conserved cellular programs with therapeutic relevance. Finally, our dataset provides a valuable resource for the epilepsy and hippocampal research communities, enabling a deeper understanding of human hippocampal organization and dysregulation in mTLE.

P1-C-85 *Activating systemic inflammation with LPS drives microglia-mediated degradation of perineuronal nets after cervical spinal cord injury in female lewis rats*

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Cervical spinal cord injury (SCI) often leads to persistent motor impairments. While rehabilitation promotes recovery, progress typically plateaus over time. We previously demonstrated that combining task-specific training with Lipopolysaccharide (LPS)-induced inflammation can attenuate this plateau in a rat model of chronic cervical SCI by increasing neuroplasticity. The underlying mechanisms of how LPS-induced inflammation increases plasticity remain unclear. The current study utilized two complementary experiments involving 64 adult female Lewis rats. All animals received a C4 dorsolateral spinal quadrant transection. Following a 10-day recovery, rats received a single LPS injection (1.5 mg/kg), saline, minocycline (35 mg/kg), or a combined LPS+minocycline treatment. Five days post-treatment, spinal cords were collected for analysis. PNN integrity, microglial activity, and lesion extension were evaluated using immunolabeling and high-resolution confocal imaging. Additionally, Imaris-based 3D reconstructions were utilized to visualize microglia engulfment of PNNs. Collectively, these experiments demonstrate that systemic LPS-induced inflammation after cervical SCI significantly reduces PNN density. We show that inflammation drives PNN remodeling, with microglia acting as primary mediators. The role of microglia was confirmed as their pharmacological inhibition with minocycline preserved PNN integrity. Together, these results indicate that controlled inflammation facilitates a permissive environment for neuroplasticity via microglial-mediated PNN degradation, a mechanism that likely explains the attenuation of the functional recovery plateau observed in our prior research.

P1-C-86 *Acute intermittent hypoxia improves blood-brain and blood-spinal cord barrier integrity in the experimental autoimmune encephalomyelitis model of Multiple Sclerosis*

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We have shown 7d of daily acute intermittent hypoxia (AIH) therapy begun at near peak disease (clinical score (CS) 2.5) reduces inflammation and promotes repair and remyelination in both sexes in the experimental autoimmune encephalomyelitis (EAE) mouse model of multiple sclerosis (MS). However, the mechanisms driving AIH-induced repair remain unknown. As both EAE and MS have disrupted blood-brain (BBB) and blood-spinal cord (BSCB) barriers, we investigated if AIH enhances barrier integrity as a potential mechanism. MOG35-55 EAE was induced in female and male C57BL/6 mice. At CS 2.5, mice received either 7d daily AIH (10 cycles of 5 min 11% O2 alternating with 5 min 21% O2) or normoxia (control – 2 hrs 21% O2) treatment, being sacrificed 7d post-last treatment. Impact of AIH on BBB and BSCB integrity was assessed for fibrinogen extravasation, fluorescent tracer-based barrier permeability and CD3+ve T-cell presence. AIH-treated mice had significantly less fibrinogen leakage in both cortex and spinal cord tissues, lower permeability indices, and reduced numbers of T-cells indicating improved BBB and BSCB integrity. Further, evaluation of tight junction proteins, ZO-1 and claudin-5, in lumbar spinal cord indicated significant AIH-associated remodeling of ZO-1 and claudin-5. The results support that AIH improves both BBB and BSCB

integrity in EAE, with comparable effects observed in female and male mice. This provides a mechanistic link between AIH treatment and the observed enhanced neurorepair, that may be applicable to other pathologies. MS Canada and UofS CoMRAD funded.

P1-C-87 *Acute intermittent hypoxia mobilizes trkA NGF receptors to the plasma membrane of sensory neurons*

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Acute intermittent hypoxia (AIH) consists of breathing brief, alternating cycles of air at normal (21%) and hypoxic (11%) oxygen levels. It is a novel, non-invasive therapy we've shown enhances peripheral nerve regeneration; however, underlying neuronal mechanisms remain unclear. Nerve Growth Factor (NGF) through its receptor trkA provides guidance cues for regenerating sensory axons. Previous work in our lab shows that increased neural activity (via drops in pH or direct electrical stimulation [ES]) mobilizes ~50% more trkA to the plasma membrane of adult rat sensory neurons in 30 minutes, enhancing NGF sensitivity. Because AIH similarly increases neural activity, we posit that AIH increases trkA mobilization to sensory neuron plasma membranes, thereby enhancing NGF responsiveness. In vitro delivery of a 5-cycle AIH or Normoxia control treatment (70 minutes) to adult Lewis rat primary sensory neuronal cultures without NGF in the media during treatment and fixation immediately post-treatment revealed significantly increased levels of trkA on the plasma membrane of sensory neurons, as detected using non-permeabilizing immunofluorescence; this is akin to previous responses to decreased pH and ES. How this impacts cellular responses to NGF, downstream signalling pathways, regenerative growth potential and whether increased mobilization is from internal stores is currently being investigated. Defining the cellular mechanisms by which AIH enhances peripheral nerve regeneration will assist in optimizing AIH protocols for clinical translation. CIHR PJT183666 & UofS CoMGRAD funded.

P1-C-88 *Adenosine restoration improves pericyte-regulated retinal blood flow in glaucoma*

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Vascular dysfunction is an early feature of glaucoma. Pericyte-regulated capillary hemodynamics decline before retinal ganglion cell (RGC) death, yet the mechanisms remain unclear. Here, we hypothesize that impaired adenosine signaling contributes to early blood flow abnormalities, as adenosine is a key regulator of vascular tone. Glaucoma was induced in Ng2-DsRed mice using an ocular hypertension (OHT) microbead model. Retinal adenosine levels were measured by liquid chromatography–mass spectrometry (LC-MS) and extracellular adenosine in the RGC layer using an AAV-delivered GPCR-activation–based adenosine sensor (GRABAdo). As adenosine kinase (ADK) regulates adenosine availability, we assessed its expression by immunohistochemistry and inhibited its activity pharmacologically or by siRNA. Capillary retinal blood flow was measured in vivo using two-photon laser-scanning microscopy (TPLSM). LC-MS revealed that OHT reduces retinal adenosine before RGC loss. Consistently, GRABAdo imaging showed decreased extracellular adenosine in the RGC layer. ADK expression was markedly increased in RGCs and Müller glia, suggesting enhanced adenosine degradation. Importantly, the inhibition of ADK could restore extracellular adenosine levels and, significantly, improve blood flow in pericyte-associated capillaries. These findings indicate that early ADK-driven adenosine reduction contributes to microvascular dysfunction in experimental glaucoma. Restoring adenosine bioavailability through ADK inhibition represents a promising therapeutic target to preserve microvascular function in glaucoma.

P1-C-89 *Age- and idiopathic Parkinson disease-associated mitochondrial impairment in induced neurons*

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Studies in human post-mortem brain suggest altered mitochondrial homeostasis in healthy aging and Parkinson's disease (PD). To study mitochondria-related phenotypes linked to aging and PD, we used direct neuronal reprogramming of human fibroblasts to induced neurons (iNs), which keep the aging signature of the donors. We have reported age-related autophagy defects leading to pathological alpha-synuclein accumulation in PD patients' iNs, making iNs a system of choice to investigate age- and PD-related phenotypes. Here, in healthy donors' iNs, we show that older males display a lower basal mitochondrial membrane potential (MMP), and that older iNs display a sex-independent increase in mitochondrial fragmentation (MF). Following mitophagy induction with CCCP, iNs also show a sex-independent age-associated accumulation of mitochondria in autophagic structures (LC3+, LAMP1+), suggesting mitophagy impairment. Decreased mitophagy in older iNs was confirmed by mitochondrial mass quantification. Preliminary data show that idiopathic PD-iNs have lower basal MMP and higher basal MF compared to matched controls. Following CCCP exposure, PD-iNs show an accumulation of mitochondria and of mitochondria in early autophagic structures (LC3+), pointing towards mitophagy defects. These results suggest alterations in mitochondrial homeostasis with aging, which are exacerbated in PD. Ongoing experiments aim at investigating the underlying mechanisms of these mitophagy defects. This study will shed light on the age-related changes in mitophagy, and how this relates to the pathophysiology of PD.

P1-C-91 *Alterations in motor cortical circuit recruitment and dorsal striatal glutamate signaling during a motor task in a mouse model of Huntington's disease*

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Voluntary movement requires coordinated corticostriatal signaling and is impaired in Huntington's disease (HD). We studied 6-8-month-old zQ175 mice and WT littermates (6 WT, 5 zQ175) in a lever-pull task in automated home-cage and head-fixed settings. Thy1-jRGECO1a mice (red Ca^{2+} indicator; excitatory neuron–selective) were imaged transcranially through intact-skull cranial windows, and received dorsal striatum (DS) AAV1-iGluSnFR (green glutamate sensor) plus an angled optical fiber for photometry, enabling simultaneous cortical Ca^{2+} imaging and DS iGluSnFR transients. In home-cage, zQ175 had lower success and more overshoot failures (impaired movement refinement/feedback control). Under head fixation, engagement and success were similar. Cortical activity showed robust primary motor activation after pull onset in both genotypes, but reduced secondary motor (M2) recruitment in zQ175. DS iGluSnFR signals were pull-locked with similar peak amplitude/latency, but slower decay in zQ175, consistent with sustained excitatory drive and/or slowed clearance. Whole-cell current-clamp in M2 pyramidal neurons found no differences in resting potential, rheobase, or frequency-current (F-I) curves, arguing against altered intrinsic excitability. Overall, results support circuit-level corticostriatal incoordination in zQ175. Ongoing work will test whether disrupted M2 connectivity drives these dynamics and whether targeted M2 activation rescues circuit signatures and performance.

P1-C-92 *Altered BDNF and TrkB levels in cerebellar Purkinje cells may contribute to ataxia in a Christianson syndrome mouse model*

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Ataxia is a feature of Christianson syndrome (CS), a rare X-linked neurological disorder caused by loss-of-function of the Na+/H+ exchanger NHE6. This exchanger is involved in endosomal pH control, which is essential for the trafficking of cargo, such as tropomyosin receptor kinase B (TrkB). In the hippocampus of CS mice, the Brain-Derived Neurotrophic Factor (BDNF)-TrkB pathway is dysregulated due to TrkB mistrafficking.

Recently, altered BDNF-TrkB pathway has been implicated in abnormal cerebellar connectivity and ataxia. Hallmarks of ataxia are Purkinje cell (PC) firing deficits and eventual death. In CS, cerebellar development appears normal at postnatal day (P)25. PC death starts at P35 only in the anterior cerebellum, followed by ataxia at P60. Surprisingly, higher anterior and posterior PC firing rates are seen at P25. Interestingly, adding synaptic blockers abolishes these deficits, suggesting dysregulated synaptic inputs in CS cerebellum. We hypothesized that an altered BDNF-TrkB pathway causes abnormal cerebellar connectivity, leading to impaired PC activity in CS. Using immunostaining, we found higher BDNF levels in anterior and posterior PCs and higher TrkB in posterior PCs at P25. Also, increased excitatory climbing fiber inputs using vGluT2 were found on anterior and posterior PC somata at P25, suggesting their improper elimination. Together, these findings suggest that dysregulation of the BDNF-TrkB pathway could contribute to aberrant cerebellar connectivity and PC dysfunction in CS ataxia.

P1-C-93 *Applying machine learning with neuroimaging biomarkers to detect Parkinson's disease and cognitive impairment*

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Up to 62% of individuals with Parkinson's disease (PD) experience cognitive impairment. An early diagnosis could reduce caregiver burden and increase treatment rates. However, there is currently no standard biomarker for PD that can be used in clinical practice. Numerous studies have found that imaging is instrumental in the tracking of PD and that machine learning can assist with detection, although many machine learning models cannot be validated past the research stage. It is possible that MRI can be used with machine learning to distinguish stages of PD and to identify cognitive impairment. This research aims to 1) develop a validated MRI-based machine learning model to identify PD and 2) evaluate whether MRI-based models can detect cognitive decline. The sample includes around 1000 subjects acquired from the Parkinson's Progression Markers Initiative. To assess the MRI, I will use a convolutional neural network structure, which can analyze images without losing anatomical connections. Models will be constructed using the Python programming language. Data will be split into training, validation, and test sets. The neural network will first be created to distinguish patients with PD from healthy patients and from patients with prodromal PD. Through machine learning, I will create a model that can be adapted into clinical settings for diagnosis and assessment of PD. If a model can be implemented into clinical practice, more patients with PD may receive treatment to delay progression and reduce the effect of symptoms on the patient's wellbeing.

P1-C-94 *ARB2A-loss of function as a putative cause of Amyotrophic lateral sclerosis (ALS) in mice*

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ARB2A is crucial for transcriptional regulation and alternative splicing, and a decrease in its activity is linked to CHARGE syndrome (CS), a disorder causing congenital anomalies. A Knockout-mouse model created to understand ARB2A biological function had no CHARGE-like defects suggesting a molecular compensatory mechanism when ARB2A functional levels fall below a key threshold. Interestingly, ARB2A interacts with SOD1, FUS, TDP43 whose loss of function is associated with amyotrophic lateral sclerosis (ALS), a neurodegenerative condition which attacks motor neurons, causing loss of muscular control. A 59-year-old man with progressive speech and gait impairment consistent with ALS was found to be heterozygous for a frameshift variant in ARB2A, a gene highly expressed in the cerebellum. DVC cage data supports the hypothesis that ARB2A-KO mice's compensatory mechanism depletes with age, leading to ALS-like neuromuscular degeneration, as these mice aged 8-12 months are significantly less active. Therefore, this study aims to examine locomotor impairments of ARB2A-KO mice (ALS model) using various behavioral tests (Open Field, Rotarod and Wire-hang cage) and to define the foliation development defects in the cerebellar vermis using specific markers.

Our preliminary results showed that 8-month KO mice show hypoactivity, reduced motor coordination and balance, with malformations in lobules IV-V, VI, IX, a considerable decrease in the PC number of the lobule VI, and a remarkable disorganization of PC in the lobule X. In conclusion, ARB2A is linked to various disorders, depending on protein levels/function. Low protein levels are associated with late-onset ALS, while moderately low levels are linked to CS.

P1-C-95 Assessing the neuroprotective effects of dutasteride in an α-synucleinopathy mouse model of Parkinson's disease

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Parkinson's disease (PD) is a neurodegenerative disorder marked by progressive loss of dopaminergic neurons in the substantia nigra and shows higher prevalence in men, suggesting sex hormones may influence its pathophysiology. Estrogens and progesterone have shown neuroprotective effects in PD models, including mitigation of α-synuclein–related toxicity. We hypothesized that dutasteride, a 5α-reductase inhibitor that blocks the conversion of testosterone into dihydrotestosterone (DHT) and may shift steroidogenesis toward estrogens, could confer neuroprotection by modulating sex hormone balance and attenuating α-synuclein–related pathology. Using PrP-A53T transgenic mice, we implanted subcutaneous placebo or dutasteride pellets (7.5 mg each) designed for 60-day sustained release. Pellets were replaced once, providing a total of 120 days of continuous exposure. We assessed anxiety-like behaviors, quantified plasma DHT levels using ELISA, and analyzed striatal α-synuclein accumulation and tyrosine hydroxylase (TH) expression by immunofluorescence. Dutasteride reduced circulating DHT to levels below the assay's detection limit, suggesting effective 5α-reductase inhibition, but did not alter anxiety, α-synuclein accumulation, or TH expression. These preliminary results indicate that while dutasteride modulates androgen/estrogen balance, this shift alone may be insufficient to confer neuroprotection in this synucleinopathy model, and the study could be repeated using other α-synucleinopathy models or alternative experimental conditions to further explore its potential effects.

P1-C-96 *Astrocytic adaptations foster stress resilience by regulating BBB function*

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Major depressive disorder (MDD) is a severe psychiatric illness; yet only 30% of individuals diagnosed with MDD fully recover with current treatments, suggesting contributions from non-neuronal mechanisms. Blood-brain barrier (BBB) integrity loss is observed in MDD and in animals exposed to chronic social defeat stress (CSDS), a mouse model of depression. Astrocytes, major component of the BBB, undergo morphological changes in MDD, such as reduced end-feet coverage of blood vessels. Here, we explore astrocytic adaptations in stress-induced BBB dysfunction and depression. Male mice were subjected to 10-day CSDS, resulting in two subpopulations: stress-susceptible (SS) animals characterized by depression-like behaviors and resilient (RES), behaving like unstressed controls. CSDS induces BBB hyperpermeability in a region and sex-specific manner, leading to depressive-like behaviors in SS but not RES animals. Reduced expression of gap junction and glial-derived neurotrophic factor (GDNF), linking astrocytic and vascular activity, was found in the nucleus accumbens of SS male mice. In contrast, RES mice showed increased neurovascular growth factors, indicating astrocyte-mediated resilience. For mechanistic insight, primary astrocytes were treated with serum from control, SS, or RES mice before and after stress. Transcriptional profiling showed that astrocytic reactivity response to serum before stress can predict SS or RES phenotype, while after stress RES serum treatment led to an increase in GDNF. Astrocytic functional analysis showed a distinct calcium signaling pattern between RES and SS during social stress evidencing phenotype-specific astrocyte response to stress. Overall, our results indicate that astrocytes modulate neurovascular function and contribute to MDD-associated alterations, representing a promising target for novel therapies for mood disorders.

P1-C-97 *Asymmetric parietal cortical atrophy in a patient with RAB39B-associated Parkinsonism: A novel truncating variant*

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IntroductionLoss-of-function variants in RAB39B (Ras Analogue in Brain 39B) cause X-linkedintellectual disability and early-onset Parkinsonism; however, whether RAB39B mutationcan lead to late Parkinsonism remains unclear. Recently, we identified a 57-year-oldmale with lifelong mild cognitive impairment who developed atypical RAB39B-likeParkinsonism late in life. Here, we ask if a novel variant of RAB39B underly these lateParkinsonism symptoms. Methods We conducted neurological exams, performed MRI/CT imaging over five years, andsequenced the patient's genome. ResultsThis patient had right-predominant tremor, mild bradykinesia craniofacial dysmorphisms,and initially responded to levodopa. Brain MRI demonstrated bilateral paramagneticdeposits in the substantia nigra and globus pallidus, with diffuse asymmetric corticalatrophy affecting the left parietal lobe. CT imaging excluded basal ganglia calcifications. Over a five-year follow-up, motor fluctuations, autonomic dysfunction, mooddisturbances, dysphagia, and sleep disorders developed, with stable cognitive function;asymmetric parietal atrophy without progression persisted. Genetic analysis identified anovel truncating RAB39B variant. Conclusion Our study identifies a novel RAB39B variant linked to late onset Parkinsonism withstable asymmetric parietal atrophy and paramagnetic deposits. Static cortical changessuggest a neurodevelopmental substrate rather than progressive neurodegeneration.

P1-C-98 *Autologous T cells form significant ICAM-1-mediated contacts with primary CNS myeloid cells in neuroinflammation*

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Multiple sclerosis (MS) is an inflammatory demyelinating disease of the CNS. Chronic active lesions feature a rim of activated microglia/myeloid cells and T cells, are associated with disability progression. Whether T cells-CNS myeloid cell interactions contribute to neuroinflammatory in MS remains unclear. Intercellular adhesion molecule-1 (ICAM-1) regulates T cell contact and tissue retention. As ICAM-1+ T cells and CNS myeloid cells expressing its ligand LFA-1 are enriched in MS lesions, we hypothesize that ICAM-1 mediates harmful T cells-CNS myeloid cell interactions. Live imaging of co-cultures of primary human CNS myeloid cells (from 2 progressive MS and 3 non-inflammatory neurological disease donors) with autologous or allogeneic T cells was performed to characterize T cells-CNS myeloid cell inetractions and assess the impact of ICAM-1 neutralization on T cells. T cells motility and contact behavior were analyzed using Imaris and flow cytometry. CD4+ and CD8+ T cells establish prolonged contacts. Both autologous and allogeneic T cells displayed reduced mean speed and increased meandering index. Autologous CD4+ formed longer contacts (>45min) and more frequently crawled on CNS myeloid cells, whereas CD8+ contacted more cells, displayed short (<15min) and long contacts with predominant scanning behavior. ICAM-1 blockade increased T cells motility and reduced CNS myeloid cell activation. ICAM-1-dependant interactions between autologous T cells and CNS myeloid cells contribute to chronic neuroinflammation in MS and may represent a therapeutic target. MS Canada/CIHR.

P1-C-99 *Axonal propagation failure and axon initial segment disorganization in the purkinje cells of a mouse model of arsacs*

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Autosomal recessive spastic ataxia of the Charlevoix-Saguenay region (ARSACS) is an inherited ataxia prevalent in Quebec. Studies of a mouse model of ARSACS in which the gene Sacs has been knocked out (ARSACS mice) show that cerebellar Purkinje cells exhibit changes, including in axonal morphology. We explored axonal function in ARSACS using ARSACS and wild-type littermates (WT) mice. Using 2-photon targeted simultaneous dual electrophysiological recordings from the soma and axon of Purkinje cells expressing GFP, we measured the fidelity of propagation of action potentials. Action potential propagation in ARSACS axons was profoundly impaired at disease onset (~p40), when motor deficits are mild. While failures were low in WT axons (<1% of action potentials failed), in ARSACS mice axonal failures were high: an average of 15% of action potentials fail (**p<0.01). In many cases, action potential propagation failure increased steeply with distances from the soma – often to >90% – suggesting that axonal propagation is passive rather than active in ARSACS axons. We investigated factors that might contribute to axonal impairment and found evidence of disorganization of scaffolding molecules within the axon initial segment (AIS). Given the severity with which Purkinje cell action potential propagation is affected early in disease progression, our results suggest that axonal dysfunction is an important contributor to ARSACS pathology, and thus could be a vital target for treating ARSACS, and possibly other neurodegenerative diseases as well.

P1-C-100 *Baseline microstructural integrity of nigrostriatal and mesolimbic pathways predicts freezing of gait conversion in Parkinson's disease*

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Background: Freezing of gait (FOG) is a disabling Parkinson's disease (PD) symptom associated with falls and limited treatments, highlighting the need for early prediction. We examined baseline microstructural integrity of parcellated nigrostriatal and mesolimbic–cortex circuits in FOG-free PD patients to identify changes preceding FOG onset. Methods: Ninety-four treatment-naïve PD patients from the Parkinson's Progression Markers Initiative (PPMI) were followed for 8.4 years and classified as FOG converters (PD-FOG; n = 53) or non-converters (PD-nFOG; n = 41) using longitudinal UPDRS II/III scores. Nigrostriatal and mesolimbic–cortex pathways, including the striatum and ventral tegmental area/substantia nigra pars compacta (VTA/SNc), were parcellated using automated tractography. Diffusion MRI metrics, mean diffusivity (MD) and fractional anisotropy (FA), were extracted from white-matter bundles and gray–white matter interfaces. Elastic Net modeling was applied. Results: PD-FOG patients were more often male (71.7%) and older at PD diagnosis. The final model showed good discrimination (AUC = 0.827) and identified male sex, higher motor severity (UPDRS III) and anxiety scores, reduced FA in executive, limbic, and rostral motor subregions, and increased MD in the limbic subregion as FOG conversion predictors. Parcellated imaging outperformed unparcellated models (AUC = 0.781 vs 0.672). Conclusion: Parcellated dMRI metrics detect structural changes years before FOG onset, and combined clinical–imaging models improve early FOG prediction.

P1-C-101 Behavioral and multi-omic analysis of neurodevelopmental disorder-linked neurexin 2α knockout mice

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Neurexins (Nrxn) are a family of presynaptic cell adhesion molecules that have been extensively studied for their role in synapse organization and have been linked to neurodevelopmental disorders (NDD). Here,

we conducted large genomic studies of schizophrenia patients and discovered protein-truncating variants in NRXN2. We further characterized Nrxn2α knockout (KO) mouse behaviors in various aspects, such as socialbility, learning and memory, motor, and sensory functions. Both male and female KO mice exhibit enhanced anxiety, and motor deficits. Somatosensory assessments revealed hypersensitivity to noxious cold in both male and female KO mice, whereas only males showed capsaicin induced thermal hypersensitivity. In particular, male KO displayed restricted interest in novel objects. Interestingly, we also observed atypical visual processing in both male and female KO. Multi-omics approaches were employed to further assess the effects of loss of Nrxn2a at multiple levels. Transcriptomic analysis of male mice in different brain regions, including hippocampus, striatum, and medial prefrontal cortex, suggested subtle but altered pathways mainly involved in trans-synaptic signaling. Proteomic analysis further suggested Nrxn2a interactome and confirmed transcriptomic data. In conclusion, our study presented that Nrxn2α KO mice exhibit sex-dependent NDD-like behaviors and altered trans-synaptic signaling, potentially through interactions with NMDA receptor–associated pathways.

P1-C-102 *Beta-parvin and it's role in vascular remodeling and blood flow regulation following ischemic stroke*

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Ischemic stroke is a vascular event resulting from an obstruction in a cerebral blood vessel. This in turn leads to a gradient of hypoxia not only impacting the initial infarct site, but also the surrounding tissue. In response to ischemia, the vascular endothelium upregulates expression of signalling pathways that regulate cell adhesion, angiogenesis, inflammation and phagocytic activity. This leads to the recruitment of immune cells, poor microcirculation, degradation of the blood-brain barrier (BBB) and angiogenesis. Recent transcriptomic work from our lab indicated that beta-parvin is upregulated in disease conditions associated with poor microcirculation and neuroinflammation. Beta Parvin is expressed primarily in endothelial cells and is known to regulate cell migration and adhesion. In order to understand what role Beta Parvin might play in disease conditions such as stroke, we first examined the expression of this protein at different time points after stroke. Immunohistochemistry assays showed that beta-parvin expression was upregulated in the peri-infarct region after 24 hours, corresponding to the acute phase of tissue damage and inflammation. However, this expression subsided over the subsequent days, in which the immune response and repair mechanisms become activated. Ongoing experiments are focused on understanding the role that beta-parvin plays in regulating vessel width, blood flow, and BBB permeability after ischemic stroke.

P1-C-103 *Brain-wide activity-dependent hemodynamic changes accompanying persistent cortical tactile sensory adaptation and its impairment in a mouse model of Rett syndrome*

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Rett syndrome (RTT) is a neurodevelopmental disorder caused by MECP2 mutation. As a transcription factor MeCP2 plays a vital role in maintaining neural circuits and activity-dependent plasticity. In RTT model mice we have shown dysfunction of cortical sensory adaptation (CSA), a form of activity-dependent plasticity. After 45 min of repetitive hindlimb stimulation responses to test pulses measured in contralateral somatosensory cortex (ssCTX) with field potentials and intrinsic optical imaging (IOS) decreased 40% compared to pre-adaptation in control (WT) and RTT mice. Testing up to an hour after cessation of continuous stimulation the early field and IOS responses remain persistently adapted in WT but quickly revert to pre-adaptation levels in RTT mice. It was unknown whether persistent CSA extends to distantly connected brain regions or if blood flow dynamics change with persistent CSA. We now find that the impaired persistence of CSA extends to the ipsilateral ssCTX in RTT mice. Unexpectedly, we also find that persistent CSA in WT mice is accompanied by a large global, stimulus-induced overshoot of the IOS signal that starts about 1 sec after test pulses, which was absent pre-adaptation and is largest in retrosplenial and frontal cortex. This IOS overshoot is consistent with a global increased stimulus-induced perfusion of tissue that develops in response to

repetitive neural activity. In RTT mice however, this global, overshooting IOS response does not develop in response to repetitive stimulation suggesting dysfunction in activity-dependent neuro-vascular coupling in RTT.

P1-C-104 *Brain-wide C-Fos signatures underlying individual differences in chronic pain*

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Chronic pain persists in some individuals long after tissue healing, while others recover fully from similar injuries, reflecting substantial inter-individual variability that remains poorly understood. To identify the neural substrates underlying this variability, we combined behavioural phenotyping with whole-brain activity mapping in a mouse model of neuropathic pain. Outbred CD1 mice (n = 52 female, 10 male) underwent chronic constriction injury (CCI) of the sciatic nerve and were assessed for sensory sensitivity using cold plate assays. This revealed pronounced heterogeneity in chronic pain phenotypes. Females exhibited significantly longer and more variable injured hind paw withdrawals compared to males ($p < 0.01$). To link behaviour to neural activity, c-Fos expression was quantified across 1,277 brain regions using ABBA, QuPath, and BraiAn. Linear regression analyses revealed strong correlations between withdrawal behaviour and activity in canonical pain-related regions, including the periaqueductal gray ($R^2 = 0.42$), basomedial amygdala ($R^2 = 0.49$), orbital cortex ($R^2 = 0.55$), and anterior cingulate cortex ($R^2 = 0.35$). Significant correlations were also observed in lesser-studied regions, including the nucleus of Darkschewitsch and supramammillary nucleus, implicating novel contributors to pain vulnerability. Together, these findings demonstrate that individual differences in chronic pain expression are associated with distributed supraspinal circuits, highlighting both established and unexpected neural substrates of vulnerability and resilience.

P1-C-105 *BTK inhibition prevents microglia-mediated demyelination induced by multiple sclerosis patient antibodies*

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Microglia/macrophages are the predominant immune cells in multiple sclerosis (MS) demyelinating lesions, but their role in demyelination is unknown. To visualize microglia during immune-mediated demyelination, we developed an in vivo model of cortical focal demyelination using pathogenic MS patient-derived recombinant antibodies. Longitudinal in vivo two-photon microscopy revealed substantial myelin and oligodendrocyte loss that depended on epitope specificity, complement, and an intact Fc region. Microglia rapidly enveloped intact myelin sheaths, leading to sheath loss, likely via microglial phagocytosis, while single-cell RNA sequencing revealed a demyelination-associated microglial signature. Parallel changes were observed in MS lesions, where microglia enveloped myelin sheaths and similar genes were upregulated. Prophylactic administration of a brain-penetrant inhibitor of Bruton's tyrosine kinase (BTK) limited microglial transcriptional changes and prevented myelin loss following microglial envelopment. These findings directly implicate microglia in immune-mediated demyelination and support BTK inhibition as a therapeutic strategy to modulate microglial response to prevent demyelination.

P1-C-106 *Calcium permeability of NMDARS in GRIN1-related neurodevelopmental disorders*

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Within the central nervous system, the slow component of excitatory neurotransmission is mediated by postsynaptic NMDA receptors (NMDARs). Inward flux of Na+ and Ca2+ and outward flux of K+ are central to NMDARs via the coincidence detection of simultaneous presynaptic glutamate release and AMPAR-mediated postsynaptic depolarization. NMDAR dysfunction has been implicated in intellectual disabilities that alter this coincident glutamatergic signaling which in turn alters synaptic plasticity during critical

neurodevelopmental time points. Synaptic plasticity depends on unique structural features of NMDARs such as voltage-dependent Mg2+ block and high Ca2+ permeability. The calcium permeation pathway in NMDARs includes three structural motifs: DRPEER (unique to the GluN1 subunit), SYTANLAAF, and the Q/R/N site. Putative Ca2+ binding sites at all three locations grant NMDARs their high degree of Ca2+ permeability. However, the exact mechanism of how Ca2+ interacts with these sites and permeates through the pore has not been fully elucidated. Using outside-out patch clamp electrophysiology, we examine how missense mutations in the GluN1 subunit perturb Ca2+ permeability, receptor gating behavior, and voltage-dependent Mg2+ block to better understand neurodevelopmental disorders.

P1-C-107 *Cannabidiol reduces the accumulation of amyloid beta plaques via cannabinoid receptor 2 and peroxisome proliferator activated receptor γ*

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Cannabidiol (CBD), a non-psychoactive compound in Cannabis, has immense therapeutic properties beneficial for central nervous system disorders, such as Alzheimer's Disease (AD). Studies suggest CBD reduces cognitive deficits associated with AD by interacting with various cannabinoid receptors, namely CB1R and CB2R, and non-cannabinoid receptors, including peroxisome proliferator activated receptor γ (PPARγ). In AD, the expression of these receptors is altered, but reported changes in the current literature remain inconsistent. To address this, we determined the localization of CB1R, CB2R, and PPARγ , in AD-compromised regions, specifically the cortex and hippocampus, and if those alterations can be mitigated by CBD treatment. In line with previous findings, CB1R immunoreactivity and expression increases in the cortex of 5xFAD mice, in comparison to wild-type (wt) age-matched control mice. In contrast, CB2R expression in 5xFAD mice did not significantly change from wt, but, following CBD treatment, expression significantly increased. Additionally, we observed PPARγ localizes inside amyloid-beta (Aβ) plaques in 5xFAD mice and PPARγ expression increases in the plaques following CBD treatment. Our research suggests the reduction of Aβ plaques and astrocytes are directly correlated with CBD-induced increased expression of CB2R and PPARγ , providing motivation to target these receptors for the treatment of AD.

P1-C-108 *CB1 receptor modulation alters dentate gyrus network activity in animal model of temporal lobe epilepsy*

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One-third of patients with temporal lobe epilepsy (TLE) are resistant to anti-seizure medications. Preclinical and clinical studies suggest that cannabinoid receptor type 1 (CB1R) is a potential therapeutic target, as CB1R activation reduces seizure activity, while CB1R overexpression in the dentate gyrus (DG) during TLE may reflect a protective response of the network. However, the effects of CB1R modulation on neuronal physiology remain unclear. Here, we used a combination of local field potential and whole-cell patch-clamp recordings to investigate the effects of CB1R allosteric modulators on the neuronal and epileptiform activity of DG cells in control (WT) and epileptic pilocarpine-treated mice (SE). Male and female C57BL/6J mice (3-6 months) were used. Two CB1R allosteric modulators were tested: GAT591 (positive, PAM; 1 μM) and GAT358 (negative, NAM; 1 μM). Epileptiform activity was induced by a pro-epileptic solution containing 4-aminopyridine (100 μM). Both PAM and NAM reduced epileptiform activity in the DG of SE mice, with no significant effects in WT mice. CB1R modulation did not alter firing of granule cells (GC) in WT animals, whereas in SE mice NAM increased GC excitability. In contrast, in WT mice both modulators suppressed mossy cell (MC) activity and accelerated depolarization block, while no effects on MCs were observed in epileptic mice. These findings identify the DG as a key site for CB1R-dependent control of network excitability in TLE. Future studies will focus on investigating the effect of hippocampal CB1R modulation on seizure development in vivo.

P1-C-109 *Cerebellar modulation of anxiety linked behaviours in neurotypical and autism spectrum mice*

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The cerebellum has recently been linked to anxiety which can be attenuated by docosahexaenoic acid (DHA). However, neither structural loci that modulate anxiety phenotypes nor the sites of action of DHA are known. Here we investigate the molecular, cellular, and anatomical contributors to anxiety using neurotypical (WT) and a mouse model with deficits in risk assessment (Fragile X; Fmr1 KO) to finely tease the cerebellum's behavioural contribution. DHA lowered baseline anxiety long after cessation of the diet. Quantification of excitatory and inhibitory proteins revealed Gat1 and Kv1.2 significantly elevated post DHA. We produced a molecular interneuron (MLI) conditional knock-out (PV-CRE x Fmr1 cKO) as well as a Purkinje neuron (PN) cKO (PCP2-CRE). PV-CRE cKO showed increased anxiety whereas the PCP2-CRE cKO showed deficits in anxiogenesis similar to the Fmr1 KO model, indicating that PN are key driver of the anxiogenic overtone. DHA was able to fully rescue the PV-CRE cKO mice behaviour whereas exacerbated the risk assessment deficit in the KO and PCP2-CRE cKO, which argues that MLI and PN have antagonistic roles in the onset of anxiety and that reduced GABA release from MLIs by DHA is sufficient to mitigate it. To address the anatomical contribution, we performed viral ablation of FMRP from PN in isolated regions of the cerebellum to produce a behaviour-correlated heat map. We then link the right hemisphere to novel exploration (crura III, VI, VII, and VIII), startle response (crux II), and freezing episodes (crux III) and the left hemisphere to novel exploration and stereotypies (crux II), sensorimotor habituation (crux VIII), and locomotion (crura VIII and IX), identifying critical cerebellar loci implicated in anxiety and DHA efficacy. Funded by CIHR.

P1-C-110 *Changes in Alzheimer's disease-associated biomarkers in post-COVID-19 patients with cognitive deficits*

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Background: COVID-19 induces long-term neurological symptoms. Because inflammation plays a significant role in COVID-19 and Alzheimer's disease (AD), we hypothesize that COVID-19 survivors could be at an increased risk of developing AD. Identifying potential molecular links between post-COVID-19 and AD can improve patient follow-up and help prevent late-onset disease. Here, we evaluated early AD-related molecular neuropathological alterations in COVID-19 survivors with and without cognitive deficits and correlated them with systemic inflammation. Method: In a longitudinal cohort of patients hospitalized with COVID-19 who returned for follow-up visits up to one-year post-COVID, we evaluated changes in plasma Abeta42, Abeta40, and total Tau using SIMOA. Plasma biomarkers were correlated with cognitive outcomes and the systemic inflammatory index (SII) during hospitalization. The Brazilian Ministry of Health and IDOR approved the study protocol. Result: Of the 43 included patients, 18 had severe disease, and 22 had an important neurological alteration during hospitalization. Up to one-year post-COVID, 18 developed cognitive alterations. However, disease severity and neurological alterations at hospitalization were not linked to post-COVID cognitive outcomes. We found that plasma Tau/Abeta42 levels were selectively elevated in patients with post-COVID cognitive deficits. Plasma Tau longitudinal changes were most influenced by SII at hospitalization and post-COVID cognitive alterations. Conclusion: Our findings link inflammation and AD-related molecular changes to post-COVID cognitive decline, urging careful follow-up of COVID-19 survivors with lingering symptoms for possible risk of future AD.

P1-C-111 *Characterizing chronic hippocampal injections of recombinant 2N4R human tau in a wild-type mouse model*

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Background: Tau pathology is an important neuropathological marker of Alzheimer's Disease (AD) and correlates closely with neurodegeneration and cognitive decline. To date, much of the work examining tau propagation has been performed using mutated tau and/or transgenic animal models. Since tau is not mutated in AD, the objective of this study is to characterize the propagation of non-mutated tau in a mouse model. Methods: Recombinant 2N4R tau preformed fibrils (2 µg) or a vehicle solution were injected in the hippocampus of 2-month-old C57BL/6J mice. Tau propagation was evaluated at different time points following single or chronic injections (24 h after one injection, or 24 h, 1, 5, 9 or 13 weeks after 5 consecutive days of injections). Hippocampal slices from 11-month-old female 3xTg mice were used as positive controls. Results: Tau hyperphosphorylation appears in the CA1 of 3xTg mice as expected. However, preliminary results suggest recombinant 2N4R human tau fibrils produces less AT8 signaling and localizes differently after chronic injection. Conclusions: Examining the propagation of recombinant 2N4R human tau in a C57BL/6 wild-type mouse model will provide novel information regarding how tau can influence neurodegeneration and cognitive decline in the early stages of AD.

P1-C-112 *Characterizing novel C. elegans models of Huntington's disease expressing the caspase-6 cleavage fragment of mutant huntingtin*

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Huntington's disease (HD) is a neurodegenerative disorder caused by a trinucleotide CAG repeat expansion in the HTT gene. HD is the most common of several polyglutamine toxicity disorders caused by CAG repeat expansion. The proteolytic cleavage of mutant huntingtin by caspase-6 is increasingly recognized as a key driver of pathogenesis. While multiple C. elegans models have been developed to study HD, fragment-specific platforms for the caspase-6 cleavage product remain lacking. To address this gap, we generated a new suite of C. elegans strains expressing the caspase-6 fragment of huntingtin with varying polyglutamine lengths (Q19, Q42, and Q79) either ubiquitously or specifically in GABA neurons. We hypothesize that expression of the caspase-6 fragment will provide a more physiologically relevant C. elegans model of HD. We are currently characterizing these novel worm models of HD to determine which phenotypic deficits are present in these models that can be used as outcome measures. We will quantify developmental rates, organismal lifespan, and motor performance. Furthermore, we will correlate these behavioral deficits with underlying cellular pathology by monitoring protein aggregation dynamics and assessing GABAergic neuron morphology and survival. This work will define quantifiable outcome measures that can be used in future studies to advance our understanding of disease pathogenesis and to identify genes and compounds that are neuroprotective. This work will establish a robust platform for future genetic and pharmacological screens to identify modifiers of HD.

P1-C-113 *Characterizing potassium chloride co-transporter 2 (KCC2) protein interactions in Huntington's Disease*

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KCC2 is the neuron specific member of the K+-Cl- cotransporter family of proteins that maintains a low intracellular Cl- concentration required for fast synaptic inhibition mediated by gamma-aminobutyric acid (GABA) in the central nervous system. Early in postnatal development, immature neurons express low levels of KCC2 resulting in high [Cl-]i and an excitatory GABA action. As development progresses, KCC2 expression is upregulated leading to reduced [Cl-]i and a shift to an inhibitory GABA action. Several neurological disorders

including Huntington's disease (HD) exhibit impaired synaptic inhibition and Cl- regulation due to decreased KCC2 expression and function. While KCC2 is heavily regulated post-translationally, it is also evident that protein-protein interactions (PPIs) of KCC2 can modulate its expression and function. Identification of the KCC2 interactome can thus provide substantial insight into its function and serve as a valuable approach to characterize the pathological mechanisms underlying disease. While HD typically manifests in adults, recent evidence suggests that human and rodent HD brains exhibit aberrant neurodevelopment at time points that coincide with the developmental GABA switch. Characterizing changes in the KCC2 interactome before and after the GABA switch is thus a critical step towards elucidating the pathological mechanisms observed during the symptomatic phase of HD.

P1-C-114 *CLCN3 regulates lysosomal homeostasis and a-synuclein accumulation in Parkinson's disease*

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Central to Parkinson's disease (PD) pathology is the accumulation of α-synuclein (α-syn) aggregates, which are linked to impaired lysosomal function. Recent genome-wide association studies (GWAS) have identified CLCN3 as a novel PD risk gene, with rare variant analyses uncovering loss-of-function variants enriched in patient populations. CLCN3 encodes ClC-3, a $2Cl^-/H^+$ exchanger localized to endolysosomal membranes, where it plays a crucial role in regulating lysosomal acidity. Pathogenic CLCN3 variants have been implicated in severe neurodevelopmental disorders and neurodegeneration, with CLCN3 knockout mice exhibiting complete hippocampal loss. Despite this evidence, ClC-3's role in PD remains unexplored. Our functional studies in iPSC-derived dopaminergic neurons reveal that ClC-3 dysfunction increases lysosomal pH, reduces glucocerebrosidase (GCase) activity, and promotes α-syn accumulation—hallmarks of PD pathology. Additionally, ClC-3 may regulate cathepsin B (CTSB), as knockout neurons exhibit increased CTSB protein levels but reduced activity. These neurons also have lower levels of Saposin C, a GCase co-activator cleaved from prosaposin by CTSB, potentially explaining the observed reduction in GCase activity. Patient-derived loss-of-function variants result in a truncation that disrupts the CBS domain of ClC-3, a region recently shown to regulate its activity via ATP binding. To further investigate this mechanism, RPE1 cell lines expressing these variants have been generated and are undergoing functional studies. Our findings suggest that CLCN3 plays a key role in lysosomal homeostasis and may protect against α-syn accumulation in PD. Understanding its function could provide valuable insights into the lysosomal mechanisms of PD and reveal new therapeutic strategies.

P1-C-115 *CNS myeloid cell activation in chronic MS and EAE is sustained by ICAM-1 mediated interactions with T cells*

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Chronic neuroinflammation causes neuroglial injury and disrupts repair in the central nervous system (CNS) of people with Multiple Sclerosis (pwMS). CNS myeloid cells and T cells accumulate at the edges of chronic active lesions; however, the contribution of their direct cell-cell interaction to CNS compartmentalized inflammation remains unclear. Intercellular adhesion molecule-1 (ICAM-1) is known to mediate immune cell contact and signaling, but its role in T cell-CNS myeloid cell interactions during MS and its animal model, experimental autoimmune encephalomyelitis (EAE), is unknown. Using single cell RNA sequencing, we found that human primary CNS myeloid cells shifted toward a pro-inflammatory profile after co-culture with autologous T cells. In silico analyses identified ICAM-1 as a candidate mediator of this interaction. Furthermore, circulating T cells from pwMS had elevated ICAM-1 expression compared to controls, with ICAM-1^+ T cells further enriched in CNS tissue. Ablation of ICAM-1 on T cells in mice led to improved clinical scores during chronic EAE, accompanied by fewer immune cells in the CNS, limited CNS myeloid cell

activation and reduced demyelination compared to littermate controls. ICAM-1 blockade on human T cells reduced CNS myeloid activation upon co-culture and promoted a transcriptomic shift towards a pro-repair phenotype. In conclusion, our results suggest that ICAM-1 on T cells promotes deleterious neuroinflammatory processes associated with chronic CNS neuroglial injury. This project is supported by the CIHR and National MS Society.

P1-C-116 *Combined effects of activity-based therapy and transcutaneous spinal cord stimulation on sub-acute spinal cord injury individuals for upper limb rehabilitation: A pilot study*

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Activity-based therapy (ABT) combined with transcutaneous spinal cord stimulation (tSCS) shows promise for upper-limb recovery after chronic spinal cord injury (SCI), but evidence in subacute populations remains limited. This study examined: (1) feasibility and daily impact of ABT+tSCS in a subacute inpatient setting, (2) sensorimotor outcomes, and (3) neuroplastic changes in motor and sensory pathways assessed using motor and somatosensory evoked potentials (MEPs, SSEPs).Twelve individuals with subacute cervical SCI (80% male; C4–C5; AIS A–D) were randomized to ABT+tSCS (n=5; 30–80 Hz, motor-facilitating intensity, C4–T1) or ABT+sham (n=5; sensory threshold); 2 withdrew for medical reasons. ABT included mental imagery, strengthening, and task-oriented exercises. Participants completed a mean of 18/20 sessions (45 min) over 8.1 weeks. Pain, fatigue, spasticity, upper extremity motor score (UEMS), and neurophysiological measures were assessed pre- (T1) and post-training (T2).Spasticity remained low (0.26±0.3), fatigue increased modestly post-session (0.6±1.7), pain (0.04±1.3) and discomfort (0.2±1.1) were minimal. UEMS gains were greater with tSCS than sham (9.2±6.5 vs. 3.8±4.7). In a subgroup, pooled analyses suggested increased MEP amplitude and reduced latency at T2 vs T1 in biceps brachii muscle. SSEP P50 showed trends toward increased peak-amplitude at C3/C4 from T1 to T2 following ulnar/median nerve stimulation. These preliminary findings support the feasibility and potential benefit of early ABT+tSCS for upper-limb rehabilitation for subacute SCI patients.

P1-C-117 *Comparative analysis of amyloid beta deposition in two different Alzheimer's disease mouse models using whole-brain two-photon microscopy*

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Alzheimer's disease (AD) is the most prevalent form of dementia, accounting for approximately two-thirds of dementia cases in individuals aged 65 years and older. At the molecular level, AD pathology is strongly associated with dysregulation of the amyloid precursor protein (APP), a transmembrane protein expressed in neurons. Mutations in the APP gene can cause excessive production of amyloid-beta (Aβ) peptides, leading to the formation of amyloid plaques, a defining microscopic hallmark of AD. To capture this amyloid pathology, 5xFAD and APPNL-G-F AD mouse models harbor APP mutations, recapitulating the progressive accumulation of Aβ plaques and associated neuroinflammatory responses. In this study, we quantified the spatial and temporal progression of Aβ plaque accumulation across brain subregions in these models. Ex-vivo two-photon tomography was used to acquire high-resolution coronal brain images. Aβ plaques were subsequently segmented from each image and the resulted image stacks were registered to the Allen Mouse Brain Atlas, enabling quantification of plaque distribution across anatomically defined structures. Our analyses revealed that Aβ plaque accumulation increased sharply with age in 5xFAD mice, whereas APPNL-G-F mice exhibited a more gradual progression. Additionally, brain regions associated with the mouse default mode network displayed higher plaque density compared to other regions, particularly at early ages. These findings highlight model-specific differences in regional and laminar vulnerability to Aβ pathology and underscore the importance of selecting appropriate models for studying AD progression.

P1-C-118 *Connectome-wide mega-analysis identifies a reproducible functional network signature of temporal lobe epilepsy*

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Resting-state functional MRI studies have reported aberrant synchronization of brain activity in patients with temporal lobe epilepsy (TLE); however, heterogeneity across findings and the lack of replication in independent cohorts have impeded consensus regarding the nature and clinical relevance of these alterations. To identify robust intrinsic functional biomarkers of TLE, we conducted the largest mega-analysis of resting-state functional connectivity to date. We analyzed multimodal MRI and deep phenotypes from 580 participants (282 TLE patients and 298 healthy controls) using both cross-sectional and longitudinal designs and tested associations with clinical features and postsurgical outcomes. Relative to healthy controls, patients exhibited reproducible patterns of hyperconnectivity (3.1% of edges) involving core regions of the default mode network and hypoconnectivity (7.4% of edges) involving temporolimbic and insular regions at baseline. Longitudinal analysis further revealed a decline in connectivity over time for hypoconnectivity edges ($t = -1.74$, $P = 0.021$). Greater hypoconnectivity was seen in patients with older age, longer disease duration, hippocampal sclerosis, and drug resistance ($r = 0.23$, $P < 0.001$). Finally, patients with persistent postsurgical seizures showed lower presurgical connectivity among unresected regions ($t = -1.81$, $P = 0.039$). Together, these findings refine the pathophysiological substrate of TLE and support the clinical potential of connectome-level biomarkers for precision assessment and surgical prognostication in focal epilepsy.

P1-C-119 *Cortical morphological correlates of apolipoprotein E4 in Parkinson's disease: Structural MRI evidence with exploratory CSF analyses from the PPMI cohort*

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Apolipoprotein E4 (APOE4) has been linked to cognitive deficits in Parkinson's disease (PD), though findings are mixed. Both APOE4 and cognitive changes have been associated with cortical morphological alterations. Yet, no study has examined the relationship between APOE4, cortical morphology, and cognition in a PD cohort. Using Parkinson's Progression Markers Initiative (PPMI) data, we investigated whether APOE4 affects cognition in PD through alterations in the cortical morphology of regions relevant to PD-related cognitive impairment in 51 PD APOE4 carriers (16 females;35 males) and 120 non-carriers (48 females;72 males). Baseline MRI scans were used to extract regional cortical morphological measures (surface area; folding and curvature indices; mean and Gaussian curvature). Group differences in the measures were assessed with ANCOVAs, and associations between the measures and 9 cognitive tests were examined. Exploratory analyses examined relationships between the measures and CSF biomarkers of PD-related cognitive impairment (amyloid, tau, α-synuclein) to provide mechanistic insight. APOE4 carriers showed increased surface area and folding index in the left angular gyrus after correction for multiple comparisons. These measures were associated with visuospatial function and memory, but not after controlling for age, sex, and disease duration, and showed no associations with CSF biomarkers. These findings suggest APOE4-related cortical morphological differences in early PD, highlighting the need for longitudinal studies to clarify their relevance in cognitive decline.

P1-C-120 *Cortical rescue of neuronal Neuroligin-2 mitigates sleep and behavioral impairments in adult knockout mice*

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Neurodevelopmental disorders (NDDs) often present with sleep disturbances which potentiate symptomatology. Neuroligin-2 (NLGN2) is a synaptic adhesion molecule regulating GABAergic transmission, yet the two NLGN2 isoforms differ in their preferential localization to GABA/glutamatergic synapses. Nlgn2 knockout (KO) mice exhibit anxiety-like and abnormal social behaviors, spend more time awake, and show massive changes in electrocorticographic (ECoG) activity. NLGN2 thus represents a strategic target to investigate the mechanisms underlying the bidirectional relationship between sleep and behavior. We here investigated whether adult manipulation of NLGN2 can affect sleep and behavior, and whether NLGN2 isoforms have similar roles. The neuronal expression of NLGN2 isoforms was manipulated in the cerebral cortex of adult Nlgn2 KO mice and wild-type (WT) littermates using adeno-associated viruses. Mice underwent ECoG electrode implantation, and signals were recorded for 24 h of baseline, 6 h of sleep deprivation, and 18 h of recovery. Anxiety-like and social behaviors were explored using the open field, elevated plus maze, and 3-chamber tests. Preliminary data suggests that adult neuronal rescue of NLGN2 in the cortex reverses the increased time spent awake, some alterations in ECoG activity, and the impaired preference for social novelty in KO mice, but not the anxiety-like behavior. Some indications for isoform-specific effects on sleep variables were observed. Overall, this work furthers our understanding of how NLGN2 shapes sleep and behavior, which is relevant to NDDs.

P1-C-121 *Could postpartum behavioral disturbances resulting from postnatal stress be related to inflammatory changes in the gut-brain axis?*

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Stress is a prominent risk factor in the development of postpartum mental health disturbances, altering responsiveness of key stress response systems. A variety of stressors have been shown to promote inflammatory activation at different body sites, including the digestive tract and the brain. The current study examined, in a mouse model, if a postnatal stressor impaired maternal care behavior, increased anxiety- and depressive-like behaviors, and changed key metrics of the gut-immune-brain axis in dams. Female C57BL/6N mice were separated from their pups for 3 hours daily from Postnatal days 2 to 14, capturing the postpartum period, whereas a subset of litters remained undisturbed. Maternal care behaviors (e.g., pup's licking and grooming) were assessed at multiple checkpoints during the stressor. Depressive- and anxiety-like behaviors were examined the day after weaning using the open field, elevated plus maze, and tail suspension tests, after which sections of the brain and the digestive tract were collected to determine inflammatory markers. Stressed dams exhibited deficits in maternal care but unexpectedly, their fear-related and passive coping behaviors were not different from their non-stressed counterparts, potentially owing to the large variability in their behaviors. Inflammatory markers in the hippocampus and colon are currently being analyzed to determine if distinct biological signatures could be associated with more pronounced stress-induced behavioral outcomes. Our findings will ultimately show if the development of postpartum behavioral impairments in response to postnatal stress could be associated with inflammatory alterations in the gut-brain axis.

P1-C-122 *CSF oligoclonal band frequency in a Cuban cohort of patients with multiple sclerosis. Comparison with Latin American countries and association with latitude*

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Background. The diagnostic sensitivity of CSF specific oligoclonal bands (OCBs) in multiple sclerosis (MS), using state of the art methods, has been clearly established to be over 95% in patients with a predominantly Caucasian background. This is not the case for other geographical regions. Objective. to assess the frequency of OCBs in a cohort of MS patients evaluated at the Institute of Neurology and Neurosurgery (Havana, Cuba), and to review the scientific literature in order to investigate the possible relationship between OCB status and latitude in the region of Latin America. Methods. Fifty-three patients (47 with definite MS and 6 with clinically isolated syndrome - CIS) were included. Isoelectric focusing with IgG immunoblotting for OCB analyses. PubMed, Scielo and Google Scholar were searched for papers containing information concerning CSF OCB status in patients with definite MS in Latin America and the Caribbean. Results. In Cuban patients with definite MS, an OCB prevalence of 87% was observed while the frequency in CIS patients was lower (67%). The prevailing pattern was that of OCBs restricted to the CSF (type 2), which was observed in 71% of definite MS patients. OCB prevalence was slightly lower, but very close to that reported in Caucasian populations. Conclusions. A prevalence of CSF restricted OCBs was slightly lower, but similar to that reported in Caucasian populations. The analysis of OCB frequency in Latin American countries revealed a possible relationship between OCB prevalence and latitude, but this must be further investigated.

P1-C-123 *Curcumin-mediated modulation of thermometabolic dysregulation in neonatal hypoxic–ischemic brain injury*

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Neonatal hypoxic-ischemic encephalopathy (HIE) remains a major cause of neonatal mortality and chronic morbidity. HIE is characterized by thermometabolic dysfunction, which exacerbates brain injury. Although therapeutic hypothermia is the current standard clinical care, its narrow therapeutic window and limited efficacy highlight an unmet clinical need neuroprotection. Curcumin is a natural polyphenol with metabolic regulatory, antipyretic, and neuroprotective properties. However, whether its neuroprotective effects involve thermoregulatory mechanisms in neonatal hypoxic-ischemic brain injury (HIBI) remains unclear. In this study, we investigated whether curcumin-mediated thermoregulation contributes to neuroprotection and explored the underlying mechanisms using the Rice-Vannucci model in postnatal day-7 mice. Curcumin administration prior to HIBI (100-300 μg/g, i.p.) significantly reduced brain tissue loss in a dose-dependent manner, with 200 μg/g identified as the optimal dosing regimen. Curcumin post-treatment (200 μg/g, i.p.) improved survival and body-weight recovery, accelerated the restoration of sensorimotor and cognitive functions, attenuated neuronal apoptosis as evidenced by reduced caspase-3/9 activation, and significantly lowered HI-induced pathological brain surface temperature following HI. Network-based target discovery and molecular docking analyses further suggested potential interactions between curcumin and mitochondrial enzymes glutaminase 2 and nicotinamide phosphoribosyltransferase, implicating modulation of mitochondrial energy metabolism and heat production as a plausible mechanism. In conclusion, these findings suggest that curcumin confers neuroprotection in neonatal HI by regulating mitochondrial thermogenesis, highlighting a potential metabolic strategy for the treatment of neonatal HIBI.

P1-C-124 *Defining the role of GBA in C. elegans models of Parkinson's disease*

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Mutations in GBA1 are the most common genetic mutations linked to Parkinson's disease (PD), the second most prevalent neurodegenerative disorder worldwide. While approximately 10% of PD patients carry the GBA1 mutations, these mutations only mildly increase the risk of developing PD. The GBA1 gene encodes glucocerebrosidase (GCase), a lysosomal enzyme responsible for glycolipid degradation and proper lysosomal function. While there are four homologous gba genes in C. elegans (gba-1, gba-2, gba-3, and gba-4), previous studies have identified gba-3 as the key gene encoding GCase activity, with loss of gba-3 leading to increased α-synuclein accumulation, a pathological hallmark of PD. Our lab has validated these findings using a fluorogenic enzyme assay, confirming that gba-3 is the functional worm homolog responsible for GCase activity. In this work, we characterized existing and newly generated worm models of PD with altered levels of gba-3 (the C. elegans homolog of human GBA1). In addition to gba-3 deletion mutants, we examined worms overexpressing gba-3 either ubiquitously or pan-neuronally. We performed phenotypic analyses assessing general health parameters, including lifespan, stress resistance, fertility, development and locomotion, as well as PD-related phenotypes such as dopaminergic neuron survival, dopamine-dependent behaviors and α-synuclein aggregation. Overall, this work advances our understanding of the role of GBA in PD and establishes novel worm models that can serve as a platform for future drug discovery efforts.

P1-C-125 *Depressive-like behaviour in a humanized knock-in mouse model of APOE, Amyloid, and Tau is sex- & APOE allele-specific*

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Mid-life depression and apolipoprotein E (APOE) ε4 allele (APOE4) carrier status are associated with an increased risk of developing sporadic Alzheimer's disease (AD). To improve early detection of AD, combining APOE genetic testing with depressive symptom assessment may enhance AD risk prediction. APOE4 is also associated with increased risk of mid-life depression and greater depressive symptoms in individuals with AD, particularly in women. However, the interaction between APOE genotype, sex, depression, and AD risk remains poorly understood. To assess APOE genotype-dependent depressive-like behaviour, two humanized mouse models were examined longitudinally. One cohort expressed human amyloid precursor protein (hAPP), tau (hMAPT), and either APOE3 (a neutral risk allele) or APOE4. A second cohort had the same genetic background but carried two amyloidogenic mutations in the APP gene (NL-F) to model amyloid pathology. Depressive-like behaviour was assessed using a touchscreen cognitive judgment bias (CJB) task, which measures depressive-like pessimistic bias by evaluating responses to ambiguous stimuli. At 8, 9, and 11 months old, female hAPP.hMAPT.hAPOE4 mice exhibited more pessimistic CJB than female hAPP.hMAPT.hAPOE3 mice, whereas males showed no genotype differences. In mice carrying the NL-F mutations, CJB did not differ across genotypes or sexes. Thus, the female hAPP.hMAPT.hAPOE4 model exhibits a sex-dependent depressive-like phenotype in the absence of amyloid pathology, supporting human studies examining how depression, sex, and APOE interact to influence AD risk.

P1-C-126 *Determining whether PD-associated lysosomal genes influence lysosomal homeostasis and stress phenotypes*

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Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by microgliosis, Lewy bodies and Lewy neurites, whose primary component is aggregated alpha-synuclein. The presence of alpha-synuclein and organelles such as mitochondria within Lewy bodies suggests impaired cellular degradation pathways in PD. As the lysosome plays a central role in the degradation of cellular components, lysosomal dysfunction has emerged as a key contributor to PD pathogenesis. GWAS, rare patient mutations, and

experimental models, have implicated multiple lysosomal genes in PD risk. However, with the exception of LRRK2 and GBA1, the mechanistic roles of these genes in PD remain poorly understood. This study aims to investigate how modulation of PD-associated lysosomal genes influences lysosomal stress and homeostatic function. Using CRISPR interference and activation, we will alter the expression of each gene in retinal pigment epithelial 1 cells and assess key lysosomal phenotypes, including lysosomal pH, proteolytic capacity, glucocerebrosidase activity, and bis(monoacylglycerol)phosphate (BMP) levels. In addition, LRRK2-mediated lysosomal stress responses and lysosomal rupture will be evaluated to determine how these genes impact lysosomal integrity. Finally, significant phenotypes will be validated in iPSC-derived microglia, a disease-relevant model for PD. Together, this work aims to advance our understanding of the genetic mechanisms underlying lysosomal dysfunction in PD and may identify novel therapeutic targets for disease intervention.

P1-C-127 *Development of a novel anti-amyloid therapeutic: An orally administrable anti-abeta-oligomer compound*

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Objective Soluble amyloid-beta (Aβ) oligomers are widely recognized as the primary neurotoxic drivers and early targets for Alzheimer's disease (AD) prevention. We have developed a protease-resistant D-amino acid Aβ-oligomer interacting peptide (D-AIP) designed to selectively neutralize toxic oligomers. D-AIP binds soluble Aβ42 oligomers (Barucker et al. 2015), neutralizes toxicity in Drosophila (Zhong et al. 2019), and crosses the blood-brain barrier (BBB) in wild-type mice via oral administration (Shobo et al. 2022). We now present new quantitative data on attenuation of total Aβ load, Aβ oligomer and downstream neuroinflammation reduction following oral D-AIP intervention in 3xTg-AD mice. Methods 3xTg-AD mice were orally treated with D-AIP from 4 to 6 months of age to target the early window of amyloid pathology. HPLC-MS was used to quantify D-AIP in brain homogenates and plasma. D-AIP and Aβ oligomers were localized in 3xTg brains by label-free MALDI-MSI. Immunofluorescence (IF) was utilized to visualize and quantify total Aβ, Aβ oligomers, and downstream neuroinflammation. Results Oral D-AIP successfully crossed the BBB and exhibited high biostability. IF revealed a significant attenuation of total Aβ load and Aβ oligomer staining in the brains of treated mice compared to controls. Importantly, this reduction in Aβ burden correlated with mitigated neuroinflammation. Conclusion These findings demonstrate that oral treatment of D-AIP enters the brain and reduces toxic Aβ oligomers in the 3xTg mouse model. Combined with attenuation of neuroinflammation, D-AIP presents a promising and safe therapeutic candidate for preventing early-stage AD progression.

P1-C-128 *Developmental alterations in a mouse model of spinocerebellar ataxia type 6*

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Spinocerebellar ataxia type 6 (SCA6) is a rare inherited neurodegenerative disease characterized by cerebellar atrophy and progressive motor coordination deficits. Surprisingly, although the mutated gene in SCA6, CACNA1A, is important in cerebellar development, motor deficits typically begin in middle age. In a mouse model, we previously showed that climbing fibre–Purkinje cell synaptic refinement is delayed between postnatal days 10-13 (P10-13), and that developing Purkinje cells exhibit altered firing without detectable motor deficits at these developmental stages. Brain-derived neurotrophic factor (BDNF) and its receptor, tropomyosin-related kinase B (TrkB), are crucial for proper cerebellar development and synaptic refinement, and are regulated by activity. We have also shown that BDNF–TrkB signalling and endolysosomal trafficking are impaired in the SCA6 mouse cerebellum at disease onset, and that modulating BDNF signalling alters Purkinje cell firing. We wondered if BDNF-TrkB signalling may be involved in changes in the developing SCA6 cerebellum. We used immunohistochemistry at P7, P11, and P21 in SCA6 and WT mice and observed a premature increase in BDNF at P11 in SCA6 mice, while differences in TrkB levels emerged at P21. We also observed increased early endosome area and colocalization with BDNF, suggesting protein trafficking

impairments exist during development. Together, these findings suggest that BDNF-TrkB alterations may contribute to developmental changes in SCA6 and highlight early molecular changes that may be linked to later disease progression.

P1-C-129 *Developmental disruption of ventral hippocampal inhibitory neurons drives hippocampal–prefrontal network dysfunction and cognitive deficits in mice*

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Schizophrenia spectrum disorders (SSD) is a broad spectrum characterized by the presence of positive symptoms, negative symptoms, and cognitive impairments. While symptoms typically emerge in early adulthood, it is hypothesised that circuit dysconnectivity begins earlier. Longitudinal studies implicate the ventral hippocampus (vHPC) as a primary locus of vulnerability, characterized by altered excitation–inhibition balance, and disrupted functional connectivity with the prefrontal cortex (PFC). These hippocampal abnormalities are closely linked to impairments in cognition, particularly working memory. Despite this, the specific inhibitory cell populations and developmental mechanisms through which hippocampal dysfunction reshapes long-range network communication remain poorly defined. Parvalbumin-positive (PV+) interneurons are fast-spiking inhibitory neurons that regulate local circuit excitability and coordinate network oscillations. Here, we test the hypothesis that selective disruption of PV+ interneurons in the vHPC during development leads to persistent alterations in vHPC–PFC network synchrony that underlie deficits in working memory. Using transgenic PV-Cre mice and adeno-associated virus–mediated delivery of diphtheria toxin A to selectively ablate PV+ neurons in the vHPC during periadolescent developmental, we combine behavioural assays with in vivo electrophysiological recordings of local field potentials in the vHPC and PFC. Our results show that selective PV+ ablation results in a significant reduction in both theta and gamma power across both the vHPC and PFC. During working memory tasks, PV+ ablation reduced vHPC-PFC coherence compared to controls. These results suggest that early-life inhibitory circuit dysfunction in the vHPC leads to persistent alterations in network communication that may underlie cognitive deficits in SSD.

P1-C-130 *Discovery of novel hyperphosphorylation sites of neurofilaments in amyotrophic lateral sclerosis mice correlating with the efficacy of novel Borsantrazole (TM)*

Nitesh Sanghai [1]

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Background:Since ALS was discovered in 1869, only two FDA-approved drugs, Edaravone and Riluzole, have shown modest clinical benefits in ALS disease progression. Recently, the FDA granted accelerated approval to tofersen based on its ability to reduce neurofilament light chain (NfL), a pharmacodynamic response biomarker. However, NfL remains a nonspecific biomarker for neurodegenerative disease diagnosis and complicates differentiation between ALS and other neurological conditions. Furthermore, none of the studies to date have explored hyperphosphorylation sites of amino acids in the cytoskeleton of neurofilaments. Objective: Our overall goal is to develop a novel ALS therapeutic, Borsantrazole (BSZ), that could modify motor disease phenotypes and demonstrate changes in the global proteome and phosphoproteome in amyotrophic lateral sclerosis mice. Methods:We conducted randomized, longitudinal efficacy studies with age- and sex-matched G37R SOD1 mice (line 42), to evaluate the (toxicity, efficacy, global proteomics, and phosphoproteomics of the BSZ) in vivo using humanized ALS G37R mice. Protocol Ref# 21-014 (AC11693). Results:Presymptomatic treatment of BSZ (10mg/kg body weight) in ALS mice demonstrated significant efficacy in modifying several clinical disease phenotypes. Moreover, using a global phosphoproteomic approach, we identified multiple novel hyperphosphorylated sites in both NfL and NfH, which were hyperphosphorylated in the vehicle treatment group compared with the BSZ treatment group. Conclusion: A longitudinal preclinical study of BSZ has demonstrated an excellent safety profile and compelling in vivo proof-of-concept efficacy. This research identified novel and well-established changes in the proteome and phosphoproteome, solidifying the therapeutic potential of BSZ as a promising new class of disease-modifying treatment for ALS.

P1-C-131 *Disrupted spatiotemporal noradrenaline dynamics in motor cortex underlie delayed motor learning in an ASD mouse model*

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Children with autism spectrum disorders (ASDs) frequently experience delays in motor development. In the 16p11.2 deletion mouse model, which mimics a common copy number variation associated with ASDs, we previously demonstrated delayed motor learning alongside abnormally elevated neuronal activity in the primary motor cortex (M1). Remarkably, activating locus coeruleus noradrenergic (LC-NA) neurons rescued both circuit deficits and delayed motor learning. In this study, we used in vivo two-photon microscopy to monitor LC-NA calcium axonal activity during motor learning and identified the temporal of LC-NA activity, in which non-behavioral related 'rapid' axonal activity (sub-second duration events) profoundly affect the behavior-induced 'persistent' axonal activity (second duration events). In addition, we performed two-photon imaging of NA sensor in M1, and we further uncovered that running-induced NA release is spatially heterogeneous and it becomes more consistent as learning progresses. However, these spatiotemporal specificities were disrupted in 16p11.2 deletion mice. Intriguingly, pharmacological and closed-loop optogenetic interventions designed to mimic the temporal and spatial NA disruptions observed in 16p11.2 deletion mice were sufficient to induce motor learning delays in WT mice. These findings shed light on previously unrecognized patterns of NA release dynamics within M1 at temporal and spatial scales, underscoring their pivotal role in motor skill learning and their disruption in ASD-related conditions.

P1-C-132 *Drug repurposing screening for spinocerebellar ataxia treatment in a C. elegans model*

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In humans, loss of coordinated movement characterizes a wide range of neurological disorders known as spinocerebellar ataxias, which result in neuronal dysfunction and death. Because spinocerebellar ataxias are rare and understudied genetic diseases, little progress has been made on developing drug therapies. Thankfully, modelling ataxia in a simpler nervous system allows for a better understanding of the causes of the disease and can facilitate the development of potential drug treatments. This research thus aims to 1) use the nematode Caenorhabditis elegans to better understand the neurological underpinnings of spinocerebellar ataxia, and 2) perform a drug screen to find hits that improve locomotion in our animal model. Using high-throughput behavioural phenotyping, we analyzed seven C. elegans mutants of ataxia-linked genes for behavioural, postural, and morphological differences compared to wild-type. One mutant, mca-3, showed large movement defects. Using a mca-3 mutant strain, we performed a drug repurposing screen of 5,632 compounds and found individual drugs and drug classes that shift mutant behaviour toward wild-type. Overall, this project takes a fast, cost-effective approach to spinocerebellar ataxia research by using the nematode C. elegans for high-throughput screening of approved drugs. This work further establishes C. elegans as a valuable model for studying spinocerebellar ataxias and provides a strong foundation for future research on drug treatments for the disease.

P1-C-133 *SeizureBiomeDB: A unified database of gut microbiome alterations in pediatric and adult epilepsy*

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The gut microbiome plays a critical role in immunity, metabolism, and brain function in health and diseases. Growing evidence links it to neurological health via the gut-brain axis. Seizure disorders are associated with distinct microbial changes that vary by epilepsy type and developmental stage, yet data are scattered across diverse studies. To address this, we developed SeizureBiomeDB, a curated, open-access database

that compiles research on gut microbiome alterations in epilepsy across animal models and clinical populations. A systemic literature search was performed from May 2025 through Augst 2025, screening the available literature and resulting in the inclusion of over 80 eligible studies that incorporated case-control designs, animal experiments, and therapeutic interventions. Extracted data included demographics, seizure type, study design, methodology, and key findings related to the microbiome. The database was built using React and PostgreSQL for secure and efficient data management. SeizureBiomeDB integrates findings encompassing 243 microbial taxa and 26 metabolites across pediatric, adult, and animal models. It is accessible via a global, searchable web platform. Interactive visualization tools, including heat maps and bar graphs, enhance data exploration. To aid interpretation, microbial taxonomy and function are linked to resources such as BacDive and MiMeDB. SeizureBiomeDB offers a structured hub to explore gut microbiome shifts across seizure subtypes. This platform underscores the significance of a centralized knowledge database in facilitating current advancements in gut microbiome research and epilepsy. Database URL: www.seizurebiomedb.ca.

P1-C-134 *Dysregulated dopaminergic signaling in the dorsal striatum: a novel approach to compulsivity in anorexia nervosa*

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Compulsivity is a central feature of several psychiatric disorders, including anorexia nervosa (AN), one of the deadliest and least understood psychiatric disorders (Van Eeden et al., 2021). AN is characterized by persistent compulsive behaviors, such as food restriction and excessive physical activity, which continue despite severe weight loss and serious health consequences. Compulsivity is considered as a disruption of the balance between goal-directed behaviors (GDB) and habitual behaviors (HB), leading to persistent inflexible habits despite negative outcomes. GDB and HB are mediated by distinct striatal subregions—respectively the dorsomedial striatum (DMS) and the dorsolateral striatum (DLS). GDB and HB are critically regulated by dopaminergic (DA) signaling. However, the contribution of DA signaling dynamic across the DMS and the DLS to the emergence of compulsive behaviors remains largely unexplored. Based on previous findings from our laboratory (Favier et al., 2020), we hypothesize that an imbalance in dopaminergic signaling between the DMS and DLS contributes to the development of compulsive behaviors. Our preliminary data suggest that chemogenetic inhibition of DA release in the DMS using inhibitory DREADDs increases compulsive grooming in mice during a modified splash test following C21 administration. If confirmed, these results would provide new insights into the neural mechanisms underlying compulsivity in AN and could open novel avenues for the development of targeted pharmacological treatments.

P1-C-135 *Dysregulation of RNA metabolism contributes to neurodegeneration and synapse pathology in multiple sclerosis*

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Neurodegeneration and synapse pathology in multiple sclerosis (MS) occur independently of inflammatory demyelination in the gray matter, but the mechanisms remain incompletely understood. Nuclear depletion of heterogeneous nuclear ribonucleoprotein A1 (A1) in neurons contributes to neurodegeneration in MS and dysregulates expression and splicing of synaptic RNAs. Thus, we hypothesize that loss of A1 function in neurons contributes to neurodegeneration independent of inflammatory demyelination through synaptic dysfunction. We modelled neuronal A1 depletion by CRISPR/Cas9-mediated A1 knockout (A1 KO) in cultured mouse cortical neurons to analyze the molecular mechanisms of synaptic dysfunction by confocal microscopy and RNA analysis. A 97% reduction of A1 protein in 14-day old neurons from high-density cultures reduced dendritic length and branching by 14% (p=0.036) and 23% (p=0.034), respectively. Neurons with A1 KO had 9% less presynapses labelled with synaptophysin (p=0.044) and a 12% increase in Homer1+ excitatory postsynapses (p=0.032). Numerous presynaptic RNAs were alternatively spliced (App, p=0.019)

and differentially expressed with A1 KO. Gene ontology enrichment analysis revealed significant alteration in neuronal action potential and calcium signalling pathways. These results indicate that A1 depletion contributes to dendritic atrophy and impacts synapse homeostasis by dysregulating RNA metabolism. These findings address a major gap in understanding the molecular mechanisms of neurodegeneration and synapse pathology that drive MS symptoms and disease progression.

P1-C-136 *Early fatigue symptom detection of MS in a string pulling EAE mouse model*

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An experimental model of human Multiple Sclerosis (MS) is obtained in the Experimental Autoimmune Encephalomyelitis (EAE) mouse. MS symptomology in the model takes a number of weeks to develop, does not fully develop in all mice, and is normally assessed with a Tail Hanging Task, which assesses hind limb function and scores it on a predetermined scale. We asked, if symptomology can be detected earlier, could treatment options be evaluated earlier? In the string-pulling task, a mouse stands on its hind legs and pulls down a string with hand over hand movements to obtain a food reward on the end of the string. Because the task assesses hindlimb, forelimb, and learned skilled motor function, we examined whether it lends itself to detecting earlier MS symptomology in the EAE mouse? Mice trained in string pulling received an EAE immunization or served as a control saline group. The EAE mice displayed an early onset of symptoms amongst the various means of detection such as pauses, hand ellipse consistency, posture consistency and body posture, which may serve as effective models for earlier MS detection.

P1-C-137 *Early hypothalamic dysfunction in Alzheimer's disease: Evidence for vascular and tanycyte involvement*

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Alzheimer's Disease (AD) is a multifactorial neurodegenerative disease. Systemic and non-cognitive symptoms are a common feature in early stages of AD, and some can be attributed to hypothalamic dysfunction. The hypothalamus is the brain center for metabolic regulation and serves as a critical interface between the brain and the periphery due to its unique anatomical position and specialized sensing cells. Despite its potential involvement in AD pathology, hypothalamic dysfunction and its underlying cellular mechanisms remain largely unexplored. In this study, using the 3xTg-AD mouse model, we combined physiological measurements and single-cell RNA sequencing to characterize alterations in hypothalamic functions and identify underlying cell type-specific mechanisms at an early pre-symptomatic stage of AD. At 3 months of age, 3xTg-AD mice exhibited sex-specific metabolic and neuroendocrine alterations. At the cellular level, we identified hypothalamic endothelial cells, tanycytes and microglia as the main affected cell types at this early stage. Subclustering analysis revealed common stress response-related alterations in capillary and arteriole endothelial cells, whereas tanycytes exhibited a strong subtype-specific inflammatory response. Our results reveal hypothalamic dysfunction in AD at both physiological and cellular levels prior to cognitive decline and classical AD pathological markers and highlight hypothalamic endothelial cells and tanycytes as understudied cell types with a potential involvement in the metabolic and systemic alterations associated with AD.

P1-C-138 *Early structural neuroimaging and multiple sclerosis polygenic risk*

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Background: Multiple sclerosis (MS) is a leading cause of neurological disability in young adults. Whether MS is driven exclusively by peripheral immune dysregulation or whether a primary central nervous system vulnerability contributes to disease initiation remains unresolved, a distinction critical for prevention

strategies. Prior work suggested that MS genetic risk may influence childhood brain myelination. We aimed to replicate these findings for the first time in an independent cohort. Methods: We analyzed 4,489 children (median age 9.9 years) from the Adolescent Brain Cognitive Development Study. MS polygenic risk scores (PRS) were tested for association with global fractional anisotropy (FA), tract-specific FA, total brain volume (TBV), and subcortical gray matter, adjusting for demographic, genetic, and environmental covariates. Results: Contrary to prior findings, MS PRS was not associated with global (P=0.93, 95% CI [-0.0316, 0.0287]) or tract-specific FA (P>0.24), TBV (P=0.32), subcortical gray matter (P=0.16), or thalamic volume (P=0.14). Gene-environment interactions including parental smoking were not significant. Conclusion: We did not replicate previously reported associations between MS genetic risk and childhood brain structure, suggesting no measurable influence of common MS genetic risk on brain structure or myelination during this developmental period. Analyses of individual variants and variant subsets with tissue-specific enrichment are ongoing.

P1-C-139 *Early synaptic degeneration and oxidative stress precede retinal ganglion cell loss in optineurin mutant mice*

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Rationale: Mutations in the Optineurin (OPTN) gene, including E50K and our newly identified N51T, are causes of severe, early-onset normal-tension glaucoma (NTG). Yet, the earliest cellular events triggered by these mutations remain poorly defined. We hypothesized that OPTN E50K and N51T mutations initiate early synaptic and functional impairments, accompanied by oxidative stress, prior to retinal ganglion cell loss. Methods: CRISPR/Cas9 OPTN E50K and N51T knock-in mice were analyzed longitudinally. Synaptic integrity (PSD95–VGLUT1), oxidative stress (DHE), glial activation (TMEM119, GFAP), RGC function (pSTR), and visual acuity (optomotor) were assessed. Results: Despite normal intraocular pressure IOP, OPTN E50K and N51T mice exhibited a pronounced reduction in PSD95–VGLUT1 colocalization at RGC–bipolar synapses. In parallel, DHE staining demonstrated markedly elevated ROS levels in RGCs compared with wild-type controls. Functional testing revealed significant decreases in pSTR amplitudes and impaired visual acuity at 12 months, which preceded RGC loss. Glial activation was demonstrated by increased GFAP immunoreactivity. Glial activation was evident, while RGC soma loss occurred only at later stages (16 months). Conclusions: OPTN E50K and N51T mutations trigger early synaptic disruption, oxidative stress, and functional impairment in RGCs before neuronal loss occurs. These results define a clear temporal cascade of early pathophysiological events in NTG, highlighting promising targets for neuroprotective intervention in NTG.

P1-C-140 *Ectosomes carrying tau are released by Parkinson's disease neurons*

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Parkinson's disease (PD) is characterized by the accumulation and intercellular spread of misfolded α-synuclein. We recently identified ectosomes, extracellular vesicles derived from the plasma membrane, as a major mechanism to transmit α-synuclein pathology in PD. Recently, misfolded tau has been implicated in PD pathology as it can directly interact with α-synuclein. Whether tau and α-synuclein interact within ectosomes to impact neuronal health in PD is unknown. Here, we utilized iPSC-derived dopaminergic neurons from PD patients carrying mutations in LRRK2. We discovered that ectosomes shed from PD neurons contain endogenous and phosphorylated tau, an indicator of tau pathology. When neurons are pretreated with aggregation prone tau fibrils, ectosomes loaded with these tau fibrils are released. We found that fibrillar tau increases the recruitment of α-synuclein into ectosomes. Finally, these ectosomes carrying tau are subsequently toxic to recipient neurons. Collectively, our data indicate a role for ectosomes in connecting tau and α-synuclein-associated pathology in PD.

P1-C-141 *Effects of a lipid metabolism-targeting treatment on recovery sleep following sleep deprivation in the 3XTG mouse model of Alzheimer's disease*

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Alzheimer's disease (AD) mouse models exhibit sleep disturbances, which constitute a risk factor for the development of AD, as well as lipid alterations. We hypothesized that a treatment modulating lipid metabolism will improve sleep quality in an AD mouse model. Triple-transgenic (3xTg) mice (mutations in App, Mapt, Psen1) and non-mutant control mice were implanted for electrocorticography (ECoG) and intracerebroventricular infusion of a stearoyl-coenzyme A inhibitor (SCDi) or a vehicle. This enzyme converts saturated into monounsaturated fatty acids, and its inhibition improves cognition and lipid pathology in the 3xTg mice. After 28 days of treatment, ECoG recordings were performed during a 6-hour sleep deprivation and recovery. Preliminary of 24-h mean time spent in wake/sleep states showed no significant effect of treatment or genotype. However, 3xTg showed more time spent awake and less time asleep (slow-wave and paradoxical sleep) compared to controls during the light period, but the opposite during the dark period. Also, the treatment increased the time spent awake and decreased time asleep (both states) during the light period but did the opposite for the dark period. The project will determine whether the animal model exhibits altered recovery after sleep deprivation and the effect of the lipid-targeting treatment on recovery sleep and on the lipid droplet profiles. This research will help to uncover the links between lipid metabolism and sleep regulation in AD and could guide the development of new therapeutic approaches targeting these interactions.

P1-C-142 *Efficacy and safety from a phase 1/2 open-label trial of GTX-102, an investigational antisense oligonucleotide for the treatment of patients with Angelman syndrome*

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Background: GTX-102 is an investigational intrathecally administered antisense oligonucleotide designed to target the UBE3A antisense transcript in individuals with Angelman syndrome, a rare neurodevelopmental disorder with no approved disease modifying treatment. Methods: GTX-102-001 (NCT04259281) was a Phase 1/2 open-label trial in pediatric participants with full maternal UBE3A gene deletion. GTX-102 was administered in 3 to 4 monthly doses followed by quarterly maintenance dosing. Results: 74 participants were enrolled across all Cohorts. In a pooled analysis of 40 Cohort 4-7 + A/B participants with available Study Day 338 (D338) Bayley-4 Cognitive Growth Scale Value data, mean (SD) change from Baseline) was 6.7 (8.6). Similar improvements were observed in Bayley-4 Receptive Communication and Aberrant Behavior Checklist – Hyperactivity/Noncompliance. Five Cohort 1-3 participants who received high-dose GTX-102 had serious adverse events of reversible lower extremity weakness (LEW). Mitigation measures (lower GTX-102 doses, dexamethasone premedication, aCSF flush after GTX-102, post-flush Trendelenburg) significantly reduced LEW incidence from 100% (5/5) in early cohorts to 4% (3/69) in subsequent cohorts. No new LEW cases occurred since the last were reported in April 2024. Conclusions: Treatment with GTX-102 resulted in rapid and progressive cognitive, communication, and hyperactivity/noncompliance improvements at D338. Phase 3 relevant doses and mitigation procedures resulted in a much lower incidence of LEW, and no new safety concerns were identified.

P1-C-143 *Reduced cerebrovascular reactivity in youth with congenital heart disease: Links with cognition*

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Congenital heart disease (CHD) is the most prevalent birth defect.1 Neonates with CHD present cerebrovascular alterations, reflected by lower cerebral blood flow (CBF)2, but these have been little studied beyond the perioperative period. We recently showed that female youth with CHD have reduced CBF compared to healthy peers.3 Cerebrovascular reactivity (CVR)4 is a measure of vascular reserve and appears more sensitive to vascular changes than CBF5, but remains understudied in CHD. Recently, a CVR technique was developed using resting-state fMRI without any breathing manipulations.4 In this study, we compared CVR across cerebral arterial territories6 between 49 individuals with CHD (26 females) and 53 controls (32 females), aged 16-26 years. Executive functioning (EF) was measured using the BRIEF-A.7 Individuals with CHD displayed lower CVR than controls in the whole grey matter and the anterior cerebral arterial territory. Females with CHD revealed lower CVR than males with CHD in the middle cerebral artery territory. A negative relationship between CVR and EF was observed in the CHD group. These findings suggest that CVR is compromised in youth with CHD, particularly in females, consistent with reduced CBF3. CVR may represent an important biomarker of cognitive processes in CHD. (Refs: 1) Liu et al., 2019. Int. J. Epidemiol.; 2) De Silvestro et al., 2023. Pediatr. Res.; 3) Easson et al., 2023. CJC.; 4) Liu et al., 2017. NeuroImage; 5) Gauthier et al., 2013. Neurobiol. Aging; 6) Liu et al., 2023. Scientific data; 7) Roth et al., 2013. Arch. Clin. Neuropsychol.)

P1-C-144 *Elucidating the Physiological Role of Amyloid Precursor Protein through multi-omics*

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Introduction: While the Amyloid Precursor Protein (APP) is central to Alzheimer's Disease (AD) pathology, its endogenous physiological functions remain incompletely understood. Shifting the focus from pathological aggregation to its native biological roles is essential for a comprehensive understanding of neurodegeneration and cellular health. Methods: To investigate these roles, we utilized a multi-omic approach combining RNA-sequencing and high-throughput proteomics. Analysis was conducted on Mouse Embryonic Fibroblasts (MEFs) and hippocampal tissue from 3-month-old female mice. This multi-system approach allows for the identification of conserved APP-dependent pathways across different biological contexts. Results: Our preliminary findings reveal significant alterations in several key biological pathways. Specifically, differential expression patterns in both the transcriptome and proteome highlight a robust involvement of APP in the regulation of the extracellular matrix (ECM) and focal adhesion dynamics. These results suggest that APP plays a critical role in mediating cell-substrate interactions and structural integrity within the hippocampus. Conclusion: By mapping the physiological landscape of APP, our data suggests that its loss of function or dysregulation may precede classic AD markers. Further analysis of these ECM-related pathways will provide deeper insight into how APP maintains homeostatic balance in the aging brain.

P1-C-145 *Neuronal growth regulator 1 as a potential target for gene expression modulation in human pluripotent stem cell models of Alzheimer's disease*

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Introduction: Alzheimer's Disease is the main cause of dementia worldwide, with symptoms that include severe cognitive impairment, learning and memory deficits. Despite this disorder severity and prevalence, there are currently no approved gene therapy-based disease-modifying therapeutical approaches to halt its progression. Previous data indicate that oligomeric amyloid β (Aβ) can bind and form a signaling complex with the Cellular Prion Protein (PrPC) and the metabotropic glutamate receptor 5 (mGluR5), activating

pathogenic signaling cascades driving dendritic spine and neuronal loss. Interestingly, we identified that the Neuronal Growth Regulator 1 (NEGR1) acts as a novel mGluR5 interacting partner and we hypothesize that modulating its expression can disrupt the Aβ/PrPC/mGluR5 pathogenic interaction in this disease. Methods: We initially screened guide RNAs for their ability to either induce or repress NEGR1 expression in human neural stem cells using the CRISPR activation and interference system. Next, we used RT-qPCR to examine if the chosen guide RNA could modulate NEGR1 expression in human cortical organoids. Results: NEGR1 #2 guide RNA was capable of inducing by 15-fold and also repressing by 3-fold NEGR1 gene expression in neural stem cells, respectively. Additionally, this guide RNA also upregulated NEGR1 expression in cortical organoids by 4.8-fold. Discussion: These findings indicate that NEGR1 expression can be modulated in human pluripotent-derived brain models. In further steps, we will evaluate if modulating this gene expression can prevent Alzheimer's disease pathology in cortical organoids.

D - SENSORY AND MOTOR SYSTEMS

P1-D-146 *Steady-state visual evoked potentials reveal visual symmetry processing in the common marmoset*

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Symmetry is a biologically important mid-level visual feature. While human and macaque studies have identified robust neural responses to various symmetry types, this processing has not been examined in other non-human primates. We present the first study of neural symmetry responses in the common marmoset. Marmosets have visual cortices that are structurally and functionally similar to those of humans and macaques, but their largely smooth cerebral cortex provides easier access to cortical areas that are often hidden within sulci in macaques. Using a Steady-State Visual Evoked Potential (SSVEP) paradigm, we recorded EEG from 32-channel surface grids chronically attached to the skulls of three marmosets. Stimuli consisted of large-field (24°) textures from two wallpaper groups: PMM (double-reflection symmetry) and P4 (four-fold rotational symmetry). By periodically alternating these patterns with phase-scrambled controls, we isolated symmetry-specific responses from low-level image-update responses, reflected in odd and even harmonics of the stimulation frequency, respectively. Both symmetry groups evoked strong image-update responses and reliable symmetry-selective responses over posterior electrodes. The temporal dynamics were remarkably similar to those established in humans. These results demonstrate that marmosets produce measurable responses to reflection and rotation symmetry. This establishes the marmoset as a viable model for studying mid-level vision and provides a foundation for future intracranial recordings of spiking activity and local field potentials.

P1-D-147 *A Drosophila model of Diabetic Neuropathy*

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Sensory neuropathy is a common complication of diabetes mellitus and is characterized by altered sensory processing and impaired nociceptive responses. High-sugar diets in Drosophila melanogaster are widely used to model diet-induced metabolic stress relevant to diabetic-like states, providing a tractable system to study how chronic metabolic challenges affect sensory behaviour. Using a Drosophila adult thermal nociception assay, we examined how a high-sugar diet (HSD) affects nociceptive sensitivity. We found that both male and female flies maintained on HSD exhibited nociceptive hyposensitivity compared to those on a normal-sugar diet (NSD). This hyposensitive phenotype persisted after flies were returned to a NSD for seven days following chronic HSD, indicating that dietary experience during early adulthood produces sustained changes in sensory-driven behaviour. These findings suggest that chronic metabolic stress can induce persistent modulation of nociceptive responses independent of ongoing dietary exposure. Expression of a constitutively active insulin receptor in nociceptors also resulted in nociceptive hyposensitivity,

suggesting that the effects we observed are due to altered insulin signalling in nociceptors. Ongoing work aims to identify transcriptional and signalling regulators that link metabolic stress to long lasting changes in adult sensory function. Together, this work supports the use of adult Drosophila as a valuable model for investigating how metabolic dysregulation may contribute to long-term sensory deficits relevant to diabetic neuropathy.

P1-D-148 *Acoustic transparency enables transcranial functional ultrasound imaging in nonhuman primates without craniotomy*

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Functional ultrasound imaging (fUSi) provides high-resolution mapping of brain hemodynamics, but its application in primates is fundamentally limited by skull-induced acoustic attenuation, often requiring craniotomy. Here, we introduce an acoustic transparency approach based on topical Ethylenediaminetetraacetic acid (EDTA) application to enable transcranial fUSi in a nonhuman primate (NHP) model. We performed fUSi (Iconeus instrument, France) in two fully anesthetized common marmosets. EDTA, an FDA-approved calcium chelating agent, was applied topically to the skull for 30 minutes using a custom 3D-printed well. In one animal, EDTA was applied after scalp incision alone, while in the second, mild skull thinning preceded application. No craniotomy was performed. fUSi was acquired in coronal and sagittal planes centered on the somatosensory cortex using established stereotaxic coordinates. Peripheral somatosensory stimulation was delivered in 30-second on/off blocks targeting the right foot. Following induction of acoustic transparency, transcranial fUSi enabled visualization of blood flow in superficial and deep vasculature previously obscured by the skull and revealed stimulus-locked hemodynamic responses. Robust activation was consistently observed in the somatosensory cortex contralateral to the stimulated limb, with weaker responses in deeper structures. This study provides the first demonstration of acoustic transparency–enabled transcranial fUSi in NHPs, establishing a key translational step toward human fUSi and an alternative to craniotomy-based imaging methods.

P1-D-149 *Action intention modulates functional connectivity: An fMRI study*

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Studies of hand control tend to focus on prehension but often ignore the final disposal of the object that ends the interaction. Our study investigates the neural correlates of object placing and grasping. Despite their reliance on equivalent target information (e.g., its location and orientation), we expected to see a difference: grasp relying more on the actual visual input, and place relying more on the mental representation of the target outcome. Our event-related fMRI study asked twenty participants to alternate between grasping and placing a rectangular object on a template presented on an inclined platform. Each trial began with a target (object/template) presented at two possible locations (left/right) and orientations (±30°). Participants waited during a planning delay before grasping or placing the object on the platform. We used a graph-theory approach to explore functional connectivity patterns in our two conditions. The brain network was segregated into three modules: a Cerebello-Occipito-Parietal Module (Mod1), a Frontal Module (Mod2), and a Sensorimotor Module (Mod3). When quantifying the modularity strength of these subnetworks, we found a higher score for grasp in Mod1 and, conversely, a higher score for place in Mod2. As expected, despite their similarity as goal-directed actions, grasp is more sensory driven, whereas place is cognitively driven. Therefore, movement intent has a major effect on brain state. In conclusion, grasp and placement share similar cortical mechanisms but emphasize different modules depending on action intention and sensory feedback.

P1-D-150 *Age-and sex-dependent modulation of descending pain control : Effects of physical activity in mice*

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Introduction : Aging is associated with a progressive decline in endogenous pain modulation (ePM) contributing to increased discomfort and movement aversion. In humans, ePM efficiency declines around the onset of gonadal aging (40–50 years), suggesting a link between pain modulation and reproductive aging. This study aimed to validate a novel behavioral paradigm to assess diffuse noxious inhibitory controls (DNIC) in mice and to examine the effects of aging and physical activity in later life. Methods : Male and female mice (3–24 months) were tested using a DNIC-like assay measuring hot-plate response latency following 60 s tail immersion in cold (0 °C) or room-temperature water. Increased latency after cold stimulation reflects effective descending pain modulation. Study 1 characterized age-related changes in DNIC across the lifespan. Study 2 examined the effects of two months of voluntary wheel running versus sedentary housing. Results : DNIC efficacy declined early, between 6 and 9 months of age, a period corresponding to reduced gonadal activity in mice, and was absent at 10 months. Physical activity increased spontaneous locomotion and reduced body weight in both sexes, but restored DNIC responses only in males. Conclusion : Although DNIC shows a similar age-related decline in males and females, its modulation appears to rely on sex-specific underlying mechanisms, as enhanced physical activity selectively benefits descending pain control in males while remaining ineffective in females.

P1-D-151 *Altered post-incision pain and subsequent disturbance of gut homeostasis in aging mice*

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In young adults, injury triggers a coordinated response involving hemostasis, inflammation, and tissue repair. But this process is impaired in the elderly, leading to prolonged pain. This study aimed to study whether a minor skin incision affects systemic and intestinal homeostasis in aging mice. Young and aging male and female mice underwent plantar incision. Mechanical allodynia was evaluated by von Frey. Inflammation profiles in the skin, serum, and colon were assessed with the Proteome Profiler Mouse Cytokine Array. Protein functional enrichments were analyzed by the STRING database. Incision-induced allodynia resolved at day12 in young mice but persisted in aging mice. In young mice, inflammation subsided in the skin and serum by day12 but increased in the colon. In contrast, aging mice exhibited delayed yet amplified inflammatory responses in all tissues at day12. Colonic inflammation was more pronounced in aging females than in aging males. Altered colonic proteins (top 15%) in aging females were enriched in the T cell proliferation/ Th17 cell differentiation, while those in aging males were associated with the myeloid cell differentiation/ mononuclear cell migration, indicating sex-specific immune responses. An incision provokes prolonged pain in aging mice, with intensified inflammation across tissues. Aging females exhibit a more severe pro-inflammatory colonic profile than males. Our findings highlight that a minor injury disrupts global inflammatory homeostasis during aging, with sexually dimorphic effects on the gut immune environment.

P1-D-152 *An ascending pathway for the relay of warm and cool sensation*

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Cutaneous thermosensation enables animals to detect changes in environmental temperature and trigger adaptive responses fundamental to survival and homeostasis. Thermal signals are encoded by peripheral thermoreceptors, integrated by spinal circuits, and transmitted to the brain through the anterolateral tract (ALT). Although thermal responses have been described in superficial dorsal horn ALT neurons, the

cellular organization and functional logic by which innocuous warm and cool information is relayed to the brain remain poorly understood. Here, we show that the expression of the transcription factor Phox2a defines a major lamina I ALT population in mice that is selectively tuned to innocuous warming or cooling. These neurons receive direct input from thermoreceptors, are shaped by local spinal circuits, and project to discriminatory and homeostatic thermosensory brain targets. Selective ablation, chemogenetic, or optogenetic manipulation of the Phox2a ALT neurons impaired temperature discrimination without broadly affecting other somatosensory modalities. Our findings contrast with prior work that predominantly characterized mechano- and thermo-nociceptive ALT subtypes, and provide evidence of a large genetically-defined neuronal ensemble dedicated to innocuous thermal transmission. Our data constitute evidence for integration and amplification of warm and cool thermal information prior to its relay to thermosensory brain regions.

P1-D-153 *An ethogram-based approach reveals the widescale behavioral impact of vision loss and provides a sensitive benchmark for assessing vision restoration*

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Background: Vision is essential for a wide range of behaviors, including predator avoidance, foraging, social interaction, parental care, and spatial navigation. As such, vision loss profoundly alters an individual's day-to-day activities. Despite this, our understanding of how vision loss reshapes naturalistic behavior remains fragmented, limiting our ability to rigorously evaluate emerging vision restoration therapies. Methods: We generated an ethogram using 5 behavioral assays—open field exploration, novel object exploration, pup retrieval (parental care), mating, and the resident–intruder task (aggression). We compared ethograms across three groups: sighted controls, congenitally blind mice lacking functional rod and cone photoreceptors, and vision-restored mice. Mice were tracked using DeepLabCut, and the machine-learning classification tool SimBA was used to identify and label behaviors. Results: Our ethogram clearly distinguished behaviors between male and female mice. Furthermore, the ethogram revealed a large number of differences between sighted and blind mice and enabled us to separate behaviors into 3 groups: visual behaviors, non-visual behaviors, and adapted behaviors. Lastly, the ethogram outperformed previous methods at assessing the efficacy of vision restoration and was able to separate mice based on the method of vision restoration. Conclusions: An ethogram-based model is a powerful tool for revealing the broad impact of vision loss and provides a sensitive benchmark of the efficacy of vision restoration approaches.

P1-D-154 *Analgesic effects of 3,4-methylenedioxymethamphetamine in the acetic acid and formalin mouse pain assays*

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Recent explorations of the analgesic effects of serotonergic psychedelics have revealed promising results. The classic psychedelic, 3,4-Methylenedioxymethamphetamine (MDMA) has displayed analgesic properties in acute thermal nociceptive assays in rat, but it is unknown whether MDMA will exhibit analgesic effects in tonic pain assays in which mice exhibit spontaneous nocifensive behaviours. To test, we examined the analgesic effects of MDMA in the acetic acid and formalin mouse pain assays. 30 minutes prior to pain assays, we systemically administered 0mg/kg, 2.5mg/kg, or 5.0mg/kg MDMA to adult male and female C57BL/6J mice. The acetic acid writhing assay (AAWA) involves the intraperitoneal injection of 1% acetic acid in dH2O causing writhing behaviour, a contortion of the abdomen and extension of the hind limbs for 30 minutes. The formalin assay (FA) involves the intraplantar injection of 2.5% formaldehyde in dH2O causing bouts of licking and biting behaviour for 60 minutes. Number of episodes and duration of writhing AAWA and licking/biting in FA were manually quantified by multiple observers. We observed a dose-dependent reduction of pain behaviour following MDMA administration in both pain assays and in both sexes. Duration of writhing in AAWA and licking/biting in FA significantly decreased in 2.5mg/kg and 5.0mg/kg groups compared to control. We observed a clear dose-dependent analgesic effect of MDMA across sexes in adult

mice. Future work can explore the site of action and the dependence of serotonergic modulation within MDMA analgesia.

P1-D-155 *Assessing local and global stereopsis using tasks of depth detection and discrimination*

Tara Nichols [1], Alexander Baldwin [1]

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Some individuals with clinically normal vision show selective deficits in stereopsis tasks, particularly when required to discriminate the direction of depth rather than simply detect its presence. This phenomenon, often referred to as stereoanomaly, has been reported in previous studies, with prevalence estimates ranging from approximately 2% to 30%, depending on the task and stimuli used. Prior work has employed stimuli that preferentially engage either local stereopsis (monocularly identifiable edges or shapes) or global stereopsis (random-dot patterns). There has been little work comparing performance (to identify stereoanomaly) between tasks using these two stimulus types. The present study directly compares local and global stereopsis across detection and discrimination tasks. Preliminary results indicate that performance on the local discrimination task diverges from the other three tasks, suggesting that it may rely on partially distinct mechanisms. In addition, performance on a clinical stereopsis screening test was not significantly correlated with any experimental task, though it was closest to significance with local detection performance. A strong relationship was observed between global detection and global discrimination performance, exceeding the level of agreement reported in some previous studies, though a larger sample will be required for direct comparison. Together, the relationships between these four tasks can form the basis of a minimal set of measurements to characterize the stereopsis phenotype of a participant.

P1-D-156 *Assessing the impact of electrode placement on auditory brainstem response waveforms*

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The auditory brainstem response (ABR) measures the electrical activity in the brainstem in response to sound stimuli. The resulting ABR traces consist of a series of waves, each representing activity in successive nuclei of the ascending auditory pathway. The amplitudes and latencies of these waves reflect the degree of synchronous neural firing in the nuclei and the axonal conduction between them, respectively. When performed on animals, sub-dermal electrodes are placed to record electrical activity evoked by the acoustic stimulus. Typically, three electrodes are used in the recording setup: an active, a reference, and a ground electrode. However, the placement of these electrodes relative to the ear may impact the amplitudes and latencies of the resulting ABR waveforms, which can in turn affect the reported thresholds. Here we tested different electrode configurations to investigate the effect of electrode placement at different anatomical sites on the resulting ABR waveforms. We conducted ABR recordings on domestic cats and presented broadband click stimuli to each subject (n=5) at intensities ranging from 20-80dB. We varied the locations of the active and reference electrodes but kept the location of the ground electrode constant. We compared wave amplitudes and latencies following the stimuli between electrode placement sites. Our findings highlight the optimal sites for electrode placement to ensure the most favourable ABR recordings. This is crucial for reliably measuring and detecting appropriate ABR waves from background noise and small changes in hearing thresholds.

P1-D-157 *At first sight: Cortical processing of restored vision following an extended period of vision loss*

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Various techniques are currently in development to restore visual processing abilities to blind individuals. However, vision loss induces significant brain plasticity, meaning that restored visual inputs will be processed differently by a previously blind brain. Though it is well-established that visual experience plays an important role in refining visual brain circuits during development, it remains unclear how prolonged vision loss alters processing of restored visual inputs in the primary visual cortex (V1). To this end, we simulated a) early blindness by dark-rearing animals from P0 to P70 and b) late blindness by subjecting animals to dark-exposure from P35 to P105. We then 'restored vision' by re-introducing mice to light conditions. Prior to, during, and following vision restoration, we performed weekly calcium imaging of layer 2/3 neurons in V1, tracking hundreds of neurons across six weeks and examining spontaneous and visually evoked activity. We find that 'at first sight', V1 tuning properties in both early- and late-blind groups deviate significantly from age-matched controls. Furthermore, longitudinal tracking of neurons reveals that tuning stability across weeks differs in restored animals compared to sighted controls. Lastly, we observe distinct functional differences between early- and late-blind cohorts. In sum, we have developed a powerful methodology that allows us to examine the impact of extended vision loss on cortical processing of restored visual inputs.

P1-D-158 *Auditory and vestibular neurotoxicity of agricultural chemicals: A global mapping of the current research*

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Agriculture is a major global economic sector. With globalization and mass production, the use of pesticides has become standard practice to meet increasing demand. However, several of these substances are known for their neurotoxic effects, particularly on the auditory and vestibular functions. Through a systematic search following the PRISMA protocol, this study aimed to map the current state of knowledge regarding the ototoxic effects of agricultural chemicals, with a focus on their impact on the auditory and vestibular health of rural workers. Twenty-five studies were included for analysis. The methodologies which have been used to investigate auditory and vestibular neural functions in these populations are diverse and heterogeneous, ranging from peripheric evaluation tools (tonal audiometry, oto-acoustic emissions recordings, etc.) to electrophysiological (ABR, P300) and perceptual explorations of central functions (GIN, DPT/DPS, PPS, RGDT, DDT). There was a major geographical imbalance in study distribution, which prevents estimation of the global prevalence of hearing loss among these workers. Finally, from a clinical neuropharmacological standpoint, the near absence of comparison groups exposed solely to noise typically prevented the isolation of the specific ototoxicity of each individual chemical. Further research is needed to fully understand the underlying mechanisms of the impacts of pesticides on auditory and vestibular function in order to insure the health and safety of exposed workers.

P1-D-159 *Auditory context modulates attentional gating during sensorimotor performance*

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Optimal motor performance relies on efficient integration of relevant sensory information into descending motor commands. The integrative process depends on both cognitive and motor factors. Past work demonstrates that shifts in attentional foci during task performance modulates sensory processing and impacts motor performance. It is possible that altering the sensory environment may also influence sensorimotor integration by changing the cognitive-motor balance. The current study examined the effect of sound on sensory gating through observing changes to incoming sensory information with

electroencephalography (EEG), during a wrist position matching task. The task involved both passive and active movements of the wrist while participants listened to no noise, white noise, pink noise, blue noise, high-tempo music, and low-tempo music. Changes in amplitude of early somatosensory evoked potentials (parietal N20-P25, frontal N30) were measured to determine effects of sound on sensory gating mechanisms. Preliminary results demonstrate a greater facilitation of N20-P25 and N30 during active wrist movement compared to passive wrist movement for all sound conditions. Additionally, the effect of attentional gating is larger for white noise, pink noise, and low-tempo music, when compared to no noise, blue noise and high-tempo music. These findings suggest that attentional facilitation of early somatosensory cortical processing is optimized by auditory contexts that promote stable, low-arousal neural states, whereas highly structured or arousing sounds may disrupt early sensory gain.

P1-D-160 *Behaviour-dependent immediate early gene activation in the mouse cerebellum*

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The cerebellum supports a wide range of motor and non-motor behaviors, yet the specific cerebellar regions and neuronal populations underlying this functional diversity remain largely unknown. Here, we mapped patterns of immediate early gene activation in the cerebellar cortex during the accelerating rotarod task, an established form of cerebellum-dependent motor learning. Using the immediate early gene c-Fos to identify cells active during the behaviour, we found significant activation throughout the vermis and in crus I of the hemispheres, specifically within the molecular and granule cell layers, compared to naive controls unexposed to the task. Inclusion of a second control group that was exposed to the rotarod apparatus but not the task revealed similar patterns of c-Fos expression linked to novelty. To separate this novelty signal from the motor component of the task, mice were habituated to the apparatus prior to testing. This habituation resulted in an overall decrease in c-Fos expression across cerebellar lobules, with significant motor activity-related differences found only in the anterior vermis. Finally, to determine how learning influences c-Fos expression patterns, mice were subjected to a multi-day motor learning paradigm in which genetic tagging of c-Fos-expressing neurons was performed on day 1, followed by c-Fos immunostaining on day 5. In this comparison, we detected no significant c-Fos signal in mice that had learned the task compared to controls. Overall, these findings reveal distinct patterns of activation associated with novelty, motor behaviour, and learning, providing a framework for linking behavior to regional cerebellar function.

P1-D-161 *Benchmarking human dorsal root ganglion organoids with cultured primary human tissue models*

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Diseases of the peripheral nervous system (PNS) are common and debilitating. While great strides in the understanding of the basic physiology of the PNS have been made, clinical translation is hampered by a lack of suitable human pre-clinical models for target and drug discovery. Organoids are synthetic tissue derived from stem cells that mimic the cell-type composition and structure of endogenous tissue. Dorsal root ganglion (DRG) organoids (DRGOs) have emerged as a promising technology to bridge the clinical translation gap for PNS disorders, however they suffer from poor fidelity and validation with respect to human DRGs. To this end, we sought to generate and optimize DRGOs. Using immunofluorescence staining and single cell RNA sequencing, we characterized the cell-type composition of our DRGOs, and validated the generation of sensory neurons and various glial cell types. Next, we measure physiological parameters using calcium imaging and patch-clamp electrophysiology. DRGO sensory neurons were electrically active and capable of generating action potentials. To directly benchmark DRGOs, we next acquired human prenatal DRG tissue. Presently, we are optimizing culture conditions for this primary human tissue. Our preliminary data suggest that these primary DRGs are viable based on neurite outgrowth and calcium imaging. Future work will focus on characterizing tissue structure using spatial RNA sequencing. We believe that these data will be essential in guiding further optimizations of DRGOs, and could provide fundamental insights into the development of the DRG.

P1-D-162 *Central integration of proprioception in controlling homolateral leg movements*

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Stable locomotion in quadrupeds depends on accurate hind limb placement. In bipedal humans, vision is used to achieve accuracy when needed. In quadrupeds, postural constraints limit visual guidance, particularly for the hind limbs. Here, the aim was to determine whether proprioceptive feedback from the homolateral forelimb, rather than vision, governs hind limb foot placement at the end of swing during quadrupedal locomotion in mice. To address this, electromyographic activity was recorded from multiple hind limb muscles during treadmill locomotion under control and perturbation conditions, with perturbations elicited by saphenous nerve stimulation to induce the stumbling corrective reaction. Kinematic analyses quantified hind limb foot placement at swing termination relative to forelimb foot placement at stance termination. The contribution of muscle spindle–mediated proprioception and supraspinal control was further tested using Egr3 knockout mice, which lack muscle spindles, as well as chemogenetic manipulations of supraspinal centers. The data show that hind limb foot placement aligns with the homolateral forelimb only during perturbation, and that this coordination requires proprioceptive feedback from muscle spindles and supraspinal processing, as propriospinal circuits alone are insufficient. Finally, the cuneate nucleus in the medulla oblongata was identified as a critical node in the supraspinal proprioceptive pathway. These findings reveal a proprioceptive mechanism that secures safe hind limb placement in response to perturbations and delineate the supraspinal pathway mediating homolateral limb coordination in quadrupedal locomotion.

P1-D-163 *Cerebellar rhomboid-3 modulates motor coordination through membrane signaling pathways in aging*

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As people live longer and lifespan increases, their health span, or the proportion of lifespan during which a person is healthy, is not improving at the same pace. It is thus urgent to identify mechanisms that expand health span. Recent studies have revealed that the protease Rhomboid-3 is the most differentially regulated gene in the aging human brain, and that it increases in aged cerebellar Purkinje cells. To understand Rhomboid-3 function, we used a Rhomboid-3 knockout (Rhom-3 KO) mouse and performed a motor coordination assay, Rotarod, in male and female mice across ages. We observed that Rhom-3 KO mice had better motor coordination across lifespan than litter-matched wildtype (WT) mice. We then showed that virally reintroducing Rhom-3 into cerebellar Purkinje cells in Rhom-3 KO mice depressed motor coordination. Together, these findings argue that cerebellar Rhomboid-3 expression contributes to declining motor coordination in aging. To understand how Rhomboid-3 affects cellular function, we used RNA sequencing in cerebella from 3 male and 3 female 10-month-old Rhom-3 KO and WT mice. We identified 255 differentially expressed genes in Rhom-3 KO mice, of which 98% were downregulated compared to WT. Gene Ontology analysis revealed that these genes were enriched for membrane-associated signaling proteins, including G protein-related pathways. These results suggest that accumulation of Rhomboid-3, perhaps acting through the overactivation of intracellular signaling pathways in cerebellar Purkinje cells, contributes to motor coordination impairment in aging.

P1-D-164 *Coherence dynamics and neural reorganization during motor sequence learning and at rest*

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Corticokinematic Coherence (CKC; cortex-proprioception) and Corticomuscular Coherence (CMC; cortex-muscle) are used to investigate interactions between brain, sensory feedback and muscles during voluntary movement. Previous work has primarily focused on simple isometric (grip) tasks, although most movements are continuous and dynamically integrated. We investigated how coherence frequency and magnitude are modulated during performance of unimanual simple (SMP) and complex (LRN) continuous visuomotor sequences. Fourteen right-handed healthy adults practiced five blocks (3 trials/sequence/block) in a single session. Coherence was computed using an optimization technique that maximized absolute coherence between cortical activity and kinematics (force) or surface EMG at each frequency/sequence. CKC was significant at 1.75 Hz for LRN relative to SMP, indicating enhanced reliance on proprioceptive feedback. We observed significant mid-beta frequencies (21-22 Hz) in CMC for LRN as compared to SMP, while no significant gamma-band differences were observed. Significant learning was observed across blocks. These findings suggest that the corticospinal system engages a stable beta-mode mechanism to ensure efficient motor output and compensate for dynamically modulated forces during continuous movement, while the absence of gamma modulation indicates that task demands may not have required higher-frequency online integration. Together, our results provide novel evidence indicating that CKC and CMC provide complementary information and play an important role in orchestrating and optimizing complex continuous movements, potentially serving as a biomarker for motor learning and plasticity. Ongoing work will examine coherence modulation with learning and resting-state connectivity pre/post training to assess functional organization of neural systems underlying sequence learning.

P1-D-165 *Combined cortical and peripheral stimulation alleviates locomotor deficits in a feline model of incomplete spinal cord injury*

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After a spinal cord injury (SCI), disrupted interactions between supraspinal, sensory, and spinal circuits result in persistent locomotor deficits, such as paw dragging. To restore these interactions, we employed electrical stimulation to engage neural circuits in real time, with the aim to assist movement. We recently demonstrated that motor cortex stimulation increases step height and reduces paw dragging in rodent and feline models of incomplete SCI. Our preliminary findings also suggest that peripheral stimulation similarly alleviates locomotor deficits. Here, we hypothesized that combining cortical and peripheral sensory stimulation would synergistically engage residual motor circuits to maximize motor efforts. In a feline model, we implanted electrode arrays in the hindlimb motor cortices, cuff electrodes around the superficial peroneal nerves innervating the foot dorsum, and electromyographic electrodes in hindlimb muscles. Cats then received a spinal contusion at T10, paralyzing both legs. Prior to and after SCI, we assessed the ability of cortical and/or peripheral stimulation to modulate locomotion on a treadmill and facilitate motor evoked potentials. We further characterized how the precise timing and amplitude of these stimulations influenced kinematic parameters and EMG activity. Our preliminary data show that combined stimulation enhances step height, reduces dragging, and increases motor evoked potentials more effectively than either approach alone. These findings highlight the potential of multi-level stimulation strategies for assisting movement after SCI.

P1-D-166 *Cortical beta-band dynamics during motor control in Tourette syndrome*

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Context: Beta frequencies are typically observed during movement execution and are known to be altered in certain movement disorders. However, few studies have explored these alterations in Tourette Syndrome (TS). Given that difficulty in modulating motor responses characterizes this condition, observable frequency-based signatures may be observable and hint at motor control mechanisms in this disorder. Objectives: (1) Compare beta EEG activation during inhibition phases between a control group and a TS group; (2) explore psychophysiological signatures specific to the TS group during stimulus-response compatibility mixed with a motor inhibition condition. Method: A group of 19 adults with TS was paired with 19 control participants based on age, sex, and handedness. Continuous EEG was recorded during a stimulus-response compatibility task with an inhibition condition. Beta frequency activity (13–30 Hz) was extracted within a 0–400 ms time window before and after motor response. Results: A higher beta amplitude was observed in the TS group in pre-motor period ($F[1,36]=5.10;p<0.05$), with a more prominent effect in the anterior frontal region during the motor inhibition condition (Group X Time X Region: $F[1.6,54.8]=3.36;p=0.05$,GGcor). Conclusion: Previous studies have also reported increased beta activity in frontal regions in TS, which is consistent with neuroimaging studies showing frontal overactivation in this population. Implications: These results could propose that beta-band EEG rhythm may serve as a psychophysiological marker of motor control processes in TS.

P1-D-167 *Cortical specificity matters: Targeted hindlimb cortical stimulation enhances locomotor recovery after spinal cord injury*

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The motor cortex exhibits a somatotopic organization where specific territories modulate hindlimb kinematics. Our previous work showed that intracortical microstimulation (ICMS) delivered to hindlimb representations during locomotion immediately alleviates locomotor deficits associated with spinal cord injury and fosters recovery of voluntary locomotor control. However, the necessity of targeting specific cortical representations remains unclear. Here, we tested whether stimulating the hindlimb-specific cortical territory, compared to non-specific stimulation or no stimulation, differentially affects locomotor recovery in cats with severe thoracic spinal contusion (T10) producing long-term bilateral locomotor deficits. After regaining weight-supported stepping, cats underwent treadmill training (20 min/day) for 3 weeks across three experimental groups: no stimulation (n = 5); ICMS targeting the contralateral hindlimb representation (n = 2); and non-specific ICMS recruiting multiple cortical representations (n = 3). Locomotor recovery was assessed on a flat treadmill, ladder treadmill, and during obstacle avoidance until four weeks post- therapy. We demonstrated that only ICMS specifically targeting the hindlimb representation significantly enhances voluntary locomotor control, particularly during complex tasks requiring precise paw placement. These results provide preclinical evidence that the functional specificity of cortical stimulation is essential for optimizing recovery, highlighting the importance of precise targeting in neuroprosthetic interventions.

P1-D-168 *Cortical states modulation of cortical activity and connectivity in congenital blind mice*

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When a sensory system is lost, an invasion of residual systems into the deprived cortical areas is observed, thus leading to changes to the cortical network. Although the existence of this plasticity is well established, the influence of cortical states, such as locomotion and wakefulness, on neuronal activity in blind animals has not been observed despite the fact that such states profoundly shape neuronal activity in healthy animals. Our objectives were to perform wide-field imaging in the somatosensory, motor, and visual cortices

in blind mice while they were awake and active. We measured calcium activity using mesoscopic imaging of the dorsal cortex in mice that underwent binocular enucleation at birth. We assessed changes in functional connectivity during periods of locomotion and wakefulness in head-fixed mice free to run on a wheel. Our results showed that connectivity changes during locomotion in blind mice were mainly characterized by a decrease in connectivity between the visual cortex and the somatosensory cortex, as well as with higher visual areas. Moreover, those changes were mainly present during the active locomotive state and not during the wakefulness state. Analysis of resting state neuronal activity also showed the cortex of blind mice was not as modulated by locomotion when compared to normal sighted mice. Overall, this research shows that cortical states modulate brain activity in a different manner in blind and sighted mice. Moreover, this modulation is also reflected in the brain's functional connectivity.

P1-D-169 *D2 receptor-expressing neurons in the gigantocellular reticular nucleus modulate locomotion and orienting movements in mice*

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The reticular formation plays a key role in motor control, containing the command systems for initiating, stopping, and directing locomotion. These commands are transmitted to spinal circuits via reticulospinal neurons. In lampreys, reticular regions are targeted by descending dopaminergic pathways (Ryczko et al. 2020 J Neurosci). However, in mammals, the reticular neurons targeted by dopamine and their behavioral roles are unknown. Here we investigated in mice the behavioral role of neurons expressing dopaminergic D2 receptors in the gigantocellular reticular nucleus (Gi), a region involved in the control of stops and orienting movements. Using RNAscope, we identified cells expressing the D2 receptor in the Gi. To activate these Gi D2-positive neurons in vivo, we unilaterally injected a virus in the Gi of D2-Cre mice, enabling Cre-dependent expression of channelrhodopsin. An optical fiber was implanted above the injection site and video recordings were done in an open-field to track body movements. Unilateral photostimulation of Gi D2-expressing neurons reduced locomotor speed and evoked ipsilateral head movements. Using high resolution axial body tracking in a linear corridor, we found that stimulation evoked body orienting movements towards the stimulated side. Altogether, our findings indicate that activation of D2-positive neurons in the Gi decreases locomotor speed and induces ipsilateral body and head orienting movements.

P1-D-170 *Decreased phase-dependant modulation in corticospinal excitability during walking in human individuals with spinal cord injury*

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The corticospinal tract plays a critical role in shaping locomotor patterns in healthy individuals, and this study aimed to characterize how spinal cord injury (SCI) alters corticospinal excitability during gait. Eleven participants with chronic SCI and eleven control participants walked on a treadmill. Transcranial magnetic stimulation (TMS) was applied over the primary motor cortex and elicited motor evoked potentials (MEPs) in both Tibialis Anterior (TA) and Soleus (SOL) during the gait cycle, which was subdivided in 10 bins. Short-interval intracortical inhibition (SICI), which reflects intracortical mechanisms was also assessed. In controls, MEP amplitudes were phase-dependent, matching electromyographic (EMG) activity ($p<0.05$ for each bin), and reciprocal modulation between TA and SOL MEPs were observed across the gait cycle ($r=-0.4416$; $p=0.0034$). After SCI, this pattern was only partly preserved: phase modulation and MEP–EMG coupling remained for TA ($p=0.027$), whereas SOL modulation and coupling ($p=0.39$) as well as reciprocal TA–SOL modulation ($r=-0.233$; $p=0.0703$) were absent. Intracortical inhibition in TA tended to be reduced in SCI but did not reach statistical significance. Phase dependant modulation of excitability in the corticospinal pathway is impaired in participants with SCI, which likely underlies the deficits observed during gait, such as decreased EMG amplitude and impaired reciprocal activation of muscles acting at the ankle.

P1-D-171 *Developing human spinal cord methodology to study pain circuits*

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Chronic pain affects more than one-third of the global population, reduces quality of life, and imposes substantial socioeconomic costs. Although preclinical studies have clarified many mechanisms underlying persistent pain, translation to patients remains limited, underscoring the need for more predictive assays and improved recognition of interspecies differences. Here, we developed a surgical approach to rapidly recover intact human spinal cord from recently deceased organ donors and evaluated the preservation of neuronal and glial populations by immunolabeling tissue from 16 donors (11 males and 5 females). In parallel, we established organotypic cultures of lumbar spinal cord slices that remained viable for several weeks and were compatible with functional assays. Using adeno-associated viral vectors, we drove somatic GFP expression in dorsal horn cells, enabling targeted whole-cell recordings from visually identified neurons (n=44; 3 males, 4 females). Neuronal capacitance, input resistance, rheobase, spike threshold, and resting membrane potential did not differ significantly by sex; however, input resistance and rheobase varied with donor medical history. To assess network dynamics, we performed calcium imaging to quantify coordinated dorsal horn activity evoked by electrical and chemical stimulation. This human ex vivo platform provides a translationally relevant approach to interrogate spinal pain circuitry and to evaluate candidate analgesics.

P1-D-172 *Differential cerebellar modulation of PA- and AP-sensitive sensorimotor circuits*

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Distinct neural substrates supporting sensorimotor control and learning in motor cortex can be probed using short-latency afferent inhibition (SAI), in which a peripheral nerve stimulus precedes transcranial magnetic stimulation (TMS) of motor cortex. Different populations of cortical neurons can be preferentially engaged by varying TMS current direction (posterior–anterior [PA] vs anterior–posterior [AP]) and pulse duration (120 vs 30 μs). The present study examined how the cerebellum, a key structure for motor learning, differentially modulates afferent projections to these neuronal populations. First dorsal interosseous motor-evoked potentials (MEPs) were elicited using PA120 or AP30 TMS. SAI was induced by median nerve stimulation 21 ms prior to TMS. Cerebellar conditioning pulses were delivered 3, 5, 7, or 9 ms before TMS (CBI). SAI in the presence of cerebellar conditioning was quantified as (SAI+CBI)/SAI, normalized to unconditioned TMS. Preliminary results showed that for PA120 stimulation (n=6), cerebellar conditioning produced a modest reduction in SAI across 5–9 ms interstimulus intervals. In contrast, for AP30 stimulation (n=4), cerebellar conditioning produced a larger reduction in SAI, most pronounced at 7–9 ms. These findings indicate that cerebellar TMS weakens SAI in a timing-dependent manner, with earlier effects on PA-sensitive circuits and later, stronger effects on AP-sensitive circuits, consistent with differential cerebellar modulation of distinct sensorimotor inhibitory pathways.

P1-D-173 *Differential roles of muscle and cutaneous afferents in motor recovery after spinal cord injury in adult mice*

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Epidural spinal cord stimulation is an emerging approach to enhance rehabilitation following spinal cord injury (SCI) and is believed to function via the indiscriminate activation of low-threshold sensory axons such as those of muscle and cutaneous afferents located in the dorsal spinal cord. However, whether targeted activation of specific sensory afferent populations (eg., activate only muscle afferents) also enhances rehabilitation is poorly understood. To test this, we injected Runx3flpo/+;PVcre/+ mice with intersectional AAVs to express channelrhodopsin2 (ChR2) specifically in muscle afferents and (MA) and rapidly adapting cutaneous afferents (RACA), and optogenetically stimulated these neurons via flexible biocompatible LED arrays implanted over the lumbar spinal cord. We found that simultaneously stimulating both MA and RACA

during the swing phase of walking reliably induces hindlimb flexion, whereas stimulation during the stance phase elicits hindlimb extension, consistent with amplification of phase-appropriate sensory feedback. Following a thoracic SCI, phase dependency is preserved; however, evoked motor responses increase in magnitude and are frequently accompanied by spasms, indicating an enhanced, potentially maladaptive sensory drive. Ongoing experiments aim to selectively activate either MA or RACA neurons post-SCI to determine their specific contributions to locomotor recovery. These findings may inform more precise spinal cord stimulation protocols and highlight optogenetics as a tool for investigating the role of spinal circuits in recovery after SCI.

P1-D-174 *Dimensionality of neural manifolds during adaptive motor behaviors*

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Motor behaviours such as reaching for a coffee cup emerge from coordinated activity across large neural populations that can flexibly adapt on short timescales. Neural population activity in the primate motor cortex (M1) and dorsal premotor area (PMd) are key nodes in this network. Prior work has shown that rapid motor adaptation can be achieved by specific changes in neural population states within neural manifolds. These manifolds have been shown to capture the dominant covariance in the population, but how aspects of the manifolds such as dimensionality change during motor adaptation remain unexplored. Here, we compared and contrasted the dimensionality of neural activity in M1 and PMd during baseline motor performance and epochs of motor learning (adaptation to predictable force-field and visuomotor rotation perturbations during a cued center-out reaching task). We estimated both the linear and non-linear dimensionality using established methods over the course of adaptation to the perturbation. Our preliminary analyses confirm that variation in dimensionality between M1 and PMd remains stable over days of baseline motor performance. We further demonstrate that dimensionality may be flexible during motor adaptation to enable flexible output and meet task demands.

P1-D-175 *Disruption of glomerular map formation in the accessory olfactory system impairs chemosensory processing and social behavior*

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Chemosensory signals play a fundamental role in guiding innate behaviors in mice, including mating, territoriality, and aggression, through specialized olfactory subsystems, such as the vomeronasal system. Chemosignals activate distinct subsets of glomeruli in the accessory olfactory bulb (AOB), suggesting that glomerular maps may contribute to the interpretation of chemosensory information driving these behaviors. Here, we investigate the consequences of altering glomerular map organization on sensory processing and social behavior in male and female mice by ablating the expression of the cell adhesion receptor Kirrel3 in basal vomeronasal sensory neurons (VSNs). Conditional ablation of Kirrel3 in VSNs led to a marked reorganization of the posterior AOB, characterized by altered specificity of VSN innervation and enlarged glomeruli. Despite retaining the ability to discriminate male from female urine, Kirrel3-deficient mice exhibited significantly reduced vomeronasal acuity to chemosignals, which is associated with a loss of male-directed aggression in both male and postpartum female mice. Functional mapping of neural activity revealed attenuated responses in mitral cells of the AOB, as well as in aggression-related brain regions, including the medial amygdala and ventromedial hypothalamus. These findings underscore the critical role of glomerular map integrity in the vomeronasal system for maintaining chemosensory acuity and regulating social behaviors. Furthermore, this study provides insight into how molecular disruptions in sensory neuron connectivity can reshape neural circuits and behavioral outputs.

P1-D-176 *Distinguishing modality-specific and shared cognitive networks in a low-dimensional neural space*

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Change detection, the ability to identify novel deviations in sensory input over time, is critical for adaptive behavior. Although auditory and visual change detection rely on distinct input sensory pathways, they also engage shared cognitive processes such as attention, prediction, and working memory. Here, we investigated how modality-specific and modality-general processes are organized within a shared low-dimensional neural subspace. We analyzed the fMRI component of simultaneous EEG–fMRI data from 17 healthy participants performing auditory and visual oddball tasks in separate sessions (OpenNeuro; Walz et al., 2018). Functional connectivity matrices were constructed using Pearson correlations across regions defined by the Glasser atlas. Partial least squares (PLS) regression was then used to project connectivity patterns from both modalities into a common low-dimensional space comprising four latent variables (LVs), interpreted using LV loadings and graph-theoretical measures. Two sets of dominant latent variables emerged. In the first set, LV1 captured a network including primary sensory, sensorimotor, and spatial attention regions present in both modalities, and LV2 revealed a modality-invariant network spanning default mode, dorsal attention, and frontoparietal systems, consistent with higher-order cognitive control and memory processes. These two LVs captured orthogonal networks, indicating separable contributions of sensory integration and higher-order cognition. In contrast to the first set, the second set, LV3 and LV4, showed modality-specific connectivity patterns, reflecting enhanced segregation within auditory or visual networks. Together, these findings demonstrate that change detection engages both shared and modality-specific network architectures, effectively disentangled within a low-dimensional functional connectivity framework.

P1-D-177 *Diverse neuronal responses to visual precision in cat cortical area 21A: Unraveling the complexity of orientation processing*

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Our research investigates the impact of visual stimuli precision on orientation processing in higher cortical areas. Specifically, we examined cortical area 21a in cats, often considered the equivalent of primate area V4 within the hierarchical organization of visual processing. 'MotionClouds' (MC), pseudo-natural stimuli, were used to explore orientation precision's effects on neuronal responses. MC precision is governed by four parameters: the orientation, the spatial frequency (SF), Bθ and Bsf. We analyzed responses from 411 neurons in area 21a, seeking patterns in orientation precision processing. Our findings reveal a large range of neuronal responses. A significant proportion of neurons (56%) exhibited peak discharge at the highest precision levels, indicating a preference for finely-tuned stimuli. In contrast, 33% displayed maximum discharge at lower precision levels. Within the high-precision group, there were varied responses: 39% were highly sensitive to the highest precision, 16% showed a gradual decreasing activation with reduced precision, and 44% had increased firing rates at two precision levels. The lower precision group also presented variability: 60% of neurons had peak activation at sub-maximal precision, while 40% increased activation towards lower precision. These results highlight a broad spectrum of precision response profiles in higher cortical visual areas and suggest a pivotal role for the cortical ventral stream in precision processing. However, the question of how the cortex utilizes this precision information to influence visual perception remains open. Our study contributes to the understanding of cortical visual processing, emphasizing the complexity and variability in neuronal response to visual precision.

P1-D-178 *Do blind mice recover better from a stroke than healthy mice?*

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Neuroplasticity allows the cerebral regions to take control over different functions after a lesion. In blind individuals, the visual cortex can contribute to tactile and motor functions, and this phenomenon is known as crossmodal plasticity. Since in blind people, a bigger proportion of the brain is responsible for motor/tactile functions, we could expect that a lesion in the sensorimotor cortex could have less impact on the sensorimotor functions compared to non blind individuals. Conversely, , in blind individuals, a stroke in the visual cortex could cause sensorimotor impairment than in a sighted subjectThe aim of this study is to measure the sensorimotor impairments of blind and control mice, before and after photothrombotic lesions targeted into the visual or sensorimotor cortex. Sixty young mice were used. Half the mice were enucleated at birth. Each half was divided in three groups: Sham, sensorimotor stroke and visual stroke. Baseline sensorimotor functions were assessed using behavioral tests including: the adhesive tape task, the texture preference test and the grid walking test. Then, photothrombotic lesions were induced, and sensorimotor assessment was continued for 8 days post stroke. At the end, the brains were collected, cleared and imaged using lightsheet fluorescent microscopy to measure the size of the strokes and to perform correlation analysis between lesion size and the level of sensorimotor deficit. The behavioral assessment showed a constant significant ($p<0.05$) sensorimotor deficit in blind and healthy mice in both stroke conditions, and the recovery post stroke was also constant across groups. This led to the conclusion that the cortex reorganisation in blind mice is not enough to better recover from a stroke.

P1-D-179 *Dorsomedial higher visual cortex is a locus for visual attention in mice*

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Visual attention enhances detection of stimuli most relevant to the task at hand. Consistent with this view, electrophysiological work in non-human primates shows that attention improves visual neural sensitivity to cued stimuli. It is widely believed that such improved sensitivity is driven by modulation signals from higher cortical regions. However, the identity of such higher cortical areas and their targets in posterior visual cortical areas are poorly defined. To address this issue, we widefield imaged GCaMP6f signals from the entire dorsal cortex while mice visually searched for vertical bars presented at cued locations within checkerboard noise. By correlating GCaMP6f signals across the cortex to stimulus features at various screen locations, we found cue-dependent gain to vertical stimulus energy in a patch of dorsomedial higher visual cortex. The improved sensitivity to cued stimuli in this area appeared with training and was not present in untrained mice. Although primary visual cortex showed orientation tuning, it showed no measurable cueing effects. Ongoing optogenetic and anatomical tracing experiments aim to determine the necessity of this region for visual attention and to identify its inputs. Overall, these results establish a cortex-wide imaging paradigm to identify attentional sources and sinks in the mouse cortex, and identify novel areas involved in attentional computations.

P1-D-180 *Dynamic coupling between the action-mode network and sensorimotor cortex during human motor learning*

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Effective motor learning requires a dynamic interplay between specialized sensorimotor circuits and higher-order control networks. How these systems coordinate their activity across the distinct phases of learning-from initial adaptation to consolidated performance and subsequent relearning-remains poorly understood. Here, we investigated the evolving functional coupling between the Action-Mode

Network (AMN), a domain-general system for goal-directed action, and the Somatomotor Network (SMN) throughout a multi-day visuomotor adaptation task. Using manifold learning techniques to characterize the low-dimensional geometry of changes in AMN-SMN functional connectivity, we observed a series of robust, task-dependent network reconfigurations. We found that initial, error-driven learning was marked by significant manifold contraction, reflecting heightened functional integration between the AMN and SMN with the broader higher-order association cortices. However, as learning performance plateaued, the AMN disengaged, leading to manifold expansion and greater functional segregation, while the SMN remained in a persistently integrated state, forming a latent signature of the newly acquired motor memory. Notably, this entire temporal pattern of network dynamics was reinstated during relearning on the next day. Furthermore, we found that the degree of functional integration during the initial learning phases on both days was related to individual differences in learning and relearning performance. Together, these findings establish a hierarchical framework where the AMN dynamically couples and decouples with the SMN to meet the changing demands of skill acquisition, consolidation, and memory-guided retrieval, providing new insights into the large-scale sensorimotor network mechanisms that guide motor learning.

P1-D-181 *Dynamic intra-hemispheric premotor–motor functional connectivity during precision grasp in macaques*

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Neural activity underlying hand movement is distributed across the primary motor (M1), dorsal premotor (PMd), and ventral premotor (PMv) cortices. While these areas are known to coordinate for tasks such as grasping, the dynamic intra-hemispheric connectivity between them remains poorly understood. We hypothesize that connectivity patterns between these motor areas adapt dynamically to facilitate movement execution. We simultaneously recorded neural activity from the hand representation of M1 (one hemisphere) and bilateral PMd and PMv in three rhesus macaques performing a precision grip task with either the contralateral or ipsilateral hand. Functional connectivity was assessed using time-resolved cross-correlation between well-isolated neurons, examining temporal alignment with behavioral markers and lag-dependent connectivity. Significant correlations were quantified using Z-scores. We compared M1-PMv, M1-PMd, and PMv-PMd connectivity by measuring coupling strength and directionality resulted from incidence and magnitude of Z-scores. Data were analyzed for each monkey and pooled for group-level analysis. Marked shifts in connectivity were observed throughout the task phases. At the population level, coupling strength peaked during the reaction and reaching phase and the late grasp period, regardless of which hand was used. Lag analysis, used as an indicator of directionality, revealed a dynamic shift in influence: premotor areas initially led M1 during high-connectivity periods before the directionality of the interaction reversed. This study characterizes the temporal dynamics of motor network interactions. These findings provide a framework for identifying disruptions in neurological disorders and inform the development of targeted neuromodulation and therapeutic strategies.

P1-D-182 *Effect of norepinephrine release in movement refinement during directional reaching*

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The motor cortex (MC) plays a crucial role in controlling reaching movements, but the neuronal mechanisms leading to refinement of this behavior remain elusive. Previous work has shown that norepinephrine (NE) is released onto the MC during motor execution suggesting a role for NE in movement refinement, along with its known role in behavioral flexibility and the processing of salient cues. Here, we trained head-fixed mice to reach toward a fixed spatial target and then assessed their ability to adapt their movement to a novel spatial goal, by introducing a previously untrained target location. During task performance, we monitored NE signals in the MC using fiber photometry to measure GRABNE fluorescence. Our preliminary results revealed an increase in NE release at movement onset and in response to a reward-predicting cue. Moreover, tracking

of paw movements showed that NE release correlates with movement execution and targeting accuracy. To establish causality, we will photo-inhibit locus coeruleus NE neurons at cue onset or during movement. We expect these manipulations to selectively impact reaction time or movement kinematics, revealing the distinct contributions of cue-evoked and movement-related NE signals respectively. Future directions should explore how norepinephrine modulates neural plasticity in the MC during the refinement of a motor action. Together, these findings will advance our understanding of how neuromodulators support adaptive motor control.

P1-D-183 *Effects of early blindness on odor discrimination and cortical activity in mice*

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Sensory loss induces compensatory plasticity that can enhance processing of spared modalities. While much work has focused on how early vision loss can affect tactile and auditory systems, much less is known about its influence on olfactory processing. Here, we examine how congenital blindness alters odor discrimination and cortex-wide sensory activity in head-fixed mice. Sighted and congenitally blind mice (GNAT1/2 mutants; both sexes) were trained on a two-alternative forced-choice task to discriminate between two odors and their mixtures. Mice start a trial by holding a wheel with their front paws, and upon odor presentation, indicate their choice for the dominant odor by steering the wheel either left or right. In addition, we performed widefield calcium imaging over dorsal cortex in mice expressing GCaMP8s during passive presentation of odors and visual stimuli, as well as during the odor discrimination task. Both groups successfully learned the task. Compared to sighted controls, blind mice learned faster and showed improved discrimination of odor mixtures, shown by a steeper relationship between performance and mixture ratio. Preliminary widefield calcium imaging results suggest significant cortical alterations to odor processing following vision loss. These findings show that vision loss is associated with enhanced olfactory discrimination. Ongoing experiments aim to examine cortical activity during task performance and to causally test the role of cross-modal cortical activity in driving behavioural performance increases seen in early-blind mice.

P1-D-184 *Electrophysiological biomarkers of thermal pain in the insula revealed by stereo-electroencephalography*

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Introduction: Converging evidence suggests the insula is a critical hub for central processing of pain stimuli. Deep brain stimulation of the posterior insula is hypothesized as a potential target for refractory chronic pain but requires better understanding of pain neurophysiology within this region. Characterization of electrophysiological signatures of pain might enable development of adaptive, network-guided neuromodulation. This study aimed to identify local field potential (LFP) biomarkers of thermal pain in the insula and other pain matrix regions using stereo-electroencephalography (SEEG). Methods: Five patients undergoing SEEG monitoring for drug-resistant epilepsy received hot and cold noxious thermal stimulation to the forearm. After preprocessing and artifact rejection, power spectral density was computed across frequency bands. Stimulus-related spectral changes were assessed using Wilcoxon signed-rank tests. Results: Heat stimulation increased gamma/high-gamma activity in both the anterior and posterior insula, alongside decreased delta and alpha power in the posterior insula. Only the posterior insula exhibited increased gamma/high-gamma activity with cold stimulation (all $p < 0.05$). Heat increased gamma and decreased theta/alpha activity within the amygdala, whereas cold stimulation increased theta activity in the orbitofrontal cortex (all $p < 0.05$). Conclusion: Thermal nociception produces region and frequency-specific LFP signatures within the insula. These biomarkers may support development of neuromodulation strategies for chronic pain.

P1-D-185 *Electrophysiological differences in auditory processing in the inferior colliculus of Cntnap2 knockout rats*

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The Cntnap2 knockout (KO) rat exhibits a loss-of-function mutation of a gene that encodes contactin-associated protein-like 2 (CASPR2), a cell adhesion molecule highly involved in neurodevelopment. Loss-of-function mutations in Cntnap2 in humans cause a syndromic neurodevelopmental disorder with core symptoms of autism spectrum disorder (ASD). Accordingly, the KO rat shows core ASD symptoms, including alterations in auditory sensory perception, which has been supported by hyperresponsivity and temporal processing differences in multiunit in vivo electrophysiological recordings in the auditory cortex. We tested if similar characteristics are present at the inferior colliculus (IC), a midbrain region of the ascending auditory pathway. We recorded multiunit activity during an auditory steady-state response paradigm of five different modulation frequencies in the IC of anesthetized adult KO and wildtype rats to assess responsivity, entrainment, and temporal processing. We found that KO multiunit clusters in the IC have increased firing rates at the higher modulations and delayed responsivity, which supports that a loss of Cntnap2 function can cause auditory processing differences at the IC. We are currently pursuing in vivo electrophysiology with simultaneous social testing to explore how the IC connects auditory processing and oxytocin-mediated social behaviour. We hope to demonstrate for the first time how loss of Cntnap2, by altering auditory processing in the IC, moderates social behavioural circuitry development, which is also heavily implicated in ASD pathophysiology.

P1-D-186 *Elucidating mechanisms of cell-type–specific noradrenergic modulation in motor cortex circuits of 16p11.2 deletion mice to rescue delayed motor learning*

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Autism spectrum disorder (ASD) affects 1 in 60 children and is typically marked by social, communicative, and behavioral impairments. However, motor delays are often seen in individuals with 16p11.2 deletion (+/-), one of the most common genetic causes of ASD. Noradrenaline (NA) is a strong modulator of neuronal activity, and many ASD symptoms can be attributed to maladaptive activity of locus coeruleus (LC). Our lab recently uncovered a role for dysregulated LC-NA function in motor learning delays in the 16p11.2+/- mouse model of ASD. We previously showed delayed motor learning linked to abnormal pyramidal neuron (PN) activity and reduced NA levels in primary motor cortex (M1), which was rescued by chemogenetic LC-NA activation. Here, we investigated the NA dynamics and neuronal activity in M1, and the mediating adrenoceptor (AR) pathways involved. RNAscope revealed increased α2-AR expression in parvalbumin (PV) interneurons relative to PNs. Simultaneous dual-channel 2-photon imaging revealed differential responses of PV neurons to behavior-induced NA release in 16p11.2+/- mice during motor learning. Pharmacological testing showed that α2-agonist guanfacine, but not α1- or β-agonists, restored both motor learning and PN activity. Given the α2-AR role in modulating HCN channels on dendritic branches, we performed 2-photon imaging and found guanfacine enhanced 16p11.2+/- PV dendritic activity during running. These results identify PV α2-AR signaling as a key mechanism in regulating the dysfunctional motor circuits and highlight a potential treatment for ASD motor symptoms.

P1-D-187 *Estrous cycle modulates cortical auditory responses across species*

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Introduction. Female mammals undergo cyclical physiological and behavioral changes driven by hormonal fluctuations. However, whether and how the estrous cycle modulates auditory sensory processing and

the activity of distinct neuronal populations remains poorly understood. Here, we investigated auditory responses across reproductive phases in mice and humans. Method. We recorded EEG activity in men and women and intracortical local field potentials (LFPs) in male and female mice. Female participants were tested during two phases of their estrous cycle characterized by low estradiol (E2) levels (early follicular phase in women; late estrus in mice) and high E2 levels (late follicular phase in women; proestrus in mice). To assess causality, female mice additionally received systemic injections of estradiol or saline during the late estrus phase. Results. Across species, females in high-E2 phases exhibited reduced baseline gamma power and weaker auditory entrainment (AE), stimulus-specific adaptation (SSA), and responses to deviant sounds. In female mice during low-E2 phases, acute estradiol administration reduced baseline gamma power, AE, and SSA, supporting a causal role of estradiol in shaping these auditory cortical responses. Single-unit recordings further revealed that baseline firing rates of putative fast-spiking interneurons were selectively increased during high-E2 phases. In addition, both evoked firing rates and spike–LFP coherence during 40-Hz auditory steady-state stimulation were significantly reduced during high-E2 phases. Conclusions. Together, these findings demonstrate that auditory processing is robustly modulated by estrous cycle across species and highlight the importance of hormonal status when assessing auditory perception in mouse models and in women with psychiatric disorders.

P1-D-267 *Large Glutamatergic Neurons in the Lateral Cerebellar Nuclei Are Essential for Motor Coordination and Cognitive Function in Mice*

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Introduction: Cerebellar nuclei (CN), composed of four bilateral pairs, represent the primary output of the cerebellum and play a central role in motor and cognitive processing. Increasing evidence links CN dysfunction to ataxic disorders such as Friedreich's Ataxia (FA). However, their compact organization and strong integration with the cerebellar cortex have made it difficult to isolate their specific contributions. We selectively ablated glutamatergic neurons (GNs) in the lateral CN to define their functional role. Methods: Vglut2-Cre mice received unilateral stereotaxic injections of AAV-FLEX-EGFP-DTR into the lateral CN, followed by diphtheria toxin administration to selectively ablate GNs. Motor function was assessed using rotarod, beam walking, footprint, and Montoya staircase tests. Cognitive performance was evaluated using open field, T-maze spontaneous alternation, and novel object recognition tests. Immunolabeling with anti-SMI32 confirmed selective neuronal loss, while GABAergic and glutamatergic synaptic markers were used to assess circuit integrity. Results: GN-ablated mice exhibited motor deficits, including reduced rotarod performance and impaired beam walking, with increased traversal time and step number. Cognitive impairments were also observed, including reduced spontaneous alternation, altered exploratory behavior. Synaptic markers analyses revealed alterations in both inhibitory and excitatory inputs, suggesting disrupted connectivity within cerebellar circuit. Conclusion: These findings identify lateral CN, GNs as critical regulators of motor and cognitive function. The observed circuit disruptions provide mechanistic insight into cerebellar output dysfunction and may contribute to the early pathophysiology of FA, highlighting potential targets for therapeutic intervention.

E - HOMEOSTATIC AND NEUROENDOCRINE SYSTEMS

P1-E-188 *Role of basolateral amygdala neurons activated by sleep deprivation on risk- and mood-related behaviours*

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Sleep deprivation (SD) differentially impacts men and women, as men increase risk-taking and women report mood disruptions. To counter SD-related deficits, we must identify brain regions compromised by sleep loss. Preliminary screens of the neuronal activity marker c-Fos from whole-brain tissue clearing revealed

the amygdala as a novel SD-activated region. As the amygdala is sexually dimorphic and may underlie mood-related deficits, we (1) defined the spatial distribution of SD-activated amygdala cells in male and female mice and (2) determined their role on SD-impacted behaviours. We mapped c-Fos+ amygdala cells rostrocaudally in male and female wildtype mice after rest (control), 4-h SD, or 2-h recovery sleep (RS) post-SD. SD increased the total number of c-Fos amygdala cells in male but not female mice. In males, c-Fos increased in several amygdalar subnuclei with SD but reversed with RS. In females, SD persistently increased c-Fos in the anterior basolateral (BLAa) and intercalated amygdala (IA). As the IA is amorphous, we trapped the excitatory hM3Dq DREADD receptor in SD-activated BLAa cells of Fos-cre mice. Chemogenetic activation of SD-activated BLA cells did not alter nesting or grooming behaviour or open field exploration, but it increased open arm time in male but not female mice on the elevated zero maze. Male SD-activated BLAa cells thus reduced anxiety, which may underlie sex differences in SD-induced risk-taking. These findings highlighted BLAa sensitivity to SD especially in male mice and point to amygdalar candidates contributing to the effects of sleep loss.

P1-E-189 *Agouti integrates environmental cues to regulate paternal behaviour*

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Paternal care is rare among mammals and the neural mechanisms governing its emergence are poorly understood. We leveraged the natural paternal behaviour of African striped mice (Rhabdomys pumilio) and combined it with brain-wide cFos quantification, single-nucleus RNA-sequencing, virally mediated gene perturbation, and environmental manipulation to dissect the neural basis of natural variation in male parenting. We find that socio-environmental conditions drive individual variation in male alloparenting such that post-weaning social isolation increases paternal care while social living in higher density groups increases infanticide. This natural variation in care corresponds to neural activity in the medial preoptic area and changes in correlated activity across brain regions. Within the medial preoptic area, expression of agouti signaling protein (Agouti) in neurons is increased by group housing and is negatively associated with care, and overexpression of Agouti reduces care and enhances infanticide in previously tolerant animals. Naturalistic manipulations further reveal that Agouti integrates long-term housing conditions rather than food availability/hunger. Our findings reveal that variation in male paternal care reflects context-dependent regulation of conserved hypothalamic and melanocortin signaling mechanisms rather than the presence or absence of paternal capacity. We are continuing to explore the socio-environmental influences integrated by Agouti in terms of development, and we are further characterizing Agouti's function throughout the striped mouse brain.

P1-E-190 *Brain-wide Klb expression in a novel Klb-cre mouse line*

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Beta-klotho (KLB) is an obligate co-receptor for diverse actions of fibroblast growth factor (FGF) 19 and FGF21 including food preference, glucose tolerance, metabolism, and cognition. Their diverse functions imply widespread KLB expression, thus transgenic tools to isolate Klb-expressing cells are necessary to define cell-specific function. Additionally, FGFs exert sex-dependent effects, but Klb expression was only defined in males. We generated a Klb-cre mouse line to (1) determine brain-wide Klb expression and (2) elucidate sex differences in Klb expression. Retro-orbital delivery of a Cre-dependent virus encoding GFP in male and female Klb-cre mice captured brain-wide Klb expression in the adult brain. We mapped GFP-immunoreactive (GFP-ir) cells along the entire rostrocaudal axis of the brain and found abundant GFP-ir cells in the cortex, thalamus, and midbrain that were similarly distributed in male and female mice. We validated Klb hybridization in GFP-ir cells, as over 80% of GFP-ir cells expressed Klb mRNA. Majority of GFP-ir cells expressed low levels of Klb mRNA, so GFP expression was independent of Klb abundance. However, high-Klb GFP cells were more abundant in female Klb-cre brains, especially in the medulla, and we also confirmed the

prevalence of high-Klb in the medulla of female wildtype mice. In sum, we validated a specific and sensitive Klb-cre line to reveal brain-wide Klb expression and region-specific sex differences. This work presents a novel tool to interrogate the roles of FGF19 and FGF21 in a region-specific manner.

P1-E-191 *Cannabidiol regulates EGFR and GPER levels in a Glioblastoma model in vitro*

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Glioblastoma is the most aggressive malignant brain tumor characterized by high proliferation, invasiveness, and resistance to therapy. Glioblastoma patients have a bad prognosis, with approximately 18 months of survival. Epidermal growth factor receptor (EGFR) and G protein-coupled estrogen receptor (GPER) are involved in cell division, invasion, and apoptosis of several malignancies, and both are present in glioblastoma cells. Cannabidiol (CBD) has demonstrated anti-cancer properties. CBD has an inhibitory action on the tyrosine kinase domain of EGFR; however, the EGFR/GPER-associated signaling involved in glioma growth remains unclear. This study investigates the concentration of EGFR and GPER and their role in the proliferation of C6 cells treated with varying doses of CBD. We cultured C6 cells, and we added 5, 10, 20, and 40 µM of CBD for 48 hours. We quantified EGFR and GPER concentrations by ELISA. We analyzed cell viability by MTT assay and cell proliferation by immunofluorescence. Cell viability decreased significantly at 40 µM CBD compared to 10, 20 µM, and the control. EGFR levels at 5 and 20 µM were lower than at 40 µM CBD; however, no significant difference was observed compared to the control. GPER levels were lower at 20 µM with respect to the control. The percentage of Ki67-positive C6 cells decreased in a dose-dependent manner under the effect of CBD. Overall, these preliminary data support an antiproliferative effect of CBD in C6 in vitro, and this Phyto-cannabinoid could be a therapeutic target for Glioblastoma.

P1-E-192 *Developing behavioural paradigm to study state-dependent stress sensitivity in awake head-fixed mice*

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How does the brain determine the magnitude of the stress response? Although core stress circuits are hardwired, sensitivity to sensory inputs is highly variable and shaped by internal brain states. Understanding how brain state modulates sensory responsiveness requires paradigms that simultaneously measure behavioural and physiological stress outputs together with neural activity. Here, we developed a novel behavioural paradigm to examine behavioural and physiological responses to sensory stimuli before and after acute stress in awake, head-fixed mice. Mice were habituated to head fixation over 10 days, then presented with a visual stimulus before and after a stress-triggering air-puff event, enabling quantification of state-dependent changes in sensory sensitivity while maintaining compatibility with electrophysiological recordings. Behaviour was analyzed using automated pose-based tracking, with validation against manual scoring for detection of position, struggle, and freezing. In parallel, we implemented a custom piezoelectric pressure-sensor platform to detect subtle movements not reliably captured by video alone. Using these complementary measures, we found that mice exhibit significantly enhanced responses to sensory stimuli following stress exposure. We are extending this paradigm by incorporating electrocardiogram and electromyogram recordings to quantify autonomic and muscle activity. Ongoing work will integrate this framework with electrophysiological recordings to determine how state-dependent neural dynamics regulate post-stress sensory sensitivity.

P1-E-193 *Differential calbindin and calretinin expression in subfornical organ neurons of rats and mice*

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The subfornical organ (SFO) is a sensory circumventricular organ that plays a crucial role in regulating body fluid balance, thirst responses, blood pressure, and cardiovascular homeostasis. SFO consists of two functionally distinct subregions: the dorsolateral shell located externally and the ventromedial core located internally. However, the anatomical organisation of the SFO has not yet been fully elucidated. This work compared the anatomical organisation of the SFO between mice and rats. Immunohistochemical images of calbindin and calretinin were obtained from three male C57BL/6 mice and three male Wistar rats. Staining intensity was quantified by measuring pixel density within defined regions of interest. Pixel density data were plotted and fitted with a fourth-degree polynomial (quartic) to the calbindin and calretinin densities for each species (all $R^2 \geq 0.90$) . Our findings revealed a clear regional differentiation in the rat SFO such that calbindin positivity was concentrated in the ventromedial core region, whereas calretinin positivity was concentrated in the dorsolateral shell region. In contrast, the immunoreactivity of calbindin and calretininin the mouse SFO did not show a distinct core–shell separation and exhibited a more diffuse expression profile. These results suggest that the anatomical organisation of the SFO differs between species.

P1-E-194 *Effects of an oxytocin receptor antagonist (OTRA) on estrogens' facilitative effects on social recognition (SR) in the medial prefrontal cortex (MPFC) of female mice*

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Objective: Social recognition (SR), the ability to discriminate between familiar and novel conspecifics, is a fundamental social behaviour supported by the medial prefrontal cortex (mPFC). Rapid, non-genomic actions of 17β-estradiol (E2) in the infralimbic (IL) and prelimbic (PL) mPFC facilitate SR in female mice, but the receptor mechanisms underlying these effects remain unclear. This study aimed to determine whether oxytocin receptor (OTR) signaling is required for estrogen's rapid enhancement of social recognition in the mPFC. Methods: Adult ovariectomized female mice received stereotaxic guide cannulae targeting the IL and PL mPFC. In Experiment 1, a dose–response study examined the effects of intra-mPFC infusion of an oxytocin receptor antagonist (OTRA; 25, 50, 75, or 100 nM) on SR to identify a subeffective dose. In Experiment 2, the identified subeffective OTRA dose was administered prior to intra-mPFC E2 or vehicle. Treatments were delivered 2 minutes apart and 15 minutes before testing. Social recognition was assessed using a validated difficult paradigm sensitive to rapid estrogenic effects. Social memory was quantified using investigation ratios, and non-social behaviours were assessed as controls. Results: Data collection is currently underway. The ongoing experiments are designed to determine the dose-dependent effects of oxytocin receptor antagonism in the mPFC and to assess whether blocking oxytocin receptors alters estrogen's rapid facilitation of social recognition. Full analysis will be completed prior to the conference. Conclusion: This study will test whether oxytocin receptor signaling is required for estrogen's rapid facilitation of social recognition in the medial prefrontal cortex, addressing a key gap in current models of fast neuroendocrine regulation of social cognition.

P1-E-195 *Effects of vaporized Δ9-tetrahydrocannabinol exposure on the behavioral and neuroendocrine consequences of acute stress*

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Cannabis use—via smoking or vaping—is a common strategy to cope with stress. Although widely perceived as stress-relieving, cannabis may exacerbate stress-related consequences, underscoring the need to define its underlying neurobiological effects. Corticotropin-releasing hormone (CRH) neurons in the paraventricular nucleus of the hypothalamus (CRH-PVN) orchestrate behavioral and endocrine

stress responses, with corticosterone (CORT) as a primary hormonal output. Endocannabinoids modulate CRH-PVN neuron activity during stress, yet both anxiolytic and anxiogenic outcomes have been associated with altered endocannabinoid signaling. However, how exogenous cannabinoids influence stress recovery and long-term outcomes remains unresolved. Here, we tested whether acute post-stress exposure to Δ9-tetrahydrocannabinol (THC) alters stress-induced anxiety-like behavior, aversive memory, and neuroendocrine output. Mice were exposed to acute stress or left unstressed, then immediately exposed to vaporized THC (10%) or vehicle. THC increased immobility following vaping, an effect attenuated by prior stress, and reduced stress-induced elevations in circulating CORT. However, THC failed to modify anxiety-like behavior in the dark–light test 24 hours later or aversive memory recall 48 hours post-stress. To identify mechanisms underlying these transient effects, we examined in vivo CRH-PVN activity. Calcium imaging revealed rapid modulation of CRH-PVN neuron activity by THC. Together, these findings reveal a dissociation between acute neuroendocrine modulation and long-term stress recovery, highlighting the complex interaction between stress and exogenous cannabinoid signaling.

F - COGNITION, EMOTION AND MOTIVATION

P1-F-196 *ATP administration enhances sensitivity to outcome devaluation in the dorsomedial but not dorsolateral striatum in rats*

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Increasing evidence suggests that neuroinflammation can alter behavioural flexibility; however, the mechanisms through which inflammatory signalling affects corticostriatal circuits remain unclear. Microglia, the resident immune cells of the central nervous system (CNS), become activated during chronic neuroinflammatory states, including those associated with diet-induced obesity (DIO). Activated microglia can release adenosine triphosphate (ATP), an important signalling molecule that acts on purinergic receptors and influences glutamatergic transmission. This study aimed to determine whether ATP signalling within the dorsal striatum is sufficient to alter behavioural control and whether its effects are region-specific. If ATP signalling is increased in DIO, this may contribute to behavioural impairments. Adult male Long-Evans rats were trained on an instrumental outcome devaluation task, in which responding is assessed after the value of a previously earned reward is reduced, to distinguish goal-directed from habitual behaviour. Sensitivity to outcome value was measured following localized ATP or saline infusions into the dorsomedial striatum (DMS), which supports goal-directed action, or the dorsolateral striatum (DLS), which supports habitual responding. Contrary to the initial hypothesis, ATP infusion into the DMS did not disrupt goal-directed behaviour. Instead, rats remained sensitive to outcome devaluation, with ATP-treated animals showing an enhanced devaluation effect relative to saline controls ($F(1,5)=11.749$, $p=0.019$). In contrast, ATP infusion into the DLS tended to reduce sensitivity to devaluation ($F(1,6)=4.063$, $p=0.09$). Together, these findings demonstrate region-specific effects of ATP on behavioural control and suggest that ATP alone is insufficient to explain inflammation-related behavioural inflexibility.

P1-F-197 *A comparison of canonical and informed basis set modelling of the haemodynamic response during N-back cognitive testing*

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General Linear Models (GLMs) are used to analyze event-related functional magnetic resonance images. While GLMs traditionally use a fixed canonical function to model the haemodynamic response (HRF), there is increasing evidence of HRF shape variability across individuals, brain locations, and tasks. This study compares bilateral frontal and parietal HRFs (representative data from left frontal area shown below) modelled using both the canonical HRF alone (model 1) and the canonical HRF with its first and second temporal derivatives (model 2) while participants (n = 14) performed a Human Connectome Project working

memory paradigm (0- and 2-back). Condition differentiation increased when amplitude was modelled with model 2 (4.5x10-4 +/- 3.7x10-4) compared to model 1 (5.8x10-4 +/- 4.0x10-4; t(13) = 7.6, p < 0.001, two-sample t-test). In addition, the 2-back condition showed increased reaction times (919 +/- 60.5 ms) compared to the 0-back condition (706 +/- 99.3 ms; t(13) =8.6, p < 0.001, paired t-test). The 2-back condition also showed increased HRF latency (3.3 +/- 0.1s) compared to the 0-back condition (3.1 +/- 0.1s; t(13) = 5.2, p < 0.001, paired t-test). Reaction time had stronger correlation with HRF latency (r = 0.66, p < 0.001) than amplitude (model 1: r = 0.36, p = 0.06; model 2: r = 0.38, p = 0.05). Our results suggest that HRF modelling using multiple basis functions can provide a more sensitive model of HRF amplitude, resulting in greater discernment between task conditions. HRF latency estimates also provide behavioural correlates not reflected in HRF amplitude alone.

P1-F-198 *A mechanical analogy for the observed oscillations in choice behavior of a population facing a time-varying reward*

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Here we report on different behavioural strategies that emerge in a population when confronted with time varying rewards. Our investigation uses a two-lever choice task to study decision-making in which participants must repeatedly choose between an immediate, but variable reward, or a constant but delayed one. The reward on the immediate reward goes inversely with its selection frequency. For rats carrying out this task, we find two behavioural groups: patient rats who choose to wait for the constant reward, and impatient rats who prefer immediate, and overall, less rewards. Analysis of the choices from each group shows that their decisions oscillate back and forth over time in a regular pattern. Stochastic simulations of this task using a reinforcement learning (RL) framework reproduce experimental observations. Using a mean-field approximation we show that the RL equations for the population dynamics can be approximated by a set of ODEs, which for the given task map to that of a damped harmonic oscillator. This mechanical analogy shows how oscillations in decision preferences occur at characteristic frequencies determined by how strongly the individual values reward, akin to the spring stiffness, and their learning rate, that is analogous to the inverse mass. There is a biasing force that moves the equilibrium toward either waiting or impatience. The spring analogy indicates that there are intrinsic limits to how rapidly agents can adjust their preferences while maintaining stable decision dynamics.

P1-F-199 *A MRI study of metabolic and cerebrovascular health*

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There is clear evidence that adiposity is associated with markers of decreased brain health. It is also now well-established that high fat and sugar diet can blunt dopamine signaling and alter functional brain responses independently of changes in adiposity. However, few studies have examined associations between diet and brain structure. Examining subcortical brain structure may provide insight into long-term adaptations of dopamine-related circuits arising from habitual dietary exposure. As part of the Brain and Body Cohort (BBC) study, we investigated whether habitual dietary fat and sugar intake is associated with subcortical brain volumes independently of adiposity. In 50 participants (aged 33–55 years; mean age = 41.3 ± 7.2 years; 21 men, 29 women; mean BMI = 25.7 ± 4.6 kg/m^2), total Dietary Fat and Sugar (DFS) questionnaire scores, reflecting fat and sugar intake, were related to MRI-derived subcortical volumes estimated using FreeSurfer, using general linear models adjusted for age, sex, and body fat. Higher DFS scores were positively associated with bilateral caudate volume (left: $\beta = 0.00118$, FDR-p = 7.7×10^{-4}; right: $\beta = 0.00111$, FDR-p = 7.7×10^{-4}), while associations in the pallidum did not survive correction for multiple comparisons, and no significant associations were observed for other subcortical regions. These findings provide evidence that dietary fat and sugar intake may shape striatal structure independently of adiposity, highlighting a potential neurobiological pathway through which diet could influence reinforcement processes relevant to eating behavior.

P1-F-200 *Acute and delayed effects of psilocybin on prefrontal cortical neuronal activity*

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Psilocybin, a psychedelic drug and selective serotonin receptor agonist, shows therapeutic promise as a novel treatment for psychiatric disorders. However, its mechanisms of action and effects on neural circuit activity remain poorly understood. The prefrontal cortex (PFC) is a key region of interest for psilocybin's therapeutic effects given its high serotonin receptor density and altered function in psychiatric disorders. Previous work has found that psilocybin rapidly and persistently increases PFC dendritic spine growth, mirroring its reported fast-acting and long-lasting therapeutic effects. Because psilocybin binds to all serotonin receptor subtypes, heterogeneous downstream effects at a neuronal level are expected. Yet, the acute single-cell level effects of psilocybin on neuronal activity underlying changes in plasticity have not been elucidated. To investigate the acute and delayed effects of psilocybin on PFC neuronal activity, we performed single-photon calcium imaging with a miniature microscope to acquire longitudinal, single-cell resolution recordings of PFC neuronal activity in the homecage before and for several days following psilocybin administration. Using both single-cell and population-level analyses we identify heterogeneous and time-varying effects of psilocybin on individual neurons in the acute phase and persistent alterations in population dynamics. These findings elucidate acute neuronal effects underlying psilocybin's neuroplastic effects and further describe psilocybin's persistent effects on PFC network-level activity.

P1-F-201 *Acute psilocin alters aversive memory retention and extinction learning in Drosophila melanogaster*

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Psychedelic drugs such as psilocybin and its active metabolite, psilocin, have gained attention as tools to treat disorders like phobias, anxiety, or PTSD and is involved in modulating memory processes in mammals; however, the mechanisms underlying these effects of psilocybin are not fully understood. Since many of the molecular and cellular mechanisms of learning and memory in Drosophila are evolutionarily conserved, we hypothesize that if we can reproduce psilocybin's effects on retention and extension of aversive memories in Drosophila, this will open the way to investigate the underlying mechanisms of psilocybin on memory. To assess this, we trained flies in a T-maze to associate one odor (CS+) with electric shock, while a second odor (CS−) remained neutral. Psilocin (2 mM) was acutely administered either before training or after training. We used odor preference at different intervals to assess memory retention. To induce extinction learning we repeated non-reinforced CS+ presentations and assessed extinction recall. Our data show that psilocin administered after conditioning significantly increased aversive memory retention at all time points, whereas pre-conditioning psilocin had no detectable effect. Notably, psilocin administered after training enhanced the extinction of adverse memories. Together, these timing-dependent effects support a role for psilocin in modulating post-training processes across aversive and extinction phases. These results highlight Drosophila as a tractable model to uncover conserved mechanisms of psychedelic action on fear-related memories.

P1-F-202 *Adolescent n-acetylcysteine intervention attenuates neurobehavioral deficits following prenatal THC exposure*

Nicholas Hamati [1], Enzo Perez-Valenzuela [1], Leandro Val Sayson [1], Marieka Devuono [1], Matthew John Jones [1], Amanda Kunst [1], Madeline Machado [1], Haseeb Mahmood [1], Marwa Idrissi [1], Daniel Hardy [1], Walter Rushlow [1], Steven Laviolette [1]

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Cannabis use during pregnancy is increasing, yet the long-term neurobehavioral consequences of developmental Δ9-tetrahydrocannabinol (THC) exposure and the potential for postnatal intervention remain incompletely understood. During critical windows of brain development, THC is known to increase oxidative stress and neuroinflammation. The present study examines whether adolescent supplementation with the antioxidant N-acetylcysteine (NAC) can mitigate behavioral alterations induced by prenatal THC exposure.

Pregnant Wistar rats received an edible THC exposure model (10 mg/kg/day) from gestational days 7-21. Offspring were administered NAC in drinking water (0.9 g/L) during adolescence (postnatal days 30-51) and then assessed across behavioral models measuring anxiety-related behavior, locomotion, cognition, social interaction, and sensorimotor gating from postnatal days 60-90. Prenatal THC exposure produced persistent, sex-dependent alterations in behavior, including changes in risk assessment, locomotor activity, social recognition, and prepulse inhibition, without evidence of global cognitive impairment. Adolescent NAC supplementation partially normalized THC-induced behavioral alterations, with stronger effects observed in male offspring. These findings suggest that prenatal THC alters neurodevelopmental trajectories in a domain- and sex-specific manner, and that adolescence represents a window for intervention. Ongoing work will investigate molecular correlates of these effects, focusing on redox balance and neurotransmitter signaling in the mesocorticolimbic system.

P1-F-203 *Age-related differences in learning rate across memory tasks*

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Canada's population is rapidly aging. Aging is associated with declines in cognitive abilities that support learning; notably, declarative and procedural memory, which rely on distinct neural systems. It is unclear if these systems are differentially affected by age, as few studies have directly compared learning rate across declarative, procedural, and complex (mixed) memory tasks between young and older adults. We hypothesize that older adults will demonstrate lower learning rates than young adults, in a task-dependent fashion. The present study examines learning rate in declarative, procedural, and complex memory tasks in 150 healthy participants, including 75 young adults (18–40 years) and 75 older adults (60–75 years). Learning was assessed using three memory tasks: the Grid Location Task (declarative memory), the Motor Sequence Learning task (procedural memory), and a piano task incorporating both declarative and procedural components. Learning rate was quantified using performance slopes across trials for each task. Our results clarify how learning changes with age, explore how age differentially affects declarative and procedural learning, and quantify their relative effect on a more naturalistic task that requires both systems. This work is important for understanding cognitive aging and may help guide targeted interventions to preserve learning and memory in older adults.

P1-F-204 *Aging reduces scale-free temporal persistence of resting BOLD signals independent of cerebral blood flow: Evidence from 550 adults in HCP-A*

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Scale-free temporal organization (long-range temporal correlations) is a core property of intrinsic brain activity and is thought to support sustained coordination and information integration across distributed networks. In aging, however, BOLD-based measures of temporal persistence may be confounded by cerebrovascular change. Here we leverage the unique pairing of resting-state fMRI and arterial spin labeling (ASL) in the HCP–Aging to test whether age-related reductions in the Hurst exponent (HE; DFA-based index of temporal persistence) primarily reflect vascular perfusion decline or an intrinsic shift in brain dynamics. We analyzed 550 adults spanning midlife to oldest age. HE was estimated in 55 LPBA40 regions; perfusion was extracted from gray-matter, partial-volume–corrected CBF maps, and analyses were constrained to cortical gray matter to mitigate structural mixing effects. Across the whole brain, HE declined linearly with age, indicating progressively weaker temporal persistence. Although CBF also decreased with age, global CBF was not associated with global HE. Regionally, age-related HE reductions were widespread, largest in lateral prefrontal and insular cortices, and remained robust after accounting for sex, systolic blood pressure, and regional CBF. Mediation analyses provided little evidence that perfusion explains the age–HE association: indirect effects (Age → CBF → HE) were small and spatially restricted, with detectable partial mediation primarily in bilateral gyrus rectus. No age × CBF interaction survived correction. These findings show that the aging brain exhibits a broad breakdown of scale-free temporal persistence that is not explained by baseline

perfusion decline, supporting HE as an intrinsic marker of functional brain aging and demonstrating the value of integrating ASL-CBF to constrain vascular interpretations of BOLD-derived dynamics.

P1-F-205 *Altered neuronal lactate dehydrogenase a expression in mice results in age-dependent changes to spatial memory and region-specific changes to the lipid profile*

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The cellular mechanisms that underly memory consolidation in the brain are bioenergetically demanding. Since glucose utilization in the brain declines with age, neurons rely on alternate metabolites such as lactate and lipids as fuel sources to sustain synaptic activity. Lactate production is primarily governed by lactate dehydrogenase-A (LDHA) activity, the rate-limiting enzyme catalyzing pyruvate to lactate conversion. Proper lactate levels within neurons are necessary for lipid synthesis, which is needed to support membrane biogenesis and axonal growth. Neuronal lipid droplet formation also occurs to sequester peroxidised lipids or provide energy reserves during stress. The present study suggests that neuronal-specific LDHA levels are elevated with age. The effects of neuronal-specific ldha induction and knockout on spatial learning and memory were also examined. Elevated neuronal-generated lactate promoted learning in young female mice, while memory impairments were observed with aged male neuronal ldha-induction mice. In contrast, spatial contextual memory was improved in old ldha knockout mice compared to age-matched controls. Levels of neutral lipids and lipid-droplet-associated protein perilipin2 were reduced within hippocampal neurons of induction mice but increased in knockout mice compared to controls. These findings suggest that elevated neuronal lactate production may interfere with protective LD formation to preserve memory in older animals, thus providing a novel perspective on the role of lactate and lipid processing on memory across lifespan.

P1-F-206 *An intrinsic evolving hippocampal scaffold guides the encoding of novel spatial memories*

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Computational models suggest the hippocampus maintains an adaptive generative model of the world, where spontaneous offline activity reflects sampling from learned priors. New experiences update these priors, which subsequently influence future learning. This framework unifies two hippocampal phenomena: “preplay”—pre-experience sequential activity reflecting the prior—and “representational drift”—the continuous evolution of a spatial map, which is seen as a structured adaptation rather than noise. A key prediction is that the evolution of offline and online neural activity must be coordinated during learning. To test this, we used longitudinal miniscope calcium imaging and LFP recordings to track dorsal hippocampal CA1 neurons in mice for weeks before and during the learning of a novel environment. We found that offline hippocampal activity patterns around sharp-wave ripples (SWRs) evolve daily in a structured manner. Critically, the neural code during the first encounter with the novel environment was significantly more similar to the offline patterns from the immediately preceding sleep sessions than to those from days earlier. Furthermore, the similarity between offline activity on any two days was significantly correlated with the representational similarity of the encoding sessions that followed. Our results provide direct evidence that learning is guided by a slowly evolving intrinsic scaffold, revealing how the hippocampus balances stability and plasticity.

P1-F-207 *Anatomical and functional investigation of VGLUT3-positive projections from the median raphe nucleus to the lateral septum in anxiety modulation*

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Elsa Lalot, Lina Elvers, Suzanne van der Veldt, Justine Fortin-Houde, Guillaume Ducharme, Bénédicte AmilhonAffiliations:1) CHU Sainte-Justine Research Center, Montreal, Quebec, Canada2) Département de Neurosciences, Université de Montréal, Montreal, Quebec, CanadaThe lateral septum (LS) integrates afferents from multiple brain regions, including the raphe nuclei (RN), and contributes to region-specific functions such as spatial coding in the dorsal LS and emotional regulation in the ventral LS. RN–LS projections include glutamatergic axons expressing the vesicular glutamate transporter type 3 (VGLUT3), which often form pericellular baskets around LS neurons. Using immunohistochemistry, we mapped VGLUT3-positive terminals along the rostro-caudal LS and quantified colocalization with serotonin (5-HT). VGLUT3 density was highest in the ventral LS, whereas VGLUT3/5-HT overlap was strongest in the dorsal LS. Retrograde tracing in VGLUT3-Cre mice identified inputs from several RN subregions, including the median raphe nucleus (MnR). Two-color tracing revealed limited overlap between VGLUT3 projections to the LS and the ventral hippocampus, indicating pathway-specific organization. Additional VGLUT3-positive inputs originated from the bed nucleus of the stria terminalis, nucleus incertus, and pontine central gray. These findings demonstrate that multiple, anatomically segregated VGLUT3-positive pathways innervate distinct LS subregions and suggest that VGLUT3-positive circuits contribute to affective behaviors such as anxiety and motivation.

P1-F-208 *Artificial reactivation of a cocaine-associated engram in the dorsal dentate gyrus attenuates cocaine prime-induced reinstatement of drug-seeking*

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Relapse-prevention strategies aim to reduce the likelihood and severity of drug relapse following abstinence, largely by targeting cravings that drive drug-seeking. Drug-seeking can be precipitated by stress, drug-associated cues, or re-exposure to the drug itself. We are interested in the contribution of drug-related memories to relapse. Memories are stored as hippocampal representations and can be genetically tagged and optogenetically manipulated in mice. Here, we tagged dorsal dentate gyrus (dDG) neurons involved in encoding a first exposure to cocaine using the TetTag system in male and female C57BL/6 mice. Using conditioned place preference (CPP), we tested whether optical reactivation of these cocaine-encoding cells could substitute for a cocaine prime to reinstate CPP following extinction. We compared reinstatement induced by optical reactivation alone, a cocaine prime alone, or a saline-tagged control, and additionally tested whether concurrent cocaine priming and optical reactivation produced additive effects. We found that optical reactivation of a cocaine-related dDG engram alone did not reinstate CPP for the drug-paired context. Strikingly, however, when optical stimulation was delivered concurrently with a cocaine prime, reinstatement was blocked. These findings suggest that reactivation of neurons encoding a first cocaine exposure may exert a protective effect against relapse. We also examined locomotor outcomes and found that reactivation of neurons encoding the first cocaine exposure did not alter locomotion, whereas reactivation of neurons encoding the fourth cocaine exposure increased locomotor activity, consistent with sensitization. This effect was stronger when stimulation occurred in the original drug-paired context.

P1-F-209 *Assessing probabilistic reward sensitivity in an early-life stress rodent model*

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Random ratio (RR) reinforcement schedules—central to slot machine payout structures—produce higher rates of responding than fixed-ratio (FR) schedules with equivalent reward rates. Despite this well-established effect, few studies have directly compared choices between RR and FR schedules. The present study assessed 48 male and female rats on a schedule preference task designed to measure attraction to random reinforcement by holding an RR schedule constant while progressively reducing the response requirement of an FR alternative across blocks. As continuing RR preference is evaluated against increasingly favorable FR alternatives, preference for RR may indicate risk-prone behavior. In the present study, we examined this schedule preference in two groups of animals: one exposed to early-life stress and a control group. Based on evidence from human studies linking early life stress to increased risk of addiction and related outcomes, we expected the early-life stress group to show a stronger and more enduring preference for the random schedule. All rats showed a robust initial preference for RR. Preliminary analyses revealed a group-level effect of early-life stress on increased overall RR preference across blocks, reflecting increased and sustained attraction to probabilistic reinforcement despite increasingly favorable FR alternatives. These findings suggest a potential rodent model for studying how early life stress influences behavioral features relevant to addiction risk.

P1-F-210 *Astrocytes integrate noradrenaline inputs to modulate fear memory specificity*

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Astrocytes, the most abundant glial cells in the brain, regulate neuronal circuits and behavior. Through their complex morphologies, astrocytes integrate peripheral and central cues to influence learning and memory. We previously found that genetic perturbation of amygdala astrocytes results in fear generalization, suggesting a critical role for astrocytes in tuning memory specificity. However, how astrocytes integrate learning-related neural activity to regulate this process remains unknown. Here, we identify a role for astrocytic integration of noradrenaline (NA) inputs in the basolateral amygdala (BLA) during the formation of specific fear memories. Using ex vivo two-photon calcium imaging in astrocytes expressing a genetically encoded calcium sensor, we found that among multiple neurotransmitters tested, astrocytes preferentially respond to NA with robust calcium responses via Gq-coupled α1-adrenergic receptors. Using fiber photometry, we further show that astrocytes are activated during both fear learning and recall in behaving animals. To test the functional role of NA signaling, we used a novel viral-mediated α1-receptor knockdown to block astrocytic responses to NA. This manipulation abolished astrocyte calcium activity during learning and recall and was sufficient to induce a complete loss of discrimination between aversive and neutral cues. Together, these results demonstrate that astrocytes play a central role in determining fear memory specificity by enabling discrimination between neutral and aversive stimuli.

P1-F-211 *Basolateral amygdala astrocytes encode anxiety states*

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The basolateral amygdala (BLA) has long been implicated in the regulation of emotional states, including anxiety. However, while previous experiments have demonstrated the important role of BLA principal neurons in driving anxiety-related behaviors, population-level recordings suggest that principal neurons encode broad exploratory states rather than anxiety per se. This discrepancy questions whether anxiety is indeed represented within the BLA, or if the BLA reflects a broader representation of behavioral states. Here, using simultaneous in vivo calcium recordings in both astrocytes and principal neurons, we find that in contrast to neurons, astrocyte activity provides a stable and scalable representation of threat-induced anxiety across an array of behavioral tasks. We find that the magnitude of astrocyte response to anxiogenic

stimuli is modulated by the individual anxiety levels of animals, and that exploration of anxiogenic environments can be decoded across multiple tasks using astrocyte activity alone. Through causal manipulation approaches combined with fiberphotometry recordings, we then demonstrate a causal role for BLA astrocyte calcium in anxiety processing by showing that driving astrocytic Ca2+ effectively increases anxiety-related behavior. Finally, we uncover the signalling mechanisms underlying astrocytic anxiety coding. Using 2-photon imaging and pharmacological experiments in brain slices, we find that BLA astrocytes almost exclusively respond to norepinephrine. We then demonstrate in vivo that knocking down astrocytic alpha1 adrenergic receptors abolishes astrocyte anxiety coding and reduces anxiety-like behaviors. Altogether, our results establish a role for BLA astrocytes as key computational elements of anxiety circuits, and could pave the way for innovative astrocytes-targeting treatment for anxiety disorders.

P1-F-212 *Behavioural ratings of appetitive conditioning in adolescent anorexia nervosa: Interim analysis*

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Hypothesis:Reward processing has been found to be disrupted in anorexia nervosa (AN), but whether symptom severity impairs learning of reward associations remains unclear. In this study, we examined whether psychopathology, indexed by eating disorder severity (EDE-Q), anxiety (STAI), mood disturbance (POMS), depression/anxiety/stress symptoms (DASS), and reward sensitivity (BAS) are associated with degree of appetitive conditioning. We predicted that those with greater symptom severity would have with weaker appetitive learning. Materials and Methods:Participants included a preliminary sample of individuals with AN (n = 14), weight-restored AN (WR; n = 21), and healthy controls (HC; n = 20). Participants completed an fMRI-based appetitive conditioning task during which the CS+ (a neutral shape) was paired with an appetitive US (the sound of baby laughter), while the CS− (same shape, different colour) was not. Participants rated valence of each CS before and after the conditioning task. We fit linear mixed models across all participants (AN, WRAN, and HC) to examine whether continuous clinical measures (same model) were associated with changes in CS+ relative to CS− valence. Results and Conclusion:None of the clinical variables were significantly associated with reward learning. BAS showed a nominal association with reward learning ($F(13,38) = 2.06$, uncorrected $p=.042$), but this effect did not survive correction for multiple comparisons. Although data collection is ongoing, these findings thus far suggest that appetitive conditioning processes may operate independently of broad psychopathology measures.

P1-F-213 *CA1 time cell dynamics during interval timing in a mouse model of Schizophrenia*

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Schizophrenia (SZ) is characterised by cognitive impairments including a prominent but understudied time perception deficit (e.g. judging the duration of intervals). However, little is known about the neural circuitry underlying timing in SZ. Timing deficits have been attributed to aberrant hippocampal network activity. A candidate neurobiological mechanism supporting interval timing in the hippocampus are time cells, i.e. neurons activated at specific timepoints, forming sequences encoding elapsed time during a delay period. We hypothesized that disrupted time cell activity in the hippocampus underlies temporal deficits in SZ. We tested this hypothesis using the Df16 mouse model of the human 22q11.2 deletion, the strongest genetic risk factor for SZ. To assess interval timing, we trained Df16 mice on a head-fixed temporal bisection task. Mice were first trained to discriminate between long and short intervals between cues for water rewards. They were tested using trials with intermediate durations to assess subjective perception of time. Compared to wild-type littermates, Df16 mice overestimated intervals, displaying reduced temporal accuracy. Using two-photon calcium imaging we recorded CA1 activity, tracking the same neurons across days as mice learned the task. Ongoing analysis will compare the emergence and stability of CA1 time cell sequences throughout short and long delays between mouse genotypes. Our results will provide a putative mechanism for disrupted temporal perception in Df16 mice, linking hippocampal circuit dysfunction to disorganised cognition.

P1-F-214 *Can imaging biomarkers reliably predict persistent post-concussion symptoms following mild traumatic brain injury? A pilot study*

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Approximately one in four patients with mild traumatic brain injury (mTBI) experiences chronic post-concussion symptoms (PCS); a mosaic of cognitive, behavioural, and somatic problems that cause functional deficits for three months or more post-injury. Despite its high incidence, no method for predicting chronic PCS exists in this patient population, and the neurological basis for these prolonged symptoms remains to be understood. Thus, we aim to use multimodal MRI data from mTBI patients in the acute (≤ 7 days) and subacute (1 month) phases to predict symptom outcomes in the chronic phase. The present pilot study uses a cohort of 25 neurologically intact participants (mean age 24.21±3.42, 12 female) with no history of brain injury or psychiatric illness to validate this methodology. MRI markers of neuroinflammation, resting-state functional network connectivity, and white matter density and integrity were collected at both acute and subacute timepoints, alongside cognitive markers and symptom scores. Three months after the initial timepoint, a brief interview was conducted to quantify the presence of chronic PCS using a validated symptom scale. Imaging biomarkers from the acute and subacute timepoints, as well as cognitive and behavioural data, were used to establish preliminary norms for later comparison with mTBI patients. Future studies will expand to characterize how aberrations from these norms underlie distinct symptom profiles in acutely injured patients and explore which of these altered imaging signatures are predictive of PCS outcomes.

P1-F-215 *Cannabinoid type 1 receptor (CB1R) blockade in adolescence alleviates the effects of adolescent social instability stress (SS) on social interaction and social reward motivation in female rats*

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We previously found that adolescent social instability stress (SS; daily 1-hr isolation and novel cage partner pairings from post-natal days (P) 30-45) reduced adolescent social interaction and adult social motivation in female rats. Here, we tested whether repeated treatment with AM251 (a cannabinoid type-1 receptor (CB1R) antagonist) would attenuate SS-induced social deficits in female rats based on evidence that repeated blockade of CB1R increased social interaction when tested days after treatment had ended. SS or CTLs (control; no SS) received AM251 or vehicle from P30-45 to block CB1R activity during adolescence. AM251 increased social interaction when tested 5 days later in SS rats and was without effect in CTL rats. Two weeks later, in a social operant conditioning test in which rats would nose-poke to access a stimulus peer, there was no effect of either SS or AM251 on training days. SS reduced social motivation in a progressive ratio test relative to CTLs (as previously shown), and AM251 increased social motivation in SS rats and had no effect in CTL rats. Dopamine (DA) receptor abundance was investigated because of the role of the DA system in reward motivation. There was no effect of SS or AM251 on DA receptor abundance in the medial prefrontal cortex and nucleus accumbens as determined by western blotting. Together, these findings suggest that disruptions in adolescent CB1R signaling underlies SS-induced social deficits, and that adolescent CB1R blockade buffers against the effects of adolescent social stressors in female rats.

P1-F-216 *Characterizing ventral hippocampal neural dynamics during heroin and cocaine self-administration and drug-seeking using fiber photometry*

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Contextual memories strongly influence relapse vulnerability in substance use disorders. The ventral hippocampus (vHPC) encodes contextual information and links it to reward; however, the dynamics of vHPC activity during drug-taking and relapse remain poorly defined. This study aims to characterize vHPC neural

dynamics during drug-taking and context-driven drug-seeking after abstinence. Male mice (n=6) underwent stereotaxic surgery to express GCaMP8s in the vHPC and to implant an optical fiber for real-time fluorescence recording. Mice also received jugular catheterization for intravenous self-administration (IVSA) of heroin (0.05 mg/kg/inf) or cocaine (0.5 mg/kg/inf) under a fixed-ratio 1 schedule. Fiber photometry recordings were collected during drug-taking (day 8 of IVSA) and drug-seeking after abstinence, assessed as lever pressing without reinforcement at 24 hours and 30 days post-IVSA. Event-related calcium transients were quantified by aligning peri-event activity to each lever press. Drug self-administration was associated with time-locked increases in vHPC calcium activity around reinforced lever presses. During abstinence tests, drug-seeking was accompanied by elevated vHPC activity, trending toward greater activation following prolonged abstinence compared to early abstinence ($p < 0.05$). These findings indicate that the vHPC is dynamically engaged during drug-taking and abstinence-associated drug-seeking. Increased activity following prolonged abstinence may reflect evolving context-linked motivational processes that could contribute to relapse vulnerability.

P1-F-217 *Chronic adolescent stress reprograms stress-responsive connectivity and socioemotional behaviors throughout the lifespan*

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Exposure to chronic stress during adolescence, a period marked by heightened brain plasticity, increases the risk of emotional dysregulation and neuropsychiatric disorders in adulthood, yet neural mechanisms and sex-specific outcomes remain unclear. Here, we show how adolescent chronic unpredictable stress (CUS) affects adult stress susceptibility and brain-wide functional connectivity. Male and female C57BL/6 mice were exposed to a CUS paradigm from postnatal day (PND) 28-40. Immediately after stress, adolescent CUS increased social interaction time selectively in females, with no clear effects in anxiety-like, cognitive, or stress coping behaviours. In adulthood (>PND 70), mice with or without adolescent CUS exposure were subjected to an acute footshock stressor (10 shocks; 2 seconds each) followed by behavioural testing to assess stress susceptibility. Male and female mice with a CUS history exhibited impaired social behaviour, and enhanced risk-taking behaviours. Neural activity associated with acute stress was examined using cFos immunohistochemistry in stress-related brain regions, revealing baseline sex differences and overall reduction in significant functional connections in CUS mice, with female CUS mice having a much higher reduction overall. These findings show that adolescent CUS influences stress susceptibility in adulthood and results in sex-dependent reduced connectivity in associated neural circuits, providing insight into mechanisms underlying sex-specific risk for neuropsychiatric disorders.

P1-F-218 *Chronic modulation of SDK1+ prefrontal neurons alters reward learning strategies*

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Sidekick-1 (Sdk1) has been implicated in depression risk and stress resilience in both human genetic studies and rodent models. We previously identified Sdk1 as a hub gene within a molecular network regulating stress resilience in reward-related brain regions, yet the functional contribution of Sdk1-expressing neurons to behaviour remains poorly understood. Using unpublished work from our lab, we identified a population of deep-layer prefrontal cortex (PFC) neurons expressing Sdk1 and sought to determine their role in reward-guided decision-making. Sdk1-Cre mice received PFC injections of Cre-dependent excitatory or inhibitory DREADDs. Animals were trained on a probabilistic reversal learning (PRL) task in which lever presses yield chocolate milk rewards with varying probabilities. For the first five days of PRL, mice received C21 to chronically activate or inhibit Sdk1+ neurons; behaviour was then tracked for an additional ten days without C21 to assess persistent effects. Across multiple behavioural metrics, chronic excitation of Sdk1+ neurons enhanced reward learning, whereas chronic inhibition impaired reward learning. To characterize underlying behavioural strategies, we applied a generalized linear model–hidden Markov model (GLM–HMM) with

Bernoulli observations to infer latent decision-making states as a function of task covariates. Our previous work identified three discrete strategies in this task: reward-learning, reward-achievement, and stickiness. Chronic excitation of Sdk1+ neurons increased the probability of occupying the optimal reward-learning state, while inhibition decreased reward-learning and promoted the stickiness state. Together, these results demonstrate that Sdk1-expressing PFC neurons modulate reward-learning strategies and may contribute to neural mechanisms supporting stress resilience.

P1-F-219 *Chronic voluntary consumption of cannabinoids in C57BL/6 mice*

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The majority of pre-clinical cannabinoid work to date has focused on injection or oral gavage of cannabinoids. However, in humans, cannabis is primarily consumed by inhalation or oral ingestion. Recently, a voluntary oral consumption model that used THC dissolved in Ensure chocolate gelatin to monitor the acute effects of a cannabinoid in mice was developed. The long-term, or chronic, pharmacodynamic and pharmacokinetic effects of cannabinoids in pre-clinical models remain understudied. Therefore, advancement of the model proposed by English et al. into a chronic treatment paradigm is needed to assess behavioural and physiological effects, drug tolerance, and bioaccumulation. Mice were individually housed and given Ensure chocolate pudding that contained 10 mg/15 mL of cannabinoids (THC or CBD) daily for 14 days. Mice underwent behavioural and physiological testing and blood collection on alternating days (every 48 hours). Weight data along with behavioural data will be presented, including movement, body temperature, and pain perception. All treatment groups were evaluated, comparing sex as well as treatment group. Among the physiological measurements made, reduced body temperature and nociception were observed in THC-consuming males and females compared to control. Pharmacokinetic data will be compared to behavioural data to see whether drug concentrations align with behavioural effects. Establishing this animal model allows our group to explore the long-term benefits and harms of cannabis using an approach that more closely resembles real-world cannabis use.

P1-F-220 *Circuit-specific noradrenergic dynamics are associated with stress susceptibility in a learned helplessness model*

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Stress exposure is a major risk factor for depression and related disorders, yet the neuromodulatory mechanisms that bias individuals toward resilience or vulnerability remain incompletely understood. The locus coeruleus–noradrenergic (LC–NE) system broadly innervates cortical and limbic circuits involved in coordinating cognitive and emotional responses to stress. However, whether region-specific NE dynamics during aversive experiences differ between resilient from stress-susceptible individuals remains unclear. To address this question, we monitored real-time extracellular NE signaling in the medial prefrontal cortex (mPFC) and amygdala (AMY) of male mice using fiber photometry with the genetically encoded GRABNE sensor. Mice underwent a learned helplessness paradigm, a widely used animal model of depression, consisting of inescapable footshock training followed by escapable shock testing. Behavioral performance during escape trials (escape latency and failure rate) was used for k-means clustering to classify animals into resilient and susceptible groups. Real-time dual-site fiber photometry data showed that in the mPFC, susceptible mice exhibited significantly reduced NE responses, quantified as area under the curve, relative to resilient animals. In contrast, in the AMY they were comparable between resilient and susceptible mice. These findings suggest that stress susceptibility may reflect an imbalance in noradrenergic engagement across prefrontal and limbic circuits, with potential implications for understanding neuromodulatory targets in stress-related mood disorders.

P1-F-221 *Claustro-cortical communication is disrupted by increased kappa opioid signaling in chronic pain*

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Increases in kappa opioid signaling in the brain contributes to the pathophysiology of chronic pain. Recent preclinical evidence has pointed to kappa antagonism as a potential therapy for chronic pain, reversing circuit dysfunction in pain processing centers. The claustrum, which has the densest expression of kappa opioid receptors (KOR) in the body, was recently shown to regulate pain processing through feed-forward inhibition of the anterior cingulate cortex. This communication is depressed in chronic pain, contributing to pain hypersensitivity. Given the rich presence of KOR (an inhibitory G protein coupled receptor), we hypothesize that increased KOR signaling in the claustrum is the mechanism by which chronic pain decreases claustro-cortical communication, and inhibiting this signaling will rescue pain hypersensitivity. We found that claustrum microinjection of a kappa antagonist did not affect acute nociception but did prevent mechanical allodynia induced by hind-paw injection of complete Freund's adjuvant. Microinjection of the antagonist after the establishment of allodynia completely reversed pain hypersensitivity, suggesting KOR signaling is necessary for maintaining chronic pain. To confirm this was specific to the claustrum, the Oprk1 gene was knocked out of claustrum projections in KORFLOX/FLOX mice. Deletion of claustrum KOR prevented mechanical allodynia similar to the antagonist. Together, these results highlight claustral KOR signaling as a critical feature of chronic pain, further supporting KOR antagonists as a potential therapeutic for chronic pain.

P1-F-222 *Closing in on the quarry of a 72-year search: the cellular origins of MFB reward signals*

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The directly activated "first-stage" neurons that give rise to the rewarding effect of medial forebrain bundle (MFB) stimulation have eluded identification for over 70 years. Although MFB self-stimulation depends on dopamine (DA) transmission, the rewarding effect arises primarily from direct activation of non-dopaminergic neurons. When rats work for optical activation of midbrain DA neurons, but not for electrical activation of the MFB, dopamine-transporter (DAT) blockade reduces the stimulation strength required to produce a reward of given intensity. Psychophysical, electrophysiological, and lesion studies suggest that the somata of at least some first-stage neurons are in the basal forebrain. We expressed ChR2 or ChroME2f in basal forebrain neurons and implanted optical fibers at classical MFB self-stimulation sites. Optical stimulation in these rats mirrored the rapid acquisition of operant responding and vigorous performance observed in rats working for electrical MFB stimulation. In rats expressing ChroME2f, the effectiveness of the optical stimulation grew steadily as the pulse frequency was increased to values as high as 120 Hz. The effect of DAT blockade paralleled the results obtained in rats working for electrical MFB stimulation: willingness to pay opportunity costs increased, but the stimulation strength required to produce a reward of given intensity remained constant. These findings implicate non-dopaminergic, MFB-projecting basal forebrain neurons in the first stage of the MFB reward substrate and bring us closer to identifying these long-sought neurons.

P1-F-223 *Comparative evaluation of the degree of transparency of AI-based transcription tools*

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Cognitive and social sciences make an extensive use of recorded interviews, which must be transcribed in order to be analyzed. This process of verbatim transcription is highly time-consuming and comes with many constraints, such as inter-judge variability and human errors due to exhaustion, especially when analyzing

large corpus of data, thus limiting the efficiency of this strategy. The rise of Artificial Intelligence (AI) could possibly provide an answer to these limitations. In the recent years, several AI-based transcription tools have been developed. However, notably due to their recency, a direct comparison of these tools is still lacking. By centering our analyses on the concept of transparency, we conducted here a comparison of fourteen AI-based transcription tools that can be used in the context of cognitive and social sciences. Through the use of a multifactorial analysis grid, the fourteen tools were compared for the type of the AI engine, the openness of the code, the characteristics of the language training, the reported efficiency of tool, and the (cyber)security of the data. Overall transparency increased with the recency of the tool. Transparency of the AI engine and of the language predicted overall transparency of the tool. Security appears to be a growing concern for these tools. These comparisons represent one of the first steps to help researchers to critically and optimally select AI-based transcription tools for their future study.

P1-F-224 *Cortical switching dynamics shape delta activity under propofol anesthesia*

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Delta-frequency activity is a defining feature of brain states associated with reduced or absent consciousness, like NREM sleep and general anesthesia. In sleep, delta activity shows slow oscillations (SOs, <1Hz) and slow waves (SWs, 1-4Hz). Recent work introduced transition frequency (speed of negative-to-positive deflection) as an amplitude-independent marker of cortical state switching, revealing slow and fast switching SWs during sleep. Whether similar dynamics are equally present under general anesthesia remains unclear. High-density EEG (128-channel) was recorded for ≥5 min during stable propofol anesthesia in eight adults before surgical incision. Propofol was administered via target-controlled infusion, targeting 2.0μg·mL^{-1} and adjusted to maintain a BIS of 45–55 (increments of 0.2mcg/ml). Delta events were detected per channel, classified as SOs/SWs, and transition frequency was computed. Transition frequency distributions differed importantly between wave types: SOs exhibited a largely unimodal distribution with limited variability (IQR=0.252 Hz), mostly concentrated under 1Hz, whereas SWs showed a broad, bimodal distribution (IQR=1.467 Hz), with a separation around 1.7Hz. These findings indicate that anesthetic delta activity is structured by distinct transition-dynamic regimes with slow and fast switching SWs clearly present under propofol anesthesia. This suggests that switcher dynamics are not exclusive to sleep homeostasis, but may reflect intrinsic modes of cortical switching that persist during pharmacologically induced unconsciousness.

P1-F-225 *Vocal development in a social context in common marmosets*

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Understanding the complexity of vocal communication is essential to study social behaviours and neurological disorders, providing an insight into cognitive and neural processes underlying social interactions. With their social organization, and complex vocal repertoire, common marmosets (Callithrix jacchus) are the ideal model to study vocalization and its development. In this study, I aim to understand the complexity and development of marmosets' vocalization. Hence, I recorded groups of marmosets sharing common features (age, sex, group affiliation). I developed a XGBoost-based algorithm in python to predict the sex and age of adult marmosets based on acoustic features extracted across 4 call types: long-distance (phee, twitter) and contact calls (trill, food call). The model achieved good accuracy and identified key voice features contributing to sex and age discrimination. I am examining longitudinal changes in vocalization among young marmosets (4 to 24 months old) using UMAP dimensionality reduction to visualize and quantify developmental trajectories based on acoustic features. I was able to observe possible call subtypes forming cluster more distinct and with stronger familial signature at 10 compared to 4 months old. Using this model, I can record families in a natural setting, allowing discrimination between adult and infant vocalizations and study vocal development from birth. Ultimately, I aim to understand how vocal features develop in a social

context and apply this to neurodevelopmental models to better characterize vocal impairments and improve diagnostics.

P1-F-226 *Cross-linguistic comparison of brain response to speech predictability in English, Mandarin Chinese, and French narratives*

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Recent research suggests autoregressive large language models (LLMs) share three computational principles with the human brain: continuous expectation formation before word onset, surprise responses to prediction errors after word onset, and context-dependent representation. These parallels allow LLMs to serve as a computational framework for studying language processing. However, previous neuroimaging evidence remains largely confined to single-language studies, typically identifying responses to surprisal in the temporal lobe and entropy in the frontal and parietal cortex. Here, we investigated the universality of these mechanisms across English, Mandarin, and French narratives. We analyzed the trilingual 'Le Petit Prince' fMRI dataset using four multilingual LLMs (Llama, Qwen, Mistral, and Bloom) to estimate word-level metrics. A conjunction analysis across all languages and models identified shared neuro-computational bases. Surprisal positively modulated the superior temporal gyrus (STG). Regarding uncertainty, we observed a divergent pattern: high uncertainty (entropy) was associated with increased activation in the STG, precuneus, and posterior cingulate cortex, whereas low uncertainty tracked with the activity in the inferior frontal operculum, middle frontal gyrus, medial superior frontal gyrus, and inferior parietal lobule. Additionally, high entropy reduction modulated activity in the STG and Heschl's gyrus. These findings suggest the brain's predictive architecture for natural language is remarkably consistent across typologically diverse languages, supporting a universal computational basis for speech processing.

P1-F-227 *Cross-species sensitivity to reward schedules: Ratio and delay variability in reward seeking*

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Unpredictable reward (i.e., a random-ratio schedule) is often preferred over predictable reward. But what about "uncertainty" influences decision making: variability in response cost or variability in outcome timing? To test this, we used an animal decision making task in which rats chose between a random ratio (RR) and a fixed-ratio (FR) reward schedule. We quantified RR preference by measuring how often animals chose RR over an FR option that became progressively less effortful. We contrasted this with a parallel test in which rats chose between fixed vs variable delays, matched to the temporal profile of the ratio task. Rats showed a robust preference for RR even when FR became substantially easier, whereas they showed minimal bias towards variable delays. To replicate these findings in humans, college-aged participants chose between two concurrently available response options (RR vs FR) in an analogous operant choice task. Two studies (N1=45 and N2=101 participants) failed to show a consistent RR bias either in choice behavior or a subjective rating measure; however, small gender-specific biases were observed. By identifying whether response variability or timing variability better predicts persistent choice, this work helps clarify dissociable components of uncertainty that influence reinforcement-guided decision making.

P1-F-228 *Deficits in contextual remapping underlie the tendency to generalize fear: Implications for post-traumatic stress disorder*

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Women are disproportionately vulnerable to developing Post-Traumatic Stress Disorder (PTSD), yet the neurobiological mechanisms underlying this susceptibility remain poorly understood. A core symptom of PTSD is fear generalization, in which fear learned in a specific context is inappropriately expressed in safe contexts. We propose that fear generalization reflects impaired memory-updating, characterized by a failure to remap trauma-related memory traces in the presence of new information (e.g., safety signals) and their persistent reactivation outside the original trauma context. Memories are stored as hippocampal engrams, providing a tractable framework for examining memory flexibility. Here, we investigated sex and individual differences in fear-related engram remapping within the dorsal dentate gyrus using WT male and female mice from both inbred (C57BL/6) and outbred (Swiss Webster) strains. Fear memory ensembles were tagged using the TetTag system, followed by immunohistochemistry and fluorescent confocal microscopy to quantify engram overlap. Mice were pre-exposed to a neutral context (B), fear conditioned in a distinct context (A) during which the fear engram was tagged and tested 24 hours later in either the conditioned (retrieval) or neutral (generalization) context, followed by testing in the alternate context. Brains were then collected to assess overlap. In parallel, mice were pre-screened using an acoustic startle reflex (ASR) assay to classify individuals as stress-susceptible or resilient prior to fear learning. We predict that fear generalization is associated with impaired engram remapping. We further predict that ASR-based pre-screening reliably predicts both behavioral fear generalization and engram-level remapping deficits.

P1-F-229 *Differential activation of lateral septum subregions during social and nonsocial novelty detection*

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Social recognition memory allows animals to identify and remember interactions with others. It is crucial in various social behaviors and is impaired in disorders such as schizophrenia and autism spectrum disorder. It relies on the hippocampus, particularly the dorsal CA2, ventral CA1, and dorsal CA1 regions, as well as on the lateral septum. Interestingly, these hippocampal areas send dense projections to the lateral septum. Yet, the role of hippocampus–lateral septum pathways and the contribution of distinct lateral septum subregions to social recognition memory remain unclear. We used c-Fos immunohistochemistry to quantify lateral septum activation in male and female mice after interaction with a familiar or novel conspecific or object, allowing dissociation of social from non-social novelty processing. We found that c-Fos activation in the lateral septum varied by region, subdivision, and condition, but not by sex alone. In both the dorsal and ventral lateral septum, activation was highest during interaction with a novel non-social object. In the ventral lateral septum, interaction with a novel conspecific elicited significantly lower activation than interaction with a familiar cagemate in the same testing context. Overall, our results show that the lateral septum responds differently to social and non-social novelty. These insights provide a foundation for further exploration of the lateral septum in novelty detection and recognition of objects versus social target and have implications for understanding social deficits in neuropsychiatric disorders.

P1-F-230 *Differential limbic system activation during passive processing of emotional and non-emotional music and smells: An ALE meta-analysis*

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It is known that music and smells elicit emotions via activation of the limbic system. However, it remains unclear whether this activation also occurs systematically for non emotion-related music and olfactory stimuli. To clarify this issue, we performed a series of Activation Likelihood Estimation (ALE) meta-analyses based on whole-brain fMRI studies in healthy adults exposed to emotion- and non emotion-related music and olfactory stimuli. Our main finding was that emotional music and olfactory stimuli, as well as non emotion-related olfactory stimuli, consistently activate regions of the limbic system, whereas non emotion-related music does not. This supports the notion that olfactory processing automatically recruits affective, mnemonic, and motivational circuits due to its direct anatomical projections from the olfactory bulb to the amygdala, piriform cortex, and entorhinal regions. In contrast, the recruitment of emotional circuits by music appears contingent upon task demands and stimulus characteristics. These results help clarify mechanisms underlying the differential processing of emotional and non-emotional stimuli in auditory and olfactory perception, with implications for understanding sensory-related neurophysiological mechanisms and cognitive processes relevant to mental health conditions such as stress, major depressive disorder, bipolar disorder, and post-traumatic stress disorder.

P1-F-231 *Discovering translational behavioral strategies of reward processing across species*

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Probabilistic reversal learning tasks are widely used to study reward sensitivity and cognitive flexibility in humans and rodents, yet it remains unclear whether the behavioral strategies guiding performance are conserved across species. To address this, we used a state-based modeling approach to characterize latent reward-related strategies in humans and mice. Human participants completed a computerized two-choice task with probabilistic monetary feedback, while mice performed an equivalent operant task with probabilistic chocolate milk rewards. Choice behavior was analyzed using a generalized linear model–hidden Markov model (GLM-HMM) to infer hidden behavioral states from recent outcomes. In both species, a three-state model provided the best fit and identified two reward-sensitive states: a reward-achievement state driven by recent reinforcement and a reward-learning state reflecting contingency acquisition. GLM weights were strongly correlated across species for reward-learning ($r = 0.99$, $p < 0.0001$) and reward-achievement ($r = 0.92$, $p = 0.003$), indicating conserved behavioral strategies. Engagement of the reward-learning state was associated with increased reward efficiency in both species, and a contingency sensitivity index confirmed that this state most closely approximated optimal performance. Dynamic modeling further showed that the posterior probability of the reward-learning state followed a logistic growth trajectory in both humans and mice (RMSE = 0.03 and 0.05, respectively). Although humans reached steady-state occupancy more rapidly, these findings demonstrate a shared reward-learning strategy operating on different timescales across species, supporting the translational value of this paradigm for studying reward-related behavior and its disruption in neuropsychiatric disorders.

P1-F-232 *Dissociable roles of DG and CA1 engram ensembles in context-specific rule retrieval in mice*

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The ability to select appropriate behaviours based on environmental context is fundamental for survival. While the hippocampus stores contextual representations via sparse ensembles of neurons (engrams), the specific functional contributions of the dentate gyrus (DG) and CA1 to context-guided behaviour is unclear.

Here, we investigated the information encoded by DG and CA1 engrams using a context-odour discrimination task (Coelho, Mocle et al., Sci Adv, 2024). We used activity-dependent labeling to tag engrams in either the DG or CA1 during exposure to a “tagged” context. Mice subsequently learned that one of two odours predicted rewards in this context, with reward contingencies reversed in a “non-tagged” context. To determine the necessity and sufficiency of these engrams, we used chemogenetics. Reactivation of either the DG or CA1 engram was sufficient to induce tagged-context behaviour even when mice were tested in a novel context or even in the non-tagged, indicating that DG and CA1 context-tagged engrams are sufficient for memory retrieval. Silencing the DG engram in the tagged context resulted in randomized digging behaviour, indicating a failure to use or discriminate contextual information. In contrast, silencing the CA1 engram did not induce random behavior; rather, it abolished preference for the tagged-context odor and biased digging toward the odor associated with the non-tagged context. Our results suggest that both DG and CA1 engrams can drive context-specific behaviour, but they encode fundamentally different types of information.

P1-F-233 *Distinct neural dynamics during encoding differentiate fast and slow episodic retrieval*

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Episodic memory is the ability to encode and retrieve specific events with spatial and temporal context. Traditional remembered–forgotten contrasts obscure variability within successfully remembered events. Here, retrieval response time (RT) is used to index encoding efficiency. Healthy participants completed an EEG episodic memory task (n=15) in which static image stimuli were presented (encoding phase) and later tested (test phase). Testing comprised 192 trials per participant (96 studied, 96 novel). Behavioral analyses focused on studied images correctly identified as old. Participants remembered an average of 78 studied images (56 hit-hit: correct item+location; 22 hit-miss: correct item only). Mean test-phase RT across all trials was 0.92±0.07 s. Fast and slow conditions were defined using within-subject RT quartiles and differed reliably (fast: 0.75±0.07 s; slow: 1.26±0.12 s, $p=9.79\times10^{-11}$). Correct studied items were mapped to encoding trials and split by RT. EEG analyses showed a larger late positive component during encoding for fast versus slow trials at parietal electrode Pz (500–700 ms; fast: 6.12±6.37 μV; slow: 3.49±8.29 μV; p=0.04), with similar patterns at P3 and P4. Time–frequency analyses revealed greater theta power (4–7 Hz, 250–550 ms) at Pz during encoding for slow versus fast trials (z-score: fast=1.35, slow=2.01; p=0.03). These findings demonstrate that retrieval latency captures systematic neural differences during episodic memory formation, revealing variability in encoding efficiency within successfully remembered events.

P1-F-234 *Distinct roles of Vglut2+ and Vglut2- VTA dopamine neurons during social Interactions*

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Social interactions are rewarding to humans and other mammals, but some conditions including autism spectrum disorder result in decreased social motivation. Neuromodulators like dopamine (DA) contribute to the motivation to interact with others. Dopamine cells have heterogenous gene expression and projection patterns within the brain, suggesting distinct functions. One such population of DA neurons expresses Vglut2, a gene that encodes a vesicular glutamate transporter. Vglut2+ neurons of the ventral tegmental area (VTA) project predominantly to the nucleus accumbens shell whereas Vglut2- neurons of the VTA project predominantly to the nucleus accumbens core, which have shown distinct responses to reward, aversion and saliency. Here we investigated the function of these populations during natural social behaviour. Using intersectional genetics, we expressed calcium indicators to distinct dopamine populations (Vglut2+/Dat+, Vglut2-/Dat+) and recorded their activity during the three-chamber social preference assay. We found that Vglut2-/Dat+ neurons showed increased activity to social stimuli. Conversely, the Vglut2+/Dat+ population showed increased activity only to social novelty. We then used chemogenetics to inhibit each population during this task. We found that inhibition of Vglut2+/Dat+ neurons did not alter social preference in any

phase, while inhibition of Vglut2-/Dat+ neurons decreased the total time spent interacting with social targets. The results of this study suggest that Vglut2+/Dat+ neurons differentially contribute to social motivation in mice.

P1-F-235 *Dopamine D1 receptor activation is necessary for object memory destabilization in female mice*

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Object memory destabilization occurs when an active memory becomes unstable due to the successful engagement of a process known as prediction error (PE). This process causes a memory to become labile, allowing it to be modified based on information that is presented during that period of instability. Past research has shown that this process involves dopamine (DA), and we have previously reported that inhibition of D1 receptors (D1Rs) in the perirhinal cortex (PRh) of male rats prevents object memory destabilization and updating. In the current study, we assessed the generalizability of these findings to female mice. Since very little reconsolidation work has been done on females, we first established the basic reconsolidation effect, demonstrating that the NMDA receptor antagonist MK-801 (0.1 mg/kg, ip) inhibits object memory reconsolidation in young adult female C57Bl6/J mice. Next, we found that the D1R antagonist SCH23390 (0.1 mg/kg, ip) prevents this effect, suggesting blockade of object memory destabilization. Thus, D1Rs are necessary for object memory destabilization in both male and female rodents. We will next assess involvement of muscarinic cholinergic receptors, which we have also implicated in this process in males, followed by investigation of potential interactive effects between dopaminergic and cholinergic signalling. This research aims to provide a more concrete understanding of the dynamics surrounding long-term memory storage and modification.

P1-F-236 *Dopamine dynamics in nucleus accumbens core during the odour span task in rats*

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Working memory is the short-term retention and manipulation of information necessary for cognition. The neural circuits involved in the limited capacity of working memory are not thoroughly understood. We have recently shown a role for dopamine D2 receptors in the nucleus accumbens (NAc) core in mediating working memory and potentially its capacity using the odour span task (OST) in rats. The OST is a well-established test of working memory capacity which relies on an incrementing non-match-to-sample rule; rats identify a session-novel odour among familiar odour stimuli to receive a food reward. After each correct response, an additional odour is introduced. To investigate real-time NAc core dopamine dynamics underlying OST behaviours, adult rats (n=4 per sex) underwent stereotaxic surgery to implant an optic fiber and infuse a viral vector containing the dopamine sensor GRAB-DA3m under control of an hSyn promoter into the NAc core subregion. Fiber-photometry recordings were taken with synchronized video of OST behaviour. Across 33 recorded sessions, rats achieved an average span of 8 odours before making an error. Analysis of z-scored NAc core dopamine traces during OST trials revealed significantly reduced area under the curve in the 2 seconds following an incorrect response compared to correct and sample responses. Similarly, maximum value was significantly reduced in the 2 seconds after incorrect responses compared to correct responses. Ongoing work seeks to identify differences between high- and low-memory load trials and train additional rats to increase sample size.

P1-F-237 *Dopamine pathways in temporal task acquisition: Evidence from chronic and acute disruptions*

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Temporal-processing deficits in time perception, anticipation, and prediction are frequently observed across conditions including schizophrenia, ADHD, and Parkinson's disease. In this work, we investigated the role of subpopulations of striatal dopaminergic neurons, grouped by dopamine receptor type, in interval timing and the acquisition of temporal tasks. We confirm that these subpopulations make separable contributions to temporal performance and learning. Three cohorts of transgenic mice were trained on a licking-based fixed-interval reward anticipation paradigm. Experimental groups included animals with targeted impairments in dopamine signaling, including D1 receptor (D1R)- and D2 receptor (D2R)-type knockouts (KOs). To track how behavior emerged across training, we applied a novel periodization framework designed to capture learning trajectories. Dopamine transmission-deficient mice showed impairments that depended on the acquisition stage. D2R KO animals failed to habituate to the task procedure, while full D1R KO mice - and mice lacking D1R in D1R/D2R co-expressing neurons - did not develop anticipatory licking. These pathway-specific effects were supported by pharmacology in trained WT cohorts using selective D1R or D2R antagonists: D1R blockade reduced anticipatory licking in a dose-dependent manner, while D2R blockade produced a general reduction in task engagement. Periodization revealed distinct learning trajectories for each pathway, indicating that these dopaminergic subpopulations differentially shape time perception and temporal learning.

P1-F-238 *Dopaminergic control of predictive memory in the subiculum*

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Associative memory allows the brain to link environmental cues to rewarding or aversive outcomes, forming predictions that guide adaptive behavior. Dopamine plays a central role in this process by signaling the relevance of experiences and shaping which associations are learned and maintained. However, how dopamine influences the circuits that support predictive memory remains unclear. We investigate the subiculum, the main output of the hippocampus, which is ideally positioned to transform memory representations into predictions that guide behavior. Within this circuit, we focus on Chrna2 GABAergic interneurons, which express dopamine receptors and finely regulate the activity of subiculum circuitry. We show that these interneurons are required for successful memory retrieval, revealing their essential role in predictive associative behavior. Interestingly, dopamine levels in the subiculum also increase during memory retrieval, and these interneurons receive convergent dopaminergic inputs from the VTA and LC. Together, these findings identify a newly identified dopaminergic-subiculum circuit that contributes to predictive associative memory and may provide insight into how its disruption may contribute to psychiatric disorders such as schizophrenia, addiction, and depression.

P1-F-239 *Monkeys choose to make mistakes*

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When engaged with a task, humans and other animals occasionally make seemingly irrational decisions known as "lapses", even in static and well-learned environments. Because they deviate from reward-maximization, these suboptimal decisions are often attributed to disengagement, distraction or sensorimotor noise. However, a growing body of literature is supporting the idea that lapses could be caused by the same exploratory processes that help us learn in uncertain environments. Because there are multiple mechanisms for exploration, we do not know if lapses are truly intentional decisions that are related to the subject's hidden objective, or else the result of some noise process involved in exploration. To tease these hypotheses apart, we used a novel reward learning task in which decisions are made serially rather than simultaneously. We found that 2 rhesus macaques sacrifice objective reward in order to

generate lapses, even in fully deterministic reward conditions. These results suggest that lapses can indeed be subjectively valuable, selective decisions in this species. However, these results also challenge current models of decision making, which do not allow for lapses after learning when there is no ambiguity in reward outcomes. We show that an ideal, reward-maximizing agent would always wait for the best option to appear once it has been identified in this task. To understand lapses, we developed a novel model that optimally trades off maximizing reward rate with a fixed drive for sampling information. This model can account for the occurrence of lapses, even when monkeys have learned the value of options and when there is no ambiguity in reward outcomes. These results suggest that lapses of task performance can be explained by an intrinsic and enduring motivation to seek information, both when it is useful and when it is not.

P1-F-240 *Dynamic regulation of foraging behavior by the habenulo-raphe pathway*

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The midbrain dorsal raphe nucleus (DRN) is a hub-like network that receives substantial afferent connections and provides widespread efferent connections. This architecture makes serotonin (5-HT) neurons well positioned to broadcast salient signals that act as modulatory variables for learning and action selection. Recent work has identified one such signal as a prospective representation of near-future reward value, a key quantity of reinforcement learning. It is unclear whether this signal tracks environmental contingencies and is incorporated into policy selection to regulate behavior. Among the many inputs to the DRN are glutamatergic projections from the lateral habenula (LHb), a region involved in aversive processing and proposed to encode negative outcome expectations relevant for value updating. In this study, we investigate how the LHb–DRN pathway influences decision-making using a spatial navigation task, the Hidden Food Maze (HFM), in which animals must balance exploitation of learned reward locations with exploration under uncertainty. In vivo fiber photometry experiments revealed ramping dynamics of cortical 5-HT release as animals approached hidden food pellets, consistent with an increasing state-value signal as reward proximity increases. Optogenetic stimulation of the LHb at frequencies known to inhibit the DRN rapidly disrupted the navigational policy. Specifically, LHb–DRN stimulation induced longer travel paths, altered hole-checking strategies, and increased angular deviations from optimal trajectories. These effects persisted beyond stimulation and are consistent with the hypothesis that the DRN regulates state transitions between exploitation and exploration. Together, these results suggest that the LHb–DRN pathway plays a critical role in behavioral flexibility by modulating state transitions through serotonergic control of policy selection.

P1-F-241 *Dynamics of catecholamine release in the pre-frontal cortex of adult mice during associative learning*

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Associative learning depends on linking actions or contexts to a reward. While dopamine (DA) classically signals reward prediction error, norepinephrine (NE), implicated in novelty signaling and potentially in updating learned associations, may play a complementary role. Both catecholamine signals converge in the medial prefrontal cortex (mPFC), a region critically involved in learning and decision-making, yet how DA/NE signals shapes associative learning within this region remains unknown. Here, we tracked NE and DA signals in the mPFC using GRABNE2m and GRABDA3m as mice learned an auditory cue and reward association. Our preliminary results show that NE and DA signals are highly correlated, increasing after the cue or reward, and showed only modest modulation during learning, with stable cue responses and minor reductions in reward responses with expectation. Both signals also increased following an air puff, suggesting that mPFC catecholamines primarily encode stimulus salience over reward prediction error. The strong NE-DA correlation further raises the possibility that both signals arise from a common axonal source. To test this, we are photo-inactivating locus coeruleus NE neurons to assess their contribution to NE and DA signals during learning. Altogether, these studies will clarify the origins and roles of mPFC catecholamines in associative learning.

P1-F-242 *Early life adversity induces changes in palatable food-seeking behaviors and the mesolimbic system in a sex-dependent manner*

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Experiencing early life adversity may predispose to stress-related mental health disorders, possibly by disrupting the establishment of neurobiological processes involved in motivated and reward-seeking behavior. While several of these disorders are more prevalent in females, the specific processes underlying this sex bias are not clear. This study examined if maternal separation during the early postnatal period, an established model of early life adversity, promoted changes in behavior and the mesolimbic system in a sex-dependent manner. C57BL/6N pups were separated from their mothers for 3 hours daily from Postnatal Day (PD) 2 to PD14 while another group of litters remained undisturbed. Body weight and food intake were determined at different times before and after weaning. Palatable food-seeking behaviors were determined in early adulthood by assessing the motivation to eat calorie-dense food in a modified open field. Anxiety- and depressive-like behaviors were also determined in the elevated plus maze and tail suspension test, after which brain sections were collected to analyze dopaminergic and neurotrophic markers. Male offspring ate more, gained more weight, and were generally less active than their female counterparts, irrespective of whether they were stressed in early life. In contrast, maternally stressed mice sought more palatable food in an environment considered risky, irrespective of sex. Dopamine receptors and neurotrophins in the nucleus accumbens were differentially affected by the early life stressor and sex. These findings suggest that early life adversity may increase risk-taking behaviors to obtain palatable foods, potentially through sex-specific changes in the mesolimbic system.

P1-F-243 *Effect of Exercise on Sleep Microarchitecture, netwrok dynamic, connectivity and dendritic spine morphology in the case of sleep restriction: a translational approach*

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Background: Sleep restriction (SR) impairs hippocampal memory consolidation by disrupting Sharp-Wave Ripples (SWRs). While chronic exercise (EX) provides cognitive resilience, the circuit-level mechanisms remain elusive. Recent studies identify the hippocampal CA2 region and its somatostatin-expressing (SST+) interneurons as critical initiators of SWRs.Objectives: We hypothesize that chronic exercise protects memory against SR by strengthening CA2-SST+ inhibitory control, thereby stabilizing ripple dynamics during the consolidation window. Methods: Mice underwent 4 weeks of treadmill exercise or sedentary housing. Spatial memory was assessed using Barnes Maze and Object Location Tasks. Following acquisition, mice were subjected to 6 hours of SR. Optogenetics was used to inhibit CA2-SST+ interneurons during the post-learning period to test their necessity in the exercise-induced rescue. Results: we expect SR-SED mice to show significant memory deficits and reduced SWR frequency, while SR-EX mice maintain performance. We predict that exercise increases synaptic inputs onto CA2-SST+ cells, ensuring robust SWR initiation despite sleep loss. Importantly, optogenetic inhibition of CA2-SST+ INs should abolish the protective effects of exercise. Conclusion: This research highlights a specific CA2 inhibitory circuit as a mediator of exercise-induced resilience, suggesting that physical activity safeguards consolidation by stabilizing hippocampal oscillations.

P1-F-244 *Emotion aware generative AI for simulating cognitive behavioral therapy dialogue and affective regulation*

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Affective dysregulation, driven by impaired top-down modulation of cortico-limbic circuits, underlies anxiety, depression, and digital addiction by reducing prefrontal cortex's ability to regulate amygdala-driven emotional responses. While Cognitive Behavioral Therapy (CBT) can strengthen these regulatory pathways via cognitive restructuring and behavioral activation, access to clinicians and limited session frequency restrict

its impact. Scalable tools modeling emotion regulation are thus needed to support individuals between therapy sessions. We developed a neuroscience-guided generative AI system that simulates CBT-consistent dialogue and tracks affective dynamics. Therapist–patient exchanges (n=229) from a Beck Institute transcript were labeled using a transformer-based emotion classifier. Emotional cues and therapist inputs were integrated into prompts for GPT-2, which was fine-tuned with LoRA (r=8, α=16) to condition generation on affective cues. A real-time interface was implemented in Gradio. The model produced emotionally congruent responses aligned with CBT principles such as Socratic questioning, validation, and reframing. Perplexity improved from 4.39 to 2.31. Affect-trajectory analyses showed converging emotional resolution across multi-turn dialogues. A crisis detection module flagged escalating negative affect with 96% precision, and human reviewers rated 83% of outputs as clinically coherent. These findings show that affect-informed generative AI can emulate regulated therapeutic dialogue and may enhance future digital mental-health tools.

P1-F-245 *Effects of sustained cannabis abstinence on depressive symptoms: Preliminary analyses*

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Introduction While people often use cannabis to cope with depression, longitudinal studies suggest that cannabis use is associated with the development and increase of depressive symptoms. Previous studies in adults with psychiatric comorbidities found that depressive symptoms improved with 28 days of cannabis abstinence. This study aims to examine if these findings extend to adults without comorbidities. Methods We recruited adults (N=45; 18-55 years old) with CUD or daily or almost daily cannabis use, a baseline positive cannabis urine toxicology, and no co-occurring Axis 1 disorders. Participants were randomized (3:2 ratio) to an abstinence group (CAN- n=26) or cannabis-as-usual control group (CAN+ n=19). Depressive symptoms were assessed weekly with the Hamilton-Depression Rating Scale. Cannabis abstinence was biochemically verified via twice-weekly urine assay of THC-COOH and encouraged with contingency management and behavioural support. Results Twenty-two participants (85%) in the CAN- group sustained 28 days of cannabis abstinence and were included in the analyses. Groups did not differ in demographic, substance using variables or baseline HAM-D scores [CAN- mean=2.68(4.24), CAN+ mean=2.79(2.88)]. Relative to CAN+, depressive symptoms in CAN- did not change following 28 days of cannabis abstinence [F(4,156) = 1.76, p =.15]. Conclusion These findings suggest that short-term abstinence alone is unlikely to confer antidepressant benefits in non-comorbid populations and previously reported improvements may depend on baseline symptom severity or psychiatric comorbidity.

G - NOVEL METHODS AND TECHNOLOGY DEVELOPMENT

P1-G-246 *A direct comparison of EEG/EMG and EEG/Accelerometer approaches for mice sleep staging*

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Sleep scoring in mice has traditionally been performed using electroencephalography (EEG) combined with electromyography (EMG), which provides high-resolution classification of wake, slow-wave sleep (SWS/NREM), and rapid eye movement (REM) sleep based on neural activity and muscle tone. However, EMG implantation is an invasive technique, motivating an interest in accelerometer-based alternatives. In this study, we compare EEG/EMG and EEG/accelerometer (EEG/Acc) sleep scoring to determine whether accelerometers located on the headstage can be a valid substitute for EMG in standard vigilance-state classification. To address this, EEG, EMG and Acc were simultaneously recorded in mice (n = 6) and segmented into 4-second epochs. Seven trained scorers labeled each epoch using a custom MATLAB interface into Wake,

SWS or REM using either EEG/EMG or EEG/Acc data. Scorers completed a structured training set (3hr EEG/EMG; 3hr EEG/Acc) and were evaluated against a consensus reference set generated by three experienced scorers. Agreement between EEG/EMG and EEG/Acc labels were quantified using epoch-by-epoch accuracy, confusion matrices, F1 scores, and Cohen's kappa. Our results suggest EEG/Acc scoring to be largely equivalent to EEG/EMG for broad vigilance states, supporting accelerometer-based sleep staging as a less invasive alternative. These findings aim to demonstrate that accelerometer-based sleep scoring provides a performance comparable to traditional EMG-based methods.

P1-G-247 *3D spatial analysis of purkinje cell distributions in the macaque cerebellum*

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The cerebellum (CB) contains over 50% of the brain's neurons and supports a wide range of behaviour through topographically organized reciprocal connections to most cerebral cortical regions (via cortico-ponto-cerebellar loops). CB computational microcircuits are primarily composed of granule (integration of inputs from the cerebral cortex and brainstem) and Purkinje cells (PC, output), but their relative topographic densities are unknown. Previous work focused on overall CB cell counts or small regions, meaning that there is no comprehensive mapping of relative densities across microcircuits and regions or between white and grey matter. To explore potential relationships between cell types across the CB, we imaged a single CB hemisphere of the macaque (Nissl stained, 398 50µm slices, .343x.343µm in-plane), performed cell-counting using a convolutional neural net machine learning pipeline (PyTorch, StarDist), achieving ~90% positive detection using only ~5000 manual PC annotations (QuPath), and reconstructed cell counts in 3D to perform spatial analysis. Our pipeline accurately differentiates between granular, PC, and oligodendrocytes in macaque CB. Preliminary results indicate a decrease in granule cell density at the folial base that may be linked to lower PC densities in these regions. Our approach provides detailed 3D maps of cell densities in grey and white matter for regional comparison, which will allow future work to investigate the relationship between region-specific cell distributions and behaviour, cognition, and evolution.

P1-G-248 *A brain–spine interface for state-dependent stabilization of blood pressure after spinal cord injury*

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Spinal cord injury (SCI) disrupts descending sympathetic control, leading to recurrent hypotensive episodes that substantially increase cardiovascular and neurological risks in millions of people globally. Our lab has previously shown that targeted epidural electrical stimulation (EES) can restore blood pressure (BP) following SCI, and a next step is to further refine this therapy enabling biologically driven automatic delivery based on the states of subjects. Here, we report the development of a brain–spine interface (BSI) for state-dependent BP control based on brainstem signals. In rat models of thoracic SCI, we identified that the high-gamma band in the rostral ventrolateral medulla (RVLM) that reliably encode hypertensive and hypotensive states as well as BP error signals. These features were used to implement a state-dependent controller in which RVLM-derived signals dynamically modulated EES parameters, coupling brainstem autonomic state with spinal sympathetic output. This architecture enabled a digital bridge for BP control using conventional neural electrodes and clinically relevant EES hardware.BSI performance was validated in freely moving rats using fibre photometry combined with continuous arterial telemetry, capturing BP regulation across ethologically relevant states. In parallel, optogenetic activation of RVLM C1 neurons produced rapid increases in arterial pressure, establishing a mechanistic pathway for central modulation of sympathetic output. To support translation, minimally invasive stentrode recordings in pigs are planned for scalable access to central autonomic signals in a large-animal model. Together, these findings establish a multi-scale, state-dependent BSI for autonomic regulation, and define a mechanistically grounded pathway toward automated BP stabilization after SCI.

P1-G-249 *A Canadian guidance framework for integrating social determinants of health in aging and Alzheimer's disease research*

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Dementia risk and outcomes are unevenly distributed across populations in Canada, reflecting inequities driven by social and structural determinants of health (SSDH). Despite their importance across the lifecourse, SSDH are inconsistently measured in aging and dementia research, and no Canadian guidance exists for their systematic integration. We used a multi-pronged approach combining: (1) participatory engagement with community partners; (2) a review of SSDH data collection across 23 Canadian longitudinal studies; (3) a national public survey of Canadian adults (N = 600); and (4) a Delphi study with experts (n = 27) to prioritize SSDH indicators. Findings are being triangulated with community partners to co-develop an open-access guidance framework. Community engagement informed the project from inception, identifying determinants of brain health that were incorporated into later phases. The review revealed substantial variability in SSDH collection: demographic variables were commonly assessed, whereas economic, environmental, and psychosocial factors were infrequently or partially captured. Public respondents identified income, financial security, and stress as major influences on health, despite their inconsistent measurement in cohorts. Experts prioritized a core set of SSDH—many rarely collected in existing studies.By identifying misalignment between what matters to communities, the public, and experts and what is currently measured, this work provides an empirical foundation for a national SSDH guidance framework to support equity-driven dementia research.

P1-G-250 *A computational pipeline for identifiability and parameter recoverability in cognitive models*

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Computational models are widely used to explain behavior and link latent processes to neural measures. Two standard safeguards are simulation and parameter recovery, which extend classic power analysis to complex models that lack analytical solutions, revealing misspecified models, coding errors, and non-identifiable parameters before real data are collected. In practice however, these steps are often implemented with ad hoc scripts, making results inconsistent. Thus, we take a bootstrap approach and present a modular diagnostic pipeline (Python package soon) that standardizes simulation and recovery analyses and provides actionable checks for model validity and recoverability. The pipeline helps researchers evaluate whether a model can be reliably fit under realistic noise and data constraints, and how experimental design choices affect identifiability. Specifically, it characterizes error as a function of trials (T) and fixed budget constraints (B) with varying number of participants (N) (B=N x T), and summarizes parameter interactions through correlation matrices and derived summaries. To make non-identifiability interpretable, it includes richer pairwise diagnostics, such as density maps, bias vector fields in 2D parameter subspace. In a Kalman-bandit case study, the diagnostics reveal parameter non-identifiability and budget dependent recoverability. Together, these outputs help researchers pinpoint why recovery fails and choose designs that make targeted mechanisms reliably identifiable before collecting data.

P1-G-251 *A neuronal waveform classification assay to characterize inhibitory and excitatory bursting characteristics in MEA data: Erinacine A as a model drug*

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Lion's mane (Hericium erinaceus) is a nootropic medicinal mushroom growing in popularity among health-conscious consumers with evidence showing neuroprotective effects across neurodegenerative disease models. Erinacine A (EA), an abundant and biologically active compound found in Lion's mane mycelium, acts as a potent stimulator of growth factor synthesis and influences neuronal systems activity. In vitro, cortical neuronal systems activity was measured by culturing neurons derived from male or female rat pups on multi-electrode arrays (MEA), followed by spike sorting and subsequent waveform analysis. Neurons were then classified into two neuron classes, putative inhibitory (PI) and excitatory (PE) neurons, using a novel classification script. We showed that the concentration of EA (0, 10nM, 100nM, 1µM) and sex influenced neuronal systems activity, with the most robust effects occurring at 100nM. PE neurons showed a significant increase in the number of spikes and bursts compared to PI neurons across both sexes. In the female-derived neurons, significant increases in the mean firing rate across both neuron classes were observed while, conversely, the inter-spike interval increased in male populations. These findings show EA can induce neuron-type and sex-dependent alterations in neuronal activity.

P1-G-252 *A novel non-obese mouse model of obstructive sleep apnea with transient inspiratory flow limitation*

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Background: Obstructive sleep apnea (OSA) affects ~1 billion people worldwide and is associated with intermittent hypoxia, a key driver of neural dysfunction, autonomic imbalance, and cognitive impairment. Up to 20% of patients are non-obese and exhibit distinct mechanisms and reduced response to standard therapies. Existing rodent models rely on obesity, intermittent hypoxia alone, or invasive airway manipulation and do not reproduce transient upper airway obstruction typical of non-obese OSA. Methods: We developed a non-invasive mouse model of reversible upper airway narrowing to investigate neural responses to obstructive events. Non-obese C57BL/10J mice received a single nasopharyngeal inoculation of glycerol (30%, 20 µL) to induce localized airway swelling and increased inspiratory resistance. Breathing was recorded in conscious animals using whole-body plethysmography. Airway obstruction was quantified using enhanced pause (Penh) and prolonged inspiration events (PIE), defined as inspiratory durations ≥2× the mean. PIE occurred predominantly during quiet breathing, a low-variability state used as a surrogate for sleep-like conditions. Locus coeruleus (LC) activation was assessed using c-fos in tyrosine hydroxylase–positive neurons. Results: Glycerol increased Penh and produced reproducible PIE during quiet breathing. Preliminary findings suggest increased c-fos expression in LC noradrenergic neurons following obstructive challenges. Conclusions: This low-cost, non-invasive model enables investigation of brainstem responses to physiologically relevant airway obstruction and intermittent hypoxia, providing a platform to study neural mechanisms and neuromodulatory targets in non-obese OSA.

P1-G-253 *A systematic comparison of mprage and bravo T1-weighted MRI pulse sequences*

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Structural MRI is widely used to study brain alterations in substance use disorders, yet methodological heterogeneity, particularly differences in T1-weighted acquisition sequences, may limit reproducibility. Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) and Brain Volume Imaging (BRAVO) are commonly used sequences, but their comparability in substance-using populations remains unclear. In a within-subject design, 115 young adults with substance use underwent both MPRAGE and BRAVO scans during the same 3T MRI session. Scan quality was rated using Human Connectome Project guidelines. Cortical

thickness, surface area, and cortical and subcortical volumes were estimated using FreeSurfer v8. Reliability and sequence differences were assessed using intraclass correlation coefficients and paired t-tests. Associations between brain structure and cannabis use measures (CUDIT total, frequency, severity, and urine tetrahydrocannabinol positivity) were examined using partial correlations adjusted for covariates and compared across sequences.MPRAGE scans showed higher subjective quality than BRAVO, though the effect size was small. Structural measures demonstrated excellent reliability across sequences, with systematic differences in absolute estimates: BRAVO yielded higher cortical thickness, whereas MPRAGE produced larger surface area and volumetric estimates. Brain–cannabis use associations were highly concordant across sequences, with minimal differences in correlation strength. These findings indicate that both sequences provide reliable but non-interchangeable structural estimates, highlighting the importance of acquisition sequence selection and transparent reporting in psychiatric and addiction neuroimaging.

P1-G-254 *Addgene Data Hub: a platform for sharing AAV and antibody experimental data*

Ashley Waldron [1]

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Addgene is a nonprofit repository for DNA-based biological materials and serves as a hub for community resources, such as our 150,000-plus plasmid collection. Our repository also includes plasmid-derived adeno-associated viral vectors (AAVs) and recombinant antibodies – two versatile tool-types used in a range of applications in the neurosciences. Both AAV and antibodies exhibit significant performance variability dependent on experimental conditions, production parameters, and biological context. However, publications typically lack sufficient technical details to replicate an experiment and rarely report negative results, limiting researchers' ability to predict tool performance in their systems or learn from unsuccessful approaches. To address these challenges, Addgene developed the Addgene Data Hub, a user-friendly platform for researchers to contribute and access experimental data generated using AAV or antibodies distributed by Addgene. The Data Hub currently contains 150 AAV reports describing chemogenetic, optogenetic, and other types of viral tools used in neuroscience research in diverse experimental contexts, alongside >500 antibody reports covering the entire antibody collection. By reducing the burden on contributors to share technical details and by making those details broadly accessible to the research community, the Data Hub serves as a valuable resource for improving reproducibility and transparency, which are essential to accelerating research and discovery.

P1-G-255 *An atlas of parvalbumin interneuron diversity in mouse visual and somatosensory cortex*

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Parvalbumin-positive (PV) interneurons are key regulators of experience-dependent plasticity, yet their molecular and anatomical classifications are not fully reconciled. Single-cell transcriptomics reveals substantial heterogeneity, while anatomical studies tend to group PV cells into a single class. Traditional morphological classifications are largely descriptive, emphasizing dendritic and axonal arbors. In contrast, when the soma of PV cells is analyzed, quantification is usually limited to size, neglecting how shape contributes to cortical organization. Large-scale analyses of PV cell morphology are needed to determine whether anatomical diversity is comparable to molecular diversity and to support reproducible classification with unbiased approaches and standardized benchmarks. We developed a data-driven workflow to quantify and classify PV interneuron morphologies at single-cell resolution, generating a benchmark dataset of 14,274 cells from mouse S1 and V1. Using a semi-unsupervised annotation strategy, we assigned morphologies to interpretable categories. We showed soma shapes are associated with particular dendritic and axonal patterns, and laminar organization of PV cells depends on factors beyond size, with shape strongly influencing spatial distribution. Our results reveal PV soma morphology exhibits structural variation comparable to that reported in molecular studies. Additionally, our dataset serves as a high-resolution atlas of PV interneuron morphologies in the mouse sensory cortex.

P1-G-256 *An open-source closed-loop behavioural control system for the raspberry Pi*

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Modern neuroscience experiments require parallel monitoring and synchronization of multiple data streams including behaviour, video recording and neurophysiology. Thus, experimental control is a growing challenge. Some open-source options are affordable, but rely on simple micro-controllers which limit experimental complexity. Other open-source options are flexible but require a deep understanding of software development and computer networking. Commercial solutions offer superior performance but can be prohibitively expensive, especially for running multiple concurrent experiments. We propose an affordable, accessible, and versatile system that integrates inexpensive and user friendly microprocessors (Raspberry Pi 5) and micro-controllers (Teensy 4.1). The Pi 5 paired with a Data Acquisition device facilitates coordination and synchronization of multiple data streams for robust experimental control while micro-controllers manage high-speed stimulus delivery. Our preliminary tests achieved sub-microsecond round-trip communication across devices. To aid adoption, we will develop an intuitive User Interface for experimental control, visualizations for online behaviour monitoring, and host the software as an open-source project on the Raspberry Pi app store. Our system is modular, as adding new functionality relies only on the Teensy which is widely supported and easy to program. We will use our system for closed-loop experiments where naturalistic behaviours can be studied in response to dynamic sensory input, the computational demands of which are unattainable with most existing systems. Merging open-source adaptability with unprecedented affordability and performance will enable high levels of experimental control both for our lab and the broader neuroscience community.

P1-G-257 *An optogenetic and imaging approach to study noradrenergic modulation of neuro-vascular coupling*

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Noradrenaline (NA) released from the locus coeruleus (LC) modulates brain-wide neuronal activity and connectivity. NA also induces vasoconstriction, suggesting a direct role in regulating cerebral blood flow. However, the mechanisms by which NA vasoconstricting effects lead to modulation of neuronal connectivity remain unknown. To disentangle noradrenaline interactions with neurovascular coupling, we developed a mesoscopic imaging system that can simultaneously record neuronal calcium activity and blood volume across the cortex of an awake mouse. Simultaneously, we perturbed cortical NA levels through optogenetic activation of the NA-expressing neurons at the level of the LC. By controlling NA levels, we aim to reveal the causal effects of NA neuromodulation on neurovascular coupling. We hypothesize that these effects may vary across cortical regions upon different patterns of activation of the LC, reflecting region-specific modulation of neurovascular coupling by NA. Our preliminary data show a decrease in both calcium and blood volume in the motor cortex during periods of induced NA release. This decrease was more pronounced during 6 Hz tonic and 16 Hz phasic LC stimulation compared to 3 Hz tonic stimulation, despite the 16 Hz phasic condition delivering the same total number of pulses as the 3 Hz tonic condition. This approach will allow us to characterize the influence of LC-mediated brain states on neurovascular coupling, informing on the importance of context-dependent interpretation of BOLD fMRI signals.

P1-G-258 *Bio-imaging strategy to follow the infectious pathway of adeno-associated viruses in neurons*

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Adeno-associated viruses (AAVs) are indispensable viral vectors in neuroscience since they are non-pathogenic and allow the specific infection of a panoply of cells. Furthermore, their DNA and capsid can be modified to develop recombinant adeno-associated viruses (rAAVs). rAAVs are the vehicles of choice for the delivery of optogenetic tools inside neurons. Some rAAVs can also cross the blood brain barrier and represent an interesting avenue for central nervous system (SNC) gene therapy. However, while rAAVs enable multiple clinical and fundamental research applications, the infection pathway of the viral particle itself remains very intricate. The efficiency of this process can still be greatly improved, and further knowledge on this mechanism is required to contribute to the optimal development, characterization and use of rAAVs. Thus, the goal of this project is to develop a bio-imaging strategy to follow the infection process of rAAVs inside neurons. First, rAAVs and subcellular regions will be labelled with fluorophores to allow their localization with fluorescence microscopy. Then, the success rate of the infectious process steps will be quantified and compared between rAAV serotypes. The infection of neurons will be studied in priority considering the SNC gene therapy potential of rAAVs. The results obtained with this imaging strategy are essential to our understanding of the AAV infection process and will lead to a more efficient and optimal development of new rAAVs. This knowledge will then open the door to new studies and contribute to the use of viral vectors in neuroscience.

P1-G-259 *Brain dynamics associated with noxious stimulation under general anesthesia are characterized by changes in redundancy and synergy measured using EEG*

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Inadequate control of anesthesia depth can expose patients to noxious events during surgery, particularly when anesthesia is insufficient. Recent fMRI studies have shown that information-theoretic measures—particularly synergy, the information emerging from interactions between brain regions, and redundancy, their shared information—are sensitive to anesthesia depth. After extending this framework to EEG, here we test whether these measures can also detect brain responses to nociceptive stimulation during general anesthesia. High-density EEG (128 channels) was recorded from eight surgical patients receiving propofol anesthesia titrated to maintain a Bispectral Index (BIS) between 45 and 55. Data were analyzed using the Integrated Information Decomposition (ΦID) framework, which decomposes information shared between EEG sources and their future states into unique, redundant, and synergistic components. To assess clinical applicability, we examined left–right and frontal–posterior scalp partitions using a subset of 24 electrodes only. EEG activity was compared before and after a 30-sec tetanic stimulation of the ulnar nerve. Noxious stimulation significantly modulated redundant ($t = -2.75$, $p = 0.028$) and synergistic information ($W = 3$, $p = 0.039$) along the front–right axis, but not across hemispheres, with values shifting toward patterns previously observed in wakefulness. Together, these findings support the potential of information-theoretic EEG metrics as signatures of nociceptive processing and analgesia disruption, advancing EEG-based pain monitoring in the operating room.

P1-G-260 *Correction of the APP London (V717I) mutation using an optimized prime editing system*

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Alzheimer's disease (AD) is driven in part by extracellular accumulation of amyloid plaques. Pathogenic mutations that alter amyloid precursor protein (APP) processing cause early onset Familial Alzheimer disease (FAD) and represent promising potential targets for gene therapy. Although most current therapeutic strategies target downstream pathological hallmarks like amyloid-β accumulation, correction of causative mutations remain mostly unexplored.Prime editing (PE) is an advanced CRISPR-based technology gene therapy tool capable of introducing precise nucleotide modifications in the genome without generating double-strand DNA breaks. The aim of this project is to correct the APP London mutation (V717I), one of the most common FAD-associated mutations. To enable efficient optimization of enhanced prime editing guide RNAs (epegRNAs), we first generated a suitable cellular model. Using optimized epegRNAs designed to introduce the London mutation, we established a homozygous HEK293T cell line carrying the London mutation. This cell line was subsequently transfected with plasmids expressing the prime editor, various epegRNAs, and single nicking guide RNAs. During epegRNA design, three silent mutations were incorporated to disrupt protospacer-adjacent motifs (PAMs) and to generate clusters of silent edits close to the target mutation to increase cellular mismatch repair evasion. Under optimized conditions, correction efficiencies of up to 50% were achieved in the HEK293T model. To assess delivery using RNA-based systems, RNA transfection with resulted in 45% editing efficiency of PAM-disrupting silent mutations in the SK-N-MC cell line and in patient-derived fibroblasts resulted in 58% editing efficiency. Our Future experiments will extend this approach to fibroblast-derived neurons and to the knock in London mouse model.

P1-G-261 *Cerebral vein segmentation in quantitative susceptibility maps using physics constrained deep learning*

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The brain relies on oxidative metabolism to function, and many diseases affect cerebral oxidative metabolism. Oxygen usage can be quantified using Quantitative susceptibility mapping (QSM) of cerebral veins. QSM offers strong venous contrast due to the paramagnetic susceptibility of deoxyhemoglobin and is widely available through standard MRI. Venous QSM can be used to estimate oxygen usage without gas challenges, providing a route for non-invasive metabolic imaging. However, current QSM-based venous segmentation methods rely on hand-tuned vessel filters or manual delineations, which struggle to capture small cortical veins and require substantial user input. The scarcity of ground truth vein labels has further limited the adoption of deep learning for QSM venous analysis. This work presents a physics-constrained deep learning framework for venous segmentation on QSM images. The model builds on an attention-gated U-Net architecture by employing two unsupervised losses: (1) a susceptibility-based physics loss enforcing consistency between predicted venous susceptibility and the measured phase-derived field, and (2) a Hessian-derived Frangi loss encouraging tubular morphology and vesselness. Rather than mimicking manual labels, the model learns to identify veins by leveraging the underlying susceptibility physics and vascular morphology, which is especially effective when ground truth is limited. The proposed model achieved an average Dice score of 0.7805 on the validation dataset, demonstrating superiority over current methods and enabling metabolic imaging applications.

P1-G-262 *Characterization of neuronal subpopulation and network activity in the external globus pallidus*

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Introduction: The external Globus Pallidus (GPe), a central structure within the basal ganglia, plays a crucial role in decision-making. Although recent advances have revealed its connections with internal and external basal ganglia structures and identified distinct neuronal populations little is known about how these neurons interact to form the GPe's internal microcircuitry. Our purpose is to characterize network neuronal activity in the GPe by establishing standardized extracellular multi-unit recordings and exploring the contribution of different neuronal subtypes to network dynamics. Methods: Recordings were obtained from slices of adult mouse GPe using the MEA2100-Mini and 3D-MEA plate. We used WaveClus for sorting, and clusters were analyzed for firing rate, stability and low and high-firing patterns. Baseline activity was recorded for 20 min, followed by burst biphasic stimulation. Results: We identified low- and high-firing profiles consistent with known GPe subpopulations, including PV and Npas1. Stimulation experiments are ongoing. Conclusions: Our approach enables consistent recording of spontaneous and evoked GPe activity, and provides insights into how local circuits contribute to basal ganglia function.

P1-G-263 *Connectivity, complexity, and chaos in the ageing brain: Synthesis of the literature*

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Every human, irrespective of the geographic region and politics, should have the opportunity to lead a long and healthy life. By the year 2030, one in six individuals worldwide is projected to be aged 60 years or older, with this age group growing from 1 billion in 2020 to 1.4 billion. The ageing brain as the most complex and the paramount organ that determines one's quality of life and autonomy, calls for deeper inquisition. Chronological ageing is intertwined with alterations in white matter architecture, structural connectivity, and reorganization of neural dynamics that cannot be fully captured by macroscopic atrophy or univariate spectral measures. This synthesis of the literature published in the past 25 years maps the critical research gaps, converging results, and trends across electroencephalography (EEG) and diffusion tensor imaging (DTI) modalities employing the complexity, chaos, and connectivity metrics. Investigating these measures provides a complementary view on how ageing reshapes the neural system and whether the compensatory mechanisms result in decreased cognitive, sensory, and motor control performance. We also aimed to investigate hybrid measures that could encompass two or more methodological families as they would enhance the sensitivity to early and subclinical ageing patterns.Finally, we conclude that entropy-based measures and hybrids such as fuzzy entropy integrated with DTI-informed architectures represent a powerful yet low-cost framework for analyzing the dynamical changes of the ageing brain and for identifying which factors distinguish healthy ageing from pathological trajectories.

H - HISTORY, TEACHING, PUBLIC AWARENESS AND SOCIETAL IMPACTS IN NEUROSCIENCE

P1-H-264 *Augmented reality for teaching neuronal signaling in undergraduate psychology*

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Traditional lecture-based methods often limit engagement and comprehension of complex neurobiological concepts such as the neuronal action potential. This pilot study evaluated whether an augmented reality (AR) teaching tool could improve understanding and engagement compared to conventional 2D model-based instruction in an undergraduate psychology course. Students (N=50) were randomly assigned to either an AR

or control group. The AR simulation, developed in collaboration with the Douglas College Computer Science Department, allowed students to visualize voltage changes while manipulating ion movement, voltage-gated channels, and Na+/K+ pumps in real time. The control group learned the same material using 2D foam models representing the same key components of the neuronal membrane. Students then completed a short test and survey assessing learning comprehension and engagement. Analysis showed high test scores for the AR group, indicating superior conceptual understanding. Students rated their AR learning experiences as engaging and easy to follow, with no significant differences in perceived difficulty or interest between groups. Findings demonstrate that AR can be an effective and practical tool for neuroscience education, supporting students' grasp of neuronal processes through interactive, embodied learning.

P1-H-265 *Characterizing prognostication practices after drug toxicity-related post-cardiac arrest brain injury*

Harjeev Sudan [1], Brian Grunau [1], Stuti Sheth [1], Stefanie Blain-Moraes [1], Judy Illes [1], Mypinder Sekhon [2], Brittany Dennis [1], Jacob Hutton [1], Donald Griesdale [1]

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Objective: Drug toxicity (OD) is a common cause of post-cardiac arrest brain injury (PCABI). Most deaths among patients admitted to intensive care units (ICU) occur following withdrawal of life-sustaining treatments (WLST). We sought to compare adherence to prognostication guidelines between OD- and non-OD-related cardiac arrest patients. Methods: We identified out-of-hospital cardiac arrests via the British Columbia Cardiac Arrest Registry (Jan. 1, 2023 – Dec. 31, 2024) who: 1) survived to ICU admission; and 2) died after WLST due to PCABI. We classified patients as OD-related if diagnosed as such by ICU clinicians and otherwise as non-OD. We defined guideline adherence based on the 2023 Canadian Cardiovascular Society Position Statement: 1) the presence of ≥2 poor prognostic findings; and 2) ≥72 hours between return of spontaneous circulation and WLST (approx. time of death). We compared between-groups differences and performed the Fisher's Exact Test. Results: We included 150 patients: among OD- and non-OD-PCABI patients, ≥2 prognostic findings were present in 51/79 (65%) and 41/71 (58%), respectively; and WLST occurred after ≥72 hours in 55 (70%) and 39 (55%), respectively. Overall, prognostication was guideline-adherent for 46 (58%) OD- and 33 (46%) non-OD patients (difference -12%; 95% CI -28, 4.2; p=0.19). Conclusion: Adherence to prognostication guidelines prior to WLST is low in both OD- and non-OD-PCABI, but we did not detect a difference between groups. The heterogeneous practices underscore the need for standardized approaches in end-of-life decision-making.

P1-H-266 *Convergence: Transforming knowledge translation through transdisciplinary art-science collaboration to foster critical thinking and cognitive connection with brain research*

Nour Chahine [1], Connor O'donnell [1], Cristian Zaelzer [2], Trish Osler [2]

[1] McGill University, [2] The Convergence Initiative

The Convergence Initiative is an independent Canadian non-profit dedicated to advancing neuroscience through the cross-pollination of science and the fine arts. Central to this mission is "Arts + Neuroscience + Society" (DART 631/3 AA), an accredited two-semester course at Concordia University's Faculty of Fine Arts. The program partners neuroscience graduate students from the RI-MUHC with fine arts undergraduates to move beyond the deficit model of science communication. By adopting a two-way engagement model, the framework facilitates authentic interactive exchanges through the transverse sharing of knowledge, giving the public a voice and humanizing the scientific process. The curriculum features a Fall semester focused on bridging knowledge gaps between domains, followed by a Winter semester dedicated to transdisciplinary team-based project completion. Learning is evaluated through diverse outputs, including 3-minute video presentations, curatorial work in museums, and visual journals. The process culminates in a professional exhibition and public symposium where complex concepts such as synaptic plasticity or neurodegenerative pathology are translated into immersive artistic works.By utilizing art as a powerful tool to translate scientific inquiry into an accessible, experiential language, Convergence provokes critical inquiry into the

societal impacts of neuroscience. Trainees develop vital communication skills, moving from transactional dissemination to a transformative, dialogue-based research-creation approach. This presentation details our methodology for transdisciplinary teaching and demonstrates how engagement-based sci-art outreach fosters a more scientifically literate society.

POSTER SESSION 2

A - DEVELOPMENT

P2-A-269 *Developmental axonal swellings formation depends on extracellular calcium signalling*

Bruna De Souza [1], William Mattana Dos Santos [1], Alanna Watt [1]

[1] *McGill University*

Axonal development and the establishment of contacts between neurons are crucial for formation of functional brain circuits. We have demonstrated that axonal swellings appear transiently on cerebellar Purkinje cell axons during postnatal development where they enhance the fidelity of action potential propagation. We have previously shown that sub-saturating concentration of tetrodotoxin (low TTX; 2.5 nM) that produce axonal failures in spontaneously-firing Purkinje cells enhance the formation of axonal swellings. This supports a model in which action potential propagation failure triggers axonal swelling formation. But what is the signaling mechanism that triggers their formation? We aimed to address this pharmacologically using low TTX to enhance their formation combined with specific channel blockers and molecular inhibitors. We observed that the formation of swellings was impaired both in the absence of extracellular Ca2+ and when voltage-gated Ca2+ channels were blocked (Nifedipine 100uM, Agatoxin 100nM and Apamin 100uM). But not when IP3R, responsible for intracellular Ca2+ release, were blocked (Xestopongin C 1uM). Intracellularly, inhibition of calmodulin (Calmidazolium 1uM) also impaired axonal swelling formation. Our results suggest that Ca2+ signaling through voltage-dependent channels is required for the formation of axonal swellings during cerebellar development.

P2-A-270 *Fate-restricted embryonic precursors define gray and white matter astrocyte specification in the spinal cord*

Caterina Sister [1], Guillermo Lanuza [1]

[1] *Fundación Instituto Leloir*

Astrocytes display two canonical morphologies—protoplasmic in the gray matter (GM) and fibrous in the white matter (WM)—yet recent transcriptomic studies indicate that their heterogeneity is far more extensive. In the developing mouse spinal cord, discrete dorsoventral progenitor domains within the ventricular zone generate astrocytes that populate both GM and WM. This complexity raises the question of how distinct astrocyte identities are established despite their shared developmental origin. We hypothesized that ventricular precursors are heterogeneous and become fate-restricted to generate either GM or WM astrocytes. To test that, we performed in vivo lineage tracing using two complementary approaches: tamoxifen-inducible expression of fluorescent reporters in GlastCreER mice, and the Mosaic Analysis with Double Markers (MADM) system, a Cre-loxP–based strategy inducing intrachromosomal recombination to reconstitute chimeric fluorescent proteins (Tomato and GFP).Sparce fate mapping revealed that astrocyte clones are frequently composed of two daughter cells of the same subtype (either GM or WM), sharing morphology, molecular marker expression, and spatial position. These pairs appear to originate from symmetric divisions occurring after migration near-final settling location. Our study reveals that, in addition to dorsoventral patterning, astrocyte diversity is established by distinct embryonic precursors within each progenitor domain that selectively generate GM or WM astrocytes. These results shed light on the differentiation programs underlying astrocyte heterogeneity.

P2-A-271 *Fetal microglia show sex-specific neurodevelopmental responses to maternal stress during pregnancy*

Alexandra Lawson [1], Matthew Rosin [1], Jessica Rosin [1]

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The prevalence of neurodevelopmental disorders (NDDs) has increased dramatically, with growing evidence linking prenatal maternal stress to these conditions. Across diverse maternal stressors, immune dysregulation emerges as a common feature, suggesting that fetal microglia— the immune cells of the brain—may detect changes in the intrauterine environment and influence neurodevelopment. Previous work from the Rosin lab demonstrated a male-specific sensitivity of hypothalamic microglia to maternal stress; however, the cellular mechanisms underlying this vulnerability remain unclear. Accordingly, our overarching goal was to characterize baseline sex and regional differences in fetal hypothalamic microglial phenotypes; including morphology, movement, and phagocytic activity, and determine how maternal stress alters these dynamics. Using a variety of quantitative approaches to assess both static and live microglial morphologic and functional phenotypes, we demonstrate that maternal stress induces a male-specific shift in microglial morphology from ameboid to ramified within the paraventricular nucleus (PVN) of the fetal hypothalamus, with males also showing increased microglia-neuron interactions. Intriguingly, live-cell imaging suggests that baseline sex differences exist with respect to microglial phagocytic activity within the PVN, as well as sex- and time-specific morphological and phagocytic response to maternal stress. These findings demonstrate sex- and region-specific microglial responsiveness to prenatal maternal stress and highlight the dynamic nature of these cells.

P2-A-272 *Floor plate derived netrin-1 is an instructive long-range guidance cue for commissural axons in the embryonic spinal cord*

Melissa Pestemalciyan [1], Celina Cheung [2], Chao Chang [3], Karen Lai Wing Sun [2], Stephanie Harris [1], Reesha Raja [4], Daryan Chitsaz [2], Jean-François Cloutier [1], Artur Kania [3], Timothy E. Kennedy [2]

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The distribution and functional significance of long-range axon guidance cues remain controversial. Netrin-1 is essential for commissural axon extension to the ventral midline of the neural tube. It remains unclear, however, to what extent netrin-1 protein functions as a long-range or short-range cue in the embryonic spinal cord, nor has it been determined if netrin-1 protein has an instructive function in vivo that directs axon migration, or is merely permissive and required for axon extension. Here, we address how netrin-1 protein is distributed in the developing spinal cord and how that distribution influences axon guidance. In early embryonic chick spinal cord, only floor plate cells express NTN1, yet the distribution of netrin-1 protein extends ~200 µm dorsal of the floor plate, exemplary of a long-range cue. In the embryonic mouse spinal cord, NTN1 is expressed by cells in the floor plate and ventral ventricular zone. We show that selective deletion of NTN1 from floor plate cells in mouse flattened the gradient of netrin-1 protein within ~200 µm of the midline and altered commissural axon trajectories across the same distance. In gain-of-function studies, we demonstrate that ectopic expression to change the distribution of netrin-1 in the embryonic spinal cord is sufficient to redirect commissural axons. These findings reveal that netrin-1 secreted by floor plate cells is distributed as a long-range cue in embryonic chick and mouse spinal cord, and demonstrate that the distribution of netrin-1 protein instructs the direction of commissural axon extension.

P2-A-273 *Free fatty acid receptor GPR120 regulates dopamine neuronal development and social behavior*

Shingo Nakajima [1], Juliette Thene [2], Akari Tomita [2], Stephanie Fulton [3]

[1] CR-CHUM, [2] CRCHUM, [3] Université de Montréal

Omega-3 polyunsaturated fatty acids (ω-3 PUFAs) are essential for brain development and their deficiency increases the risk for neurodevelopmental and psychiatric disorders. G-protein coupled receptor 120 (GPR120), a receptor for ω-3 PUFAs, is expressed on dopamine neurons of the ventral tegmental areas and modulates their activity. Here, we examined how GPR120-mediated fatty acid sensing affects dopamine neuronal development and related behaviors. Constitutive GPR120 KO mice and wild-type littermates were used for morphological and behavioral analyses. Dopaminergic development was evaluated in primary midbrain cultures derived from pups (P0-2) and brain slices of adult mice by tyrosine hydroxylase (TH) staining. Anxiety-like, exploratory and social behaviour were assessed using the elevated plus maze, open field test, social interaction, and marble burying test in male and female adult mice. Chronic intracerebroventricular infusion of GPR120 agonist was performed via osmotic pumps in adult male C57BL6/J mice fed an ω-3 PUFA deficient diet. Primary dopamine neurons lacking GPR120 exhibited reduced branching while GPR120 agonist treatment enhanced neurite complexity. Dopamine axon varicosity area was reduced in the medial prefrontal cortex, but not in the NAc, of GPR120 KO mice. Both male and female GPR120 KO mice showed decreased social interaction without changes in anxiety- or repetitive-like behaviors. Chronic pharmacological GPR120 activation increased social interaction. These findings suggest that lipid sensing though GPR120 promotes dopaminergic maturation and regulates social behavior. Supported by a NSERC Discovery grant to SF.

P2-A-274 *From brain age deviations to developmental trajectories in adolescence*

Anthony Gagnon [1], Marie Brunet [1], Maxime Descoteaux [1], Larissa Takser [1]

[1] University of Sherbrooke

Background. Normative modeling of brain development enables quantification of individual deviations in maturation. The brain age gap (BAG), the difference between MRI-predicted age and chronological age, offers an individualized metric of neurodevelopment. However, consistent patterns across psychiatric disorders remain elusive, and its ability to predict developmental trajectories within continuous models of cognition and behavior has not been examined. Methods. Using longitudinal data from the Adolescent Brain Cognitive Development Study (ages 9-15, n=9,074), we built 8 region-specific brain age models using volume, cortical thickness, and surface area from the Brainnetome adolescent atlas. Psychiatric diagnoses were derived from parent-reported questionnaires. Multivariate linear regression assessed case-control differences and cross-sectional continuous cognitive/behavioral profiles. Developmental trajectories were identified using a multivariate joint latent-class mixed model, and associations with BAG values were tested using multinomial logistic regression. Results. Children with ADHD showed negative BAG across multiple regions (Cohen's d: -0.12 to -0.08). Subcortical BAG emerged as a transdiagnostic indicator of younger-appearing brains (d: -0.07, pfdr = 0.024). Older-appearing brains were associated with a high-cognition, low-symptom profile, whereas younger-appearing brains were linked to a low-cognition profile. Three trajectories were identified: stable, towards externalizing, or internalizing behaviors. Widespread positive BAG predicted evolution towards internalizing behaviors but reduced the likelihood of the externalizing trajectory. Conclusions. Integrating BAG with continuous cognitive and behavioral profiles yielded a plausible framework for early identification of atypical trajectories, which may contribute to personalized psychiatry.

P2-A-275 *Guidance cue integration by growth cones: spatial regulation of microRNAs*

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[1] Brock University

Growth cones, located at the tip of growing axons, sense and interpret various guidance cues (repulsive or attractive), which facilitate axonal pathfinding, which is important during both development and regeneration. Retinoic acid, the metabolite of Vitamin A, is an important guidance cue required for brain development and regeneration in many species. Utilizing regenerating molluscan CNS neurons, we have previously shown that retinoids induce attractive growth cone turning in a non-genomic manner, requiring local protein synthesis and a non-coding RNA, microRNA-124. This study shows that exposure to multiple guidance cues affects growth cone behavior; growth cones show diminished responses to retinoic acid following their exposure to dopamine. Guidance cue integration requires rapid and precise control over the growth cone cytoskeleton and can involve signaling through RhoGTPases. We have thus determined the role of a Rho-associated protein kinase ROCK (a downstream effector of RhoA-GTPases and target of miR-124) in both dopamine and retinoic acid-mediated growth cone behaviours. We also show how signaling integration of the different guidance cues affects the spatial and temporal expression of miR-124. Given the role of local protein synthesis and its control by miRNAs in mediating growth cone responses, we are now examining where de novo protein synthesis occurs during changes in growth cone behavior. These experiments provide insights into the signaling pathways involved in cue integration during axon pathfinding.

P2-A-276 *Gut–brain axis dysregulation produced by adolescent edible Δ 9 tetrahydrocannabinol (THC) exposure*

Marieka Devuono [1], Eva Corsini [1], Selena Chiarini [2], Jenna Flemming [1], Chiara Fricano [3], Erynn Lonnee [1], Marta De Felice [1], Elyanne Ratcliffe [2], Daniel Hardy [1], Walter Rushlow [1], Steven Laviolette [1]

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Cannabis use during adolescence is associated with increased risk of later psychiatric disorders, yet usage rates remain high. Adolescence is a vulnerable period when exposure to Δ-9-tetrahydrocannabinol (THC) can disrupt the endocannabinoid (eCB) and serotonin (5-HT) signalling, systems that regulate mood, inflammation, and gastrointestinal (GI) function. Their disruption may contribute to the frequent co-occurrence of psychiatric and GI symptoms. Therefore, to investigate the contribution of gut–brain axis disruption to the long-term impact of adolescent THC exposure, we used a rat model of adolescent edible THC exposure that produces sex-specific affective and cognitive behavioural deficits in adulthood. Electrophysiological recordings revealed that adolescent THC exposure increased glutamatergic activity in the prefrontal cortex (PFC) of both sexes and increased ventral tegmental area (VTA) dopamine signalling in males. Using PCR, we quantified eCB, 5-HT, and inflammation related gene expression in the intestines and mesocorticolimbic regions in adulthood. In the small intestine, adolescent THC decreased Diacylglycerol Lipase α, Peroxisome Proliferator Activated Receptor γ, and increased Cyclooxygenase 2 mRNA expression, suggesting alterations in the eCB system and inflammatory signalling. PCR analysis in the brain is ongoing. These findings demonstrate that adolescent THC exposure produces enduring changes in brain and gut function. Gut–brain axis dysregulation may represent a key mechanism contributing to the long-term consequences of adolescent THC use.

P2-A-277 *Transcriptomic and protein expression analyses of early differentiating neurons in the developing mouse cerebellar nuclei*

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The cerebellar nuclei (CN) play crucial roles in sensorimotor integration and cognitive function, and their developmental trajectory may influence neurodevelopmental disorders. Traditionally, early CN neurons are thought to arise at embryonic day 9.5 (E9.5) from the rhombic lip. Here, we characterize the α-synuclein (SNCA) expressing mesencephalon-derived neurons that emerges before E9 in the nuclear transitory zone

(NTZ; the precursor to mature CN). Using SncaGFP transgenic mice, EdU incorporation assay revealed that SNCA⁺ NTZ neurons are highly proliferative at E9-E9.5, and they are the only NeuN⁺ differentiated cerebellar neurons between by E12. Single-cell RNA sequencing data analysis (GSE118068) of postmitotic SNCA⁺ neurons at E10 and E12 revealed a distinct molecular profile, with differential gene expression and gene ontology enrichment highlighting involvement in axonogenesis at E10 and in neuron differentiation and axon guidance by E12. Enriched cellular components included the growth cone, axon terminus, and both pre- and postsynaptic membranes. Spatiotemporal transcriptomic profiling using Visium HD (10x Genomics) is being used to map spatially resolved transcriptional programs of SNCA⁺ NTZ neurons and integrate their molecular states with early cerebellar nuclei organization. In conclusion, we characterized the early differentiated NTZ neurons that predates canonical CN neuron development. Their unique temporal profile and gene expression suggest a foundational role in cerebellar circuit formation.

P2-A-278 *How do substantia nigra dopamine neurons grow such a complex axonal arbor? An in vitro exploration*

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Dopamine (DA) neurons of the substantia nigra pars compacta (SNc) are known to establish a distinctly arborized axonal domain, with a much larger number of axonal release sites compared to other types of neurons. Ventral tegmental area (VTA) DA neurons show a more modest axonal arbor. This characteristic has been suggested to contribute to the elevated vulnerability of SNc DA neurons and other affected neuromodulatory neurons in Parkinson's disease (PD). Little is known about the cellular and molecular developmental mechanisms that underly such axonal complexity. Our global hypothesis is that a unique cell-autonomous mechanism drives axonal branching in DA neurons, but that glial and neuronal-derived signals also contribute. To tackle this question, primary postnatal neurons obtained from transgenic mice expressing tdTomato selectively in DA neurons were examined using immunostaining and confocal imaging. Our results reveal that by 3 days in vitro, SNc DA neurons have developed a larger axonal arbor compared to VTA neurons. Activity-dependent mechanisms seem to be at play at this early stage because DA neurons already fire at a rate of approximately 2 Hz and blocking firing with tetrodotoxin reduces axonal development. We also find that axonal arbor growth is more dependent on glial-derived secreted factors than the dendritic arbor during early stages of postnatal development in culture. This project will provide a better understanding of the development of DA neurons, which could ultimately help to identify new strategies to reduce their vulnerability in PD.

P2-A-279 *Identification of a novel mirror movement causing gene: A recurrent MCF2 variant which disrupts DCC binding and subcellular relocalization leads to congenital mirror movements*

Dennis Drewnik [1], Andrea Accogli [2], Victoria Veas Roy [1], Patricia Yam [1], Nassima Addour-Boudrahem [2], Jean-Francois Michaud [1], Sabrina Schlienger [1], Judith St-Onge [2], Oriane Trouillard [3], Caroline Dubacq [4], Emmanuel Roze [3], Catherine Fallet-Bianco [5], Joke

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Neuronal wiring in the developing nervous system relies on axon guidance, a process enabling axon pathfinding to target cells. Disruption of axon guidance results in a wide spectrum of defects including congenital mirror movements (CMM) and corpus callosum agenesis (CCA). Axon guidance signaling pathways, such as Netrin-1/DCC, act through guanine nucleotide exchange factors (GEFs) to activate Rho GTPases, which regulate axon pathfinding. MCF2 is an X-linked gene that encodes a GEF which activates the GTPases Rac1 and Cdc42. We identify a recurrent hemizygous MCF2 variant [c.31C>T p.(R11W)] in two unrelated cases displaying axon guidance and corticospinal defects: an adult male with CMM and an unrelated male fetus with CCA and abnormal corticospinal tract decussation. Through biochemical and cellular studies, we demonstrate that MCF2 interacts physically with DCC and is able to induce DCC subcellular relocalization. The MCF2 R11W variant disrupts the interaction with DCC, is less efficient at relocalizing DCC, and has decreased GEF activity.

To test whether the MCF2 R11W variant is sufficient to cause a CMM-like phenotype in mice, we generated knock-in mice harbouring the MCF2 R11W variant. Hemizygous male MCF2 R11W mice showed increased mirror movement-like behaviours compared to wildtype, as assessed through the cylinder reaching test. Together these data demonstrate that MCF2 is a novel DCC interacting protein. Furthermore, our data suggests that the MCF2 R11W variant may impair axon guidance by impacting DCC signalling, a key regulator of motor control lateralization.

P2-A-280 *Ikaros family members network drives neuronal diversification in the mouse developing retina*

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During CNS development, neural progenitors generate different cell types in a strict chronological order, and any perturbance in this birth order impairs the development of functional circuits. In the mammalian retina, amacrine cells (ACs) are the most diverse neuronal cell type, comprising over 60 subtypes. This diversity is pivotal for the processing of electrical inputs from photoreceptors to ganglion cells, allowing perception of motion and direction selectivity. However, the molecular mechanism behind it remains poorly understood. Here, we investigated how transcription factors from the Ikaros family (Ikzf1/2/4) cooperate to drive amacrine cell diversification. We identified that, beyond the already described early temporal factor Ikzf1, another Ikaros transcription factor, Ikzf2, is expressed by retinal progenitor cells(RPCs), suggesting a role in cell fate decisions. Accordingly, we report that overexpression of Ikzf2 in late-stage RPCs in vivo robustly promotes the generation of GABAergic ACs. Conversely, combined inactivation of Ikzf2 and Ikzf4 leads to a reduction in the number of GABAergic AC produced in retinal explants. Finally, we show that deleting Ikzf2 and Ikzf4 in late-stage RPCs abolishes the ability of Ikzf1 overexpression to trigger early temporal identity and induce ACs, suggesting a genetic interaction between Ikzf1 and Ikzf2/4. These results suggest that Ikzf2 is a key component of an Ikaros protein network that temporally defines the early competence window, more specifically regulating the production of AC subtypes.

P2-A-281 *In vivo measurement of glutamate and gaba in the pediatric anterior cingulate cortex: Feasibility and preliminary findings*

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Background: Social and environmental conditions in childhood have been linked to brain development differences, yet neurochemical measures remain underrepresented in pediatric imaging studies. The anterior cingulate cortex (ACC) is stress-sensitive and involved in emotional regulation. To investigate neurochemical differences, this pilot study measured Glutamate using Point RESolved Spectroscopy (PRESS) and GABA using edited MEscher–GArwood Point RESolved Spectroscopy (MEGA-PRESS). Methods: Thirty-three youth (8–16 years) completed MRI scanning on a Siemens 3T scanner. Glutamate PRESS and GABA MEGA-PRESS data were acquired from the ACC. Spectra were processed using the Gannet pipeline, including frequency and phase correction, metabolite modeling, voxel co-registration, tissue segmentation, and tissue-corrected quantification relative to water. Statistical analyses were performed in SPSS. Results: Mean glutamate levels were 4.91 i.u. (SD = 0.43), whereas mean GABA levels were 4.52 i.u. (SD = 0.98). Pearson correlation analysis indicated a significant moderate negative association between glutamate and GABA concentrations across participants ($r = -0.361$, $p = .039$), suggesting that higher glutamate levels were associated with lower GABA levels in the ACC. Conclusion: PRESS and MEGA-PRESS MRS successfully quantified glutamate and GABA, respectively, in the pediatric ACC. Glutamate levels were higher than GABA, and glutamate concentrations were moderately negatively correlated with GABA, suggesting an inverse relationship between these metabolites in this stress-sensitive region. These preliminary findings provide neurochemical data that can inform future studies of stress, adversity, and brain maturation in youth.

P2-A-282 *Inflammation profiles induced by mechanical ventilation in the developing brain*

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Background: About 6000 children/year require mechanical ventilation (MV) in the PICU. While lifesaving, MV can cause ventilator-induced lung injury (VILI), trigger systemic inflammation, and disrupt cerebral homeostasis, potentially leading to ventilation-induced brain injury (VIBI), a critical issue during early neurodevelopment.Hypotheses and objectives: This study aims to implement an innovative translational project to explore the prevalence and mechanisms involved in VIBI in children. Methods: Intubated lambs were ventilated for 8 h under 4 conditions combining low vs high tidal volume (LVt/HVt) and stable vs unstable pH. Blood and whole brains were collected. Inflammatory, injury, and BBB biomarkers were assessed by RT-qPCR and ELISA, and microglial activation was quantified by 3DMorph. Results: Preliminary data (n = 4 lambs) show a trend toward increased plasma S100b, a damage biomarker, in the HVt/unstable pH group, accompanied by higher plasma cytokines, consistent with a systemic inflammatory response. Brain IL-8 expression was higher in the brainstem and cerebellum, with increased tight-junction and tissue-injury proteins, supporting propagation of systemic inflammation to the brain only 6 hours after MV initiation. 3DMorph indicated a more quiescent microglial phenotype in LVt/stable pH lambs, with greater ramification, longer branches, and more terminations than HVt/unstable pH. Conclusion: These preliminary findings suggest that maintaining stable pH, particularly with LVt, may be less deleterious and more protective for the developing brain in this lamb model.

P2-A-283 *Investigating associations between maternal prenatal nutrition and neurocognitive development in early childhood*

Stefanie Perrier [1], Chuan-Heng Hsiao [2], Emily A. Rodriguez Cuevas [2], Ankush Kesri [2], Faith Nassiwa [2], Sanhita Sunil Sawant [2], P. Ellen Grant [1], Kathleen T. Durant [3], Sarah U. Morton [1], Yangming Ou [1]

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The first 1000 days of life represent a period of rapid brain development characterized by high metabolic demand and environmental sensitivity. Despite growing interest in maternal prenatal nutrition, much remains unknown about how early life nutritional patterns relate to child neurocognitive outcomes. Using data from the Environmental influences on Child Health Outcomes (ECHO) initiative (National Institutes of Health, USA), we examined associations between maternal nutrition in pregnancy (nutrient intake, healthy eating indices, supplement use) and early childhood cognitive scores [Bayley Scales of Infant and Toddler Development 3rd ed. (n=883), Peabody Picture Vocabulary Test 3rd ed. (n=517), Stanford-Binet Intelligence Scales 5th ed. (n=582)], in addition to key sociodemographic variables. Multivariate machine-learning regression models with feature selection were used to identify sets of variables jointly associated with each outcome. When examined without contextual factors, several dietary variables were selected (e.g., iron, folate, calcium, vitamin K, fatty acids, and maternal fish consumption; mean absolute percentage error (MAPE) per outcome: 9.4, 11.4, 12.5%). However, when sociodemographic and family-related covariates factors were considered, prediction error was slightly lower (MAPE per outcome: 8.9, 11.1, 12.1%), and prenatal dietary variables provided little additional predictive information. Future studies are needed to clarify how maternal prenatal nutritional patterns relate to neurocognitive outcomes within complex sociodemographic contexts.

P2-A-284 *Investigation of Endothelial Deficits in Models of SYNGAP1 Haploinsufficiency*

Leya Aubert-Tandon [1], Ziying Liu [2], Tyler Renner [2], Caroline Vergette [3], Amber Morton [1], Moises Freitas-Andrade [4], Julie Ouellette [2], Baptiste Lacoste [4]

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Blood vessel health is critical for brain maturation, as blood vessels supply growth factors, nutrients, and oxygen, and protect against pathogens. Early cerebrovascular deficits may cause lifelong neuronal impairments. Building on our previous work showing that endothelial cell (EC) dysfunction leads to

functional changes in a 16p11.2 deletion mouse model of autism and considering growing evidence that EC dysfunction contributes to neurodevelopmental disorders (NDDs), we aimed to investigate its role in SYNGAP1-related disability (SRD). SRD is caused by mutations in the SYNGAP1 gene, leading to a lack of functional SynGAP protein, resulting in cognitive impairment, seizures, and communication deficits. We hypothesize that SYNGAP1 haploinsufficiency alters EC structure and function, which we explore using in vitro and in vivo approaches. Preliminary data using SYNGAP1-deficent human-induced ECs (hiECs) from SRD patient-derived iPSCs reveal altered VE-cadherin distribution, more junctional protrusions and gaps, and altered angiogenic activity in vitro. Transcriptomics identified 325 up- and 118 downregulated differentially expressed genes in hiECs. Based on these results, we will further assess hiEC integrity and conduct metabolomics to better characterize the impact of SYNGAP1 in ECs. We will also examine cerebrovascular structure, blood-brain barrier (BBB) ultrastructure, blood flow dynamics, and behaviour in EC-specific Syngap1 deletion mice. This project aims to clarify the role of SYNGAP1 in ECs and expand our understanding of cerebrovascular health in NDDs.

P2-A-285 *It's all in the vessels: the neonatal brain vasculature provides a unique combination of molecular cues to neural stem cells that alters with age*

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Postnatally, neural stem cells (NSCs) reside in the subventricular zone (SVZ), where they receive signals from their environment to regulate their behaviour. In the adult, the brain vasculature has been identified as an important regulator of NSC maintenance, proliferation, and differentiation. It is currently unclear how the vasculature interacts with and affects NSCs during the neonatal period. We hypothesize that the neonatal vasculature prevents hyperproliferation and differentiation of NSCs to maintain the NSC pool. Our objective is to investigate the role of vascular signalling cues onto NSCs across the lifespan. Utilizing single-cell RNA sequencing, we examined transcriptional changes of mouse neonatal and adult SVZ vascular cells and conducted ligand-receptor modelling to predict whether vascular ligands signalling onto NSC receptors differ with age. Based on the top 50 differentially expressed genes, the neonatal vasculature showed a distinct transcriptional signature compared to the adult, upregulating Igf2, Pdgfb, and Pdgfd. We selected key ligands of interest to test in vitro to investigate their influence on NSC function. In initial experiments, these ligands added to mouse cortical precursors reduced the amount of neurogenesis. These results suggest that the neonatal SVZ vascular niche is transcriptionally different from the adult and that the unique molecular cues expressed by neonatal vascular cells may help to maintain the NSC pool. Future work will investigate how this unique combination of factors influences NSC behaviour in vivo during this critical period of brain development.

P2-A-286 *Longitudinal study of neurovascular and cognitive health in aging mice*

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Aging is a complex process marked by a decline in both cerebrovascular and cognitive health, yet the causal relationship between these systems remains unclear. This ongoing study aims to investigate the temporal progression of neurovascular dysfunction and cognitive decline in aging mice using a comprehensive longitudinal approach. The central hypothesis of the study is that the progressive degradation of neurovascular integrity contributes to cognitive decline and that vascular changes precede and precipitate neuronal dysfunction and cognitive impairments. To investigate this, transgenic mice expressing the calcium indicator GCaMP6s equipped with a long-term cranial window will be monitored throughout their lifespan using optical imaging techniques. The study will utilize two-photon microscopy and wide-field imaging to capture both neuronal activity and vascular dynamics at different spatial scales. Behavioral and cognitive assessments will complement these measurements to correlate neurovascular changes with cognitive performance. Longitudinal data acquisition is actively progressing, and preliminary findings indicate that

our methods are effective. This project offers an integrative approach, combining structural and functional neuroimaging with behavioral analysis, to advance our understanding of the relationship between vascular health and cognitive decline in aging. The findings are expected to contribute to the broader sense of age-related brain changes with potential translational implications for human health.

P2-A-287 *Metal co-exposure alters sensory and social behaviors in C. elegans with a loss-of-function mutation in neurexin*

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Mutations in the key synaptic gene neurexin, and developmental exposure to heavy metals, manganese (Mn) and nickel (Ni), significantly impact juvenile health. However, we know little about the impact of heavy metal exposure on mutations in synaptic genes. Previous studies have revealed that mutations in the neurexin gene decrease synaptogenesis and alter sociality; moreover, exposuresthem to Ni and Mn are detrimental to neurons. Given this, we asked whether exposure to Mn and Ni exacerbates the neurodevelopmental and behavioral phenotypes of C. elegans with a loss-of-function mutation in neurexin. We treated age-synchronized larval stage-1 worms (N2 (wt), nrx-1 [tm1961], and nrx-1 [ok1649]) with Mn (0, 2.5, 5, 10 mM) and Ni (0, 1, 2, 3 mM) for 1 hour and allowed to grow for 48 hours at 20°C. We measured mitochondrial health using MitoTracker Red dye, and we assessed developmental rate, NaCl chemotaxis, clumping and bordering behaviour. We found that Ni treatment at high concentration exacerbated developmental deficits indicated by reduced body length in both ok1649 (14.7%) and tm1961 (14.5%) mutant strains when compared to their controls. Moreover, mutant strains failed to exhibit normal NaCl associative learning, even at baseline. In all strains, Mn treatments caused increased [N2 (65.2%), ok1649 (88.2%), tm1961 (38.7%)] mitochondrial reactive oxygen species, and abnormal increase in clumping and bordering.Taken together, our results demonstrate that exposure to heavy metals increases the detrimental effects of mutations in synaptic genes.

P2-A-288 *Microglial/macrophage androgen receptor knockout produces ADHD-like phenotype in male mice*

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Neurodevelopmental disorders (NDDs), including attention deficit/hyperactivity disorder (ADHD), are diagnosed more often in males, with an approximately 3:1 male-to-female ratio. One hypothesis for this disparity is the prenatal androgen surge in male fetuses, which masculinizes some brain regions while defeminizing others. Brain development is partly regulated by the neuroimmune system, particularly microglia, the brain's resident macrophages. Importantly, both central and peripheral macrophages, including placental Hofbauer cells, exhibit sex-specific characteristics. These findings suggest that androgen signaling in macrophages may contribute to behaviors associated with NDDs. To test this, we selectively deleted androgen receptors (AR) in microglia/macrophages and assessed early-life behaviors relevant to NDDs. Two mouse models were examined: a microglia/macrophage-specific AR knockout (mARKO) and a neural progenitor AR knockout (nARKO). Mice underwent behavioral testing for social and repetitive behaviors, followed by qPCR analysis of prefrontal cortex tissue to assess NDD-related gene expression. In a separate cohort, placentas and brains from fetal day 17.5 mARKO and wild-type mice were collected for cytokine and metabolomic analyses. Social behavior did not differ between groups; however, mARKO mice displayed persistent hyperactivity along with reduced expression of dopamine transporter (DAT), serotonin receptor Htr1a, and brain-derived neurotrophic factor (BDNF), markers associated with ADHD. Preliminary cytokine analyses revealed increased IL-6, IL-12p70, LIX, and MIP-2 in mARKO placentas, indicating altered inflammatory signaling. These findings suggest that androgen receptor signaling in macrophages contributes to ADHD-like phenotypes and supports the use of mARKO mice as a model for ADHD research.

P2-A-289 *Mlp60a and Sallimus are required to restrict branching of developing dendritic arbors*

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Regulating the growth and arborization of complex dendrites is crucial for the proper development of neural circuits. Spire, a filamentous actin (F-actin) nucleation protein, is required for forming new dendrite branches in Drosophila class 4 dendritic arborization (c4da) sensory neurons.1 We used mass spectrometry to identify Muscle LIM protein at position 60a (Mlp60a) and Sallimus (Sls) as potential Spire-interacting proteins, though neither had been linked to dendrite development.Mlp60a and Sls are known to crosslink F-actin within muscle cell z-discs and are critical for myocyte development.2,3 The mammalian ortholog of Sls (Titin) interacts directly with the Mlp60a ortholog CSRP3 in cardiac muscle z-discs.4 In c4da neurons, we found Mlp60a::GFP localized to the cell nucleus and puncta within dendrites. RNA interference (RNAi)-induced loss of Mlp60a in c4da neurons increased new branch formation, resulting in more terminal branches and greater total arbor length. This was suppressed in spir hemizygotes, suggesting a requirement for Spire in ectopic branch initiation. Initial imaging of Sls-GFP lines indicates Sls presence within c4da neurons. RNAi knockdown of Sls increased the number of terminal branches and total arbor length, mirroring the effects of Mlp60a loss. These findings provide the first evidence for roles of Mlp60a and Sls in nervous system development. Ongoing experiments will explore the effects of Spire, Mlp60a, and Sls interactions on F-actin levels, distribution, and dendrite dynamics.1Hatton and Marquilly et al. 2025. 2Wishard et al. 2023. 3Knoll et al. 2002. 4Knoll et al. 2010.

P2-A-290 *Modeling early-life adversity in Wistar rats: Effects of maternal dietary fiber during lactation on offspring development*

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Diet during early life plays a crucial role in supporting development. Modifying maternal diet during lactation can alter milk composition, which may in turn influence offspring development. In this study, we investigated the effects of maternal dietary fiber on offspring development. Wistar rat dams were assigned to one of three diets during lactation: fiber restricted (0.4% cellulose), fiber enriched (30% cellulose), or control (5% cellulose). Offspring were assessed for weight trajectory, sensory and motor development, ultrasonic vocalizations, and anxiety-related behaviour during postnatal days (PND) 1-21. Enriched offspring showed greater overall increase in weight compared to restricted offspring. Enriched offspring showed accelerated sensory development, as indicated by earlier ear and eye opening compared to restricted and control groups. Sex specific effects were also observed, with females more affected in ear opening and males more affected in eye opening. For motor development, fiber enriched offspring showed reduced grip strength on PND 14 and reduced righting reflex latency on PND 5. Ultrasonic vocalizations were not affected by maternal diet. In conclusion, these findings indicate that maternal dietary fiber can influence offspring trajectories including somatic, sensory, and motor development, with some effects being sex specific.

P2-A-291 *Morphological evidence suggestive of a hierarchical mode of glial cell diversification and intrinsic developmental plasticity within the murine enteric nervous system*

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Enteric glial cells represent a highly heterogeneous cell population residing both within and outside the ganglia and inter-ganglionic fiber bundles that form the core networks of the enteric nervous system (ENS). The classification of enteric glia in various subtypes is still mainly based on their particular location and associated morphological attributes. We recently reported that these “topo-morphological” enteric glia subtypes gradually appear during early postnatal development in healthy wildtype mice, under the influence

of structural tissue changes that occur during this period. This process is also influenced by the source of ENS progenitors, with notable biased contributions by Schwann cell precursors (SCPs). This prior work further suggested the existence of a hierarchical program of spatiotemporal differentiation, whereby intra-network enteric glia of the myenteric plexus sequentially give rise to nearby extra-network enteric glia as well as to more distant intra- and extra-network enteric glia of the submucosal plexus. To learn more about enteric glia diversification, we reasoned that the Nr2f1Spt/Spt mouse model of Waardenburg syndrome type IV could be particularly informative, as the absence of ENS in the colon of these mice is specifically due to premature glial differentiation of ENS progenitors before birth. Our new analyses of the ENS-containing ileum from these mice now also reveal abnormal acquisition of enteric glia diversity after birth. These alterations of enteric glia diversification are in agreement with the previously proposed hierarchical differentiation model in wildtype mice.

P2-A-292 *Integration of human and mouse single-cell transcriptomes of the developing cerebellum nominates cells-of-origin for Group 3 and 4 medulloblastoma*

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The cerebellar rhombic lip neurogenic niche is critical for glutamatergic neurogenesis, and dysregulated differentiation of rhombic lip lineage cells is hypothesized to cause medulloblastoma (MB), a malignant pediatric cancer lacking targeted therapies. Humans have an expanded rhombic lip subventricular zone compartment not seen in mice or macaques, and the common Group 4 subtype of MB is hypothesized to arise by dysregulation of the EOMES+ unipolar brush cells (UBC) generated by this compartment. However, it is unknown whether humans have unique UBC populations not seen in the mouse and, if so, whether Group 4 MB tumour cells resemble these UBC populations. We integrated 336,598 human and mouse single-cell transcriptomes of the developing cerebellum (9–21 post-conception weeks in humans and E10–P14 in mice) and identified two subpopulations of UBC that are enriched in the human samples, relative to mice. One of these populations, which we term UBC 1, predominates at 11 post-conception weeks, is predicted to be driven by OTX2, SOX4, and SOX11, and is enriched for axonogenesis and neurodifferentiation pathways. We analyzed 27,735 single-cell transcriptomes from eight MB tumours and recapitulated the observation that Group 4 MB cells best resemble UBC. We then found that two-thirds of Group 3 and Group 4 MB UBC-like cells best resemble human-enriched UBC 1 cells. Gene regulatory network analysis revealed that top regulators of Group 4 MB tumour cells include EOMES, SOX4, and SOX11. Our work provides initial evidence for human-enriched UBC states, and suggests that SOX4 and SOX11 may drive neurogenesis in UBC and gene expression in a subset of Group 4 MB tumour cells. We are currently expanding this work to a single-cell multiome atlas of 60 primary MB tumours.

B - NEURAL EXCITABILITY, SYNAPSES, AND GLIA: CELLULAR MECHANISMS

P2-B-293 *Characterizing the effects of diazepam on tau hyperphosphorylation and spatial memory in a mouse model*

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Background: Diazepam is a benzodiazepine prescribed to the elderly. Pre-clinical research has shown that benzodiazepine use increases tau hyperphosphorylation, a biomarker and neuropathological marker of Alzheimer's Disease (AD). Studies using data from the Québec health insurance registry (RAMQ) report that its prescription correlates with increased risk of AD, but not all studies replicate these findings. This study aims to elucidate the relationship between benzodiazepine prescription, tau hyperphosphorylation and dementia risk. Methods: 6-, 12-, 18-, and 24-month-old male and female C57BL/6J mice were injected with either 2 or 10 mg/kg of diazepam and sacrificed 1 or 7 hours after injection. Mice from the 7-hour group performed Morris Water Maze and Y-Maze tests 6 hours after injection. Brain, plasma, and erythrocytes were

collected for analysis. Results: Preliminary data suggest mice given diazepam spend less time in the platform area compared with controls during the probe test which is in agreement with previously published work. Western blots will be performed on collected brain samples to determine if these behavioural differences are associated with increased tau hyperphosphorylation. Conclusions: This preliminary work begins an examination into the effects of benzodiazepines on tau hyperphosphorylation. These findings will have implications into understanding the mechanisms of tau hyperphosphorylation and dementia.

P2-B-294 *Functional characterization of CG17698, a novel memory suppressor gene*

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The neuroscience field has long recognized the existence of genes essential for proper memory processes to occur. The same applies to genes that are not strictly required, but contribute to memory acquisition, retention, or retrieval. However, over the past several decades, scientists have also identified the opposite side of the coin: genes that, apart from their canonical functions in the cell, somehow suppress various aspects of learning and memory through different mechanisms. In an independent RNAi-based memory screen in Drosophila melanogaster, CG17698 was identified as a suppressor of intermediate memory. We have since validated this finding and found that CG17698 affects memory acquisition and/or intermediate memory across several neuronal populations. We show that CG17698 is expressed in multiple brain regions, including those critical for associative memory formation, storage, and retrieval. Interestingly, knockdown of CG17698 in dopaminergic or mushroom body neurons also alters synaptic vesicle pools. Drosophila CG17698 is orthologous to mammalian Camkk1, which has been implicated in regulating synaptic plasticity, and in modifying and remodeling the underlying neural circuits either directly or via its downstream targets. We hypothesize that CG17698 may play similar roles in Drosophila and, therefore, aim to further elucidate its function in regulating memory and modulating neuronal synaptic vesicle pools.

P2-B-295 *Gator1-dependent MTORC1 hyperactivity drives the development of neuronal communication*

Maéline Muller [1], Imane Hadj-Aissa [1], Antoine Desmeules [1], Laetitia Marcadet [1], Martin Lévesque [1], Chantelle Sephton [1], Paul Dutchak [1]

[1] *Université Laval*

Mutations in GATOR1 complex subunits, NPRL2, NPRL3, and DEPDC5 have been associated with a wide spectrum of familial focal epilepsies and autism spectrum disorders (ASD). GATOR1 controls mTORC1 activation depending of the nutritional status of the cell, particularly intracellular amino acid levels, by function as a GTPase-activating protein complex toward a RAG proteins, and inhibiting mTORC1 activity when amino acid levels is low. We show that disease-linked mutations in the NPRL2 subunit can restrict the function of GATOR1 complex and its inhibitory function on mTORC1, resulting in the hyperactivation of downstream cellular growth signalling. While GATOR1 loss-of-function mutations directly impact the amino acid sensing role of mTORC1, few studies have focused on the impact of these mutations on the homeostatic coordination of mTORC1 regulation with the PI3K/AKT-dependent growth factor signalling pathway. Using a combination of pharmacological tools, we discovered that specific mutations in the NPRL2 subunit of GATOR1 renders cells resistant to mTORC1 inhibition caused by PI3K inhibition, in neuronal and non-neuronal cells. To further investigate the biological contribution of GATOR1 in neuronal development and function, we generated a NPRL2 knockout model using primary neuron culture. Those neurons lacking NPRL2 expression, developed exaggerated neuronal firing activity, reminiscent of seizure activity in vivo. Collectively, our studies show a novel function of GATOR1-dependant amino acid-signalling in the development of hyperactive neural network formations.

P2-B-296 *GATOR1-dependent signaling in astrocyte metabolic reprogramming and neurotransmitter recycling: phenotypic insights and mTOR-targeting therapy*

Imane Hadj-Aissa [1], Maéline Muller [1], Laetitia Marcadet [1], Antoine Desmeules [1], Jorge Soliz [1], Chantelle Sephton [1], Paul Dutchak [1]

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Epilepsy affects more than 50 million people worldwide, and nearly one third of patients are resistant to available anti-epileptic drugs, underscoring the need for disease-modifying therapies. Mutations in the GATOR1 complex, composed of NPRL2, NPRL3, and DEPDC5, are a major cause of focal epilepsy. GATOR1 negatively regulates mTORC1, a key regulator of cellular metabolism and growth. Under amino acid deprivation, GATOR1 inhibits mTORC1 via RAG-GTP hydrolysis; however, GATOR1 mutations lead to constitutive mTORC1 activation. In the human brain, GATOR1 mutations frequently occur in a mosaic manner. While neuronal dysfunction has been significantly studied, the role of astrocytes remains unclear. Here, we show that GATOR1 loss of function alters astrocyte morphology and mitochondrial organization in a mouse model and in astrocytic cell lines. In vivo, GATOR1-deficient astrocytes induce progressive astrogliosis by 5 months of age, leading to lethality between 5 and 8 months. At the cellular level, astrocytes display elevated reactive oxygen species and mitochondrial electron transport chain dysfunction, consistent with hyperactive mTORC1-signaling. Given the limitation in anti-epileptic treatments, we developed a novel therapeutic strategy targeting mTOR using antisense oligonucleotides (ASOs). ASO treatment restores cellular homeostasis and results in a robust rescue both in vitro and in vivo. These findings identify astrocytic mTOR dysregulation as a key pathogenic mechanism and support ASO mTOR targeting as a promising therapeutic approach for drug-resistant epilepsies.

P2-B-297 *GDNF-induced neuroregeneration in Hirschsprung mice occurs through non-canonical signaling in diverse enteric neural progenitor subtypes*

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Hirschsprung disease (HSCR) is a severe congenital disorder defined by the absence of the enteric nervous system (ENS) in the distal bowel. Although surgical treatment is life-saving, it often leads to persistent bowel dysfunction and long-term complications. To overcome these limitations, we are developing a regenerative approach based on rectal delivery of the neurotrophic factor GDNF (glial cell line–derived neurotrophic factor). We previously showed that postnatal GDNF enemas in HSCR mice induce the stable formation of a functional ENS derived from tissue-resident neural progenitors. Here, we aimed to elucidate the cellular and molecular mechanisms underlying this remarkable regenerative process. Using single-cell RNA sequencing, pharmacological inhibition, and genetic lineage-tracing approaches, we analyzed GDNF-treated and untreated HSCR mouse models. We demonstrate that GDNF-induced neurogenesis is mediated by NCAM1 and its downstream effector FAK, rather than the canonical GDNF receptor RET. In addition, we identify an unexpectedly broad pool of ENS progenitors responsive to GDNF, comprising at least three distinct populations: neural crest–derived Schwann cell precursors, enteric glia, and a previously unrecognized non–neural crest–derived population. These progenitors display distinct neurogenic potentials, and all three are required to generate balanced proportions of cholinergic and nitrergic neurons. Together, our findings support the broad applicability of GDNF-based therapy for HSCR patients, including those carrying RET variants, and provide important insights for selecting optimal progenitor sources in future ENS regenerative and cell-based therapies.

P2-B-298 *Glial coverage of neuromuscular junction predicts motor performance in humans*

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Amongst important factors contributing to the development and progression of age-related muscular deficits are the alterations of the neuromuscular junctions (NMJs), a tripartite synapse composed of the presynaptic nerve terminals, the postsynaptic nicotinic receptors located on the muscle fiber and perisynaptic Schwann cells (PSCs). Rodent studies have revealed alterations of the neuromuscular junction (NMJ) with age. However, healthy human NMJ, remains largely understudied, particularly regarding its three synaptic components and their relationship to functional capacity during aging. Biopsies of the Vastus lateralis from a small cohort of active young and older adults, that underwent comprehensive functional testing, were obtained with a needle biopsy optimized for the sampling of NMJs. Our analysis supports that NMJs of older active individuals presented a higher level of partial denervation than previously reported. PSC coverage was variable even in younger individuals but, importantly, was the best predictor of motor performances in older individuals. In our dataset, the standard Timed Up and Go (TUG) test emerged as the most informative functional measure for detecting neuromuscular alterations associated with aging. Here, we provide a novel way to study human data and propose new perspectives about human NMJ alterations and functional predictors in aging. Our data challenge both concepts of a stable NMJ throughout the human lifespan and that its innervation is the best predictor of motor performance. This study advances our understanding of the glial contribution to NMJ health and aging in humans and suggests that strategies aimed at preserving glial cell integrity may help mitigate age-related declines in neuromuscular function.

P2-B-299 *Glial-specific glutamate transporters required for sleep regulation in drosophila*

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Sleep is essential for life, yet its biological mechanisms remain largely unknown. While sleep research has traditionally focused on neurons, glial cells are emerging as key regulators. Drosophila melanogaster is a powerful model: it exhibits sleep-like behaviors, shares conserved genes linked to human sleep disorders, and contains glial subtypes resembling mammalian glia. In the fly brain, astrocytes infiltrate synaptic regions, ensheathing glia (ENS) wrap neuropil areas, and cortex glia (CTX) surround neuronal cell bodies. We found that reduced expression of the glutamate transporter Eaat1 in ENS and CTX decreases sleep, whereas its reduction in astrocytes causes arrhythmic sleep without altering total duration. Calcium dynamics in ENS are strongly associated with homeostatic sleep pressure, and ENS express the glial-specific vesicular glutamate transporter DVGLUT2, enabling modulation of aversive learning via vesicular glutamate release. Whether this transmission mechanism also regulates sleep remains unclear. We hypothesize that Eaat1 regulates sleep by linking ambient glutamate uptake in ENS to calcium-dependent, DVGLUT2-mediated vesicular release. Using glial-specific GAL4-driven RNAi and the drug-inducible GeneSwitch system, we show that both constitutive and adult-specific knockdown of EAAT1 and DVGLUT2 significantly reduce sleep. These findings suggest ENS operate a sleep-promoting glutamate cycle in which uptake and vesicular release are critical for maintenance. By identifying this glia-to-neuron signaling pathway, our work demonstrates that non-neuronal cells actively orchestrate behavioral states through precise neurotransmitter recycling, establishing a framework for how glial glutamatergic dysfunction may contribute to sleep disorders.

P2-B-300 *GluA2-lacking AMPA receptor-Auxiliary complexes offer a diversity of polyamine block sensitivity*

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The majority of fast excitatory neurotransmission in the mammalian brain is mediated by AMPA subtype ionotropic glutamate receptors, which are critical for the learning and memory mechanisms of Hebbian plasticity and glutamatergic synapse homeostasis. Canonically AMPA receptors (AMPARs) are divided into two distinct functional groups based on their Ca2+-permeability and polyamine block sensitivity through RNA-editing at the channel pore region of GluA2 subunit. Our recent work has shown that GluA2-containing AMPARs form a continuum of polyamine-insensitive ion channels with varying degrees of Ca2+ permeability. However, polyamine block sensitivity of GluA2-lacking AMPARs is not yet well studied. Here we show that the degree of polyamine block can be differentially regulated by AMPAR auxiliary subunits (i.e TARPs, GSG1L and CNIHs) within a spectrum, where TARPs and CNIHs similarly attenuate polyamine block, whereas GSG1L enhances it, indicating an unexpected diversity in how AMPAR auxiliary subunits regulate polyamine block sensitivity through distinct structural and functional mechanisms. Moreover, our proteomic data shows that about 68% of cerebellar AMPARs are GluA2-lacking receptors, mainly by GluA1 and A4 subunits with certain auxiliary subtypes and stoichiometry. The native GluA2-lacking AMPARs exhibits variety of polyamine sensitivity and Ca2+-permeability, suggesting a unique role of AMPAR auxiliary subunits regulating pore properties. Taken together, our work deciphers the composition and function of cerebellar GluA2-lacking AMPAR-auxiliary complexes and offers mechanistic insight into the diversity of polyamine block sensitivity.

P2-B-301 *Glutamate-releasing immature inhibitory terminals in the auditory brainstem contain distinct excitatory and inhibitory synaptic vesicles*

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[1] *McMaster University*

Many synapses release multiple neurotransmitters, though the function of co-transmission is often unknown. During a brief period in postnatal life, immature glycinergic terminals in the auditory brainstem release glutamate onto cells in the lateral superior olive (LSO). Transient glutamate release is enabled by expression of the vesicular transporter VGLUT3, and knockout of VGLUT3 leads to perturbed developmental refinement of the glycinergic circuit. Slice patch physiology strongly suggests that glutamate and glycine are packaged into distinct vesicles, though questions remain about vesicle organization and whether the vesicular transporters associated with glycine (VIAAT) and glutamate (VGLUT3) indeed occupy distinct vesicles. To assess vesicle identity at these co-transmitting synapses, we collected rat tissue at the peak of VGLUT3 expression (postnatal day 10-12), immunolabeled for VGLUT3 and VIAAT, expanded 10-fold, and collected confocal image stacks of synapses onto LSO cells in the expanded gels. Label for VGLUT3 and VIAAT appeared in bright clusters of expected size for immunolabeled vesicles. Less than 10% of all segmented putative vesicle signal exhibited any overlap, and the majority of putative vesicles (~80%) exhibited zero overlap of VGLUT3 and VIAAT signal. Our data are consistent with co-transmitting terminals in which VIAAT and VGLUT3 occupy distinct, albeit interspersed, vesicles.

P2-B-302 *Heterochronic myeloid cell replacement reveals the local brain environment as a key driver of microglia aging*

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Aging is the key risk factor for cognitive decline and impacts the brain in a region- and cell type-specific manner. Microglia in the white matter and cerebellum are considered among the fastest aging cell type; however, it remains unclear whether this phenomenon is mediated by intrinsic mechanisms or is primarily driven by age-related changes in neighbouring cells. Here, we describe a scalable and genetically modifiable system for heterochronic myeloid cell replacement, enabling the in vivo reconstitution of young and

aged mouse brains with intrinsically young immune cells. Using confocal and in vivo two-photon imaging, proteomics, and single-cell and spatial sequencing, we find that reconstituted myeloid cells in the brain adopt region-specific morphological and transcriptional profiles of microglia expression including a low-density, immune-vigilant state specific to the cerebellum. Strikingly, in aged brains, reconstituted cells rapidly acquired aging phenotypes, particularly in the cerebellum, indicating the local environment as a primary driver of microglia aging. To this end, we identified STAT1-mediated interferon signaling as one key axis controlling microglia aging in the cerebellum, whereas loss of STAT1 significantly prevented this aging trajectory in reconstituted cells. Spatial transcriptomics analysis combined with genetic cell ablation models identified rare and regionally restricted natural killer cells as the source of interferon signaling necessary for regulating microglia aging signatures in the cerebellum.

P2-B-303 *High-throughput optogenetic mapping of prefrontal layer 2/3 microcircuits*

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The brain operates through interconnected neural circuits organized into hierarchical networks in which structure constrains function. Understanding brain function therefore requires mapping synaptic connectivity, yet conventional methods are slow, limiting productivity. Here we introduce optomapping, a high-throughput connectivity mapping approach that is ~100× faster than traditional multiple patch-clamp techniques. Using optomapping, we quantified layer-2/3 excitatory microcircuits of the prefrontal cortex (PFC), an associative area, using primary visual (V1) and motor (M1) cortex as reference input/output areas. AAV9-CAG-DIO-STChroME-P2A-mRuby was injected into the cortex of postnatal day (P) 0–2 Emx1-Cre mice to drive soma-targeted expression of the opsin ChroME in pyramidal cells (PCs). In acute slices prepared at P18–26, we performed whole-cell recordings from PCs or inhibitory basket or Martinotti cells while sequentially activating hundreds of candidate presynaptic PCs using near-IR femtosecond-laser spiral scans. This enabled systematic measurement of synaptic connectivity, strength, and dynamics. The PFC had ~2× stronger recurrent excitation in layer 2/3 than V1 or M1 ($p < 0.01$), whereas V1 and M1 were similar. In the PFC, connectivity was more spatially localized around the postsynaptic neuron, with a strong preference for within-layer connections. Together, our findings suggest stronger local excitation in PFC, consistent with circuit specializations supporting association cortex processing.

P2-B-304 *Hippocampal place cell remapping during spatial reward learning*

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Navigation is a necessary process for living organisms to locate resources, find mates, and avoid predators. The dorsal CA1 of the hippocampus encodes an animal's location during spatial learning and memory. Specialized pyramidal neurons called place cells preferentially fire when an organism is in a specific location. These cells remap depending on environmental factors; how spatial encoding changes longitudinally across a multi-day reward-location learning paradigm remains unclear. We used in vivo calcium imaging to observe dorsal CA1 cell firing while mice conducted a spatial learning task in search of food rewards. We injected a CRE-dependent adeno-associated virus (AAV) which encodes for a genetically-encoded calcium indicator, GCAMP6F, into the dorsal CA1 of CAMK2a-cre mice before implanting a GRIN lens dorsal to the injection site. We recorded fluorescent calcium transients via an Inscopix nVue data acquisition system. We identified place cells in dCA1 that were attuned to the locations of the food rewards and measured their ability to remap when the reward locations were changed. We also correlated place cell activity with historical reward locations. We quantified recruitment of non-place, non-reward cells into the place cell group. Our study will elucidate the cellular dynamics of navigation over time, and future work will apply our findings to the study of navigation in healthy and disease states.

P2-B-305 *Hormetic thermal stress confers benefit and promotes adaptive resilience in C. elegans*

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Stress, a fundamental biological response, can range from mild to severe. While it is known that severe stress is harmful, we know less about how mild stress (hormesis) induces beneficial responses. Since dopaminergic and cholinergic neurons in Caenorhabditis elegans are implicated in response to severe thermal stress, therefore, we asked if these neuronal populations also respond to hormetic stress.Synchronized L1 larvae were assigned to four groups: Control, Low Thermal Stress (LTS) group (30 °C for 45 min), High Thermal Stress (HTS) group (37 °C for 1 h), and LTS + HTS group (30 °C for 45 min followed by 37 °C for 1 h). After exposure, worms recovered at 20 °C for 48 h before assessments. We quantified survival rates, developmental rates, body length, locomotion, mechanosensory behavioral response, and we used fluorescent microscopy to measure neuronal degeneration. Thermal stress (37 °C for 1 h) significantly reduced survival (23.2%), body length (814.5 µm), and locomotor activity (4.9 min^{-1}) compared with control values (82.9%, 1723.5 µm, and 23.1 min^{-1}, respectively), impaired sensory behavior, and induced degeneration of dopaminergic and cholinergic neurons ($p < 0.05$). In contrast, the hormetic stress (30 °C for 45 min) group showed no significant difference from the control in all evaluated parameters. Worms pre-exposed to hormetic stress before severe heat exposure showed better results in all evaluated parameters compared to the HTS group. These findings indicate that hormetic thermal stress enhances adaptive resilience in C. elegans and supports neural health.

P2-B-306 *Identifying GluN1 subunit N1-cassette residues controlling N1-cassette regulated function*

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NMDA receptors (NMDARs) are glutamate/glycine-gated ion channels with two GluN1 and two GluN2 subunits. GluN1s exist as splice variants: GluN1a lacks the exon4 encoded N1 cassette, while GluN1b contains it. The 21-amino acid N1 cassette (residues 191-211) at the ATD/LBD interface confers regulatory properties of NMDAR function, though the critical residues are not fully elucidated. We generated N1-cassette mutants library, expressed them in HEK293 cells, and performed patch-clamp recordings to define amino acid constraints on cassette control of allosteric regulation, gating, and glycine-dependent non-ionotropic signaling. We found that deletion of residues S191-Q195 in the N1 cassette prolongs NMDAR decay time, restores glycine-induced internalization, and converts spermine inhibition into potentiation. Moreover, substitution of S191 and K192 with alanine restores glycine-induced internalization without affecting deactivation kinetics or spermine regulation, highlighting potential contribution of these residues. Substitution of K207A and R208A accelerates channel deactivation and enhances polyamine sensitivity, while glycine-induced endocytosis remains unchanged. Notably, K211A mutation induces spermine potentiation, while preserving K211 and substituting remaining N1-cassette residues retains spermine regulation. These findings demonstrate N1-cassette sequences critical for NMDAR allosteric regulation, suggesting that targeting this domain could provide a novel strategy for modulating synaptic signaling.Supported by funds to MWS from CIHR and the Krembil Foundation.

P2-B-307 *Identifying the MHCI interactome during typical synapse development and following immune stimulation*

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Increasing evidence points to a central role for immune-related genes and responses in Autism Spectrum Disorder (ASD) pathogenesis. Mutations in interleukin-1β (IL-1β) signaling pathway genes have been linked to ASD, and altered expression of immune genes including IL-1β, its receptors, and major histocompatibility

complex I (MHCI) molecule have been reported in postmortem ASD tissue. Moreover, maternal infection increases ASD risk four- to seven-fold. We recently discovered that MHCI may be a shared molecular hub downstream of diverse genetic and environmental ASD-related insults. In the central nervous system, MHCI molecules negatively regulate synapse stability, density, E/I balance, and NMDAR function, and IL-1β-induced synapse loss requires neuronal MHCI alterations. However, little is known about the mechanisms underlying MHCI-mediated synapse loss. We hypothesized that identifying the full MHCI interactome would reveal links between immune and synaptic signaling following IL-1β increases. We performed an unbiased proximity proteomics screen to identify MHCI (H2-Kb and H2-Db) protein interactors in developing neurons at baseline and after IL-1β treatment. Primary neuronal cultures were infected with AAV containing TurboID constructs (TurboID-HA-H2Kb, TurboID-HA-H2Db, or HA-TurboID control) driven by a hSyn1 promoter to biotinylate interacting proteins specifically in neurons. Following IL-1β or vehicle exposure, biotinylated proteins were collected and analyzed by mass spectrometry. This analysis identified novel neuron-specific MHCI interactors and IL-1β-dependent changes in the MHCI interactome, providing mechanistic insight into an ASD-associated pathways and revealing candidate proteins for validation as potential therapeutic targets.

P2-B-308 *Impact of MDGA2 haploinsufficiency on dendritic spine architecture in the dentate gyrus*

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The dentate gyrus (DG) is a critical yet understudied component of the hippocampal trisynaptic circuit, gating cortical inputs, supporting adult neurogenesis and playing critical yet understudied roles in neural pathologies underlying autism spectrum disorder (ASD). While robust alterations in dendritic spine density and morphology have been well characterized in CA1 and CA3 pyramidal neurons of MDGA2 (MAM domain containing glycosylphosphatidylinositol anchor 2) heterozygous autism mouse models, the impact of MDGA2 loss on synaptic structure and function within the dentate gyrus remains unknown. In this study, we used Golgi-stained tissue to investigate how MDGA2 haploinsufficiency affects dendritic spine density and morphology in dentate gyrus granule cells across key neurodevelopmental timepoints. Analyses focused on dendritic segments within the middle and outer molecular layers, which receive distinct medial and lateral perforant path inputs from the entorhinal cortex. By extending established spine-level analyses to the dentate gyrus, this work aims to clarify how loss of the rare synapse suppressor MDGA2 alters dendritic spine properties within a pertinent but underexplored hippocampal subregion critical for learning and memory, further revealing the nature of neural circuit and structural changes underlying ASD.

P2-B-309 *Impact of the CA1-specific deletion of Sigma-1 receptor on neuronal activity and behavior*

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The sigma-1 receptor (S1R) is a ligand-operated, transmembrane chaperone protein widely expressed throughout the body, with higher concentrations in the brain, that can act as an atypical auxiliary subunit of various voltage-gated ion channels. While complete S1R knockout in mice does not appear to impair basic physiological functions or behaviors, S1R becomes critical under challenge, particularly during learning and neuronal plasticity. This suggests its involvement in hippocampal neuronal activity essential for memory organization and consolidation. Current mouse models, which rely on global S1R silencing, do not allow for region- and neuron-specific analysis. To address this, we crossed a Cre/LoxP-based conditional S1R knockout mouse model with the r4ag11 transgenic line, which expresses Cre recombinase in CA1 and partially in the dentate gyrus (DG) under the CaMKIIα promoter. This approach allowed for region-specific deletion of S1R in CA1 and partial deletion in the DG. To investigate S1R's role in hippocampal activity and memory processes, we performed whole-cell patch-clamp recordings of CA1 pyramidal neurons and behavioral tasks assessing learning and mood regulation. While synaptic excitability remained unchanged, intrinsic excitability increased in males but remained unaffected in females. Interestingly, the knockout induced

sex-specific effects on first spike latency. Our findings suggest that S1R modulates neuronal excitability in a sex-dependent manner, with potential implications for hippocampal-dependent behaviors.

P2-B-310 *Inflammation during development alters axonal morphology and microglial engulfment activity in D. Rerio*

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Inflammation during development has been linked to many neurodevelopmental disorders (NDDs). A prevalent theory on the role of inflammation in NDDs is that there is defective pruning of axon branches by microglia, the brain's main resident immune cell. Microglia surveil the central nervous system (CNS) to clear pathogens and debris but are also known to monitor neuronal function and provide neuroprotection thereby contributing to healthy CNS development. Dysregulation of these cells patrolling the CNS in development can have serious and lasting effects on neuronal circuit formation. However, it remains unknown if there are critical periods for inflammation and microglial activation to shape the developing nervous system. Using the zebrafish (D. rerio) visual system as an accessible model system for studying brain development, neurons were sparsely labeled to identify individual cells in a transgenic microglia-labeled fish line. Pericardial injection of lipopolysaccharide (LPS), a bacterial wall mimetic, was conducted on relatively mature 6 day-postfertilization animals. After a 2-hour recovery period, the optic tectum was imaged using two-photon microscopy. Retinotectal axons were assessed for changes in morphology and length, and axonal engulfment and phagocytosis by microglia in normal vs. inflammatory conditions were quantified. Preliminary results are consistent with published literature at younger stages; inflammation is associated with increased axon branching, decreased axon length, and attenuated microglial phagocytic activity.

P2-B-311 *Investigating a role for netrin-1/DCC signaling in excitatory homeostatic synaptic upscaling*

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Neuronal circuits require homeostatic mechanisms to counterbalance destabilizing forces and maintain physiologically stable firing rates. Homeostatic synaptic scaling allows neurons to maintain the relative weight of synaptic inputs, while adjusting overall firing levels in response to long-term perturbations in activity. The secreted protein netrin-1 and the netrin receptor deleted in colorectal cancer (DCC) are made by neurons and enriched at synapses in the mature mammalian brain. Recent studies have identified essential roles for neuronal netrin-1 and DCC in long-term potentiation (LTP), a classic form of activity-dependent Hebbian plasticity. Netrin-1 is sufficient to potentiate synapses and induce synaptic insertion of AMPA receptors. As such, netrin-1 is a candidate to regulate homeostatic upscaling, a process that requires similar increases in post-synaptic strength. The present study investigates the involvement of netrin-1 in homeostatic upscaling associated with long-term decreases in neuronal activity. We have demonstrated that netrin-1 is secreted following long-term silencing of activity induced by tetrodotoxin (TTX). Further, using genetic knockouts of netrin-1 or DCC we have shown that each protein is required for the increase in miniature excitatory post-synaptic current (mEPSC) amplitude that follows chronic TTX exposure. Ongoing investigations are examining the signaling downstream of DCC involved in TTX-induced upscaling. These findings aim to identify a novel mechanism involved in homeostatic plasticity and a convergence point with Hebbian plasticity.

P2-B-312 *Dysfunctional somatodendritic AMPA receptor signaling in Fragile X Syndrome Cerebellum*

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Fragile X syndrome (FXS) is the most common single-gene cause of inherited intellectual disability and autism. Affected individuals and preclinical mouse models show brain hyperexcitability, although the underlying mechanism is poorly understood. Here we show that loss of Fragile X Messenger Ribonucleoprotein (FMRP) alters dendritic signaling and excitability in cerebellar molecular layer interneurons (MLIs - stellate cells). We observed a large but briefer excitatory postsynaptic potential (EPSP) in Fmr1-/- stellate cells (SCs) following excitatory parallel fiber (PF) stimulation. We demonstrate that the change in EPSP halfwidth is caused by an increased GABAergic transmission. The enlarged peak amplitude in Fmr1-/- SCs is due to a combination of abnormal TEA-sensitive potassium channels (Kv and Kca) functions. Pharmacological block of Kv and Kca channels converted the EPSP profile in WT SCs to that of Fmr1-/- mice. Additionally, pharmacological openers of Kv and Kca channels further attenuate EPSP amplitudes in both WT and Fmr1-/- SCs at varying degrees. These findings further validate the importance of two potassium channels in EPSP regulation. Interestingly, introduction of an N-terminal fragment of FMRP into Fmr1-/- SCs not only makes the EPSP a more potent response to pharmacological openers, but, more importantly, restores the EPSP amplitude to the WT mouse level. Contrary to conventional understanding, our study demonstrates that this AMPA-mediated signaling deficit in FXS can be corrected acutely by a fragment of FMRP via translationally independent mechanisms.

P2-B-313 *Investigating the effect of behavioral context on time cell dynamics and formation*

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Pyramidal neurons in the hippocampus quickly become tuned to different environmental cues (cue cells) and behavioural contexts, such as space (place cells) or time (time cells). Even though this tuning to specific behavioural features is critical for memory formation, the mechanisms underlying its rapid formation remain unclear. A novel candidate mechanism is “behavioral time-scale synaptic plasticity” (BTSP) whereby hippocampal neurons undergo a large depolarization, known as a ‘plateau potential’, while a mouse is in a specific location, followed by the emergence of a stable tuned spiking at that location. However, beyond place cell formation, it is unclear if time cells can also be tuned by BTSP. To address this question, we utilized 2-photon calcium imaging to record thousands of CA1 pyramidal neurons across days while headfixed mice learnt a non-spatial delayed odour discrimination task. After training, we find an increased number of time cells, with temporal tuning to the delay period, compared to naïve exposure to the task. An increased number of these time cells was tuned by putative BTSP events. Additionally, a higher rate of time cell tuning and associated BTSP events were observed after the rewarded odour versus non-rewarded one. The number of tuned cells, and their tuning strength, correlated with task performance. Finally, using 2-photon voltage imaging, we recorded membrane potentials of CA1 pyramidal cells during the same task, capturing the dynamics of subthreshold plateau potentials leading to tuned cells, and confirming that BTSP could tune time cells. Overall, we present novel learning-related dynamics of time cell formation in the hippocampus, as well as a potential mechanism behind this tuning.

P2-B-314 *Investigating the effects of probiotics on corticospinal excitability*

Malaikah Ahmad [1], **Faith Adams** [1], **Karishma Ramdeo** [2], **Chloe Drapeau** [1], **Mary Ann Ingrid Sader** [1], **Jiyeon Park** [1], **Aimee Nelson** [1]

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Emerging research supports the bidirectional connection between the brain and gut microbiome via the gut–brain axis, with growing evidence that microbial activity can influence neurotransmitters. Various Bifidobacteria and Lactobacilli species synthesize γ-aminobutyric acid (GABA). In vitro studies have previously demonstrated that probiotic supplementation with L. brevis and L. plantarum produces increases

in GABA and decreases in glutamate concentrations in the colon. As a result, this study aimed to investigate whether probiotic supplementation impacts corticospinal excitability and the propensity for short-term plasticity induced by repetitive transcranial magnetic stimulation (rTMS) in humans. Thirty healthy adults (15 males, 15 females) completed four visits as part of a randomized, double-blinded, placebo-controlled crossover design. Participants consumed either a probiotic (120 billion CFU per capsule) or placebo for 28 days, followed by a one-month washout period before crossing over to the alternate condition. TMS was used to assess corticospinal excitability and inhibition with motor evoked potentials (MEPs) and short-interval intracortical inhibition (SICI), respectively. Furthermore, the effect of the probiotic on the propensity for rTMS induced plasticity was assessed via the delivery of intermittent theta burst stimulation (iTBS) and measuring changes in MEP amplitude before versus following iTBS. As reduced GABAergic function and cortical disinhibition are prevalent in mood disorders and chronic pain conditions, this research will inform on the potential for microbiome-based interventions to alter the excitability of the nervous system.

P2-B-315 *Investigating the role of adaptor protein ShcD in oligodendrocyte development and myelination*

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Oligodendrocytes are the myelinating cells of the central nervous system, essential for rapid action potential propagation. Mature myelinating oligodendrocytes (OLs) are formed from their precursors, oligodendrocyte progenitor cells (OPCs). The oligodendrocyte lineage is highly spatiotemporally regulated by various growth factors involved in receptor tyrosine kinase (RTK) signalling pathways. Adaptor protein ShcD is enriched within the OL lineage, with expression highest in OPCs and progressively decreasing across differentiation. ShcD is involved in numerous RTK pathways with established roles in oligodendrocyte development and function. Although RTK signalling in the OL lineage has been well studied, the role of ShcD therein has yet to be fully elucidated. Utilizing ShcD wildtype (WT) and knockout (KO) mice, we investigated the role of ShcD in OL development and function. By probing adult mouse brain tissue, we found ShcD to have a region-specific influence on OL lineage marker expression. Additionally, we generated primary ShcD WT and KO OPCs capable of differentiation to mature OLs. The loss of ShcD significantly reduced the migration capacity of primary OPCs relative to their WT counterparts. Current work investigates the expression of OL lineage markers within the developing brain when rapid myelination occurs. Our findings highlight the importance of ShcD in oligodendrocyte dynamics, prompting further investigation into its mechanisms.

P2-B-316 *Investigation of transcriptomic changes in the anterior cingulate cortex in a mouse model of chronic neuropathic pain*

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Chronic pain impacts 25% of Canadians aged 15 and above, disproportionately affecting women and other people with ovaries (67% of individuals with chronic pain).Despite this, preclinical research has historically used male rodents. Neuropathic pain affects up to one-third of those experiencing persistent pain. The anterior cingulate cortex (ACC) is believed to be a hub for pain-induced long-term changes, with studies showing neuroplastic changes in the ACC rapidly after injury.Understanding the mechanisms involved in pain in the ACC and the biological processes driving the transition from acute to chronic pain are essential for improving diagnosis and treatment. This study investigated differential gene expression (DGE) in the ACC of female and male mice using the spared nerve injury (SNI) model of neuropathic pain.Adult (8 weeks old) C57BL/6 female and male mice underwent SNI and control procedures. Mechanical allodynia was assessed using the Von Frey test before injury, and prior to ACC sample collection at 5, 14, 30, and 60 days post-injury. Bulk RNAseq was employed, and DGE analysis of SNI over sham was performed using DESeq2.Despite comparable levels of mechanical allodynia in response to SNI, RNAseq analysis ($p<0.05$, $log2FC>0.5$) revealed distinct sex-dependent transcriptional profiles over time. These findings indicates that neuropathic pain induces sexually dimorphic transcriptional changes in the ACC, underlining the importance of including both

females and males in chronic pain research to better understand the molecular mechanisms underlying pain chronification.

P2-B-317 *Long-range amygdala-prefrontal engram projection supports remote fear retrieval*

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The ability to generate long-term memories is a critical aspect of adaptive behavior, with profound implications for psychiatric disorders, including post-traumatic stress disorder and anxiety disorders. Long-term memory retrieval is supported by distinct neuronal ensembles active at the time of learning, known as engrams, which are located in multiple brain regions. While it is known that engram neurons display preferential structural and synaptic connectivity with other engrams, the behavioral contributions of long-range engram-engram projections are less clear. Here, we investigated the role of engram neuron ensembles within the medial prefrontal cortex (mPFC) and of basolateral amygdala (BLA) engram projections to the mPFC in supporting remote contextual fear memory retrieval in mice. Using targeted viral approach and activity-dependent labelling combined with optogenetic and chemogenetic tools, we found that mPFC-projecting engram neurons in the BLA and mPFC are necessary for remote contextual fear memory retrieval. Remote fear retrieval also induced an increase in engram-engram synaptic connectivity between BLA and mPFC at a single neuron level. Our findings indicate that remote contextual fear memories are supported by a distributed engram network that relies on BLA-mPFC connectivity. These data suggest that the reactivation of long-range engram projections is a key mechanism underlying the persistence of fear memories, highlighting the importance of leveraging this framework to uncover novel memory encoding and retrieval mechanisms across distributed brain networks.

P2-B-318 *Mapping CCK-projections from the edinger-westphal (EW) and their function*

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The Edinger-Westphal nucleus (EW) is a midbrain structure traditionally associated with autonomic regulation, but the role of its centrally projecting neurons in pain processing remains unclear. Cholecystokinin (CCK)-expressing neurons within the EW form a distinct neuropeptidergic population with connectivity patterns that suggest a role in nociceptive modulation. Here, we mapped the EW afferent and efferent projections and examined the behavioural impact of selectively manipulating EW-CCK neuronal activity. Circuit-mapping approaches were combined with chemogenetic manipulation to bidirectionally modulate EW-CCK neuronal excitability using excitatory or inhibitory designer receptors exclusively activated by designer drugs (DREADDs). Thermal and mechanical nociception, conditioned place preference, social interaction, and anxiety-like behaviour were assessed to capture both sensory and affective aspects of pain. To study the impact of neuropathic pain on EW function, rodents underwent spared nerve injury (SNI) followed by behavioural testing. Circuit-mapping revealed EW projections to the superior colliculus, periaqueductal gray, and mammillary bodies. Chemogenetic excitation of EW-CCK neurons increased c-Fos expression compared with the inhibitory and control groups, confirming effective neuronal modulation. However, behavioural effects of EW-CCK manipulation were modest or absent across tests. Together, these data define the connectivity of EW-CCK neurons and constrain their contribution to pain-related behavioural outcomes.

P2-B-319 *Mechanisms of laminar organization of hippocampal excitatory synapses*

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Hippocampal circuits develop by precise assembly of synapses in discrete dendritic layers. The molecular determinants of laminar selectivity remain poorly understood. Leucine-rich repeat transmembrane proteins (LRRTMs) regulate excitatory synapse development and plasticity, positioning them as key mediators of input-specific connectivity. Across development, LRRTM1 and LRRTM2 show distinct temporal and laminar expression. In adult mice brain, LRRTM1 is enriched in stratum radiatum (SR) and LRRTM2 in stratum lacunosum moleculare (SLM) and the dentate gyrus molecular layer. Conditional deletion of Lrrtm1 in adult dorsal CA1 (Lrrtm1-dCA1-cKO) reduced synaptic transmission and impaired long-term potentiation (LTP) at CA3-CA1 synapses in SR, whereas inputs in SLM were unchanged. Re-expression of LRRTM1 restored basal synaptic strength and LTP. Lrrtm1-dCA1-cKO mice exhibited reduced freezing and diminished CA3-CA1 network dynamics in a fear memory test, indicating weakened network activation. Blocking AMPA receptor endocytosis using the GluA23Y peptide rescued both LTP in SR and fear memory. In the fear memory test, control (GluA23S) mice showed impaired fear memory and relearning, while GluA23Y rescued these deficits. Our findings demonstrate that LRRTM1 functions as a lamina-specific regulator of CA3–CA1 synapses in stratum radiatum, where it stabilizes AMPA receptors to maintain synaptic strength and plasticity, thereby sustaining circuit dynamics and fear memory.

P2-B-320 *Mechanistic insight into mild traumatic brain injury induced circadian and sleep abnormalities in mice*

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Traumatic brain injury (TBI) is a bump, blow, or jolt to the head that disrupts normal brain function, with mild traumatic brain injury (mTBI; Glasgow coma scale 13-15), accounting for 70–90% of all cases. Despite its prevalence, mTBIs often go undetected by standard neuroimaging. Aside from the more recognized side effects of mTBI such as cognitive impairment and headaches, 1/3 of mTBI patients have dysautonomias and commonly exhibit circadian rhythm and sleep dysfunctions. Circadian rhythms are ~24 hour cycles regulated by the suprachiasmatic nucleus (SCN), which synchronizes peripheral clocks and maintains physiological cycles. The objective of this study was to determine the underlying hypothalamic mechanisms that cause mTBI-induced circadian deficits and sleep abnormalities. Using a lateral head impact model of mTBI, we found that 1. Late-night mTBIs produced phase advances in activity and wake-associated temperature rise onset as well as an overall increased sleep. 2. There is an advance in the firing onset of SCN vasopressinergic (SCNVP) neurons following mTBI. 3. Wake-promoting lateral hypothalamic orexin (LHOrx) cells become less active after mTBI. In conclusion, these findings indicate that mTBI induces circadian phase shifts, likely driven by aberrant activation of SCNVP neurons at a time of day when they are typically quiescent. Secondly, mTBI increases sleep during both the inactive and active phases in mice, concomitant with reduced c-Fos staining of wake-promoting LHOrx.

P2-B-321 *Mef2 transcription factors enable microglial support of brain vasculature functions*

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Introduction: Previous epigenomic data from our group suggest that the transcription factors MEF2 (a/c/d) are essential for maintaining microglial homeostasis. Loss of MEF2 activity dysregulates genes critical for neurovascular unit (NVU) function, including PDGFB, P2RY12, and TREM2. We hypothesized that microglial

MEF2 regulates NVU function and contributes to cerebral small vessel disease (CSVD) pathophysiology. Methods: MEF2 was selectively depleted in microglia of CX3CR1-CreERT2:MEF2^flox mice, with tamoxifen-treated CX3CR1-CreERT2 mice used as controls. Immunohistology assessed microglia (Iba1), astrocytes (GFAP), and endothelial cells (CD31) under basal conditions. CSVD-like hypoperfusion was induced by unilateral ligature of the left common carotid artery. Cerebral blood flow (CBF) was measured using laser speckle contrast imaging and laser Doppler. Postmortem immunohistology assessed reactive microglia (Clec7a) and astrocytes (GFAP). Results: In the striatum, knockout mice showed increased microglial density in females and increased astrocytic and endothelial cell areas in both sexes under basal conditions. With hypoperfusion, knockout mice exhibited reduced CBF at 1 and 14 days compared to controls, along with increased astrocyte area and reactive microglial density. Conclusions: Microglial MEF2 transcription factors are critical regulators of NVU integrity and function. Their loss disrupts microglial support of vascular and glial cells, thus revealing a novel mechanism contributing to CSVD and identifying MEF2 as a potential therapeutic target.

P2-B-322 *Microglial TNF signaling is required for behavioral and cognitive deficits in a rodent model of post-traumatic stress disorder*

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Post-traumatic stress disorder (PTSD) is a debilitating mental illness that follows trauma and leads to persistent alterations in cognition and emotional regulation. Current treatments, including SSRIs, are slow and ineffective for many patients, highlighting the need for novel therapeutic strategies. Neuroinflammation has emerged as a promising avenue for PTSD treatment.Elevated levels of the pro-inflammatory cytokine tumor necrosis factor-alpha (TNF) have been reported in PTSD patients and rodent stress models.
Our laboratory previously showed that acute stress induces a sustained increase in TNF in the ventral hippocampus, enhancing AMPA receptor–mediated glutamatergic transmission and driving anxiety-like behavior. The role of TNF in chronic stress, however, remains unclear. Using the single prolonged stress (SPS) paradigm, a rodent PTSD model, we found persistent anxiety-like behavior and cognitive impairments lasting at least 8 weeks, accompanied by elevated TNF in the hippocampus and frontal cortex. SPS failed to induce deficits in TNF knockout, TNF receptor 1 knockout, or microglial TNF–deficient mice. MDMA, a compound under clinical investigation for PTSD with reported anti-inflammatory effects, rescued anxiety-like behavior when administered after SPS, suggesting that modulating inflammatory signaling contributes to its efficacy. These findings identify microglial TNF as a promising therapeutic target for PTSD.

P2-B-323 *Microglial trogocytosis in activity-dependent axonal pruning in the visual system during development*

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Existing research suggests that microglia, immune cells of the nervous system, play a role in neural circuit formation. Microglia are thought to do this through trogocytosis, which is the partial phagocytosis of cells. Live imaging shows that microglia may remodel synapses by consuming particular branches of a neuron's axon terminal. This mechanism could change neuronal wiring by weakening specific connections between neurons. The mechanisms deciding which neurons undergo trogocytosis are still unknown. One potential mechanism is neuronal activity. Trogocytosis may be a competitive mechanism for degrading weaker synapses relative to its' neighbors. We expressed tetanus toxin to genetically silence transmitter release in a subset of tadpole retinal ganglion cells (RGC) to examine the effects of synaptic activity on trogocytosis rates and axon morphology. Furthermore, we will examine if axon morphological changes following suppression of neuron activity are dependent on microglia. We will deplete microglia using PLX3397, a pharmacological inhibitor of the colony-stimulating factor 1 receptor and examine if this prevents the changes to axon morphology. Trogocytosis remains an understudied mechanism that may be important for proper wiring of neural circuits. By understanding how microglia interact with neurons, our work may also provide further knowledge into their contributions to neurological disorders.

P2-B-324 *Miglustat protects against demyelination of smaller diameter axons and promotes myelin formation*

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Multiple sclerosis (MS) is an autoimmune disease characterised by phases of axonal demyelination that eventually provokes axonal degeneration. Miglustat (Zavesca™; Actelion Pharmaceuticals) is a drug approved for the treatment of Gaucher genetic disease, designed to inhibit pathological accumulation of glycosphingolipids in cells. In the EAE mouse model for MS, Miglustat has been shown to inhibit astrocyte-mediated inflammation in the CNS. To test its impact on demyelination, we treated mice with Miglustat during a cuprizone (CPZ)-induced demyelination protocol. Brain sections were immunolabelled for myelin, astrocyte and microglia specific proteins to assess demyelination and potential effects of Miglustat in the corpus callosum. Spectral confocal reflectance (SCoRe) imaging was used to quantify global myelin integrity and myelin debris. Using transmission electron microscopy, we measured G-ratio, myelin thickness, major dense line number and periodicity to characterise myelin ultrastructure. Oligodendrocytes cultured in vitro in presence of miglustat showed increased signal for myelin basic protein (MBP). Our findings indicate that miglustat can directly act on oligodendrocytes to promote myelination. Miglustat treatment during demyelination increased myelin thickness and axon diameter, and inhibited microglial phagocytic capacity, specifically protecting smaller axons from demyelination. Further investigation will be required to determine if protection conferred by Miglustat during demyelination may promote remyelination following the end of CPZ treatment.

P2-B-325 *Mitochondrial calcium & hydrogen peroxide interact to control nonselective cation channels in aplysia neuroendocrine cells*

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Changes to intracellular Ca^{2+} or reactive oxygen species (ROS) can alter neuronal activity by gating ion channels. In bag cell neurons of the sea snail, Aplysia californica, channels opened by these messengers generate prolonged depolarization and action potential firing known as an afterdischarge to drive egg-laying hormone secretion and reproductive behaviour. Important here are two cation currents: a voltage-dependent current gated by hydrogen peroxide (H_2O_2) and a voltage-independent current activated by mitochondrial Ca^{2+}. The latter can also be opened by liberating Ca2+ following collapse of the mitochondrial membrane potential with FCCP (carbonyl cyanide 4 trifluoromethoxyphenyl-hydrazone). Because FCCP-induced uncoupling can also increase ROS, including H_2O_2, we examined interactions between these pathways. Using cultured bag cell neurons and whole-cell recording, FCCP elicited an ~25 mV depolarization from a resting potential of -60 mV. Similarly, at a holding potential of -60 mV, the FCCP-evoked current was ~-750 pA, which was reduced by ~60% with prior H_2O_2 exposure. Conversely, if FCCP was delivered first, the H_2O_2-induced current was enhanced by 3-fold, which was reduced by intracellular Ca^{2+} buffering with EGTA, suggesting Ca^{2+} dependence. With regards to redox, the H_2O_2-induced current was reduced by 3-fold in the presence of the mitochondria-targeted antioxidant, MitoTEMPO. For Aplysia, neuroendocrine cell activity and the resulting secretion of reproductive hormone may be influenced by the interaction between ROS and mitochondrial Ca^{2+}.

P2-B-326 *Modality-specific neurovascular coupling via layer-segregated arteriole networks*

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The brain’s vascular system regulates energy supply and responds dynamically to neural activity through neurovascular coupling. Brain mapping techniques, such as fMRI, use vascular signals as proxies for neuronal activity and assume a consistent one-to-one coupling. Here, we show that neurovascular coupling is

modality-dependent: distinct sensory inputs engage specialized arteriole types, to produce layer-specific blood flow patterns. Using multi-scale optical imaging, we compared neuronal and vascular responses to innocuous touch vs. optogenetic nociceptor activation. Despite similar neuronal activity, nociception-induced hemodynamic signals were halved. This effect was mediated specifically by small and shallow penetrating arterioles, and results were reproduced in silico. These findings reveal a new principle of neurovascular organization, wherein arteriole type and termination depth dictate localized blood delivery, challenging uniform interpretations of fMRI signals.

P2-B-327 *Modulation of interneuronal functioning and perineuronal nets by microglia in female ovariectomized mice*

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Menopause is characterized by the decline in peripheral female gonadal hormones, such as estrogen and progesterone, and is frequently associated with a decline in emotional and cognitive abilities. A withdrawal of female gonadal hormones has been shown to reduce the functioning of inhibitory GABAergic neurons, required for the synchronized firing of neurons across regions that facilitates network dynamics. Microglia are implicated in the shaping of neuronal circuits, for example, through the phagocytosis of inhibitory synapses and perineuronal nets (PNNs) ensheathing fast-spiking interneurons, modulating their firing properties. Female gonadal hormones directly bind to microglia, modulating their functioning, with estradiol withdrawal potentially inducing an excessive degradation of neuronal connections. To investigate the effects of hormonal depletion on microcircuit functioning, 3-month-old female C57BL/6J mice will be subjected to ovariectomy (OVX), the bilateral removal of their ovaries, or sham OVX, the placement of a surgical incision without removal of the ovaries. Measurements will be conducted at three time points: at 30 days, 60 days and 90 days post-OVX. Behavioural domains assessed will include anxiety (open field) and learning and memory (novel object recognition). High-throughput epifluorescence microscopy will be used to investigate microglial modulation of inhibitory microcircuits and PNNs. Automatized measurements of microglial morphological features and proximity to interneurons and PNNs will be performed to provide functional insights into microglial mechanisms (N:6/condition).

P2-B-328 *Neocortical microcircuit changes associated with fragile x syndrome*

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Fragile X syndrome, the most common form of inherited intellectual disability, is associated with over 10x the average risk of seizures. Seizures have been linked to changes in local circuits. However, it remains unclear precisely how local circuits are altered in Fragile X brains, which makes seizures difficult to treat. A key reason why circuit alterations linked to Fragile X remain unknown is that current connectivity mapping methods are too slow. We therefore created optomapping, a high-throughput 2-photon optogenetic circuit mapping method that is ~100-fold faster than multiple patch-clamp recordings. We used this method to identify primary visual cortex circuit changes associated with increased seizure propensity in Fragile X. We expressed soma-targeted ChroME in neocortical pyramidal cells (PCs) via neonatal infection of either Emx1-Cre control mice or Emx1-Cre;Fmr1-/- Fragile X mice. In acute slices from P18-P27 mice, we evoked PC spiking using near-IR femtosecond-laser spiral-scan photostimulation. While patch-clamping layer-5 excitatory PCs as well as inhibitory basket and Martinotti cells, we drove surrounding PCs with the laser to identify differences in excitation/inhibition balance. Preliminary results indicated an increase in the number and strength of connections between layer-5 PCs in Fragile X. Altered excitation in local circuits may thus underlie increased seizure propensity in Fragile X. Given conserved cortical circuit motifs across mice and humans, these results may help guide the development of seizure therapies for Fragile X syndrome.

P2-B-329 *NeuroD1-AAV9 astrocyte-to-neuron reprogramming improves motor function and neuron-to-glia balance following ischemic stroke in non-human primates*

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After ischemic stroke, approximately 60% of survivors experience persistent motor impairments driven by irreversible neuronal loss. Ischemic injury causes astrocytic proliferation, disrupting neuron-glia balance, which limits endogenous repair and leads to chronic inflammation and neurodegeneration. Gene therapy with NeuroD1-Adeno-associated virus 9 (AAV9) is an emerging stroke treatment that induces astrocyte-to-neuron transdifferentiation. Functional recovery with NeuroD1-AAV9 has been demonstrated in pre-clinical models, including rodents and non-human primates (NHPs). The dose–response relationship for maximizing NeuroD1-AAV9 recovery remains undefined. In this study, twelve NHPs underwent middle cerebral artery occlusion. Fourteen days post-stroke, animals received intracerebral injections of NeuroD1-AAV9 using either a low-dose or high-dose protocol. Animals were followed for 9 months, during which recovery was assessed using the NHP Stroke Scale. At the endpoint, brains were collected and processed for immunofluorescence labelling of neuronal (NEUN) and glial (GFAP, IBA1) markers to evaluate astrocyte-to-neuron conversion and glial responses. Both NeuroD1-AAV9 protocols showed sustained motor improvements over nine months, with significant effects on stroke scale outcomes compared to controls. Histological analyses revealed restoration of the neuron-to-glia ratio in the ipsilateral hemisphere, characterized by a reduction in $GFAP^+$ astrocytes in both low- and high-dose groups. No significant differences in $IBA1^+$ microglial cell counts were observed. These findings show that both low- and high-dose NeuroD1-AAV9 promote recovery and neuronal restoration after ischemic stroke in NHPs, supporting dose-optimized astrocyte-to-neuron reprogramming as a translational therapy strategy.

P2-B-330 *Neurophysiological properties of subthalamic nucleus neurons expressing corticotropin-releasing hormone*

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Background: The subthalamic nucleus (STN) is an important structure within the basal ganglia receiving inputs from motor, non-motor, and limbic brain areas and is critically important for the initiation of voluntary action. A subset of STN neurons express the stress-relevant neuropeptide corticotropin-releasing hormone (CRH). Evidence suggests this neuronal subpopulation is functionally relevant for responding to stressful challenges, namely exposure to predator scent. However, little is known about the intrinsic properties of this neuronal subpopulation.Hypothesis: We predict that STN-CRH neuronal activity and excitability in young adult mice will resemble canonical STN neuronal activity. Methods: Spontaneous and current-induced activity will be characterized using whole-cell patch-clamp electrophysiology in male and female 3-month-old mice. Results: We will report on the frequency and amplitude of spontaneous and induced action potential firing, spontaneous excitatory transmission, and rebound firing following hyperpolarizing current injection. Conclusion: Characterizing this stress-responsive subpopulation of STN neurons is critical for understanding the role of these neurons in both health and disease. As the STN is one of the major targets of deep brain stimulation for Parkinson's treatment, we will build on this work with future investigation into the role of these neurons in Parkinson's disease both in the presence and absence of acute stress exposure.

P2-B-331 *Neuroplastic mechanisms underlying the antidepressant effects of psychedelics*

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Work from the Murphy-Royal lab using early-life stress (ELS) models shows astrocyte dysfunction in the amygdala and hypothalamus, highlighting astrocytes as promising therapeutic targets. Traditional antidepressants have limited efficacy, whereas psychedelics can produce rapid, durable relief in

treatment-resistant depression, potentially by remodeling perineuronal nets (PNN) around parvalbumin (PV) interneurons. Since astrocytes are major PNN producers, we hypothesize psychedelics reopen a critical period by promoting plasticity in stress circuits via astrocytic PNN regulation. This project sets out to investigate whether psychedelics such as 5-MeO-DMT (DMT) reverses depression-like behavior in mice and reveal the underlying cellular mechanisms. Methods: We examined the effects of DMT on PV and PNN structure in the lateral amygdala. Using ELS model, C57BL/6J mice received either DMT or saline injections, and brains were collected 24h later. Tissues were then stained for PV and PNN and then imaged by microscopy. Results: DMT significantly reduced the proportion of PV surrounded by PNN and decreased overall PNN coverage, indicating a loosening of extracellular matrix constraints and enhanced structural plasticity. Furthermore, this effect was more pronounced in males, suggesting sex-specific mechanisms. Conclusion: DMT modulates inhibitory circuits in the amygdala by remodeling PNN. This supports the hypothesis that psychedelics can reopen critical periods and highlights sex-specific mechanisms that may be leveraged for therapeutic strategies against stress-related disorders.

P2-B-332 *New tools to promote release of endogenous serotonin in the prefrontal cortex*

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Serotonin neurons play an important but still enigmatic role in emotional and cognitive regulation, and serotonin signalling is a therapeutic target for many psychiatric disorders. Recent optogenetic work suggests a strong and specific modulatory role in cognitive flexibility for serotonin release in the prefrontal cortex (Morgan et al., 2023, bioRxiv 2023.03.30.534775). This experiment involved a brief period of 20 Hz stimulation of prefrontal serotonin release, provoking a behavioural impact not detected in experiments with longer or repeated stimulations. This pattern suggests synaptic depression of serotonin afferents may occur in the prefrontal cortex. Here, we stimulate serotonin afferents optogenetically in brain slices of prefrontal cortex from adult Pet1cre::Ai32 mice while recording the responses electrophysiologically. Trains of low frequency stimulation yield sustained outcomes which are repeatable. By contrast, even brief trains of higher frequency stimulation show prominent depression of outcome. We investigate the properties of this plasticity, including its cross-frequency impact. We use pharmacological approaches to probe the mechanisms of this depression, revealing new tools to optimize the release of endogenous serotonin in the prefrontal cortex. These experiments in brain slices of mouse prefrontal cortex describe key regulation of serotonin signalling. This research yields insight that may help overcome challenges in vivo and ex vivo in investigating the impact of serotonin on brain function.

P2-B-333 *NMDA receptor signaling is not monolithic: Location determines plasticity function*

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NMDA receptors (NMDARs) are well-known as coincidence detectors in Hebbian learning, but this requires postsynaptic localization. Presynaptic NMDARs, however, remain controversial due to pitfalls in pharmacology and Ca2+ imaging. Thus, we used more direct techniques to test the function of distinct NMDAR pools. Immunogold EM in V1 layer 5 of P21 C57BL/6 mice revealed GluN1, GluN2A and GluN2B subunits both pre- and postsynaptically at excitatory synapses onto pyramidal cells (PCs). Consistent with pharmacology, GluN2B dominated presynaptically ($p < 0.001$).Next, we genetically deleted NMDARs sparsely by neonatal AAV-eSYN-iCre injection into NR1fl/fl mice, with MNI-NMDA uncaging confirming NMDAR loss ($p < 0.001$). Using quadruple patch in P10-P20 acute slices, we tested PC→PC pairs with NMDARs deleted (Del) either pre- or postsynaptically, versus wildtype (WT). AP5 reduced EPSP amplitude in WT→WT ($p < 0.001$) and WT→Del pairs ($p < 0.001$), but not Del→WT pairs ($p = 0.46$), showing that pre- but not postsynaptic NMDARs regulate release. Furthermore, timing-dependent long-term depression (tLTD, $p = 0.29$) but not potentiation (tLTP, $p < 0.05$) was abolished in Del→WT pairs. In contrast, tLTP ($p = 0.24$) but not tLTD ($p < 0.01$) was abolished in WT→Del

pairs. These results reveal a double dissociation in spike-timing-dependent plasticity. Finally, presynaptic NMDARs controlled spontaneous release, while postsynaptic NMDARs controlled spines and axo-dendritic branching. In summary, NMDARs do not act as a unified plasticity signal but support distinct roles depending on synaptic location.

P2-B-334 *Not only neurons; dopamine receptor signaling in microglial cells drive behaviour and neuroinflammatory state*

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Microglia play prime roles in physiology and pathology of the CNS, due to their capacity to adjust to various signals from their environment. One major signal is dopamine (DA). Study of DA functions has traditionally relied on the expression of DA receptors on neurons; however, emerging evidence suggests their expression on microglia. We aim to investigate how DA receptors D1 and D2 expressed by microglia affect immunomodulatory responses, behavior, and neuronal function in vivo. We generated microglia-specific D1 and D2 deletion models by crossing Cx3cr1CreER2 with Drd1lox/lox or Drd2lox/lox strains. Results show that microglia express D1 and D2 in the striatum, and expression increases following chronic psychostimulant administration; microglial D1KO leads to hypo-anxiety and abolishes baseline compulsive-like behavior. Surprisingly, microglial D1KO leads to reduced hyperlocomotion in response to acute amphetamine and blunts behavioral sensitization to cocaine only in female mice. Microglial D2KO mainly results in altered striatal cytokines levels.Microglia sense and respond to fluctuations in striatal DA release. Microglial D1 A. is associated with physiologic regulation of compulsive-like behavior and anxiety & B. modulates response to psychostimulants in a sexually dimorphic way. Microglial D2 plays a major role in the homeostatic striatal cytokine profile. The findings of this ongoing study will open an entirely new area of research with microglial DA signaling as a target in psychopathologies related to obsessive-compulsive traits, anxiety, and substance use disorder.

P2-B-335 *Opioid-induced hyperalgesia develops in the periphery and in the absence of proinflammatory microglia*

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Adverse side effects of opioid use, including analgesic tolerance, opioid-induced hyperalgesia, and addiction, are serious clinical challenges for pain management and opioid deprescribing. Microglia have been implicated in the development of these adverse effects, but the mechanisms through which opioids alter microglia are poorly understood. We hypothesize that alterations in spinal microglia underlie the generation and maintenance of pain hypersensitivity in opioid withdrawal. Male C57BL/6J mice were treated with escalating doses of morphine (10-40 mg/kg, i.p.) or saline for 4 days, following which pain behaviour and spinal tissue collection was performed 1 and 7 days post-drug. CD11b+ myeloid cells were isolated from spinal cords and used for single-cell RNA sequencing, while fluorescence in-situ hybridization was used to confirm the expression of the mu opioid receptor in microglia. Microglial morphology was determined via immunohistochemistry in opioid-withdrawn and saline-treated spinal cord sections. Opioid withdrawal produced hyperalgesia in mice for up to 7 days. Cell branching was reduced in opioid-withdrawn microglia alongside upregulation of the endolysosomal marker CD68. Microglia displayed a modest shift in gene expression, with an increase in genes related to phagocytosis and motility, but not inflammation. Opioid receptor expression in microglia was heterogenous. Notably, peripherally-restricted opioid treatment was sufficient to produce hyperalgesia, implying that direct microglia-opioid interactions are dispensable for hyperalgesia.

P2-B-336 *Pannexin1 homolog regulates plasticity required for adaptive learning in larval zebrafish*

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Pannexin1 (Panx1) is an integral ion and metabolite membrane channel in the central nervous system that regulates synaptic plasticity. Despite its well-documented role in ATP release and neurotransmission, downstream signalling pathways initiated by Panx1 channels, remain largely unexplored. Using 6-day-old zebrafish larvae, we have previously shown that Panx1a, a homolog of Panx1, is critical for visual habituation, with knockouts (Panx1a-/-) showing persistent startle responses compared to wild-type. We used post-hoc fosab labelling to identify brain activity hotspots that require Panx1a for habituation. We also show higher baseline transcription and reduced activity-induced fosab in localized brain regions in knockouts, suggesting the involvement of Panx1a in excitation-inhibition (E/I) balance. We demonstrate this further by pharmacologically modulating receptor signalling pathways. The results indicate that excitatory glutamatergic drive is required for habituation but does not represent the primary point of Panx1a action. In contrast, GABA antagonists destabilized habituation memory in both genotypes, with Panx1a-/- larvae disproportionately affected. At a network level, local field potential recordings in the dorsolateral pallium (hippocampus analog) and optic tectum (sensory center) indicate reversed oscillatory activity in knockouts post-habituation, suggesting disrupted network dynamics. Together, the results point towards a conserved role for Panx1 channels in scaling molecular mechanisms to network- and behavior-level plasticity. NRSC DG RGPIN-2019-06378 (GRZ)

P2-B-337 *Panx1 channel mediates TNFα-induced endothelial barrier permeability in human brain microvasculature*

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Introduction: Pannexin 1 (Panx1) is an ATP-release channel activated during inflammation. TNFα modulates Panx1 opening and alters endothelial function, but its effects on brain endothelial cytoskeleton and barrier integrity remain unclear. We investigated Panx1's role in human brain endothelial response to TNFα. Methods: hCMEC/D3 cells were treated with TNFα (10 ng/mL) for 5 and 24h. Panx1 total levels and Y198 phosphorylation were assessed by immunofluorescence and Western blot. Panx1 activity was measured by ethidium uptake and ATP release. Ca^{2+} signals used Fluo-4 AM. Occludin levels/distribution by Western blot. Permeability assessed by FITC-dextran in diffusion chamber. Results: TNFα increased Panx1-Y198 phosphorylation at 5 and 24h (higher ratio at 24h), enhancing Panx1 activity and ATP release—both blocked by probenecid (PBN) or 10Panx1. At 5h, TNFα boosted ATP-evoked Ca^{2+} signals via Panx1, prevented by blockers. At 24h, TNFα disrupted occludin junctions and raised permeability; PBN attenuated these. Conclusion: Panx1 centrally mediates TNFα-induced brain endothelial dysfunction through ATP release, Ca^{2+} signaling, occludin remodeling, and barrier leakiness. Panx1 blockade reverses effects, highlighting it as a prime therapeutic target in neuroinflammation

P2-B-338 *Pharmacological rescue of GABAergic synapse strengthening in a mouse model of Fragile X Syndrome*

Xinyuan (Cecilia) Chen [1], Siqi Wang [1]

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Fragile X syndrome (FXS) is the most common form of inherited intellectual disability and the primary monogenic cause of autism spectrum disorder. Emerging evidence implicates defective GABAergic inhibition as a crucial contributor to FXS pathology. While many findings reveal deficits in GABAA receptor function and inhibitory tone in FXS, the activity-dependent dynamic plasticity of GABAergic synapses remains largely unexplored. Our previous study identified a signaling pathway coupling NMDARs to the GABAergic system that enables synaptic strengthening in cerebellar molecular layer interneurons. In this pathway, NMDAR

activation triggers downstream nNOS-cGMP-PKC signaling, ultimately unsilencing silent synapses and potentiating the inhibitory response. Here, we identify a widespread reduction in NMDAR-mediated currents in MLIs from a FXS mouse model using patch-clamp recordings, suggesting a loss of GABAergic plasticity. Consistent with this, high-frequency stimulation fails to potentiate inhibitory responses by recruiting silent inhibitory synapses, whereas exogenous cGMP robustly restores potentiation, indicating that the deficit primarily resides at the level of NMDARs. Notably, pharmacological elevation of cGMP, particularly via the PDE5 inhibitor sildenafil, can rescue this form of inhibitory plasticity in MLIs. Together, these findings uncover an unexpected impairment of inhibitory synaptic plasticity in the FXS brain and identify cGMP signaling as a promising target for restoring E/I balance and improving therapeutic strategies.

P2-B-339 *Silent synapse recruitment drives GABAergic potentiation in the cerebellar stellate cells*

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Plasticity at inhibitory synapses enables dynamic regulation of neuronal activity, yet the synaptic basis of GABAergic potentiation is not completely understood. Previously, we identified a form of GABAergic potentiation in cerebellar stellate cells that depends on NMDAR- and GABARAP-dependent signaling, but does not require CaMKII and gephyrin. However, it remains unclear whether the resulting increase in GABAergic current arises from enhanced receptor content at individual synapses or through alternative synaptic mechanisms. To address this question, we used whole-cell electrophysiology combined with macroscopic and minimal-evoked IPSC protocols. Using α3 subunit knockout mice and intracellular pharmacological blockade, we demonstrate that this potentiation is postsynaptically mediated and selectively involves α3-containing GABA A receptors rather than α1-containing receptors. We utilized the minimal-evoked IPSC protocol, which enabled independent quantification of the contributions of event frequency and amplitude change to the plasticity. As a result, we found that potentiation was driven primarily by increased event frequency, with minimal contribution from changes in peak amplitude of GABAergic current. This result is consistent with the recruitment of previously silent synapses via a postsynaptic mechanism. Together, our project identifies silent synapse recruitment as a principal mechanism of GABAergic potentiation in the cerebellum and reveals a postsynaptic pathway that selectively engages α3-containing GABAergic synapses.

P2-B-340 *Phasic axonal dopamine release appears to involve mechanisms beyond synaptotagmin-1*

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Parkinson's disease (PD) is characterized by the degeneration of dopaminergic neurons (DAn), resulting in motor deficits. Dopamine (DA) release in the striatum is tightly regulated by vesicular calcium sensors, such as synaptotagmin-1 (Syt1). Previous studies in mice have shown that Syt1 knockout (Syt1KO) significantly reduces DA release after a single stimulation, without altering observable motor behaviors or the level of DA in the striatum. Given that DAns display spontaneous firing (1–5 Hz) and burst activity (10–50 Hz), we hypothesized that these firing modes could sustain residual phasic DA release in Syt1KO mice. To test this hypothesis, we performed cyclic voltammetry recordings on striatal slices from WT and Syt1KO mice following single stimuli or trains (burst activity at 6Hz/10Hz/50Hz). The impact of applying continuous, pacemaker-like stimulation (1Hz/2Hz/5Hz) prior to release measurements was also evaluated. DA release induced by acute stimulation was reduced by 90% in Syt1KO mice. However, DA release evoked by burst firing was reduced much less extensively. Pacemaker-like activity attenuated acutely evoked DA release in both WT and KO mice, with a twofold smaller effect in KO mice. These results are globally compatible with the hypothesis that while DA release evoked by single stimuli is dependent mainly on Syt1, release evoked by higher frequencies of stimulation also implicates other exocytosis calcium sensors. We further hypothesize that DA-dependent behaviors are sustained by multiple modes of DA secretion.

P2-B-341 *Physiological properties of VGLUT1 mediated glutamatergic neurotransmission in the Substantia Nigra*

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The substantia nigra (SN) plays a central role in mediating purposeful voluntary movement and the degeneration of dopaminergic neurons in the SN pars compacta (SNc) results in motor disorders found in Parkinson's disease. Neurons of a variety of neurotransmitter subtypes make synaptic inputs onto SN neurons yet the synaptic properties of glutamatergic inputs and their impact on neuronal excitability is not completely understood. In this study, using optogenetics we examined VGLUT1-mediated glutamatergic synaptic neurotransmission onto GABAergic neurons of the substantia nigra pars reticulata (SNr) and dopaminergic neurons of the SNc. Using a VGLUT1-Cre::ChR2 mouse line, we optogenetically stimulated VGLUT1 expressing glutamatergic presynaptic fibers and recorded SN neurons in the whole-cell patch-clamp configuration in acute brain slices.Pharmacological blockade with DNQX and APV demonstrated that excitatory postsynaptic currents in both SNr and SNc neurons were mediated by both AMPA and NMDA receptors, respectively. Application of TTX and 4-AP revealed that these responses were action potential-dependent and monosynaptic. Short-term plasticity was assessed using stimulus trains at 5Hz and 25Hz, revealing evidence of synaptic facilitation, depression, and mixed plasticity in both SNr and SNc neurons. Notably, substantial variability was observed in the magnitude of synaptic depression across recorded cells. These findings indicate that VGLUT1-mediated glutamatergic inputs to the substantia nigra exhibit heterogeneous short-term plasticity profiles, suggesting diverse effects in modulating SN neuronal excitability.

P2-B-342 *Pregnancy-induced microglia activation promotes Neural Stem Cells niche remodelling and maternal neurogenesis*

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Adult neural stem cells (NSCs) persist lifelong in specialized niches of the mammalian brain and exhibit remarkable plasticity in response to physiological demands. Pregnancy is a unique physiological state in which profound systemic, hormonal, and metabolic changes transiently remodel brain function and structure. It is shown that pregnancy triggers transient neurogenesis in the female olfactory bulb needed for pups' recognition. This results from the activation of NSCs in the subventricular zone (SVZ). However, the mechanisms underlying this NSCs activation remain elusive. Here, we investigated how pregnancy remodels the SVZ microenvironment and influences NSC behaviour. Using ex-vivo Ca^{2+} imaging followed by multiplex immunostaining, we examined niche remodelling, NSC–interactions with distinct cell types in pregnant/virgin mice. Our results reveal that pregnancy reshapes the SVZ microenvironment, increases immune cell presence, and induces niche-specific Ca^{2+} signalling patterns in NSC basal processes. These alterations were accompanied by a transient increase in NSC proliferation involving prolonged cell cycle. Furthermore, longitudinal in-vivo bioluminescence imaging in TLR2 reporter mice revealed transient microglial activation during pregnancy, suggesting a dynamic interplay between immune signalling and NSC activity. Together, these findings demonstrate that microglial activation during pregnancy could promote transient SVZ remodelling and maternal neurogenesis, providing new insights into the cellular and molecular mechanisms underlying maternal brain plasticity.

P2-B-343 *Presynaptic intracellular calcium stores modulate acetylcholine release and α4β2 nicotinic responses in layer 1 prefrontal cortical neurons*

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Cholinergic neurotransmission in the medial prefrontal cortex can modulate attention and executive function. However, it is not clear whether intracellular calcium signaling can modify acetylcholine (ACh) release and subsequent nicotinic acetylcholine receptor responses. Using whole-cell recordings and optogenetics in ChATcre-ChR2 knock-in mice to evoke acetylcholine release, we identified two types of nicotinic currents with different kinetics in layer 1 neurons: a fast transient response inhibited by the α7 antagonist MLA and a prolonged response sensitive to the α4β2 antagonist DHβE. Presynaptic calcium buffering with EGTA-AM reduced α4β2 responses but did not affect α7 currents, indicating loose calcium source–sensor coupling for ACh release mediated α4β2 responses. Manipulating calcium-induced calcium release (CICR) with ryanodine showed that high-concentration ryanodine (6 μM), which inhibits CICR via ryanodine receptors, greatly reduced the slow α4β2 response, whereas low-concentration ryanodine (1 μM), which activates ryanodine receptors, enhanced α4β2 responses. α7 responses were relatively unaffected by ryanodine. Together, these findings demonstrate distinct calcium dependencies for α7 and α4β2 nicotinic responses in layer 1 mPFC neurons and identify CICR as a key modulator of α4β2-mediated signaling.

P2-B-344 *Unsilencing the silent synapse: Evaluating mechanisms of glutamatergic synapse maturation in the retinotectal circuit of Xenopus laevis*

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Immature glutamatergic synapses are described as “silent synapses” because they express N-methyl-D-aspartate-type glutamate receptors (NMDAR) but lack α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPAR). Over the course of development, synapses mature through the postsynaptic trafficking of AMPARs, allowing the cell to more readily induce a response and transmit neural signals. It remains unclear whether NMDAR activation is required for the process of maturation and the ‘AMPAfication’ of the silent synapse. This study evaluates NMDAR-mediated mechanisms that may allow for the maturation of glutamatergic synapses in normal development. Both electrophysiology and in vivo two-photon live imaging will be used to study the development of synapses in the optic tectum of Xenopus laevis tadpoles. First, we reared tadpoles of two different developmental stages in NMDAR antagonists that target specific sites on the NMDAR to evaluate the effects on AMPAR-mediated miniature excitatory postsynaptic currents (mEPSC). Following NMDAR-antagonist rearing, mEPSC event frequency generally decreased in the later-stage animals and increased in the earlier-stage animals compared to the untreated animals of the same stage. These effects will be further explored by collecting electrical stimulation-evoked AMPA/NMDA ratios in tectal neurons in the NMDAR antagonist-reared animals to directly measure retinotectal synapse maturation. We will also image tagged AMPARs to optically detect AMPAR trafficking at individual synapses in vivo to better understand how silent synapses mature.

P2-B-534 *Changes in Excitation/Inhibition Balance Following Developmental Ethanol Exposure*

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Prenatal alcohol exposure (PAE) is a major cause of neurodevelopmental impairments and is associated with long-lasting alterations in brain function. There is evidence that PAE alters the balance of excitation/inhibition (E/I) in neuronal circuits, and this contributes to the cognitive and behavioral deficits observed in fetal alcohol spectrum disorders (FASD), however the cellular mechanisms underlying these changes remain incompletely understood. In this study, we examined synaptic E/I balance in hippocampal CA1 pyramidal neurons following PAE using whole-cell patch-clamp electrophysiology. Spontaneous excitatory and

inhibitory postsynaptic currents (sEPSCs and sIPSCs) were recorded in acute hippocampal slices from control and PAE-exposed animals. Event frequency and amplitude were analyzed to assess presynaptic activity and postsynaptic receptor function. Our preliminary data indicate a shift in E/I balance toward increased excitation following PAE, accompanied by changes in both frequency and amplitude of EPSCs and IPSCs. Additional experiments are ongoing to further validate and extend these findings. Together, these results provide mechanistic insight into how prenatal alcohol exposure disrupts synaptic regulation and neuronal network stability and may help identify potential targets for therapeutic intervention in FASD.

P2-B-535 *Profiling LTP Decay by Distinguishing the Synaptic Differences Between De Novo and Rescued Memories*

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Long-term potentiation (LTP) is a form of synaptic plasticity associated with the persistent strengthening of synapses which models how memories are formed. Under certain conditions, potentiated synapses can undergo a loss of attained strength that mirrors synaptic events associated with forgetting, referred to as LTP decay. Evidence suggests that NMDA receptors play a central role in regulating LTP decay, suggesting that erasure of synaptic information is an activity dependent process. To probe these mechanisms, I explored whether GluN2B-containing NMDA receptors contribute to theta burst stimulation (TBS)-induced LTP decay at Schaffer collateral-CA1 synapses. Extracellular field potential recordings were used to assess synaptic strength following TBS. To examine the contribution of GluN2B-containing NMDA receptors to this phenomenon, I applied a selective GluN2B antagonist (RO25-6981) 20 minutes following TBS and monitored synaptic strength over the following 70 minutes post-application. These experiments were compared to both “strong” TBS protocols which we consider an analog for de novo memory formation. To further identify molecular hallmarks associated with LTP decay, we are performing proteomic analyses of CA1 isolated synaptosomes in our de novo and rescued memory protocols. This approach may reveal hitherto unknown changes in synaptic protein complement that differ in slice models for de novo and rescued memories.

C - DISORDERS OF THE NERVOUS SYSTEM

P2-C-345 *Enhancing neuronal glucose uptake via GLUT3 protects retinal ganglion cells and visual function in glaucoma*

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Neurons require a high energy supply; to support these demands, insulin signaling increases glucose uptake and metabolism through upregulation of the GLUT3 transporter. We previously demonstrated that insulin protects retinal ganglion cells (RGCs) and visual function in glaucoma. Here, we tested whether RGC-specific GLUT3 augmentation, alone or combined with exogenous glucose, is sufficient to counter glaucomatous neurodegeneration.Glaucoma was induced in adult mice using a microbead model of ocular hypertension (OHT). GLUT3 expression was assessed by flow cytometry and immunohistochemistry. RGC-specific AAV. GLUT3 was delivered by intravitreal injection. Glucose (50% w/v) or saline eye drops were applied daily for one week. Cellpose-based automated quantification of RGCs was performed in RBPMS-stained retinas. Visual function was evaluated using optomotor response assays.OHT caused a significant decrease in GLUT3 expression in RGCs (21%) versus sham group. Assessment of RGC survival showed similar increased rescue rates among treatments (AAV.GLUT3: 24%; glucose: 21%; combined: 31%; vs. OHT). Interestingly, optomotor response analysis revealed a differential effect, with greater visual function gain in treatments involving glucose delivery, most notably in combination with GLUT3 (19% vs. control). Our data show that RGC-specific GLUT3 augmentation and glucose delivery effectively improve RGC survival and visual function. This study suggests that strategies enhancing neuronal glucose uptake and metabolism may offer neuroprotection and rescue visual function in glaucoma.

P2-C-346 *Evaluation of the implication of Parkin, microglia and CD8+ T cells in the vulnerability of dopamine neurons*

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Although growing evidence links inflammation to the onset of Parkinson's disease (PD), the underlying mechanisms are unclear. Mutations in the Parkin gene are associated with early-onset forms of PD. In addition to a role as regulator of mitochondrial quality control, Parkin acts as suppressor of mitochondrial antigen presentation by MHC-I on peripheral antigen-presenting cells (APCs). Parkin loss of function consequently leads to peripheral activation of CD8+ T cells. We hypothesize that, like their peripheral APC counterparts, Parkin KO microglia have an exacerbated pro-inflammatory profile in response to inflammatory signals, which through interactions with cytotoxic CD8+ T cells, impacts DA neurons. Our in vitro co-culture experiments show that CD8+ T cells are sufficient to induce DA neuron loss after an LPS/IFNγ stimulus. Interestingly, the presence of activated microglia accentuates this loss, particularly in Parkin KO. After an inflammatory stimulus, Parkin-deficient microglia show a similar elevation of MHC-I and phagocytic capacities compared to WT, but higher secretion of cytokines and chemokines. We are presently investigating the CD8+ T cells mechanism(s) leading to neuronal loss using blocking antibodies.Up to now, our results suggest that only a subset of the physiological properties of microglia are altered in the absence of Parkin. The results of this study will allow us to better understand the implication of microglia in regulating the vulnerability of DA neurons.

P2-C-347 *Exploring brain asymmetry in depression: Molecular insights from a single-cell study*

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Major depressive disorder (MDD) is a psychiatric disorder linked to heightened suicide risk, yet underlying biological mechanisms remain poorly understood. Atypical brain asymmetries relative to population-level have been implicated in MDD, particularly in functional and structural studies; however, molecular-level hemispheric differences have been less explored. To address this gap, we examined cell-type specific gene expression patterns in the subgenual anterior cingulate cortex (sgACC), a region involved in emotion, cognition, and strongly implicated in MDD. We performed single-nucleus RNA sequencing (snRNAseq) on mirrored postmortem sgACC tissue dissections from both hemispheres of 31 individuals without MDD and 33 with MDD that died by suicide. Nuclei were isolated from the tissues and processed using the 10x Genomics Chromium 3' workflow, enabling high-throughput profiling of mRNA transcripts and assignment to their cell of origin. We generated high-quality snRNAseq data of approximately 50B transcripts from 500K nuclei. Preliminary quality metrics and cell clustering demonstrate high technical quality, suitability for desired analyses, and expected cellular composition with clear cell-type marker genes. Ongoing analyses will assess hemispheric differences of cell-specific gene expression in healthy individuals and those with MDD. This study is the first to examine hemispheric asymmetry using snRNAseq and provides a novel framework to understand cellular and molecular asymmetry in MDD and suicide, with implications for biomarker discovery and therapeutic targeting.

P2-C-348 *Exploring kefir as a therapeutic approach for Alzheimer's disease using an in vitro β-amyloid aggregation model*

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Alzheimer's disease (AD) is a progressive neurodegenerative disorder linked to β-amyloid (Aβ) accumulation, synaptic dysfunction, chronic neuroinflammation, and neuronal death, with no effective early diagnostics or curative treatments. The gut–brain axis has emerged as an important modulator of AD pathophysiology, where fermented dairy products like Kefir shows potential to modulate gut microbiota, reduce neuroinflammation, and promote neuronal survival. This study evaluated the effects of kefir crude extract (KCE) and derived peptides on neuronal viability in an in vitro Aβ aggregation model. KCE (5 mg/mL) and 4 peptides (PW, M11, M20, and M25; 2000 µM) were tested in human astrocytes (NHA) and neuroblastoma cells (SH-SY5Y). Two experimental approaches were used: co-incubation with Aβ (1 µM) before cell exposure and treatment after Aβ aggregation and senile plaque formation. Cell viability was measured by AlamarBlue, oxidative stress by DCFH-DA staining, and immunostaining for apoptosis and functionality. Statistical analysis used Student's t-test ($p \leq 0.05$). KCE and all tested peptides exhibited no cytotoxicity, maintaining approximately 98% cell viability. In the preventive model, KCE and peptides M11, M20, and M25 significantly increased neuronal viability and effectively inhibited Aβ aggregation, whereas PW showed no protective effect. In the post-aggregation model, KCE and all peptides promoted enhanced neuronal viability. Additionally, most peptides significantly reduced intracellular oxidative stress in SH-SY5Y cells, and no positive labeling for apoptotic markers or synaptogenesis was detected in any of the experimental models evaluated. Kefir crude extract and derived peptides increased neuronal viability and reduced oxidative stress before and after plaque formation, highlighting their potential neuroprotective role in AD.

P2-C-349 *Exploring neurophysiological mechanisms and risk factors behind the development of chronic postsurgical pain after thoracic surgery using electroencephalography*

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Background: Chronic postsurgical pain (CPSP) is defined as pain that persists for more than 3 months after surgery. CPSP disproportionately impacts patients undergoing thoracic surgery, with incidence rates of up to 50%. However, the risk factors and maladaptive neurophysiological mechanisms under CPSP development remain poorly understood. Objective: To address this gap, we aimed to investigate neural mechanisms and neuromarkers associated with CPSP. Methods: 14 patients undergoing minimally invasive thoracic surgery completed neurophysiological assessments using electroencephalography (EEG) at two time points: (1) 2-3 weeks preoperatively and (2) three months postoperatively. Diagnosis of CPSP was made at three months post-surgery using a validated definition. Each assessment included resting-state EEG recordings under eyes-open and eyes-closed conditions, as well as cortical activity recorded during submaximal isometric hand contractions. Results: Preliminary analyses report differences in resting-state band power (theta, alpha, beta), event-related desynchronization (mu and beta band), and corticomuscular coherence during movement, between patients who develop CPSP versus those who do not. Conclusion: Our findings highlight potential neuromarkers associated with the development of CPSP, and provide insight into cortical mechanisms contributing to its persistence. Improved understanding of neuronal dysregulations underlying CPSP is important to inform preventative approaches and targeted therapies to reduce the burden of CPSP after thoracic surgery.

P2-C-350 *Fish oil supplementation prevents memory loss in experimental chronic liver disease*

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Introduction: Hepatic encephalopathy (HE) is a complex neuropsychiatric syndrome arising from chronic liver disease (CLD). It is characterized by cognitive impairments and associated with systemic and neurological inflammation. A promising strategy to mitigate cognitive deficits linked to HE is supplementation with omega-3 polyunsaturated fatty acids (ω3), known for their anti-inflammatory properties. Methods: Rats underwent bile duct ligation (BDL) to induce CLD and HE or sham surgery (SHAM). Five days following surgery, rats received either fish oil supplementation (FO) or saline (SAL) by gavage daily for 4 weeks. Food intake and body weight was monitored weekly. Novel object recognition test (short/long-memory) and rotarod test (motor coordination) were assessed. Plasmatic cytokines (TNF-α/IL-1β) were measured and liver injury biomarkers. Results: An improvement in short term memory was observed in BDL-FO vs BDL-SAL ($p < 0.05$). Regarding long-term memory, a global effect of supplementation was noted ($p = 0.058$) between SHAM groups and BDL groups. FO supplementation did not improve motor coordination with no difference between the BDL groups ($p = 0.207$). FO supplementation did not impact plasmatic TNF-α/IL-1β and CLD severity with no significant difference in liver injury biomarkers between BDL groups. Conclusion: ω3 supplementation improves short-term memory in 5-week BDL rats. However, the benefit of FO is not associated with a reduction in systemic inflammation or liver disease severity. These findings highlight the therapeutic potential of ω3 in managing cognitive deficits associated with HE but the mechanism of action of ω3 in CLD remains unresolved.

P2-C-351 *Fluoxetine enhances TrkB expression and function to rescue motor coordination deficits in a mouse model of spinocerebellar ataxia type 6*

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[1] *McGill University*

Spinocerebellar ataxia type 6 (SCA6) is a rare, autosomal dominant neurodegenerative disease primarily affecting the cerebellum that leads to progressive problems with motor coordination and balance (ataxia) starting at midlife. While SCA6 significantly impairs a person's quality of life, there are currently no available treatments to slow or stop this disease. We have previously shown that dysfunction in the expression and signaling of brain-derived neurotrophic factor (BDNF) and its receptor tropomyosin-related kinase B (TrkB) contributes to disease in a mouse model of SCA6. Intriguingly, fluoxetine (Prozac), an FDA-approved antidepressant, has recently been shown to act as an allosteric modulator of TrkB, facilitating BDNF-TrkB signaling. We thus wondered whether fluoxetine could mediate disease in SCA6 mice. We used a string-pull assay, in which mice engage in coordinated hand-over-hand movements, to assess motor coordination in treated and untreated SCA6 and litter-matched WT mice at disease onset (7.5 months). We observed that fluoxetine-treated SCA6 mice had a sustained and significant improvement in motor coordination, similar to WT levels, compared to untreated SCA6 mice. Using immunohistochemistry, we found that fluoxetine-treated SCA6 mice had significantly increased TrkB levels in the Purkinje cell soma compared to untreated SCA6 mice, while BDNF expression levels remained low. Our findings suggest that repurposing fluoxetine could provide a safe, affordable, and translatable treatment option for SCA6 and other ataxias where BDNF or TrkB signaling are affected.

P2-C-352 *From synaptic instability to serum biomarkers: NMJ-derived protein change in ALS*

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The lack of reliable biomarkers has hampered therapeutic development in amyotrophic lateral sclerosis (ALS), a fatal neurodegenerative disease affecting motor neurons. Common in all ALS cases, the denervation of neuromuscular junctions (NMJs) is a process that begins long before symptoms onset and characterized by prolonged cycles of denervation and reinnervation. We therefore hypothesized that this NMJ dynamism represents a valuable source of biomarkers that closely reflect disease state and progression. Proteomic analysis comparing resistant and vulnerable muscles and disease progression in SOD1G37R mouse model led to the identification of many NMJ-associated candidate proteins. We first focused on laminin β2 (LAMβ2), an NMJ-specific protein essential for structural organization. Serum LAMβ2 levels were significantly reduced at the pre-onset stage. In contrast to neurofilament-light chain (NfL), a widely used biomarker of axonal damage, LAMβ2 levels were unchanged following nerve injury, indicating disease specificity. Notably, LAMβ2 reduction was detectable as early as postnatal day 100, more than 300 days before symptom onset, where NfL was unchanged, making LAMβ2 as the earliest potential measurable biomarker. We next investigated synapse-associated protein 1 (SYAP1), involved in synaptic plasticity. Serum SYAP1 levels were significantly reduced at disease onset compared with both wild-type and pre-onset mice. Together, these findings identify LAMβ2 and SYAP1 as novel potential NMJ-biomarkers that could improve early diagnosis and disease monitoring in ALS.

P2-C-353 *Functional contributions of afferent and corticocortical projections to human motor control*

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Afferent and corticocortical projections to the motor cortex provide critical information to the motor system for planning and executing accurate movements. Circuits mediating these processes can be probed using transcranial magnetic stimulation (TMS). To investigate their functional roles in motor behaviour, the present study examined the relative contributions of afferent and corticocortical contributions during movement planning, onset, and execution. Short-latency afferent inhibition (SAI) was used to examine afferent contributions while short-interval intracortical inhibition (SICI) was used to examine corticocortical contributions during a visuomotor tracking task. Results showed a stronger effect of conditioning stimulus on SICI compared to SAI, suggesting corticocortical circuits play a more dominant role in shaping motor behaviour than afferent projections. The magnitude of difference in weighting of SICI and SAI between conditioned and unconditioned stimuli was also greater during later planning, movement onset, and movement execution compared to early planning. This would suggest that the motor plan is being modulated more during these phases by information converging on the motor system. The dominant role of SICI and modulatory role of SAI suggest differential roles of corticocortical and afferent projections to motor behaviour. Late planning modulation is likely mediated by corticocortical connections to set the initial motor plan, while movement onset and execution is likely mediated by afferent inputs to update the motor plan with sensory information.

P2-C-354 *Gene polymorphisms and metabolomics alterations in mouse models of sporadic Alzheimer's disease*

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Sporadic Alzheimer's disease (SAD) accounts for over 90% of all Alzheimer's disease cases and arises from complex interactions of multiple factors, including genetic risk factors, lifestyle cofactors such as stress and diet, and aging. These interactions leave measurable signatures in biological systems. Metabolomics, the study of small-molecule metabolites generated during metabolism, provides a powerful systems-level approach to identify biochemical alterations associated with genetic risk factors. In this study, metabolomic alterations associated with SAD-related gene polymorphisms were examined, focusing on humanized amyloid precursor-protein (hAPP), associated with amyloid protein processing, apolipoprotein E4 (APOE4), involved in lipid metabolism, and triggering receptor expressed on myeloid cell 2 (TREM2), a microglial immune receptor involved in signaling neuroinflammation. Blood serum samples were collected from male and female mice at 3, 6, and 9 months of age which correspond to early adulthood, midlife, and emergence of age-related and pathology-related changes in these models. Samples were analyzed using nuclear magnetic resonance (NMR) spectroscopy. Metabolomic spectra were compared across age, sex, and genotype to characterize distinct metabolomics profiles. Across all strains, metabolomic profile differed between 3 and 9 months of age, and genotype-dependent difference were most pronounced at 9 months, indicating increasing metabolomic divergence with age.

P2-C-355 *Genetic insights into neural mechanisms underlying sensorimotor dysfunction in familial restless legs syndrome: A whole-genome study in French-Canadian families*

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Restless legs syndrome (RLS) is a common yet underdiagnosed sensorimotor disorder affecting about 10% of the elderly population of North American and European ancestry. It causes an urge to move the legs, particularly at night, disturbing sleep and impacting mental and physical health. While the exact cause of RLS is unclear, substantial evidence supports a genetic contribution. Among French-Canadian (FC) patients with RLS, 77.1% report a positive family history, indicating a significant genetic contribution in this population. Although studies have identified potential genetic risk loci, they have not definitively established causal coding variants that segregate in multiplex families. We therefore aimed to identify rare, disease-associated variants by analyzing whole-genome sequencing data from 25 FC families. We clinically assessed affected individuals before sequencing. We processed genomic data using GATK joint genotyping and annotated with ANNOVAR to integrate functional and population frequency data. We filtered for rare, protein-coding variants predicted to be deleterious. We then identified segregating variants within families and compared them across families, as well as with the established RLS risk loci. We identified 87 variants that segregate in one family, which are present in at least one individual from another family. None of these variants are pathogenic in clinical databases. This study establishes a family-based genomic framework for RLS which could help illuminate neural circuit dysfunction and guide future neurobiological and therapeutic research.

P2-C-356 *Genome wide CRISPR activation screen unveils BAP1 as a modulator of a-synuclein fibril internalization*

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One of the hallmarks of Parkinson's disease (PD) is the presence of Lewy bodies, which contain protein aggregates including α-synuclein (αSyn). Pathological αSyn aggregates can spread between cells in the brain, contributing to disease progression. Lab-generated preformed fibrils (PFF) of αSyn are also able

to propagate transcellularly between neurons, modeling the disease. While many pathways have been proposed to facilitate the internalization of αSyn, our understanding remains limited. A genome-wide CRISPR activation screen identified BAP1, a gene genetically linked to PD risk, as a novel regulator of PFF uptake. We demonstrate that increased BAP1 specifically reduces αSyn fibril internalization, without affecting other cargos. RNA sequencing revealed that BAP1 activation differentially regulates genes involved in the cellular membrane, and specifically the extracellular matrix. In turn, we found that BAP1 activation strongly reduces extracellular binding of αSyn fibrils by downregulating heparan sulfate proteoglycans and increasing O-linked glycosylation. Finally, we validated these findings in human-derived models, demonstrating that BAP1 activation reduces αSyn fibril uptake in human iPSC-derived dopaminergic neurons, but not in iPSC-derived microglia. The cell-specific phenotype correlates with differential expression of ASXL3, BAP1's binding partner and PD risk gene. We confirmed that siRNA knockdown of ASXL3, but not ASXL1/2, increases PFF uptake. These findings shed light on the mechanism of αSyn fibril spread, revealing BAP1 as a novel regulator of this process.

P2-C-357 *Hemodynamic and electrophysiological progression of the Rose Bengal photothrombotic stroke model in mice*

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The photothrombotic stroke model is gaining popularity due to its relative simplicity, minimal invasiveness, and clinical relevance. Photothrombosis involves the delivery of an intravascular photosensitizer (Rose Bengal) followed by its photoactivation, resulting in vessel occlusion and ischemia. Using a combination of complementary optical and non-optical techniques, we characterized the physiological changes in mice undergoing photothrombosis. We report that Rose Bengal has vasoconstrictive properties, inducing hypoemia both in the brain and periphery even in the absence of its photoactivation. Conversely, we find that light, when used at photothrombosis-appropriate intensities and durations, induces large amounts of tissue heating and hyperemia even in the distal non-illuminated hemisphere. Furthermore, we show that use of the optimal photothrombotic wavelength based on the Rose Bengal absorption spectrum (yellow-561nm) produces a more consistent and pronounced drop in blood flow, and a shorter latency to the initial spreading depolarization (SD), ultimately resulting in a larger stroke. Similarly, when yellow light is used to induce a stroke in ChR2-expressing mice, the electrophysiological and hemodynamic confounds from green light cross activation of ChR2 are eliminated. Finally, we observe across cohorts that male mice have larger strokes than females. Altogether, we extensively describe important caveats and confounds concerning photothrombosis and provide a detailed characterization of its early ischemic events.

P2-C-358 *High-resolution spatial transcriptomics of the maternal brain in a rodent model of postpartum depression*

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Pregnancy and the postpartum period are characterized by remarkable neuroplasticity in the maternal brain, yet they also represent times of heightened vulnerability to mood disorders such as postpartum depression (PPD). To investigate the molecular and cellular underpinnings of this vulnerability, we employed two complementary spatial transcriptomics platforms: Slide-seq and Slide-tags, to chart gene expression changes in maternal rat brains. Our focus is exclusively on maternal tissues, enabling a detailed examination of how the peripartum brain remodels in PPD. Using a validated rodent model of PPD based on high levels of postpartum corticosterone administration, we have generated comprehensive spatial maps of limbic regions implicated in mood and cognitive regulation (e.g., hippocampus, prefrontal cortex) across multiple timepoints in nulliparous and postpartum dams. Both Slide-seq and Slide-tags offer whole-transcriptome profiling, facilitating the identification of cell type-specific transcriptomic shifts alongside region-specific

patterns of immune signaling and neuroplasticity.By integrating these cutting-edge technologies, our study offers a uniquely detailed perspective on the spatial organization of gene expression in the maternal postpartum brain. These findings lay the groundwork for uncovering novel molecular targets for PPD treatment and illustrate the power of advanced spatial transcriptomics to illuminate mechanisms of peripartum neuroplasticity in mothers.

P2-C-359 *High-throughput screening using ratiometric fluorescent-based GCase substrate to identify activity modulators of lysosomal GCase, as Parkinson's disease-associated genetic risk factor*

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Lysosomal malfunction is clearly implicated in Parkinson's disease (PD) pathogenesis. Among lysosomal factors contributing to PD is lysosomal enzyme b-glucocerebrosidase (GCase), encoded by GBA1, which hydrolyzes glycolipids glucosylceramide and glucosylsphingosine. Mutations in GBA1 are genetic risk-factor for PD, however, only ~10 % of individuals carrying GBA1 mutations develop PD. The low penetrance suggests there are genetic factors that modulate GCase activity, only a few are known. To identify them, we applied a dark-to-light substrate (LysoFQ-GBA) to probe GCase activity in a pooled genome-wide CRISPR-Cas9-KO screen in H4 cells. We found that disruption of ~50 genes impaired GCase activity, some of which were linked to PD via mutations found in GWAS data. We identified lysosomal lipid transport pathways as key regulators of GCase activity, including genes encoding lysophospholipid transporter (SPNS1) and cholesterol transporter (NPC1). Notably, a disease-associated variant of SPNS1 was linked to elevated PD risk. Functional analyses revealed that loss of SPNS1 does not alter GCase abundance but compromises its activity in lysosomes. Recently, we quantitatively measure GCase lysosomal endogenous activity using an image-based high-throughput screening in living cells to study GCase modulators in native cellular environment. Together, our findings indicate that multiple PD–associated genes converge on lysosomal mechanisms that regulate GCase function, providing insight into how GBA1-related risk intersects with broader genetic pathways contributing to PD pathogenesis.

P2-C-360 *Hippocampal interneuron dysfunction during working memory in a mouse model of schizophrenia*

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Schizophrenia is characterized by cognitive impairments including working memory (WM) deficits. WM deficits may be underpinned by aberrant inhibitory signaling from major interneuron classes like parvalbumin (PV) interneurons. Aberrant PV activation and morphology in the CA1 have been reported in the DF16A mouse model of the human 22q11.2 chromosomal deletion, the strongest genetic predictor of schizophrenia. However, physiological deficits of these fast-spiking inhibitory cells are poorly understood in-vivo, while finer morphological deficits have not been explored. Therefore, we performed in-vivo voltage imaging on double transgenic PV-Cre Df16A mice, during an olfactory WM task, followed by in-vitro confocal imaging. We recorded action potentials and subthreshold activity of multiple CA1 PV cells in parallel, at high temporal resolution and across days. Ongoing analyses suggest Df16A PV cells are hyperactive at odor onset during stimuli encoding, driven by sensitivity to salient stimuli, and hypoactive outside of odor windows. This bidirectional dysfunction may contribute to noisy stimuli encoding and poor WM maintenance. Indeed, Df16A mice exhibited learning deficits compared to littermate controls. Sholl analysis on fixed Df16A PV cells revealed significant decreases in dendritic complexity compared to controls, perhaps underpinning observed intrinsic deficits. These experiments reveal how interneuron physiological and morphological dysfunction leads to disruption of WM in schizophrenia, with implications for CA1 inhibitory circuits as future therapeutic targets.

P2-C-361 *Hippocampal short-term potentiation deficits occur in a mouse model of late-onset Alzheimer's disease*

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Two forms of NMDAR-dependent synaptic potentiation are co-induced by theta-burst stimulation (TBS) of the Schaffer collaterals. The initial phase of potentiation (short-term potentiation, STP) declines in response to baseline synaptic activation within tens of minutes and has properties that would suggest its' involvement in variable-term memory. Additionally, a stable enhancement of synaptic transmission (long-term potentiation, LTP) that can last for hours is also induced, and is accepted to be the synaptic corelate of long-term memory. Studies into changes in synaptic potentiation using animal models of Alzheimer's disease (AD) have focused on changes in LTP and rarely on STP. Moreover, these studies have primarily used early-onset AD models which reflect a comparatively small proportion of AD cases. Here we characterised both STP and LTP in the late-onset AD 2 (LOAD2) model mice compared to C57BL/6J (WT), using extracellular field-potential recordings from aged (24-32 months) acute dorsal hippocampal (DH) slices.At CA3-CA1 synapses from both the LOAD2 and WT mice, TBS induced STP and LTP. A similar amplitude of STP was induced in LOAD2 and WT slices. However, STP decayed at a significantly faster rate in LOAD2 mice ($p < 0.01$). In terms of LTP, there was a trend for an increase in LOAD2 compared to WT mice ($p = 0.09$). Overall, these results show that alterations in STP occur in the LOAD2 mice, which may reflect alterations in short-term cognitive function, which is often the first symptom of dementia.

P2-C-362 *Hypertension in Huntington's disease: The effect of propranolol treatment on symptom onset*

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Huntington's Disease (HD) is a neurodegenerative disorder characterized by a triad of motor, cognitive and psychiatric symptoms. Emerging evidence indicates that patients with HD also experience comorbid cardiovascular abnormalities, including increased systolic blood pressure. Specifically, hypertension, a sustained increase in blood pressure, has been associated with an earlier age of symptom onset in HD. Previous retroactive studies have suggested that the use of propranolol, a β-adrenergic receptor antagonist commonly used in the treatment of hypertension, can delay HD symptom onset. Thus, here we aim to further investigate the benefit of propranolol treatment in HD. To do this, we utilized a well validated knock-in mouse model of HD, the zQ175. Both male and female wildtype and heterozygous zQ175 mice were assigned to receive either propranolol hydrochloride (5 mg/kg dissolved in drinking water) or untreated water over the course of 16 weeks. During treatment, mice were subjected to a monthly behavioural battery. Preliminary findings indicate that treatment with propranolol prevented the decline in motor skills, cognition, and anxiety-like behaviour in the male zQ175 mice when compared to untreated controls. Similarly, some improvement in motor performance was observed in female zQ175 mice. Overall, these findings suggest propranolol use may alter HD associated symptom onset in the zQ175 mouse model.

P2-C-363 *Identification of pathogenic variants in the BORCS5 and BORCS8 genes associated with neurodevelopmental disorders*

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The BLOC-One-Related (BORC) complex is a ubiquitously expressed protein complex composed of eight subunits called BORCS1-8. Consistent with its role in axonal lysosome transport, mutations in BORC subunits cause neurological defects in mice. However, the physiological significance of BORC in humans remains to be determined. We have identified twelve patients with BORCS5 gene mutations and five patients with BORCS8 gene mutations, all of whom have severe neurodevelopmental disorders. Individuals affected by BORCS8 mutations exhibited global developmental delay, progressive muscle wasting, and optic atrophy. Patients

with BORCS5 mutations had brain malformations, microcephaly, optic atrophy, and progressive motor disorders. We generated a borcs8 F0 KO model in zebrafish using CRISPR/Cas9 editing. Mutant larvae showed a marked reduction in body, head and eye size, as well as a locomotor defect associated with a decrease in dorsal and ventral myotomes and shorter axons. We also developed borcs5 F0 KO models and overexpression models via RNA injection. These reproduced early morphological defects (reduced body, head and eye size), as well as locomotor abnormalities. The mutants exhibited microcephaly as well as axonal and muscular alterations. Overall, we identified mutations in BORCS5 and BORCS8 for the first time, and our results demonstrate that they are essential for the development and proper functioning of the central nervous system.

P2-C-364 *Identifying naturalistic behavioural signatures of chronic pain using keypoint-moseq*

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Chronic pain affects millions worldwide, severely reducing quality of life, and yet its underlying mechanisms and sources of individual variability remain poorly understood. To examine individual differences in chronic pain expression beyond reflexive sensory assays, the current study leveraged naturalistic behaviour following nerve injury. Female CD1 mice underwent chronic constriction injury (CCI) of the sciatic nerve, revealing large variability in cold hypersensitivity across individuals. Changes in gait, posture, movement and behavioural sequences were quantified using pose estimation and unsupervised clustering with Keypoint-Moseq, allowing identification of behavioural motifs associated with CCI. Specifically, 8 of the 37 behavioural syllables showed significant changes in frequency compared to uninjured mice. Furthermore, these motifs provide an unbiased feature set for stratifying injured animals and capturing individual differences in behavioural responses to chronic pain. Our findings reveal both prominent and subtle alterations in naturalistic behaviour following CCI and provide an ethological readout of injury-related changes in movement. By capturing how pain reshapes behaviour at the individual level, this approach links sensory hypersensitivity with changes in spontaneous behaviour and offers a way to examine distinct trajectories of chronic pain.

P2-C-365 *Illness duration-dependent subcortical iron accumulation in Schizophrenia: Findings from a quantitative susceptibility mapping study*

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Introduction: Brain iron levels are implicated in several neuropsychiatric illnesses, including schizophrenia spectrum disorders (SSD). However, current evidence on subcortical iron changes in SSD remains inconclusive, with a large variation in sample characteristics across studies. Methods: We recruited 20 chronic SSD patients and 19 healthy controls from the Centre for Addiction & Mental Health (CAMH) in Toronto, Canada. Participants underwent quantitative susceptibility mapping (QSM) with a 3T MRI to measure brain iron levels. Results: Iron levels were elevated significantly in the left hippocampus ($d = 0.998 \pm 0.34$, $pFDR = 0.02$) and nearing significance in the left putamen ($d = 0.758 \pm 0.33$, $pFDR = 0.068$) of SSD patients compared to controls, while accounting for age and sex. Interestingly, there was a significant, positive age-by-illness effect in the aforementioned areas, indicating a stronger age-related iron accumulation in SSD. Conclusion: We demonstrate elevated subcortical iron in chronic SSD and a more pronounced age-related iron deposition associated with the illness. Since our findings challenge previous reports and corroborate others, we suspect that the discrepancy can be explained by differences in illness durations in different cohorts.

P2-C-366 *Impact of Beta-amyloid oligomers on hippocampal network activity and neurotransmission*

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One of the main neuropathological hallmarks of Alzheimer's disease (AD) is the accumulation of beta-amyloid oligomers (Aβo), which begins approximately fifteen years before the onset of clinical symptoms. This early accumulation induces neuronal hyperactivity, contributing to memory impairment and neurodegeneration. Increasing evidence suggests a strong link between Aβo and excessive activation of the glutamatergic system. This study aimed to evaluate the effects of Aβo on neuronal activity and neurotransmitter release within a single animal model. A microdialysis probe was implanted into the right hippocampus of rats to allow daily administration of Aβo (0.4 µg) for 5 consecutive days and simultaneous collection of interstitial fluid (ISF). Neuronal activity was recorded using 5 electrodes, including one at the injection site. Control animals received scrambled Aβ. Neurotransmitters, including glutamate and GABA, were quantified by mass spectrometry. Immunohistochemical analyses confirmed effective delivery of Aβo into the hippocampus. Chronic Aβo administration induced a marked, time-dependent increase in delta-band power, associated with a progressive reduction of higher-frequency oscillations in the injected hippocampus compared with controls. Importantly, increased delta activity also spread to the contralateral, non-injected hippocampus. Neurochemical analyses revealed elevated glutamate and glycine levels, together with decreased glutamine concentrations in the ISF of the Aβo-injected hippocampus. We developed an innovative approach enabling simultaneous in vivo assessment of local field potentials and neurotransmission. These findings demonstrate that Aβo disrupt both neuronal network activity and neurotransmitter homeostasis, providing new insights into early pathophysiological mechanisms of AD and highlighting potential diagnostic and therapeutic targets.

P2-C-367 *Impact of chronic stress on blood-brain barrier and stress responses in adolescence*

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According to WHO, major depressive disorder (MDD) is the first cause of disability worldwide with a prevalence at 3-8% in adolescents. Despite this, biological mechanisms underlying MDD are predominantly investigated in adults. Around 40% of depressed adolescents do not or respond poorly to antidepressant treatments suggesting that causal mechanisms remain elusive. Chronic stress is an important risk factor to the development of MDD and increased peripheric inflammation is a biological signature of depression. Prolonged rise in circulatory inflammatory molecules has been suggested to damage the blood-brain barrier (BBB), a highly selective barrier protecting the brain. Since adolescence is a critical time window in the onset of depression, I investigated how chronic stress exposure impacts the neurovasculature. I take advantage of an emotional stress paradigm, social instability stress, which induces changes in sociability in adolescent male and female mice by introducing unfamiliar home cage partners. The effects of social instability are measured through anxiety- and depressive-like behavioral tests. I explore the impact of chronic stress on the neurovasculature by assessing changes in expression levels of genes associated to BBB integrity and function. Transcriptomic profiling is complemented with immunostaining and detailed morphological analysis of the neurovascular network. Deciphering stress-induced neurovascular alterations occurring during adolescence could allow a better comprehension of the biological mechanisms that underlie the development of depression.

P2-C-368 *Impact of exercise-based interventions for individuals with essential tremor: A scoping review*

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Introduction: Essential tremor (ET) is one of the most prevalent movement disorders. Exercise could be a good adjuvant treatment for ET, given its positive effects in other neurological conditions. This scoping review aimed to synthesize the existing research related to exercise-based interventions for ET, identify knowledge gaps, and suggest directions for future research. Methods: Searches were conducted in MEDLINE, CINAHL, and EMBASE. Eligible studies had to be published in peer-reviewed journals, be written in English, include an exercise-based intervention in ET patients lasting ≥ 4 weeks, and report ≥ 1 outcome variable related to ET severity, functional capacity, or manual dexterity. Results: Nine studies met the inclusion criteria. All studies used a pre-post, quasi-experimental design. Interventions lasted 4 to 8 weeks and included resistance (N=4), vocal (N=1), balance (N=1), dexterity (N=1), yoga (N=1), and physiotherapy (N=1) exercises. The mean sample size was 8.4 ± 6.0. Overall, significant improvements were found for tremor severity (4/6 studies), manual dexterity (3/4 studies), and quality of life (2/5 studies). Surprisingly, no study investigated the effect of aerobic exercise on ET. Conclusions: This scoping review suggests that exercise-based interventions may alleviate some ET-related symptoms, but the evidence remains limited due to the absence of randomized controlled trials, small sample sizes, and both short and heterogeneous intervention protocols. Additional research, namely randomized controlled trials, is warranted in this space.

P2-C-369 *Impact of hexavalent chromium on white matter integrity and cognitive function in a model of Multiple Sclerosis-like demyelination*

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Multiple sclerosis is a chronic neurological disease characterized by demyelinating lesions within the central nervous system. Although the etiology remains unclear, we know that environmental exposure to toxicants has been implicated in its pathogenesis, including heavy metals such as hexavalent chromium (Cr6+). We proposed that pre-exposure to Cr6+ would exacerbate myelin loss and cognitive dysfunction in the cuprizone model of demyelination, while also impeding remyelination and restoration of cognitive ability post cuprizone removal. To test this hypothesis wildtype (C57/BL6) mice were given intraperitoneal injections of saline, or sodium dichromate (Na2Cr2O2) for four weeks before exposure to 0.2% cuprizone in the diet for six weeks. Thereafter, the cuprizone was withdrawn to allow for spontaneous remyelination. An array of behaviour tests was conducted post-injections, post-cuprizone, and post-withdrawal. At each timepoint, a cohort of mice was euthanized for Synchrotron X-Ray Fluorescence, Histological, and Immunofluorescence imaging, and Western Blotting to identify changes in cellular integrity and inflammation. Na2Cr2O2 treated mice demonstrated increased anxiety and altered exploration. Immunohistochemical staining revealed similar myelin protein expression in mature oligodendrocytes across all groups. However, expression of tight junction protein claudin-5 decreased with Na2Cr2O2 exposure. Overall, acute Cr6+ exposure may elicit mild impairment in cognitive abilities and alter blood-brain barrier permeability.

P2-C-370 *In vivo effects of hippocampal tau pathology on brain oscillations, neurotransmission, and memory*

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Introduction: Two key neuropathological markers of Alzheimer's disease (AD) are the accumulation of amyloid-beta oligomers (Aβo) followed by hyperphosphorylation of the tau protein, two events that occur prior to the onset of clinical symptoms. In these early stages, alterations in brain oscillations are observed across various brain regions, along with dysfunction of the glutamatergic and GABAergic systems in the

hippocampus, an essential structure for memory. However, the direct impact of tau on these oscillations, as well as the role of glutamatergic and GABAergic systems in this process, remain poorly understood. Methods: An in vivo model of chronic tau protein injection into the hippocampus of awake, freely moving rats was developed. Neuronal activity was measured using Local Field Potential recordings (LFP) in key brain regions affected in AD. Simultaneously, microdyalisis enabled quantification of neurotransmitters release in interstitial fluid by high performance liquid chromatography coupled with mass spectrometry. Finally, the effect of tau protein injection on rat's memory was assessed using behavioral tests, and blood samples were collected to identify plasma biomarkers reflecting the progression of tau pathology when specific brain oscillations are altered. Discussion: Given that Aβ and tau pathologies precede clinical symptoms, detecting their specific signatures on brain oscillations, along with identifying correlated blood biomarkers, could be extremely useful as a screening tool for earlier diagnosis of AD and for monitoring disease progression in both clinical settings and therapeutic trials.

P2-C-371 *Inhibiting stearoyl-coA desaturase modulates hippocampal fatty acid composition, increases dendritic spine density and normalizes interneuron and astrocytic gene expression in the amyloidogenic 5xFAD model of Alzheimer's disease*

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Alterations in brain lipid metabolism are a central feature of Alzheimer's disease (AD), yet therapeutic strategies targeting these pathways remain underexplored. Our laboratory previously showed that inhibition of the fatty acid enzyme stearoyl-CoA desaturase (SCD) improves learning and memory in the 3xTg-AD model. Here, we investigated lipid metabolism dysregulation and the cell-specific effects of an SCD inhibitor (SCDi) in the hippocampus of the more aggressive 5xFAD.SCDi or vehicle was infused intracerebroventricularly for 28 days in 5xFAD and control mice. Hippocampi were analyzed for fatty acid composition by GC–FID, pathology hallmarks by immunohistochemistry, and dendritic spine by Golgi staining. Single-nucleus RNA sequencing was performed to characterize AD- and SCDi-induced cellular changes. Bioinformatic analyses were conducted using Seurat, with pathway enrichment assessed by GO and GSEA and, cell–cell interactions using CellChat.SCDi treatment modulated hippocampal fatty acids, and increased dendritic spine density in the absence of changes in amyloid levels. We recovered 112,122 high-quality nuclei and identified 30 clusters corresponding to major hippocampal cells. Pathway analyses identified inhibitory neurons and astrocytes as primary responders to SCDi, with correction of dysregulation in cell-cell adhesion, synapse organization, and metabolic pathways. These findings demonstrate that targeting lipid abnormalities through SCD inhibition induces cell-specific transcriptomic recovery in the AD hippocampus, highlighting SCD as a promising therapeutic target.

P2-C-372 *Integrating serum biomarkers with diffusion MRI identifies history of concussion signatures*

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Mild traumatic brain injuries, or concussions, are increasingly identified as a risk factor for neurodegenerative conditions like dementia. Because single-modality assessments often fail to capture the subtle, chronic effects of these injuries, this study used a multimodal framework to evaluate long-term outcomes. We recruited 71 community-dwelling adults (ages 50–81) to undergo comprehensive neuropsychological testing, blood biomarker analysis, and diffusion tensor imaging (DTI). Participants were stratified by history of diagnosed or self-reported concussion, frequency of injury, and contact sport participation. The assessment battery evaluated cognitive domains including memory, attention, and processing speed. Serum analysis targeted neurofilament light chain (NfL), glial fibrillary acidic protein (GFAP), phosphorylated tau (pTau-217), interleukin-10 (IL-10), and tumor necrosis factor-alpha (TNF-α). White matter microstructure (fractional anisotropy [FA] and mean diffusivity [MD]) was analyzed via tract-based

spatial statistics. Results indicated that while the concussion group displayed lower baseline serum NfL levels than controls (FDR-adjusted $p < 0.05$), elevated NfL within the injured cohort correlated with reduced white matter integrity (lower FA, higher MD) and lower verbal fluency scores. Distinct biomarker profiles emerged for specific subgroups: individuals with multiple past concussions exhibited elevated IL-10, whereas those with contact sport history showed increased pTau-217. ROC analysis demonstrated that a combined biomarker model offered the highest diagnostic accuracy for concussion exposure (AUC = 0.82 for multiple injuries). These findings suggest that multimodal evaluation is useful for detecting the nuanced, long-term sequelae of concussion in aging adults and for identifying individuals at high risk for cognitive decline.

P2-C-374 *Investigating a novel intravenous antisense oligonucleotide (ASO) therapy in a mouse model of dravet syndrome*

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Dravet Syndrome (DS) is a catastrophic pharmaco-resistant pediatric epilepsy caused primarily by SCN1A mutations, with debilitating seizures, developmental delays, high morbidity and a high incidence of Sudden Death in Epilepsy (SUDEP). Current treatments provide only partial symptom relief and fail to address the underlying genetic cause, thereby highlighting the need for effective and curative therapies. To address this, we developed and evaluated a novel intravenous (IV) antisense oligonucleotide (ASO) therapeutic enabled by QurCan Therapeutics' proprietary CNS-penetrating TERP technology in a mouse model of DS. This platform enables non-immunogenic, repeat IV dosing, active transport across the blood-brain barrier and has been de-risked for clinical applications and offers superior safety and efficacy over other viral and lipid-nanoparticle delivery platforms, without hepatotoxicity. In this study, various dosing paradigms (single and multiple pre weaning dosing) were evaluated with intravenous (facial vein and retro-orbital sinus injections) administration of C-TERP-ASO in DS mice. Our data suggests that (i) the C-TERP platform can deliver genetic cargos successfully to the brain via IV administration, and (ii) C-TERP-ASO administration reduces seizure incidence and severity, in a dose-dependent manner and (iii)the treatment increases cerebral Nav1.1 protein in a mouse model of DS. Collectively, these findings provide proof of principle for a novel non-viral intravenous ASO therapy targeting the CNS and support its potential as a disease-modifying treatment for DS.

P2-C-375 *Investigating eIF2α-mediated translational control in taste memory formation*

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Learning and memory rely on activity-dependent protein synthesis that enables synaptic plasticity and long-term circuit remodeling. The eukaryotic initiation factor 2 alpha (eIF2α) is a key regulator of translational initiation, and reductions in eIF2α phosphorylation have been shown to enhance protein synthesis and support long-term memory formation. However, the way that eIF2α-mediated translational control operates within specific neuronal populations and circuits during sensory learning remains poorly understood. This project investigates the role of eIF2α signaling in taste memory formation, focusing on the circuit activation involved in the insular cortex, medial prefrontal cortex, and basolateral amygdala. We used behavioral taste-learning paradigms to test novel, familiar, and aversive taste experiences followed by region-specific analysis using immunohistochemistry to quantify changes in phosphorylated and total eIF2α and related signaling pathways. Genetic and viral approaches were used to selectively manipulate eIF2α phosphorylation in defined neuronal populations and projection pathways, allowing assessment of cell-type and circuit-specific contributions to memory formation. Projection-specific manipulation strategies can be used to study circuit-specific translation regulation within defined neuronal populations, allowing characterization of the translational mechanisms that underly learning-related plasticity. By integrating molecular, cellular, and systems-level analyses, this work aims to reveal how translational control shapes sensory memory encoding. Understanding these mechanisms may provide insight into fundamental processes of cognitive function and create therapeutic strategies for neurological disorders that are characterized by impaired memory,

including Alzheimer's disease.

P2-C-376 *Investigating the impact of elevated blood pressure on cerebrovascular alterations in Huntington's disease*

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BACKGROUND: Huntington's disease (HD) is a dominantly inherited neurodegenerative disease primarily impacting the striatum and cortex. While central nervous system (CNS)-related pathology is a hallmark of disease, HD is also characterized by autonomic and cardiac dysfunction with elevated blood pressure (↑BP) occurring up to 25 years prior to symptom onset and correlating with worsened progression. Given that both HD and ↑BP induce inflammation and changes to the cerebral vasculature, we hypothesize that the combination of ↑BP and HD will worsen changes to the cerebral vasculature and lead to more severe neuropathology. METHODS: Immunofluorescence assays were conducted using human post-mortem tissue sections from the dorsolateral prefrontal cortex. Vessel density and morphology were assessed in male and female normotensive vs hypertensive HD samples relative to controls (n=6 per group). Blood-brain barrier (BBB) integrity was also assessed along with astrocyte morphology, given their role in BBB function as well as inflammation. RESULTS: Morphological alterations were observed in both HD and ↑BP relative to controls. However, there was an apparent interaction effect in hypertensive HD subjects. This suggests the two disease states may be altering cerebral vasculature via distinct mechanisms. Our results suggest that ↑BP impacts cerebral vascualture and may contribute to more severe neuropathology. Further investigation of underlying pathological mechanisms is warranted, as there may be implications for future adjunctive treatments targeting cardiovascular disease in HD.

P2-C-377 *Investigating the molecular function of THAP12*

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Problem. Lennox-Gastaut Syndrome (LGS) is a rare and severe form of epileptic encephalopathy, where the cause remains unknown in about 30% of cases. Recently, our lab has identified novel compound heterozygous variants in the zinc finger protein THAP12, in two patients diagnosed with LGS. THAP12 has never been previously associated with any neurological disorder and its function in neurodevelopment remains unknown. Our preliminary results have shown that a loss of THAP12 leads to embryonic lethality in mice, whereas a loss of thap12 in zebrafish results in severe neurodevelopmental defects including reductions in brain size, deficits of neural progenitor pools, and seizure-like activity (Ochenkowska et al., in preparation). Hypothesis. Based on our preliminary data, we posit that THAP12 is a transcriptional regulator of genes essential for neural progenitor cell (NPC) proliferation. Methods. Objective 1. Identify the molecular function of THAP12. Perform a molecular characterization of THAP12 in HEK293FT and iPSC-derived neural progenitor cells to identify genes regulated (ChIP-seq) and potential co-activators or interacting partners (Co-IP) involved in its function. Objective 2. Determine how a loss of THAP12 impacts differentiation outcomes. We will generate brain organoids following an unguided differentiation of patient-reprogrammed iPSCs. Immunostaining with neuronal markers alongside scRNA-seq will be employed to determine how a loss of THAP12 impacts differentiation outcomes. We will also perform MEA analysis to assess how functional maturation of synapses may be impaired. Conclusion. Throughout this project we will establish the networks governed by THAP12 across development, laying the groundwork for the development of future targeted therapies.

P2-C-378 *Investigating the presence of complement factor C6 in periventricular white matter lesions in Multiple Sclerosis disease progression*

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Complement proteins have recently been linked to multiple sclerosis (MS) due to their presence around demyelinating lesions. Preliminary data shows a consistent upregulation of complement C6 in periventricular white matter lesions (PVWML) when compared to other types of lesions. The periventricular area is thought to be especially vulnerable to lesion formation and inflammation as it is in close proximity to the blood-cerebrospinal fluid barrier (BCSFB). C6 is noteworthy as it is involved in all complement activation pathways and forms part of the membrane attack complex (MAC) . Considering our preliminary data and current literature, we hypothesize that microglia are a major CNS source of C6 in PVWML and microglial activation state influences C6 expression. This will be tested by analyzing PVWML in post-mortem brain tissue from MS patients with immunofluorescence microscopy. Furthermore, primary human microglia isolated from epileptic surgical resections were cultured under homeostatic and inflammatory conditions to assess C6 expression in vitro. Preliminary data shows C6 immunoreactivity was enriched in PVWML and co-localized with activated microglia. In vitro, inflammatory stimulation of human microglia moderately increased C6 expression relative to homeostatic conditions. These findings suggest that activated microglia contribute to local complement C6 production in PVWML, potentially augmenting MAC-associated tissue injury. Defining microglial complement regulation in periventricular regions may reveal novel targets to mitigate lesion progression in MS.

P2-C-379 *Investigation of gene–environment interactions in the progression of Parkinson's disease (PD) and multiple system atrophy (MSA)*

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A primary risk for the development of α-synucleinopathies like Parkinson's Disease (PD) and Multiple System Atrophy (MSA) is the combination of genetic and environmental factors—a complex interaction that remains poorly understood and difficult to model. Determining how these factors jointly promote disease progression remains a critical gap in the field. Here, we use both healthy and patient iPSC-derived dopaminergic neurons (DNs) and oligodendrocytes (OLs) to model PD and MSA in vitro. To examine how environmental toxicants influence disease pathogenesis, we employ Organophosphate Esters (OPEs), selected for their pervasive use, high human exposure, and proposed health risks. We find that some but not all OPEs are toxic to both DNs and OLs. Preliminary findings indicate that toxic OPEs could be influencing mitochondrial function and current experiments are exploring in-depth mechanisms by which these compounds might influence PD and MSA pathology, not only through affecting mitochondria but also the lysosome. The overarching goal of this study is to determine the influence of the environment on perpetuating neurodegenerative disorders, with the aim of informing safer chemical design and evidence-based policy.

P2-C-380 *Investigation of the long-term effects of COVID-19 on the autonomic nervous system based on neurophysiological and neuroimaging measures*

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Long COVID (LC), defined as symptoms lasting over 12 weeks post-infection, affects over 10% of people and is a major cause of disability in Canada. Alongside fatigue and breathlessness, neurological symptoms including orthostatic intolerance, dizziness, cognitive impairment, headache, and depression are common. These features suggest involvement of the autonomic nervous system (ANS), yet central mechanisms remain

unclear. Autonomic inputs converge on small brainstem and hypothalamic nuclei, which are difficult to image and crucial for linking autonomic regulation to fatigue and cognitive symptoms. Large MRI cohorts (e.g. UK Biobank) show global and brainstem volume loss after SARS-CoV-2 infection but lack the resolution to pinpoint specific nuclei or relate these changes to autonomic function. Our aim is to localize and quantify alterations in central autonomic nuclei using 7T MRI, and link these to physiological measures of autonomic function and LC symptom severity. We will recruit 200 nonhospitalized adults, including LC patients and controls. Session One will assess autonomic function by monitoring heart rate, blood pressure, respiration, and oxygen saturation at rest and during controlled challenges. Session Two will use 7T MRI to measure brain structure, rest and task activity, and microstructure. By integrating imaging, physiological, and clinical data, we aim to identify markers of autonomic dysfunction and predict symptom severity. This work will clarify the role of central autonomic circuits in LC, advance monitoring biomarkers, and guide individualized treatment.

P2-C-381 *Isoform-specific roles of ZDHHC8 in neurodevelopment and disease*

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Many neurodevelopmental disorders are characterized by disruptions in the brain's excitatory/inhibitory (E/I) balance. The palmitoyltransferase ZDHHC8 has been linked to many of these disorders, yet its cell-type–specific roles remain poorly understood. Using bioinformatic analysis of human single-cell transcriptomic datasets, we identified two previously unrecognized splice isoforms of ZDHHC8 with reciprocal enrichment in inhibitory (ZDHHC8iso1) and excitatory (ZDHHC8iso2) neurons, confirmed using fluorescence in situ hybridization. RNA-seq and RT-PCR analyses demonstrated that the canonical NCBI-annotated ZDHHC8 transcript is not detectably expressed in brain tissue, indicating that neuronal ZDHHC8 expression is dominated by these alternative isoforms. In silico motif analysis revealed that the isoforms encode proteins with distinct regulatory motifs and predicted interaction domains. Functional studies show that ZDHHC8 is required for dendritic outgrowth in excitatory, but not inhibitory, neurons. Conditional knockout of Zdhhc8 in excitatory neurons was rescued by ZDHHC8iso2 but not ZDHHC8iso1, demonstrating non-redundant isoform function. Additionally, we identified five patients with rare ZDHHC8 coding variants, including one at a splice junction, suggesting disease-associated disruption of isoform regulation. We are working on functionalizing these patient variants. Together, these findings reveal isoform-specific, cell-type-restricted functions of ZDHHC8 and implicate isoform dysregulation as a mechanism contributing to E/I imbalance in neurodevelopmental disorders.

P2-C-382 *Ketogenic diets partially restore bioenergetic pathways in the hippocampus of an Alzheimer's disease mouse model*

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Impaired brain glucose metabolism and hippocampal structural alterations are early hallmarks of Alzheimer's disease (AD). Ketone bodies can serve as an alternative brain energy source, helping restore metabolism and structural integrity. We previously showed that ketone-modulating diets improve cognition and increase hippocampal spine density in AD mouse models. To clarify the mechanisms behind these effects, we examined their impact on the hippocampal transcriptome.Triple transgenic AD mice (3xTg) and Wild-type controls (WT) were fed for six months with either a standard diet (SD), an SD enriched with medium-chain triglycerides (MCTD), or a carbohydrate-free ketogenic diet (KD). Hippocampi were collected for bulk RNA-seq analysis.Differential expression and gene set enrichment analyses revealed that 3xTg mice on SD showed 910 dysregulated pathways, characterized by increased cellular respiration and reduced developmental and morphogenetic processes. Both MCTD and KD partially restored pathways related to bioenergetics, cellular metabolism, and cytoskeletal remodeling. Notably, 3xTg mice fed MCTD exhibited a transcriptomic profile more similar to WT-SD mice, suggesting stronger therapeutic efficacy. MCTD also

normalized a broader range of pathways than KD, with specific effects on embryonic programs and organ morphogenesis. These results support ketogenic interventions, particularly MCT-enriched diets, as promising strategies to modulate hippocampal gene expression and mitigate AD-related metabolic dysfunction.

P2-C-383 *Ketone-driven modulation of mitochondrial function in FUS-ALS models*

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Disrupted energy homeostasis is an early feature of amyotrophic lateral sclerosis (ALS), with alterations in glucose utilization and lipid metabolism emerging prior to overt neurodegeneration. Dietary interventions that modulate metabolic state have shown promise in select ALS subtypes, yet the mechanisms by which alternative energy sources influence neuronal and glial function remain unclear. Here, we examined the impact of ketogenic intervention using mouse and primary neural cell models of FUS-ALS (hFUSR521G). hFUSR521G mice and littermate controls were maintained on a standard or ketogenic diet for four weeks. In parallel, primary cortical neurons and astrocytes derived from hFUSR521G mice were exposed to the ketone body b-hydroxybutyrate to evaluate cell-type–specific metabolic responses. Ketogenic intervention was associated with improvements in motor and cognitive performance in hFUSR521G mice, alongside attenuation of inflammatory signatures. Global metabolic profiling revealed diet-dependent normalization of energy expenditure, with distinct responses observed between sexes. At the cellular level, ketogenic intervention corresponded with a decrease in damaged mitochondria within the central nervous system. Consistent with these findings, ketone treatment modulated mitochondrial membrane potential in primary neural cells, suggesting that multiple neural cell types contribute to metabolic adaptation in FUS- ALS. Ongoing work will define how ketone-driven metabolic rewiring differentially impacts neuronal and astrocytic mitochondrial pathways and network dynamics.

P2-C-384 *Lipid alterations promote non-vesicular secretion of tau by hippocampal neurons*

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Lipid alterations promote non-vesicular secretion of tau by hippocampal neurons.Ju-Young Bae1,2, Iset Ilarraza Arizmendi1, Isha Ralhan1,2, Nathanael Lee2,3, Maria S. Ioannou1,2,3,41Department of Physiology, University of Alberta, Edmonton, AB, Canada2Group on Molecular and Cell Biology of Lipids, University of Alberta, Edmonton, AB, Canada3Neuroscience and Mental Health Institute, University of Alberta, Edmonton, AB, Canada4Department of Cell Biology, University of Alberta, Edmonton, AB, CanadaTau is a microtubule-stabilizing protein implicated in many neurodegenerative diseases. Tau deposition in the brain and cerebrospinal fluid is a strong biomarker of disease progression. In disease, neurons actively secrete pathological tau species via multiple mechanisms to protect themselves. Previous studies demonstrate that neurons in a healthy state also release tau as a normal, physiological process. This is important for understanding how proteins spread during the early stage of the disease, but the mechanisms of normal tau release and how it is regulated remain unclear. In this study, we discovered that modulating lipids promotes tau release by wildtype hippocampal neurons, independent of cell death. Reduced intracellular Ca2+ and the knockdown of vesicle-associated membrane protein 7 suppressed the tau release. We also identified simultaneous release of tau and lysosomal luminal protein cathepsin L – both degraded by proteinase K, indicating the absence of membrane enclosure. Our findings collectively suggest that endolysosomal exocytosis of tau is tightly regulated by lipid homeostasis.

P2-C-385 *Longitudinal characterization of alpha-synuclein on brain connectivity, cognitive, and behavioral symptoms in marmosets' model of Parkinson's disease*

Jiayue Yang [1], Tyler Cook [1], Constance Dollet [1], Maeva Gacoin [1], Justine Clery [1]

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Recent evidence suggests that misfolded, aggregated forms of alpha-synuclein (aSyn), a primary protein in the Lewy bodies of Parkinson's Disease (PD), spread through the brain in a "prion-like" manner, mediating disease progression. From a known disease epicenter, we present a common marmoset model (non-human primates) of pathological alpha-synuclein (aSyn) spreading to investigate voxel-wise alterations in functional networks using magnetic resonance imaging (MRI). 3 adult wildtype marmosets (2 males) received an injection of either marmoset aSyn preformed fibrils (PFF) (1 male, 1 female) or phosphate-buffered saline (1 male) in the left caudate and putamen. T2-weighted MRI images (0.2mm isotropic) and resting-state functional MRI (rs-fMRI) (0.8mm isotropic; Siemens 7T) images were acquired at before and every 2 months post-injection (mpi). Touchscreen (pairwise visual discrimination task) and activity data (motion videos and sleep actigraphy) were collected at each MRI time point. We have acquired data up to 6 mpi and expect to complete data collection in December 2025. By comparing the current time point (6 mpi) with the healthy baseline, the connectivity, behavioral, and sleep data showed no significant change, as expected. We found stable MRI signals, normal behaviors, and flexible cognitive abilities in healthy, pre-PFF-injected subjects. Throughout 10 mpi, we anticipate progressive alterations in these markers, which are expected to remain significantly different from the healthy baseline. Analysis of whole-brain network of functional connectivity, along with cognitive testing, pose estimation, and sleep monitoring, is currently being performed to characterize signatures of aSyn spreading and disease progression. Further immunohistochemistry is conducted in early 2026 to examine the molecular pathology underlying these MRI and symptomatology findings.

P2-C-386 *Loss of calcium-binding protein frequenin results in nociceptive hypersensitivity through changes in nociceptive circuit excitability*

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Pain is difficult to treat due to a lack of understanding of its molecular mechanisms; however, one cause is calcium dysregulation. Targeting calcium-binding proteins may provide a promising approach to treat pain as opposed to targeting calcium directly. We used a Drosophila thermal nociception model to screen mutants of various calcium-binding proteins; of the 13 tested mutants, only loss of Frequenin1 (Frq1) or Frequenin2 (Frq2) resulted in nociceptive hypersensitivity. We hypothesized that loss of Frq results in hypersensitivity either through a change in nociceptor structure or in excitability throughout the nociceptive circuit. We used CRISPR-Cas9 to tag the endogenous frq1 and frq2 genes with a flag epitope and found that both are widely expressed in the nociceptive circuit. Loss of Frq1 or Frq2 resulted in no change in the structure of the nociceptor itself; thus, we are currently exploring if loss of Frq results in changes in ascending excitability by performing calcium imaging at the nociceptor axonal endings of Frq mutant and control larvae. Using a split GAL4 approach, we also determined that Frq is expressed in descending GABAergic neurons, suggesting that Frq is modulating the nociceptive response through a change in descending inhibition. Additionally, we used CRISPR-Cas9 to generate an endogenous Frq1 or Frq2 conditional knockout to target Frq in specific subsets of neurons in the nociceptive circuit. Collectively, our data demonstrates a novel functional role for Frq1 and Frq2 in nociception through changes in excitability of the nociceptive circuit.

P2-C-387 *Machine learning-based prediction of pain recurrence following trigeminal neuralgia surgery*

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Trigeminal neuralgia (TN) is a debilitating facial pain disorder affecting 12.6 per 100,000 people annually, with 65% experiencing comorbid anxiety and depression. While surgical interventions (microvascular decompression [MVD], Gamma Knife radiosurgery [GK], and rhizotomy) provide initial relief, recurrence rates vary unpredictably, leaving clinicians unable to counsel patients on long-term outcomes. Current decision-making lacks objective tools to predict recurrence. We address this gap by developing predictive models integrating pre-surgical MRI features with clinical variables to forecast recurrence patterns. We constructed a multimodal dataset from 641 TN surgical patients at Toronto Western Hospital (398 GK, 198 MVD, 45 rhizotomy), extracting clinical variables including pain levels, recurrence events, and treatment histories. Our pipeline integrates clinical metadata with pre-surgical MRI morphometry, organizing data temporally and stratifying by surgery type. Machine learning approaches include binary classification for recurrence likelihood, regression for pain-free duration, and survival analysis for time-to-recurrence. We have established one of the largest structured TN datasets combining clinical records with neuroimaging. Our validated pipeline integrates data workflows, temporal organization, and patient stratification, supporting upcoming feature extraction and model training. By identifying patients at highest recurrence risk and predicting timing, these models can guide personalized surgical decision-making and patient counselling, demonstrating how quantitative imaging can address urgent questions in neuropathic pain management.

P2-C-388 *MALDI-TOF imaging mass spectrometry demonstrates sex- and age-dependent spatial changes in brain energy metabolism in response to amyloid stress using a mouse model of Alzheimer's Disease*

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Alzheimer's Disease (AD) is the most common form of dementia with no effective therapies to currently prevent or slow its progression. Increasing research into cerebral energy metabolism has revealed the importance of lactate as an energy substrate and signaling molecule required during neuronal activation, memory formation, normal physiological glial function, and the regulation of gene transcription through a novel epigenetic process termed histone lactylation. In this study, we spatially and temporally mapped lactate levels and histone lactylation in brain tissues of wild type and an AD transgenic mouse model using matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) imaging mass spectrometry in negative ion mode with 1,5-diaminonaphthalene (DAN) matrix as well as immunofluorescence microscopy utilizing a pan-lysine lactylation antibody, respectively. Lactate levels declined with age predominantly in male mice. The spatial relationship between lactate levels and histone lactylation suggests that both processes may contribute to microglia activation and neuroinflammation, but the need for cell-type and region-specific investigation is required to further understand the relationship between lactate metabolism and epigenetic processes during aging and in AD.

P2-C-389 *Metabolic dysfunctions may be causing selective anterior purkinje cell loss in the cerebellum of a Christianson syndrome mouse model*

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Christianson Syndrome is an incurable neurological disorder where ataxia is one of the most debilitating symptoms. In the cerebellum of Christianson Syndrome patients, an intriguing cell death pattern is seen. The primary output neurons, Purkinje cells, exhibit selective vulnerability in the anterior, while those in the posterior region remain resilient, despite being exposed to the same genetic insult. What could be

causing this patterned cell death? Anterior Purkinje cells fire at a higher frequency and have a higher energy demand than those in the posterior, suggesting energy-related issues may underlie this selective cell death. Energy imbalances are often caused by metabolic dysfunctions, which are increasingly being recognized as a factor in many neurodegenerative disorders, including ataxias. Therefore, we hypothesized that metabolic dysfunctions are causing this selective anterior Purkinje cell vulnerability. Using a multidisciplinary approach, we found a significant reduction in the essential protein Hypoxanthine-guanine phosphoribosyltransferase involved in the generation of purines, essential precursors for ATP, the energy currency of the cell. We also found that mitochondria, the major producers of ATP, had damaged cristae and were reduced in number only in the vulnerable anterior at the onset of ataxia (P60). Our findings therefore suggest that improper energy metabolism may contribute to cell death in Christianson Syndrome ataxia and could be a potential therapeutic target.

P2-C-390 *Metformin as a therapeutic intervention for Phelan-McDermid syndrome*

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Phelan-McDermid syndrome (PMS) is a rare neurodevelopmental disorder caused by deletions of chromosome 22q13 or mutations in SHANK3. PMS is characterized by developmental and speech delay, and neonatal hypotonia, with the majority exhibiting autism spectrum disorder (ASD) and intellectual disability. Impairments in memory, which plays a crucial role in forming social relationships by enriching conversational material with personal memories, further exacerbate symptoms of PMS.Most preclinical studies have focused on males, leaving an important knowledge gap regarding sex-specific mechanisms and treatment efficacy. We assessed behavioral phenotypes and molecular alterations in male and female Shank3B-/- mice, a model of PMS. We tested the therapeutic potential of metformin, an FDA-approved diabetic drug known to inhibit mTORC1 and MAPK/ERK signaling pathways, both often hyperactivated in ASD-related disorders.Shank3B-/- mice displayed autistic-like behaviors (repetitive behavior, social preference, and communication) and memory deficits, with notable sex differences in memory performance and vocalization. Metformin treatment significantly improved these deficits. At the molecular level, male Shank3B-/- mice showed upregulated mTORC1 and MAPK/ERK signaling, whereas females exhibited an increase in the eIF2α pathway; these alterations were corrected by metformin. Together, our findings reveal sex-dependent behavioral and signaling alterations in Shank3B-/- mice and support metformin as a promising therapeutic option for rapid clinical translation of PMS treatment.

P2-C-391 *Mild mitochondrial uncoupling restores neuronal resilience and preserves vision in glaucoma*

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Mitochondrial dysfunction and oxidative stress are key features of glaucoma neurodegeneration induced by ocular hypertension (OHT). MP201, a prodrug of 2,4-dinitrophenol, acts as a mild mitochondrial uncoupler that reduces reactive oxygen species (ROS) and supports cellular repair. Here, we tested whether MP201 improves mitochondrial health, promotes retinal ganglion cell (RGC) resilience, and preserves visual function in glaucoma.OHT was induced in adult mice using the magnetic microbead model, and MP201 (8 mg/kg) was administered daily by oral gavage. ROS levels were measured using dihydroethidium. Mitochondrial volume was quantified by 3D reconstruction of retinal axons in Thy1-YFP-CFP-Mito mice. PGC-1α and BDNF expression were assessed by western blot and immunofluorescence. Glial reactivity was evaluated by GFAP expression and microglial density (IBA1). RGC survival was quantified by RBPMS stereology, and visual function by the optomotor reflex.MP201 significantly improved RGC outcomes versus vehicle by: (i) reducing ROS to sham levels; (ii) restoring mitochondrial volume in axons; (iii) elevating endogenous PGC-1α and BDNF levels; and

(iv) reducing glial reactivity. MP201 also improved RGC survival and significantly improved visual acuity.MP201 restores redox balance, improves mitochondrial integrity, increases neurotrophic support, and reduces glial reactivity, collectively preserving RGC survival and visual function. These findings identify mild mitochondrial uncoupling as a promising therapeutic strategy to counter oxidative stress and vision loss in glaucoma.

P2-C-392 *Mistrafficking of KCC2 in Endolysosomal system in the hippocampus of Christianson Syndrome mouse model*

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Christianson Syndrome (CS) is an X-linked neurodevelopmental/neurodegenerative disorder. Patients have intellectual disability, autism and epilepsy. It arises from mutations in the SLC9A6 gene which normally encodes the endosomal pH regulator (Na+, K+)/H+ exchanger isoform 6 (NHE6). NHE6 maintains the accurate pH of endosomes to allow proper cargo trafficking. All mutations result in a loss-of-function for NHE6 and an overacidification of recycling endosomes is observed. Epilepsy and autism have been linked to low levels of 2 K+/Cl− cotransporter (KCC2). As KCC2 is located in recycling endosomes we investigated if loss of NHE6 resulted in low levels and or mistrafficking of KCC2 to overacidification of endosomes which could lead to autism and epilepsy in CS patients. Using immunoblotting in a murine model of CS (NHE6KO) we found that KCC2 levels were significantly lower in the hippocampi of KO vs WT at PND 21, 60, and 180. There were no significant differences in mRNA levels of KCC2 between KO and WT indicating gene transcription may not underlie the alterations in protein expression. Using immunolocalization we tested mislocalization of KCC2 in acute hippocampal slices of P60 tissue using LAMP1(lysosomal marker) and Rab11(recycling endosome marker). We found a significant increase in colocalization of KCC2 with LAMP1 in the KO and less in recycling endosomes compared to WT suggesting mistrafficking of KCC2. The present study elucidated fundamental and CS disease-relevant mechanisms in KCC2 trafficking to potentially rescue the mislocalization of KCC2 in future studies.

P2-C-393 *A role for injury-associated microglia in neural responses to cortical white matter and parenchymal damage*

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Adult neural stem cells (NSCs) in the ventricular-subventricular zone (V-SVZ) generate oligodendrocytes and interneurons, representing a potential endogenous source for brain repair. Using lineage tracing, single-cell (sc) RNA-sequencing (scRNA-seq) and sc-spatial transcriptomics, we showed that dorsal V-SVZ NSCs are activated to increase oligodendrogenesis during recovery from cuprizone–rapamycin-induced demyelination. During recovery, NSCs remain transcriptionally unchanged but the V-SVZ environment differs; dorsally localized microglia increase ~3-fold, alter ligand expression and adopt a distinct remyelination-enriched transcriptional state. Predictive scRNA-seq and proteomic-based ligand-receptor analysis identified microglial-derived IGF1 and OSM as candidate regulators of NSC activity during remyelination. These ligands promoted NSC proliferation and oligodendrogenesis in vitro and in vivo. Selective ablation of remyelination-enriched microglia during remyelination reduced dorsal precursor proliferation and oligodendrocyte precursor number, suggesting that these microglia mediate myelin repair. To assess whether similar microglia states and microglia-NSC interactions occur during other CNS injuries, we performed SVZ-lineage tracing and sc-spatial transcriptomics in a murine grey matter focal stroke model. Initial data show microglia at the infarct site with a transcriptional state resembling remyelination-enriched microglia alongside neural cells that migrated from the V-SVZ. Ongoing work asks if NSCs and remyelination-enriched microglia contribute to ischemic repair.

P2-C-394 *Modelling individual differences in chronic pain-related social behaviours*

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Chronic pain is a leading cause of disability worldwide and is associated with disruptions to social behaviour that reduce quality of life. While these social impairments vary widely between individuals, the basis of this variability remains unclear. Here, we used a mouse model of chronic neuropathic pain to examine individual variability in pain-related changes in social behaviour. Female CD1 mice underwent chronic constriction injury (CCI) of the sciatic nerve. Cold-plate testing from 7 days post-surgery revealed that mice showed high or low sensory sensitivity following injury. Social behaviour was assessed during 10-minute interactions with a younger, same-sex conspecific in a naturalistic setting. Ultrasonic vocalizations during social interactions were recorded and analysed using DeepSqueak to quantify call rates and acoustic features. Compared to uninjured controls, mice with CCI spent less time engaging in social behaviours and more time self-grooming and performing non-social behaviours. The magnitude of these social behavioural changes varied substantially across individual mice but was not strongly related to cold hypersensitivity, indicating that changes in social behaviour are largely independent of sensory sensitivity. Together, these findings demonstrate that sciatic nerve injury produces robust yet heterogeneous alterations in social behaviour, providing a basis for examining individual differences in pain susceptibility and pain-related social dysfunction.

P2-C-395 *Molecular mechanisms underlying local inhibitory control over cortico-accumbal and tegmental pathways in stressed male and female mice*

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The intricate inhibitory control over excitatory neuronal circuits in the medial prefrontal cortex (mPFC) regulates the expression of emotional stress responses. Under chronic stress, this balance is perturbed in part by a lost of glutamatergic inhibition, affecting neurons projecting to the nucleus accumbens (NAc) and the ventral tegmental area (VTA). In this work, we assessed the gradual molecular alterations disrupting connectivity between GABAergic subpopulations and cortico-accumbal and tegmental neurons in mice exposed to chronic stress. Using trans-sectional viral tracing with electrophysiological recordings in transgenic mice, we labeled mPFC-NAc and VTA projecting neurons and evaluated their communication with GABAergic interneurons. Our analysis revealed morphological and functional changes affecting PV and SST neurons and their capacity to maintain appropriate inhibitory control over both pathways in stressed males and females. Furthermore, we used snRNAseq to evaluate the molecular mechanisms underlying these alterations, revealing transcriptional changes in several cell types affecting males and females during and after chronic stress. This was associated with changes in intracellular communication cascades, including inflammatory, hormonal, and neural functional pathways, potentially underlying the changes in the inhibitory tone imposed by GABAergic subtypes over mPFC-NAc and VTA projecting neurons. Our results highlight the molecular mechanisms responsible for the gradual lost of inhibitory control over mPFC neurons projecting to these subcortical structures.

P2-C-396 *Molecular pathogenesis of juvenile ALS: Dissecting the impact of the E102Q SIGMAR1 variant on cellular homeostasis and autophagy*

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Amyotrophic lateral sclerosis (ALS) is a rare neurodegenerative disorder that affects motor neurons, leading to progressive muscle weakness, atrophy, and loss of voluntary movement. Around 80% of patients die within five years of diagnosis. Approximately 90% of adult-onset ALS (AO-ALS) cases are sporadic, with unknown causes; the remaining 10% are familial, linked to genetic variants. Juvenile ALS (JALS) is an exceptionally rare

form, with onset before age 25, compared to between 55 and 75 in AO-ALS. Since its identification in the early 1900s, JALS has received less attention. Genetics account for about 40% of JALS cases. Key genes include FUS, ALS2, SOD1, and SIGMAR1 (S1R). A rare S1R mutation (c.304G>C, p.E102Q) has been linked to autosomal recessive JALS. Like AO-ALS, JALS involves disrupted cellular homeostasis and neuronal hyperexcitability. S1R helps maintain neuronal stability by regulating autophagy and modulating ion channel activity. However, the mechanisms and effects of the E102Q variant are unclear. Using cell-based assays, we examined how E102Q affects S1R localization, autophagy, and voltage-gated potassium (Kv) channel trafficking. Our results show that E102Q promotes S1R dimerization and nuclear localization, reduces autophagic flux, and impairs Kv1.2 trafficking to the plasma membrane in response to S1R agonist stimulation. These findings offer new insights into molecular dysfunction caused by the E102Q variant in JALS, particularly its effects on autophagy and ion channel regulation, and support further research into potential therapeutic targets.

P2-C-397 *Mouse models of BCOR-associated inherited retinal degenerations uncover potential pathogenic mechanisms*

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Inherited retinal degenerations (IRD) are pathologies leading to loss of photoreceptors cells (PR), which can result in blindness. While over 330 genes have been associated with IRDs, the genetic origin of the disease remains unknown in many cases. Our lab has recently identified mutations in Bcl6-corepressor (BCOR), a gene coding for a transcriptional regulator, associated with early-onset IRD in humans. However, the molecular impairments resulting from these mutations remain incompletely understood. To investigate the role of BCOR in the retina and determine how the identified variants lead to IRD, we generated four mouse lines, each carrying a different BCOR point mutation in the same amino acid residue as the IRD patients. In these mutants, the retinal pigment epithelium displays abnormal cell morphology. We also observed an early-onset reduction in PR response, which eventually progresses to functional visual defects, replicating the pathology observed in humans. Mechanistically, our results suggest that the degeneration phenotype stems from abnormal repression of the transcription factors CRX and OTX2 by the mutated forms of BCOR, resulting in the deregulation of gene expression in retinal cells. Through our approach, we have successfully generated the first mouse models of BCOR-associated IRDs. These mutant mice will allow us to further elucidate the underlaying molecular mechanisms using genomics approaches. We also anticipate that these results will inform the development of gene therapies for this rare form of IRD.

P2-C-398 *mTOR-dependent regulation of synaptic FUS translation in ALS*

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Synaptic loss is an early pathological feature of amyotrophic lateral sclerosis (ALS), preceding cognitive and motor decline. Genetic studies in familial ALS implicate mutations in the RNA-binding protein Fused in Sarcoma (FUS), suggesting that altered RNA metabolism contributes to synaptic vulnerability. FUS regulates mRNA transport and translation, and the ALS-linked FUS-R521G mutant promotes dendritic attrition and synaptic loss, yet its impact on local protein synthesis remains poorly defined. Our previous work showed that FUS associates with stalled polyribosomes in a mTORC2-dependent manner, leading us to hypothesize mTORC2-dependent control of local translation by FUS, which is lost in ALS mutants. Here, we examined whether FUS activity at synaptic polyribosomes is regulated by the mTOR pathway. Treatment with torin1 (mTORC1/2 inhibitor) or rapamycin (mTORC1 inhibitor) increased FUS levels in the soma and neurites. However, only torin1 elevated synaptic FUS, indicating mTORC2-specific regulation. Consistently, FUS showed increased colocalization with stalled polyribosomes at presynaptic sites following torin1 treatment. The ALS-linked FUS-R521G mutant showed enhanced accumulation on synaptic polyribosomes and reduced protein synthesis but remained insensitive to mTORC2 modulation. In conclusion, mTOR inhibition increases synaptic FUS localization and its association with polyribosomes, whereas FUS-R521G exhibits elevated synaptic targeting but is insensitive to mTORC2 regulation, supporting a mechanism contributing to synaptic dysfunction in ALS.

P2-C-399 *Multimodal differentiation of MRI phenotypes in left and right temporal lobe epilepsy*

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Temporal lobe epilepsy (TLE) is a common pharmaco-resistant focal epilepsy typically associated with pathology in the mesiotemporal lobe. Increasingly, TLE is conceptualized as a network disorder, with broad impacts on the brain beyond the primary substrate. Given marked differences in cerebral morphology and function between hemispheres, it is important to systematically characterize the effects of temporal lobe lesion laterality in TLE. This study aimed to investigate inter-hemispheric differences in MRI phenotypes in left and right TLE patients. We leveraged a multisite, multimodal MRI dataset comprising 554 participants (147 left TLE; 135 right TLE; 272 healthy controls). We extracted cortical and subcortical morphological and microstructural feature maps (cortical thickness, fractional anisotropy, and apparent diffusion coefficient). ComBat-harmonized structural feature maps were used for computing vertex-wise Mahalanobis distances in each patient against a normative distribution, providing a vertex-wise multivariate structural abnormality score.TLE was characterized by widespread structural alterations relative to controls, particularly in the ipsilateral temporal lobe and hippocampus. Direct comparison found that left TLE showed more marked contralateral alterations, particularly in the temporal lobe. In the ipsilateral hippocampus, right TLE showed significantly more abnormality. We compared structural and functional disease epicenters between left and right TLE using normative connectivity data from the Human Connectome Project, finding that disease epicenters reflected analogous differences to structural abnormality. These data suggest that left and right TLE constitute a similar underlying pathology presenting differently as a function of diverging network organizations, providing additional evidence supporting the understanding of TLE as a network disorder.

P2-C-400 *Multimodal sensory training as a leverage to improve motor function in individuals with spinal cord injury*

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Spinal cord injury (SCI) affects over 1,300 Canadians annually and is associated with lifelong disability and high healthcare costs. Evidence suggests that spinal neuromodulation can enhance motor recovery by activating dorsal spinal networks involved in sensory processing. While sensory inputs are known to modulate motoneuronal excitability, rehabilitation strategies that directly target sensory pathways to improve motor outcomes after SCI remain limited. This pilot study aimed to enhance lower-limb motor function by leveraging the sensory system through a combination of transcutaneous spinal cord stimulation (tSCS) and repeated proprioceptive stimulation within activity-based training. Individuals with chronic SCI (AIS A–D, ≥6 months post-injury) completed an 8-week multimodal sensory training program combining active or sham tSCS with structured proprioceptive and functional tasks. Clinical and neurophysiological assessments were performed before, after, and one month after trainingData were collected with active tSCS in five participants. A further two participants are ongoing, and one withdrew prior to training. Preliminary analyses revealed improvements in lower-limb proprioception, with little changes in superficial sensation. Strength increased in at least one leg in all motor-incomplete participants, whereas no strength gains were observed in motor-complete participants. Balance confidence, assessed using the Activities-specific Balance Confidence scale, improved in all participants. Preliminary findings suggest clinical benefits of multimodal sensory training, primarily in individuals with motor-incomplete SCI. Ongoing analyses of somatosensory cortical activity and transcranial magnetic stimulation outcomes may help identify neurophysiological changes that predict subsequent functional recovery and guide training intensity and duration in future trials.

P2-C-401 *Multiple-sclerosis-relevant stressors converge on RBP mislocalization and neurite degeneration in primary mouse neurons*

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The RNA binding protein (RBP) hnRNP A1 is essential for neuronal function, and its mislocalization from the nucleus to cytoplasm disrupts RNA processing and contributes to neurodegeneration in multiple sclerosis (MS). Other RBPs; FUS and TDP 43, are also implicated in neurodegenerative diseases. Because MS related stressors disrupt RBP homeostasis, we examined how excitotoxic, oxidative, and endoplasmic reticulum stress affect RBP localization and neuronal integrity in primary mouse embryonic neurons. Neurons were treated with serial dilutions of glutamate, SIN 1, or thapsigargin to induce excitotoxic, oxidative, and ER stress, respectively. Using AI driven fluorescent confocal microscopy, we measured RBP cytoplasmic mislocalization, and neurite loss (as a marker of neurodegeneration). Oxidative stress elicited the strongest response, with hnRNP A1 increasing ~5.5 fold ($p=0.0001$), FUS ~3 fold ($p=0.0002$), TDP 43 ~2.2 fold ($p=0.0035$), and neurite loss of ~75% ($p=0.0014$; one way ANOVA). Glutamate excitotoxicity caused lesser effects (hnRNP A1 ~2 fold, FUS ~1.4 fold, TDP 43 ~1.3 fold; neurite loss ~75%). ER stress caused no changes in RBP localization or neuronal structure. These findings reveal stressor-and RBP specific responses, with hnRNP A1 as the most responsive RBP. We propose that oxidative and excitotoxic stress are key drivers of RBP dysfunction in neurons, which may be major drivers of neurodegeneration in MS. Next, we will inhibit AMPA and NMDA receptors and nNOS to determine whether blocking upstream pathways rescues RBP mislocalization and neurite integrity.

P2-C-402 *Mutant huntingtin reshapes mitochondrial protein interactions in Huntington's disease*

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Polyglutamine expansion of huntingtin (mHTT), a large scaffolding protein, alters its conformation and promotes misfolding, aggregation, and disruption of multiple cellular pathways. However, how mHTT affects protein-protein interaction (PPI) networks remain poorly understood. Emerging evidence suggests that HTT localizes to the mitochondrial intermembrane space, raising the possibility that its mutant form rewires mitochondrial interaction networks. We performed an integrative network analysis using curated, experimentally validated mammalian interaction data from PubMed, STRING, and BioGRID. Redundant entries were removed and protein identifiers standardized. Mitochondrial interactors were identified by cross-referencing MitoCarta 3.0 and UniProt localization annotations. Network construction and topological analyses were performed using Cytoscape.From 3144 HTT-interacting proteins, 230 mitochondrial-associated partners were identified. Comparative analysis revealed substantial remodeling of the mitochondrial interactome in disease progression. mHTT gained 80 PPIs early and 76 at advanced stages, including aberrant interactions with respiratory chain complexes I and V. Conversely, we found that 33 PPIs were lost early and 20 later, notably with OPA1 and TOMM20/22, implicating defects in mitochondrial fusion and protein import. These interactions are currently being validated in a HD mouse model. These findings demonstrate that mHTT profoundly reshapes mitochondrial interaction networks, providing mechanistic insight into mitochondrial dysfunction in Huntington's disease.

P2-C-403 *Neural markers of social interaction deficits in neurodevelopmental disorders: A normative modelling approach*

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Neurodevelopmental disorders (NDDs), such as autism, affect over 3% of children globally and are characterized by deficits in social interaction, communication, and cognition. Recent advances in neuroscience, coupled with shifts toward the neurodiversity paradigm, highlight the need to study NDDs as natural variations in brain function rather than purely as deficits. To address this, we apply normative modelling, a data-driven approach that examines biological variation across both clinical and healthy populations, to identify brain-based markers associated with social interaction impairments. Using cognitive and naturalistic task data from the Healthy Brain Network, we analyse task-based EEG data to measure neural dynamics during sensory encoding. Specifically, we focus on temporal dynamics such as the autocorrelation window (ACW) and power-law exponent (PLE) which capture how neural activity unfolds over time and have been previously linked to sensory processing and cognitive function. By comparing these markers across individuals with NDDs and the broader population in tasks, we aim to identify specific neural patterns related to social deficits. Preliminary results suggest that participants with NDDs, particularly autism, show shorter ACWs and lower PLEs compared to the population generally. Other EEG measures of task-related neural activity will be discussed, with a focus on their utility as potential biomarkers for identifying and understanding deficits in social interactions. This research contributes to the growing field of neurodiversity-affirming neuroscience by mapping neurocognitive variation in NDDs beyond traditional neurotypical comparisons. Identifying neural markers associated with social impairments could lay the groundwork for more personalized and biologically informed interventions, ultimately improving outcomes for individuals with NDDs.

P2-C-404 *Neuronal SorCS1 promotes synaptic resilience and selectively restores working memory in Alzheimer's disease*

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Alzheimer's disease (AD) is characterized by amyloid-β (Aβ) plaques, tau hyperphosphorylation, and early synaptic dysfunction that strongly predicts cognitive decline. Therapeutic strategies targeting amyloid pathology have shown limited clinical benefit, highlighting the need to identify mechanisms that preserve synaptic function in the presence of disease. Here, we investigated whether neuronal SorCS1 promotes synaptic resilience in AD. We generated an inducible, neuron-specific SorCS1 overexpression model crossed with5xFAD mice and selectively induced SorCS1 expression in forebrain excitatory neurons after the onset of pathology. Behavioral, electrophysiological, biochemical, and histological analyses were performed to assess cognitive function, synaptic transmission, and neuropathology. Neuronal SorCS1 overexpression selectively rescued short-term working memory deficits in female 5xFAD mice in the Y-maze. SorCS1 partially restored impaired basal synaptic transmission in hippocampal CA1 circuits. Excitatory synapse integrity was robustly recovered, including normalization of PSD95 and synaptophysin expression, restoration of synaptic puncta size and density, and selective rescue of β-neurexin and AMPA receptor subunits. These effects occurred without changes in amyloid plaque burden or soluble Aβ levels. In contrast, neuronal SorCS1overexpression significantly reduced tau hyperphosphorylation in the hippocampus of female 5xFAD mice and interacted with GSK3β. Together, these findings identify SorCS1 as a neuronal synaptic resilience factor that preserves excitatory synapse integrity, mitigates tau pathology, and selectively improves working memory independently of amyloid clearance, supporting synapse-centered therapeutic strategies for Alzheimer's disease.

P2-C-405 *Neuron-specific knockout of gigyf2 in mice results in autism-related behaviour and learning and memory impairments*

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Dysregulation of protein synthesis in the brain results in abnormal synaptic functioning and is studied as a major cause of autism spectrum disorder (ASD). Mutations in GIGYF2, a gene involved in mRNA translation, have been identified in individuals diagnosed with ASD. Furthermore, GIGYF2 is ranked as per the Simons Foundation Autism Research Initiative (SFARI) database as a high-confidence (category 1) risk factor gene, indicating that it highly likely to be implicated in ASD when mutated. To determine the involvement of GIGYF2 in neurodevelopment and ASD, we created a novel Gigyf2 conditional knockout (cKO) mouse model and deleted Gigyf2 in inhibitory and excitatory neurons (Gad2 and Camk2a-expressing respectively). Since the full knockout is lethal, this mouse model represents the first opportunity to study behaviour and molecular mechanisms in a homozygous Gigyf2 knockout mice. In fact, we observed increased repetitive behavior, increased anxiety, impaired social behavior and memory and learning deficits in the inhibitory Gigyf2 cKO. In comparison, our excitatory cKO model did not demonstrate disrupted behaviour in most autism-like and memory tests. From our results, we hypothesise that GIGYF2 expression in inhibitory neurons is crucial for the development of neurotypical behaviour and that when ablated it can result in autism-like symptoms. Importantly, this model needs to be further studied for the mechanism by which lack of GIGYF2 expression causes this phenotype by determining downstream protein expression of major pathways involved in ASD.

P2-C-406 *Neuroprotective effects of pyrroloquinoline quinone in folate deficiency–induced blood–brain barrier disruption*

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Folates (vitamin B9) are essential for neurodevelopment, with brain delivery mediated by folate receptor-α (FRα), the proton-coupled folate transporter (PCFT), and the reduced folate carrier (RFC) at the blood–cerebrospinal fluid barrier and blood–brain barrier (BBB). Folate deficiency (FD) results in cerebral folate deficiency (CFD) and has been associated with several neurological disorders. This study examined FD-induced BBB dysfunction and the neuroprotective potential of pyrroloquinoline quinone (PQQ), a redox-active compound that activates PGC-1α/NRF-1 signalling. Human brain microvessel endothelial cells (hCMEC/D3), an in vitro model of the BBB, were exposed to control or FD media and treated with PQQ (1–5 μM), while C57BL/6N mice received control or FD diets followed by a 10-day PQQ treatment (20 mg/kg/day, i.p.). FD increased inflammatory cytokines and chemokines, endothelial adhesion molecules, and oxidative stress markers, and reduced expression of tight junction proteins (ZO-1, occludin), accompanied by increased sodium fluorescein permeability in vivo, indicating BBB breakdown. PQQ mitigated these changes, restored tight junction expression, and upregulated RFC and PCFT via PGC-1α/NRF-1 activation. These findings demonstrate that FD disrupts BBB structure and function and identifies PQQ as a promising modulator of barrier integrity and folate transport in CFD-associated CNS disorders. (Supported by NSERC)

P2-C-407 *Neuroprotective effects of remote ischemic conditioning in a mouse model of repetitive mild traumatic brain injury*

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Traumatic brain injury (TBI) is a leading global cause of disability. Repetitive mild TBI (r-mTBI) is associated with persistent neuroinflammation and neurodegeneration, yet no treatments exist. Remote ischemic conditioning (RIC) is a non-invasive intervention shown to reduce neuroinflammation and blood–brain barrier disruption, but its effects in r-mTBI are unknown. This study evaluated the effects of RIC on r-mTBI-induced motor and cognitive dysfunction, neuroinflammation, and molecular changes. Thirty-two male C57BL/6 mice were randomized into four groups: sham/no RIC, sham/RIC, r-mTBI/no RIC, and r-mTBI/RIC.

RIC consisted of four cycles of 5-min ischemia and reperfusion applied daily to the hindlimbs for 14 days. r-mTBI was induced using a Lateral Impact Model, with one mTBI administered daily for 5 consecutive days. Neurobehavioral testing was performed 1-3 days post-injury. Neuroinflammation was assessed by immunohistochemistry for astrocytic and microglial markers in the motor cortex and hippocampus. Cytokine/chemokine levels were quantified from whole-brain homogenates, and proteomic profiling was performed using liquid chromatography-tandem mass spectrometry. r-mTBI increased foot slips on the beam walk compared to controls ($p<0.05$), an effect reduced by RIC ($p<0.05$). RIC also decreased microglial density and Iba1 mean fluorescent intensity in the motor cortex ($p<0.05$). Cytokine analyses showed significant changes in IL-1α, IL-2, IP-10, and MIP-2. Proteomic analyses are ongoing. These findings identify RIC as a potential promising prophylactic strategy for r-mTBI.

P2-C-408 *NMJ proteomic signatures underlying resistance and vulnerability in ALS progression*

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A common pathological feature of amyotrophic lateral sclerosis (ALS) is the progressive destruction of neuromuscular junctions (NMJs). NMJ denervation is one of the earliest events in ALS patients and murine models. Consistent with patient observations, our group showed that NMJs undergo a prolonged cycle of denervation and reinnervation before complete motor axon retraction. This instability is driven in part by maladaptive glial regulation of NMJ maintenance and repair.NMJ vulnerability is motor unit-dependent: fast-fatigable units, such as those innervating the extensor digitorum longus (EDL), are highly susceptible, whereas extraocular muscle (EOM) innervation remains resistant to disease progression. Together, these findings establish the NMJ as a dynamic and heterogeneous site of pathology during ALS development and progression. Our goal was to gain a better understanding of the molecular basis underlying the differential vulnerability. To this end, we performed comparative NMJ-targeted proteomic analyses of resistant EOM and vulnerable EDL muscles of wild type and symptomatic SOD1G37R mice, as well as longitudinal analyses of EDL muscles at pre- and symptomatic stages. An unbiased proteomic approach, complemented by NMJ-focused analyses, identified distinct molecular pathways related to axon guidance, extracellular matrix remodelling, and synaptic organization, reflecting denervation-reinnervation cycles preceding symptom onset. Understanding NMJ proteomic signatures will aid the identification mechanisms governing NMJ demise in ALS and potential candidate biomarkers for early ALS diagnosis and disease progression assessment.

P2-C-409 *No evidence for genetic role of the tumor necrosis factor pathway in Parkinson's disease*

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Tumor necrosis factor (TNF) inhibition is under investigation as a therapeutic strategy for Parkinson's disease (PD) and REM sleep behavior disorder (RBD), yet supporting genetic evidence is limited. We used Summary-data-based Mendelian Randomization (SMR) to test whether expression level of ten TNF-related genes were causally linked to PD risk, PD progression, or RBD risk. We also analyzed associations between common and rare variants in these genes, and performed pathway specific polygenic risk score analysis, with PD. Overall, our findings do not support a genetic link between the TNF signaling and PD or RBD, arguing against this pathway as a genetically validated therapeutic target.

P2-C-410 *Essential Tremor and BACE2: a role for oligodendrocyte-specific Aß metabolism in disease etiology*

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Essential tremor (ET) is a common movement disorder characterized by involuntary postural and action tremors, typically affecting the upper limbs. As the most prevalent movement disorder globally, ET affects ~1% of the general population and 5% of those over 65. Progressive tremors severely impair patients' quality of life, making identification of molecular biomarkers crucial for improving diagnostic accuracy and developing effective treatments.Although the etiology of ET remains unclear, growing evidence implicates the cerebellum as a primary dysfunction site due to its role in motor control, balance, and posture. Notably, insoluble amyloid β-protein oligomers (Aβs) accumulate at significantly higher levels in ET patients' cerebella compared with healthy individuals. Aβ homeostasis is normally regulated by sister proteins BACE1 and BACE2, with recent genome-wide association studies implicating BACE2 as disease-relevant for ET. Single-cell studies identified two variants associated with decreased BACE2 expression in ET patients' cerebellar oligodendrocytes. Interestingly, oligodendrocytes contribute to amyloidogenic Aβ peptide production in AD mouse models, suggesting BACE2 dysregulation in oligodendrocytes may underlie ET pathogenesis via altered Aβ metabolism. To investigate this, we performed CRISPR-Cas9-mediated BACE2 knockout in fibroblast-derived induced pluripotent stem cells, followed by 75-day differentiation into oligodendrocytes. The resulting oligodendrocytes will test the effect of BACE2 on Aβ metabolism, dendritic branching, and cell health. This in vitro model aims to probe the relationship between BACE2 function and oligodendrocyte-specific Aβ metabolism in hopes of providing new insights into ET pathophysiology, improve diagnostic precision, and guide future therapeutic interventions.

P2-C-411 *Contrasting oculomotor abnormalities in right- and left-sided Parkinson's disease using eye-tracking*

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Parkinson's Disease (PD) is a progressive neurodegenerative disease characterized by motor and non-motor symptoms. Loss of dopaminergic neurons in the substania nigra is a key feature of PD, leading to bradykinesia, tremors, rigidity, and gait changes. Motor symptoms are often lateralized in PD due to contralateral hemispheric damage, producing differences in non-motor symptoms. Oculomotor control is disrupted in PD, but the asymmetric neurodegeneration may perpetuate differences in oculomotor behaviour between right- and left-sided PD. This study aims to compare oculomotor abnormalities (saccade, pupil, blink) between right- and left-sided PD. Individuals with PD-right (n=38), PD-left (n=68) and healthy age- and sex-matched controls (n=61) were recruited through the Ontario Neurodegenerative Disease Research Initiative. PD patients were stratified based on the side with greater motor impairment. Participants completed an unstructured free-viewing task, which involved watching sequences of video clips (3-4 seconds in duration) containing scenes of nature, people, buildings, etc. Saccade, pupil, and blink measures were recorded using a video-based eye tracker, and clinical measures were collected. Preliminary data reveal differences in gaze bias, saccade behaviour, pupil size, and blink probability between PD-right and PD-left. These results demonstrate how affected oculomotor pathways can perpetuate differences in eye behaviour between right- and left-sided PD, enabling eye-tracking to aid in detection and diagnosis.

P2-D-412 *Evolutionarily conserved neural dynamics across mice, monkeys, and humans*

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On evolutionary timescales, brain circuits adapt to support survival in the ecological niche of each species. While some anatomical aspects of neural circuitry are conserved across species with distant evolutionary origins such as rodents and primates, it remains unclear whether ancestrally-related regions leverage similar neural computations, captured through neural dynamics, as these species perform common behaviors such as reaching and grasping. We hypothesise similar movements are produced through preserved neural dynamics, and tested this directly using intracortical recordings from mouse, monkey, and human motor cortex - a region prevalent throughout higher vertebrate - during motor behaviors. We compared the neural dynamics within- and across-species using Dynamical Similarity Analysis (DSA), an analytical approach to compare the rules governing the state transitions of two dynamical systems. Remarkably, we found that neural dynamics were as similar across all species as any two individuals within a species, indicating evolutionarily preserved neural computations for movement in the motor cortex. Indeed, neural dynamics were more similar across species than those across brain regions even in the same human (motor vs. somatosensory cortex) and across distinct behavioral contexts in the same monkeys (covert planning vs. overt movement). Altogether, these findings suggest strong conservation of motor cortical dynamics processes across species. We thus assert that evolution maintains effective neural computations across the phylogenetic tree even as behavioral repertoires expand.

P2-D-413 *Posterior-anterior propagation of beta bursts during motor control*

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IntroductionBeta-band oscillations (13–30 Hz) emerge as transient bursts that regulate motor control, with pre-movement bursts linked to inhibition and post-movement bursts to accuracy. Yet how these bursts propagate along the cortical posterior–anterior axis—a core hierarchy from sensory to motor processing—remains unknown. MethodsUsing MEG data from 573 healthy adults (CamCAN cohort) during a right-index-finger tapping task, we analyzed beta-burst propagation before and after movement. Bursts were detected as periods where beta power exceeded the 75th percentile for at least 100 ms, after 1/f background removal. Regional burst onset time ranks were examined via PCA. Optical flow analysis independently quantified propagation direction along the posterior–anterior axis. ResultsFrom the burst onset ranks, we found organized posterior–anterior propagation that reversed between motor phases: pre-movement, left-hemisphere bursts traveled posterior-to-anterior, right-hemisphere anterior-to-posterior; post-movement, directions reversed in both hemispheres. Optical flow confirmed this phase-dependent reversal (all $p < 1\times10-10$). These results reveal that beta bursts propagate systematically along a cortical functional hierarchy, with directional reversals reflecting a shift from feedforward motor preparation to feedback sensory integration, supported by complementary hemispheric dynamics. ConclusionThis study establishes organized burst propagation as a key mechanism of sensorimotor integration.

P2-D-414 *Exploring homeostatic plasticity as a mechanism underpinning prolonged pain*

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Homeostatic plasticity stabilizes neural networks by adjusting synaptic thresholds in response to prior activity. Disruption of this mechanism may contribute to maladaptive plasticity in chronic pain. This study examined whether prolonged experimental muscle pain alters homeostatic plasticity in the primary motor cortex. Healthy adults received repeated intramuscular nerve growth factor injections into the first dorsal

interosseous muscle to induce sustained pain lasting up to 21 days. Homeostatic plasticity was probed using cathodal tDCS combined with TMS to assess corticomotor excitability across pain development and resolution. Twenty participants were recruited (mean age 25± 5 years, range 20–37). Pain diaries showed the expected temporal profile, with peak intensity at days 2 to 4 and gradual resolution by day 21. Preliminary descriptive analyses suggest variability in homeostatic responses across the pain trajectory. Exploratory corticomotor mapping indicates individual differences in map organization during elevated pain, with partial normalization as pain resolves. Overall, prolonged pain appears to disrupt homeostatic plasticity in M1, suggesting a mechanism linking sustained pain to maladaptive cortical reorganization relevant to chronic pain.

P2-D-415 *Eye vs. hand effector-specificity in human parietal and frontal cortices*

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Humans rely on visually-guided saccades and reaches to interact with the world. Although non-human studies report effector-specific signals for saccades vs. reaches in parietal and frontal cortices, human fMRI studies often show overlapping activation, perhaps due to temporal “blurring” of closely-timed sensory, cognitive, and motor events. Here, we use an fMRI paradigm that separates these sensorimotor events to better characterize saccade versus reach networks, and to determine effector-specific activation. Participants (N = 20) performed cue-separated saccade, reach, and control tasks. Each trial included 3 events: an effector-independent target-encoding phase, and effector-dependent motor-planning and execution phases. Relative to control, encoding of visual target information engaged bilateral temporal cortex. During planning, saccades activated occipito-parietal and frontal regions whereas reaching showed a broader occipito-parietal-frontal activation pattern. During execution, both effectors activated overlapping occipital-parietal regions, with distinct frontal motor regions. Direct comparison of saccade vs. reach activation patterns during planning revealed greater reach activity in parietofrontal regions. During execution, saccades had greater activity in lateral occipito-parietal and frontal eye-field related areas while reaches had greater activity in medial occipito-parietal and left motor-related frontal regions. Together, these findings suggest distinct saccade- and reach-related activation across occipito-parieto-frontal regions during movement execution.

P2-D-416 *Factorial analysis of ensemble representation of attention and decision-making in prefrontal cortex of macaque monkeys*

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Macaque monkeys were trained with positive reinforcement to perform a visual search task with separate interleaved 2x2 factorial manipulations of attention and of response decision operations. Attention was manipulated by varying the similarity between a singleton and distractors. Response decision was manipulated by varying the discriminability of a go/nogo cue. The organization and termination rule of the two operations were previously determined using System Factorial Technology (SFT; Lowe et al, 2019). Single-units were sampled in the frontal eye field (FEF) with linear electrode arrays. Here, results are reported from an ensemble level analysis using demixed Principal Component Analysis (dPCA). The ensemble of neurons in FEF embodied reliable representations of singleton location and response decision. The separate manipulations of attention and decision operations influenced the timing of these representations. The demixed Principal Components (dPC) for attention and for decision were not entirely orthogonal. The results indicate that attention and decision processes are embodied in overlapping neuronal subpopulations rather than in fully distinct groups. Future work will determine whether variation of the dPC accounts for systematic variation of response times and how single-neuron properties relate to the ensemble representations. We will also compare these representations across different processing architectures characterized by SFT.

P2-D-417 *Feedback gains reflect unfolding decisions during ongoing actions*

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Decision-making has been shown to influence the preparatory state of the human motor system, as revealed by changes in corticospinal excitability and proprioceptive feedback gains. However, most evidence comes from paradigms in which decisions are made before movement initiation. It is unclear whether similar interactions occur in more natural situations, where decisions unfold during ongoing action. Here, we investigated whether deliberation dynamically influences motor preparation during continuous movement. Participants performed a manual tracking task in which, midway through the movement, an alternative target could appear, allowing them to either continue the ongoing action or switch to a new goal. Mechanical perturbations were applied to the arm at different times after target presentation to probe feedback gains, estimated from evoked electromyographic responses in a muscle agonist for the alternative reach. We show that feedback gains were enhanced when participants chose to switch targets, consistent with preparation for the new action. Critically, feedback gains were also transiently elevated when participants freely chose to continue tracking, compared to trials without an alternative option, indicating motor engagement during deliberation even when the alternative action was ultimately rejected. This transient effect disappeared once the decision to continue was resolved and was absent when continuation was externally instructed. These findings demonstrate that deliberation processes dynamically and continuously shape motor system state during ongoing action.

P2-D-418 *Foraging plasticity in Caenorhabditis elegans or how developmental stress leads to cautious foragers in rich environments*

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When organisms face adverse circumstances during growth, they develop adaptations to cope with them; nonetheless, the absence at maturity of these anticipated harmful conditions may mean adaptations are no longer beneficial and could even be disadvantageous in an innocuous environment. Understanding how developmental stress influences adult traits is therefore essential, and Caenorhabditis elegans is a powerful model organism to achieve this. Worms fed ad libitum (well-fed; WF) exhibit clearly defined foraging states. However, we find significant differences in them when they undergo starvation-induced dauer stage during development and consecutively receive an ad libitum diet to resume development to adulthood (post-dauer; PD). We quantify the locomotion of WF and PD worms, and consistently observed decreased exploration in PD animals. AVA, an interneuron essential in modulating reversal occurrence, exhibits distinct activity in PD animals in comparison to WF ones. Nonetheless, the underlying mechanisms behind these neurobiological and behavioural changes remain unknown.By combining video recordings of C. elegans with computer vision analysis and Hidden Markov models for behavioural scoring, alongside molecular and genetic techniques, our approach seeks to uncover how early-life starvation reshapes the neural and behavioural architectures that govern the foraging strategies of C. elegans in adulthood.

P2-D-419 *Frequency-specific modulation of beta-band dynamics by transcranial alternating current stimulation in younger and older adults*

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Motor decline in older adults accompanies changes in beta-band oscillations. Movement-related beta desynchronization (MRBD) and post-movement beta rebound (PMBR) are linked to age-related motor performance decline. Transcranial alternating current stimulation (tACS) can improve motor function, but effects vary across individuals due to stimulation parameters (e.g., frequency). Moreover, motor-related tACS studies in older adults remain limited. Quantifying tACS effects on MRBD and PMBR, and directly comparing

age groups within a unified experimental framework, is therefore essential for characterizing age-related differences in neural responsiveness and optimizing stimulation protocols for aging.Electroencephalography (EEG) was collected from 29 healthy adults (14 young, 15 older) during handgrip tasks. Participants received 1 mA high-density tACS at 20Hz/70Hz, or sham tACS, to the left primary motor cortex. EEG was recorded at baseline, 15- and 45-minute post-stimulation. Baseline data were compared between groups, and a two-way analysis of variance examined age and protocol effects on beta power changes. At baseline, older adults showed significantly higher PMBR than younger adults ($p<0.001$). Post-stimulation, no age main effect emerged, indicating comparable protocol effects across age groups. A significant stimulation type effect was observed across timepoints. Specifically, 20Hz tACS increased MRBD more than 70Hz tACS and sham at 15 minutes (all $p<0.01$), persisting at 45 minutes ($p<0.05$). Additionally, 20Hz tACS reduced PMBR compared to 70Hz and sham in older adults at 15 minutes ($p<0.05$), an effect absent in younger adults and not sustained at 45 minutes. These findings demonstrate frequency-specific, partially age-dependent modulation of beta-band dynamics, informing targeted neuromodulation strategies to improve aging motor function.

P2-D-420 *Functional brain mapping of stroke-induced cortical blindness in mice using neurophotonics*

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Ischemic strokes induce disabilities varying depending on which cortical areas are injured. Spontaneous functional reorganization comes after but frequently remains insufficient for full recovery. Mostly studied in the motor cortex, it includes changes in connectivity and functional properties of neighbouring cortical areas. We investigated if similar mechanisms were present after inducing cortical blindness with a stroke in the primary visual cortex (V1). Stroke-related visual disabilities are far less studied than motor impairments. Without preclinical models, we developed a cortical blindness mouse model using widefield calcium imaging. Cortical windows on adult Thy1-jrGECO1a mice revealed fluorescence fluctuations linked to neuronal calcium activity during rest or visual stimuli. A phothrombotic stroke in the V1 cortex was used to model cortical blindness and cortical functions were tracked for a month after.Local increase in raw fluorescence, paired with a reduction in blood flow, spontaneous and evoked cerebral activity, were direct consequences of the stroke in the V1 cortex. All functional metrics improved after a month, which was corroborated by post-mortem histology of the ischemic injury. Transient loss of visual integration was not associated with changes in the general retinotopy. The local, injured, visual network showed a permanent reduction in connections strength and centrality while cortex-wide efficiency was diminished. Our findings suggest that spontaneous functional reorganization occurs in the V1 cortex and may involve mechanisms like the motor cortex.

P2-D-421 *Functional connectivity of reticulospinal neurons within the medullary reticular formation*

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The spinal circuitry is under the control of the medullary reticular formation via glutamatergic reticulospinal neurons (RSNs). Although their role in initiating and coordinating locomotion is established, their functional organization and connectivity remain poorly understood. We hypothesized that glutamatergic RSNs are reciprocally connected within neuronal assemblies. To test this hypothesis, we combined whole-cell patch-clamp recordings with calcium imaging or optogenetics. To assess connectivity among RSNs, a Cre-dependent viral vector was injected into the lumbar spinal cord of Vglut2-Cre mice to express a calcium indicator in RSNs. Depolarization of a single RSN revealed calcium responses in neighboring neurons, with a higher probability in the most proximal cells, supporting functional connectivity among lumbar-projecting RSNs. To examine reciprocal connectivity, Cre-dependent viral vectors were injected to express a fluorophore in cervical- or lumbar-projecting RSNs and a photoactivator in the opposite population. Optogenetic recruitment of lumbar-projecting RSNs elicited action potentials and increased firing in cervical-projecting RSNs, and vice versa, supporting functional connectivity between distinct RSN populations. In summary, our

findings show that glutamatergic RSNs form interconnected assemblies at the brainstem level, which may contribute to the coordination of descending locomotor commands.

P2-D-422 *Functional contribution of glutamatergic neurons of mesencephalic locomotor region nuclei to locomotion*

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The mesencephalic locomotor region comprises the cuneiform nucleus (CnF) and the pedunculopontine nucleus (PPN). Glutamatergic neurons in the CnF preferentially drive high-speed locomotion, whereas those in the PPN are associated with slower locomotor states, raising questions about the ability of the CnF to initiate slow-speed locomotion. Clinical studies have also highlighted potential inaccuracies in electrode placement during stimulation of these nuclei, which may contribute to suboptimal outcomes. Here, we tested whether glutamatergic neurons of the CnF can initiate locomotion at slow speeds and whether electrophysiological signatures can be used to better identify stimulation sites. A Cre-dependent viral vector was injected into adult Vglut2-Cre mice to express a photoactivator in glutamatergic neurons of either the CnF or PPN. Locomotor initiation was assessed in animals at rest using kinematic analyses during one-second trains of optogenetic stimulation. Low stimulation intensities and/or frequencies applied to glutamatergic CnF neurons reliably generated slow locomotor speeds, whereas activation even at high intensities and frequencies of glutamatergic PPN neurons failed to initiate locomotion. In addition, electrophysiological recordings combined with short-pulse photostimulation revealed that activation of CnF, but not PPN, neurons elicited rhythmic locomotor-like activity in animals at rest. These findings indicate that the CnF can generate locomotion across a wide range of speeds and that electrophysiological recordings may improve electrode placement accuracy.

P2-D-423 *Impact d'une perturbation transitoire des voies corticales sur les relations fonctionnelles entre le cortex visuel primaire et le pulvinar chez la souris*

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Cette étude avait comme objectif d'examiner l'effet d'une inhibition transitoire du cortex par LM, une aire visuelle supérieure corticale, sur les interactions neuronales entre le cortex visuel primaire (V1) et le pulvinar (LP). En particulier, le taux de synchronie entre ces deux régions a été examiné via une approche combinant l'imagerie calcique et l'électrophysiologie. Des expériences préliminaires ont été effectuées sur 3 souris (n = 500 neurones) pour tester le mode d'inhibition (Cryoprobe) et le protocole expérimental. 3 autres souris (n = 287 neurones) ont été testées selon 2 types de conditions, soit sous activité spontanée ou sous activité évoquée lors de 4 phases d'enregistrements : avant, durant et 2 périodes après le refroidissement de LM. Un profil « creux » de synchronisation intrarégionale est majoritairement obtenu, démontrant une baisse de synchronisation des pics durant l'inactivation et une hausse durant les phases de récupération. La synchronisation interrégionale est diminuée durant la période d'inhibition de l'enregistrement évoqué et maintenu en spontanée. De plus, la stimulation visuelle augmente la synchronisation de 600% entre le cortex visuel primaire et le pulvinar avant l'inhibition. Ces résultats suggèrent qu'il existe une réorganisation fonctionnelle dynamique contextuelle, possiblement relayée par le pulvinar. Supp : IRSC.

P2-D-424 *In vivo characterization of strain-specific entourage effects in Psilocybe mushrooms in a rat model of autism spectrum disorder*

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Entourage effects, arising from interactions among co-occurring metabolites, are a recognized yet poorly characterized feature of plant and fungal systems. With current research focused on purified psilocybin,

the neurobiological impact of whole psilocybin-containing mushrooms has not yet been evaluated in vivo. We employed the valproic acid (VPA) rat model of autism spectrum disorder to examine whether chronic microdosing with two chemically unique Psilocybe strains produces distinct behavioural outcomes, alterations in brain systems activity, and therapeutic effects relative to pure psilocybin. Male and female adolescent VPA-exposed rats received daily voluntary oral microdoses (0.3 mg/kg psilocybin equivalent) for 31 days. Behavioural assays evaluated anxiety-like and repetitive behaviour, social interactions, and spatial and recognition memory. Local field potentials were recorded from the medial prefrontal cortex, anterior cingulate cortex, dorsal hippocampus, and nucleus accumbens to examine oscillatory activity. VPA animals showed expected behavioural and oscillatory alterations. All treatments improved subsets of these alterations. However, the two Psilocybe strains produced differentiated and non-overlapping behavioural and electrophysiological signatures, each also differing from purified psilocybin. Several sex-dependent therapeutic effects were also observed. These findings demonstrate that Psilocybe strain chemistry drives unique behavioural and brain systems activity profiles that are distinct from pure psilocybin, highlighting the importance of full-spectrum fungal composition for future whole psychedelic mushroom-based health interventions.

P2-D-425 *Investigating how an immune challenge impacts the trajectory of chemotherapy-induced peripheral neuropathy*

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Introduction: Chemotherapy-induced peripheral neuropathy (CIPN) is an unfortunate side effect of chemotherapy treatment that causes neuropathic pain. Pain resulting from CIPN can lead patients to end their treatment course early, emphasizing the need to prevent or resolve CIPN. A medication that causes CIPN is Paclitaxel (PTX), which induces immunological and neuronal changes and activates interferon (IFN) signaling. While IFNs have been shown to modulate pain, their role in promoting resolution of CIPN has yet to be elucidated. We hypothesize that interfering with type I IFN signaling will alter the natural resolution of CIPN. Methods: Male and female mice received a cumulative dose of 16mg/kg of PTX (intraperitoneally) to induce pain. Tactile stimulation of the hind paw was performed over a 6-8-week period to assess changes in hypersensitivity. Poly(I:C), a synthetic double-stranded RNA molecule that induces a type I IFN response, was injected during peak pain to determine if a secondary stimulus could alter the trajectory of CIPN. To better understand the role of IFN signaling, similar experiments were conducted in IFN-receptor knock-out mice and wild-type mice that received IFN-β. Results: We found that PTX treatment causes hyperalgesia, which resolves in both sexes. Poly(I:C) accelerated recovery from CIPN, while mice lacking the IFN-receptor did not recover. Mice that received IFN-β had faster recovery from hypersensitivity. Conclusions: These results suggest that IFNs play an important role in CIPN recovery, highlighting their potential as a future therapeutic.

P2-D-426 *Investigating the Circuit Mechanism of Steering in Isothermal Tracking of Caenorhabditis elegans (C. elegans)*

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Animals require effective navigation strategies to locate food. The nematode uses two primary navigation strategies: klinokinesis (biased random walk) and klinotaxis (steering). Nevertheless, the neural mechanisms underlying steering are less well understood. Steering involves precise cooperation among sensory neurons, interneurons, and motor neurons. Notably, the RIA interneuron plays a key role in sensory-motor coordination by limiting head bending amplitude through negative feedback. My goal is to clarify how RIA regulates sensory and motor neurons to perform sustained steering behavior. We use isothermal tracking as a behavioral model to investigate the computational rules and underlying the molecular and cellular mechanisms that govern sustained steering behavior. Previous studies have assumed that worms perform isothermal tracking by comparing temperature differences detected during head sweeps. However, our preliminary results reveal that it may be not the whole story. Our novel hypothesis is that C. elegans achieves isothermal tracking through discrete fine-tuning event during forward locomotion. Disruption of the RIA

impairs the worm's ability to fine-tune its steering, ultimately leading to a failure in isothermal tracking behavior, and it may be caused by reduction in success rate of fine-tuning. To test this assumption, we are applying calcium imaging in freely moving worms in a gradient environment.

P2-D-427 *Investigating the effects of lorazepam and baclofen on TMS evoked transcallosal inhibition*

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Transcallosal projections within the corpus callosum allow for the transfer of information between bilateral primary motor cortices (M1). These projections are essential for producing coordinated motor actions, preventing unwanted mirror activity, sculpting and fine-tuning cortical output. Transcallosal communication involves a balance of excitatory interhemispheric projections and inhibitory cortical mechanisms. In motor impairment disorders such as stroke or Parkinson's Disease, motor impairments are associated with disrupted transcallosal signaling. Characterizing the mechanisms that govern transcallosal communication is therefore essential for understanding motor control and clinically relevant disruptions of interhemispheric communication. Transcranial magnetic stimulation (TMS) can be used to probe neural circuits underlying transcallosal connectivity. Interhemispheric inhibition (IHI) is one approach whereby the motor evoked potential (MEP) elicited by TMS is reduced in amplitude when preceded by a conditioning TMS pulse delivered to the opposite M1. Currently, there remain uncertainties surrounding the pharmacological origin of IHI. We therefore pursued an exploratory, double-blind, placebo-controlled study where lorazepam (GABAA agonist) and baclofen (GABAB agonist) were administered in a healthy control population. Twenty-four participants attended three sessions where they were administered lorazepam, baclofen or a placebo. IHI was recorded in the right first dorsal interosseous (FDI) muscle before (T0) and 1.5 hours after (T1) the administration of the drug. Our results demonstrate that IHI is decreased after administration of baclofen whereas lorazepam had no effect on IHI.

P2-D-428 *Kinematic analysis of motor responses evoked by circumferential stimulation of the lumbar spinal cord in cats*

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Walking is an essential skill in everyday life, but becomes impaired in many movement disorders, such as spinal cord injury (SCI). Neuromodulation approaches, such as electrical stimulation of the spinal cord (EES), show promise in restoring leg movements after SCI. Here, we used a circumferential electrode that wraps around the spinal cord to investigate the effects of dorsal, lateral, and ventral EES on the generation of leg movements in anesthetized adult cats. We quantified leg movements by measuring kinematics using DeepLabCutTM (Mathis et al., 2018). Then, we characterized the direction, amplitude, and laterality of evoked movements before associating them with stimulation parameters. Preliminary results show that ventral stimulation evoked more movement than dorsal stimulation, with a success rate of 68% compared to 43%. It also showed greater specificity and functionality with more unilateral movements and a wider range of movement amplitudes. Ventral stimulation could also evoke specific movements at a much lower stimulation amplitude: 1A instead of 4A for a knee extension. Our preliminary results suggest that EES of the spinal cord is highly dependent on the segment and location stimulated. Moreover, stimulating the spinal cord ventrally evokes more specific movements at a lower stimulation amplitude than equivalent dorsal stimulation. Ultimately, our goal is to find optimal stimulation parameters to reconstruct a functional walking pattern that will be tested in chronic spinal-transected cats before a trial in humans.

P2-D-429 *Lateral entorhinal–piriform projections in context-dependent odor processing*

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Sensory representations in the cortex are shaped not only by stimulus features but also by contextual and behavioral signals. In the piriform cortex (PC), neurons initially tuned to odors become modulated by non-olfactory variables such as visual context, but it remains unclear which associative inputs drive this modulation. A candidate source is the lateral entorhinal cortex (LEC), a region involved in context encoding and memory that is monosynaptically connected to PC. We hypothesize that LEC projections provide contextual information to PC and that their inhibition will alter both PC coding and behavioural performance. To test this, we established an in vivo approach combining selective chemogenetic silencing of the LEC–PC pathway with neuronal recordings and behavioral monitoring. We developed a dual-virus system to express inhibitory DREADDs specifically in projection neurons. In addition, we optimized histological reconstruction to target simultaneous recordings in PC and connected regions using high-density Neuropixels probes. Currently, we confirmed dual-virus expression in LEC neurons projecting to PC, and accurate Neuropixels probe mapping. Ongoing experiments will assess how the pathway inhibition alters neural representations and task performance, and lays groundwork to test how contextual signals are integrated into olfactory circuits and how higher-order associative regions shape early sensory processing.

P2-D-430 *Lateral hypothalamic pathways drive locomotor control and recovery after spinal cord injury*

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While cortical and brainstem circuits contribute to locomotor control, the specific role of the lateral hypothalamus area (LHA) remains poorly understood. The LHA contains heterogeneous populations of glutamatergic and GABAergic neurons that project to multiple brain regions. Given the involvement of some mesencephalic reticular nuclei in locomotion, we investigated the contribution of LHA neuronal subtypes and their mesencephalic-projecting pathways to locomotor control and recovery after spinal cord injury (SCI). Cre-dependent viral vectors were injected into transgenic mice to express a photoactivator in glutamatergic or GABAergic neurons of the rostral or caudal LHA. Using kinematic analysis with optogenetics, we found that glutamatergic neurons of the rostral LHA initiated and modulated locomotion before and after SCI. In contrast, glutamatergic neurons of the caudal LHA and GABAergic of either LHA parts showed no comparable effects. In a subset of mice, mesencephalic-projecting glutamatergic neurons of the caudal LHA were more effective in initiating and modulating locomotion than those from the rostral LHA, both before and after SCI. These effects were absent for mesencephalic-projecting GABAergic neurons. Inhibition of mesencephalic glutamatergic neurons abolished glutamatergic LHA-driven locomotion before and after SCI. In summary, our findings identify selective glutamatergic LHA pathways as contributors to locomotor control and potential targets to promote motor recovery after SCI.

P2-D-431 *Localized reorganization of brain structure following early auditory deprivation*

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Early deafness is associated with enhanced visual abilities, particularly peripheral vision, which is commonly referred to as cross-modal plasticity. While functional reorganization following auditory deprivation has been widely documented, it remains unclear whether such adaptations extend to white-matter pathways and, if so, whether these reorganizations have functional consequences. To address this question, we investigated diffusion-based MRI data from 12 domestic cats (6 hearing, 6 perinatally deafened), matched for age and sex, using a combination of graph-theoretical metrics, gradient-based analyses, and network control theory applied to structural connectivity. At the global network level, most graph measures were preserved between groups, indicating overall stability of connectome organization. Regional analyses, however,

revealed localized reconfiguration, with a subset of nodes showing altered community affiliation in about 8% of cortical nodes ($p < 0.001$). To further characterize these changes, we examined the low-dimensional structure of subcortical–cortical and corticocortical connectivity using gradient-based approaches focused on auditory-related subcortical nuclei, as well as primary auditory and primary visual cortices. While the principal organizational axes were largely preserved, localized differences in gradient structure and cortical projection patterns were observed between groups. Finally, network control analyses revealed reduced energetic demands for transitions from visual cortex to frontal and prefrontal regions in the deaf brain (reductions of 1.06%; $p < 0.001$), indicating enhanced efficiency of visual-to-higher-order communication. Together, these findings suggest that early auditory deprivation induces localized yet subtle changes in structural organization and network dynamics that may support cross-modal functional adaptation.

P2-D-432 *Mechanisms of activity-dependent cortical sensory adaptation in the rodent hindlimb somatosensory circuitry*

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Animals are continuously exposed to environmental stimuli to which sensory and central nervous systems have evolved to optimize their detection and processing. Cortical sensory adaptation (CSA) to repetitive stimulation (RS) is a hallmark feature of sensory systems. Despite this, the specific neural contributions and circuitry underpinning CSA are yet to be elucidated. Electrophysiological studies from our lab investigating cortical responses to hindlimb RS show short-term CSA (stCSA) characterized by a decrease in evoked cortical response over the course of a train of 7 tactile stimuli. Sustained RS applied for 30-45 minutes augments the amount of stCSA which persists for up to an hour after the cessation of RS. Our current studies investigate the neural substrate of stCSA and the basis for its persistence following sustained RS focusing on thalamocortical and intracortical circuitry using in-vivo two photon imaging of neuronal Ca2+transients. Complex lateral and vertical interactions especially implicated in the cortex are mediated by both excitatory pyramidal cells and regulatory inhibitory interneurons including those expressing parvalbumin. Neural activity corresponding to Ca2+ reporter fluorescence was isolated to parvalbumin-expressing interneurons or pyramidal principal cells in cortical layers two to four of the primary hindlimb somatosensory cortex. The respective excitatory and inhibitory contributions to neural plasticity in the context of our stimulation paradigm yields insight into the possible mechanisms of neural adaptation in healthy adult mice.

P2-D-433 *Mechanisms of decision-making during natural interactive behaviour*

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Many studies have examined decision-making in the context of specific tasks, such as saccade or reach decisions. However, natural behaviour involves decisions both within and between tasks that are embedded in rich, continuous activity. To move toward understanding the complexity of such scenarios, we developed a new naturalistic foraging task (i.e., apple picking task) implemented using virtual reality (VR). The task allows us to examine how decisions are made both among actions of the same type (choosing an apple to reach or a tree to approach) and between different kinds of activity (deciding whether to keep picking apples or find another tree). Moreover, using VR allows us to test if existing models capture these rich behaviours without sacrificing control over experimental variables. In line with prior work, we found that both apple and tree choices were influenced by benefits (e.g., value) and costs (e.g., distance from subject). Also in line with prior work, the choice to leave a tree was well fit by predictions of optimal foraging theory, and depended on the richness of the environment. Importantly, the residuals between predictions and actual leaving times could be further partially explained by the value of new available trees, revealing an interaction between action-level and task-level decision mechanisms. Our results provide a framework for future experiments with EEG recordings and/or TMS perturbations in humans, as well as for similar paradigms in monkeys, to better address the underlying brain mechanisms of complex decision-making during natural behaviour.

P2-D-434 *Mechanisms responsible for increasing repiratory activity during locomotion*

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Respiration must continuously adapt to the conditions in which animals operate. During locomotion, for example, both breathing frequency and amplitude increase markedly. This locomotor-related respiratory acceleration is conserved across vertebrates and, in lampreys and more recently in mammals, has been shown to rely largely on central mechanisms, in particular the mesencephalic locomotor region (MLR), which projects directly to brainstem centers controlling respiration. In lampreys, substance P-expressing neurons in the MLR project to the respiratory rhythm generator and participate in respiratory modulations. However, the contribution of cholinergic neurons has remained unresolved. To investigate their role, we combined physiological, pharmacological, and anatomical approaches in juvenile and adult lampreys. Extracellular recordings of respiratory motoneurons were obtained in isolated brain preparation during MLR stimulation, with or without drugs targeting cholinergic transmission. Acetylcholine directly increased the respiratory rhythm, and MLR-induced respiratory acceleration was enhanced by physostigmine and reduced by atropine. Retrograde tracing and immunohistochemistry further revealed direct cholinergic projections from the MLR to the respiratory rhythm generator. These results demonstrate that acetylcholine plays a key role in locomotion-induced increases in respiratory activity. Suported by: NSERC and CIHR

P2-D-435 *Microstimulation of V4 domains modulates visual perception in non-human primates*

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In primates, cortical area V4 plays a key role in visual object recognition. It is organized into millimeter-scale domains that represent specific stimulus features such as shape, texture, and color. These domains are thought to serve as a critical intermediate stage between early visual areas that process simple features and higher-order regions involved in complex object representation. However, the causal influence of these domains on shape perception remains unknown. To investigate this, we trained a non-human primate to perform a delayed match-to-sample task involving discrimination of circular and radial gratings, stimuli known to evoke distinct patterns of neural activity in V4. We then applied electrical microstimulation to feature-selective domains in V4, using bipolar stimulation to confine current spread to regions with shared stimulus preferences. We found that microstimulation of V4 domains significantly biased perceptual decisions toward the stimulus that evoked the strongest neural response in the targeted region. Importantly, this bias was stronger with bipolar stimulation, where current was restricted within the V4 domain, compared to monopolar stimulation, even though total current was matched across conditions. These findings demonstrate that the topographic organization of V4 has functional significance for perceptual decision-making, extending beyond the selectivity of individual neurons. More broadly, the results suggest that applications aimed at artificially inducing specific percepts may benefit from distributing electrical stimulation across multiple sites with similar feature coding, rather than relying on isolated stimulation.

P2-D-436 *Milliseconds that matter: how temporal fine structure shapes sensory detection and discrimination*

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Perceptual thresholds for self-motion, audition, and vision often approach limits imposed by environmental noise. In contrast, detection and discrimination thresholds derived from single-neuron activity are typically an order of magnitude higher when based solely on firing rate. The potential contribution of other defining features of spike train structure in individual neurons, however, has received far less attention despite their capacity to convey critical stimulus information. We recorded single vestibular nuclei (VN) neurons in two rhesus macaques during translational and rotational motion delivered by a motion platform. We developed

a novel signal detection framework for computing detection and discrimination metrics that explicitly incorporates the fine temporal structure of neural responses. Using the Van Rossum distance to compute d' across repeated stimulus presentations, we captured millisecond-scale spike timing patterns. Thresholds derived from these distance-based metrics were markedly reduced at short timescales, yielding values far closer to perceptual thresholds than those obtained from firing rate alone. Mathematical modeling and computational analyses revealed that spike timing precision accounts for these improvements in sensitivity. Together, these results demonstrate that precise spike timing enables single vestibular neurons to detect and discriminate subtle stimulus changes, supporting the idea that temporal coding allows small neuronal populations to achieve near-behavioral levels of sensory acuity.

P2-D-437 *Müller Glia-mediated light transmission as a potential trigger for cone planar cell polarity in mice*

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Sensory organs often rely on coordinated spatial organisation to optimise function and neural output. Patterning of cellular asymmetries within the plane of a tissue is known as planar cell polarity (PCP). Recently, we discovered PCP in cone photoreceptors of mouse retinas, showing that their light sensitive cilium is systematically oriented towards the optic nerve head. Intriguingly, we found that this PCP is established by a non-canonical pathway requiring light exposure at the time of eye opening (P14). Because cones are located deep within the layered retina, it remains unclear how light reaches them to instruct PCP. A promising mechanism involves Müller glial cells, which span the full retinal thickness and have been proposed to act as optical waveguides. As Müller glia associate with cones in a stereotypic 1-to-1 fashion in mice, we hypothesize that they are responsible for patterning light transmitted to cones, thereby triggering PCP. To test this, we will emit light exclusively from Müller cells in dark-reared mice at P14 using bioluminescent tools. Conversely, we will disrupt Müller glia light transmission in light-reared mice by inducing melanin production. We predict Müller glia-driven photon emission will rescue PCP in their associated cones in dark-reared mice, whereas blocking transmission will prevent PCP despite normal light exposure. If confirmed, this would demonstrate that sensory input takes part in mammalian development and identify light as a non-molecular morphogenic cue.

P2-D-438 *Natural self-motion is actively recoded in vestibular cortex*

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Accurate perception of self-motion requires transforming vestibular inputs into neural representations suitable for perception and action. Classical models propose that this transformation is largely completed in subcortical pathways, with cortical areas primarily relaying vestibular information to support perception. Here, we challenge this view by demonstrating that neurons in the macaque parieto-insular vestibular cortex (PIVC) profoundly recode vestibular signals during natural self-motion. Using motion stimuli that reproduce head movements encountered during everyday behavior, we show that PIVC neurons do not represent stimulus dynamics through continuous, graded firing-rate modulations, as observed during conventional sinusoidal stimulation. Instead, natural motion elicits nonlinear burst firing that selectively encodes distinct motion features. These bursts reliably signal specific features of the stimulus, while the full temporal structure of self-motion can only be reconstructed by pooling activity across the neural population, revealing a distributed coding strategy. Importantly, this feature-based burst coding is absent in vestibular thalamic inputs and is not observed during artificial stimulation. Together, our findings demonstrate that vestibular cortex actively constructs distributed representations optimized for natural self-motion, indicating that cortical encoding of vestibular signals—and likely other sensory modalities—is fundamentally shaped by the statistics of the natural environment.

P2-D-439 *Neural and behavioural correlates of audiovisual gaze-orienting in common marmosets*

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[1] McGill University

Multisensory integration (MSI), the brains' ability to combine multiple senses, is critical for perception; Disrupted MSI contributes to maladaptive decision-making, illusion susceptibility, and language learning / social deficits. I use the common marmoset (Callithrix jacchus) due to their behavioural and genetic homology with humans. Evidence suggests that marmoset cortical networks are conserved, with little known about their MSI organization and function. I hypothesize that marmosets demonstrate MSI functionality in the superior temporal sulcus (STS), superior colliculus (SC), and ventral intraparietal area (VIP), demonstrating superadditivity and distinct functional connectivity (FC) and blood oxygen level dependent activity (BOLD) to multisensory stimuli. I have collected behavioral and neuroimaging data in marmosets examining MSI's effect on signal detection, gaze-orienting, BOLD, and FC. Behavioural data is collected via eyetracking and automated touch-screen interaction on a custom platform (Smart Chair, Rogue Research). A non-invasive MRI custom coil built for marmoset imaging at 7T was used (Yazdanbakhsh et al., 2025). I recorded BOLD signal changes during an audiovisual spatial orienting task (n = 3). Subjects attended to audiovisual cues over noise while stimulus reliability, temporal synchrony, and spatial congruency were manipulated. Preliminary data in two subjects demonstrates increased activation during multisensory conditions in the multisensory regions including the STS, and VIP, supporting my hypotheses regarding localization of MSI function.

P2-D-440 *Neural markers of interocular grouping during binocular rivalry with MEG*

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Binocular rivalry (BR) occurs when two incompatible images are simultaneously presented, one to each eye, and elicit perceptual alternations between image dominance and suppression. Remarkably, BR accommodates interocular grouping (IOG) such that portions of two globally coherent images shown separately to each eye, still result in frequent global pattern perception. We investigated the neural correlates of BR and IOG with magnetoencephalography (MEG). Stimuli consisted of red or green orthogonal gratings flickering at 5 or 6.67 Hz, to allow for analysis of tagged fundamental, intermodulation frequencies, and steady-state visually evoked responses (N = 25). Our design included conditions with systematically increasing grouping demands; 2 or 4 complementary patches, with vertical or horizontal meridian image divisions. Participants reported their perception of dominant or mixed percepts. IOG showed weaker fundamental power than BR in early visual cortex during perceptual dominance, while power for suppression was less affected in depth and topography. Multivariate logistic regression further highlighted differences between BR and IOG, in V1 and V2, as well as higher-order visual areas (i.e., IP and LO). A support vector machine distinguished between dominance and suppression, with the highest accuracy near the time of the perceptual alternation. Interestingly, only the conditions with high IOG demands produced higher order intermodulation frequencies, significantly correlated in V1 to alternation rate. Overall, we show evidence of a broad similarity for BR and IOG in neural representations across the visual cortex, as well as specific mechanisms of monocular image segmentation and integration for IOG.

P2-D-441 *Neuroanatomical organisation of glutamatergic reticulospinal neurons*

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Locomotion relies on spinal interneuronal circuits modulated by descending brain inputs. Glutamatergic reticulospinal neurons in the pontomedullary reticular formation play a key role in initiating and modulating locomotion, yet their topographical organization remains poorly described. We hypothesized that these neurons exhibit a predominantly unilateral projection pattern and selectively innervate cervical or lumbar spinal segments to coordinate forelimb and hindlimb movements during locomotion. Two retrograde

Cre-dependent adeno-associated viruses were injected into the cervical and/or lumbar spinal cord of adult Vglut2-Cre mice. AAV2retro-EF1-DIO-mCherry and AAVretro-CAG-Flex-eGFP were used to label glutamatergic reticulospinal neurons projecting to distinct spinal segments. Neural tissue was cryosectioned and imaged by fluorescence microscopy. Neurons expressing a single fluorophore were identified as projecting to one spinal target, whereas co-localization of both fluorophores indicated projections to multiple spinal segments. Glutamatergic reticulospinal neurons predominantly exhibited unilateral and segment-specific projections, while a subset displayed either bilateral projections spanning multiple spinal segments. These neurons were primarily located within the alpha and ventral gigantocellular nuclei of the pontomedullary reticular formation. Together, these findings indicate that glutamatergic reticulospinal neurons are spatially organized to support lateralized and segment-specific control of spinal locomotor circuits.

P2-D-442 *Quantitative study of perineuronal net plasticity in the mouse visual cortex following retinal injury and cholinergic potentiation*

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Cholinergic potentiation with the acetylcholinesterase inhibitor donepezil (DPZ) enhances cortical plasticity and perceptual learning after visual training, possibly involving parvalbumin (PV+) interneurons and their perineuronal nets (PNNs). Here, we investigated whether DPZ modulates inhibitory circuit integrity following visual impairment through structural changes of PV+ neurons and PNNs. Unilateral choroidal neovascularization (CNV) was induced by photocoagulation in adult C57BL/6 mice. Visual cortex changes were examined two and seven days post-lesion in animals receiving daily DPZ (0.3 mg/kg) or no treatment. Visual recovery was assessed using the visual cliff test. PNN and PV+ interneuron densities were quantified using immunohistochemistry combined with deep learning-based analysis. Two days post-CNV, untreated mice exhibited a marked reduction in PNN density and PV+/PNN+ cells, an effect prevented by DPZ administration. These changes were most prominent in layers 2/3 and 5, while layer 4 was unaffected. At seven days, PNN preservation persisted selectively in layer 2/3, accompanied by a reduction in PV+ neuron density, suggesting adaptive regulation of parvalbumin expression. Treated mice also showed better visual recovery and performance during the visual cliff test. Together, these findings indicate that reduced retinal input disrupts interlaminar inhibitory organization in the visual cortex and that cholinergic potentiation with DPZ preserves inhibitory circuit structure, supporting excitation–inhibition balance and cortical integration during visual recovery.

P2-D-443 *Neurovascular and corticospinal dynamics of intermittent theta burst stimulation*

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Intermittent theta burst stimulation (iTBS) is widely used to modulate brain activity non-invasively, yet its application remains limited by large inter- and intra-individual variability in outcomes. Studies investigating this variability are largely restricted to non-invasive approaches in humans and still cannot fully explain its physiological origins. Neuronal plasticity depends on specific activity patterns that are tightly coupled to vascular dynamics, suggesting that neurovascular signals may provide informative predictors of neuromodulation efficacy. Here, we provide a continuous characterization of neurovascular and corticospinal dynamics during iTBS in the rat motor cortex. We hypothesized that neurovascular signatures could be extracted and used to predict iTBS outcomes. The experimental design combines electromyographic recordings of evoked responses, which reflect changes in corticospinal excitability, with measurements of cerebral blood flow in an anesthetized rat model undergoing an iTBS protocol. First, we characterize the neurovascular dynamics of the motor cortex surrounding iTBS. Second, we evaluate the extent to which the most informative neurovascular parameters can predict the outcome of neuromodulation.iTBS induced, as expected, variable changes in corticospinal excitability. However, robust and reproducible vascular and electromyographic patterns were observed during the conditioning itself. These dynamics may provide valuable insights into how iTBS parameters directly affect online neurovascular and corticospinal dynamics,

and therefore influence the outcome of the conditioning protocol. In addition to contributing to the reliability of iTBS, this study directly impacts procedures widely used in humans that rely on measurements of cerebral blood flow to infer neuronal activity.

P2-D-444 *Noradrenaline shapes top-down inhibition of the cortex by NDNF+ neurons in reinforcement and behaviour*

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Noradrenaline (NA) plays a significant role in decision-making, behavioural flexibility, and learning. To support these behaviours, it is proposed that NA signals positive or negative reinforcement to the cortex. However, the mechanisms by which NA interacts with distinct cellular components of cortical circuits during reinforcement have not yet been studied. Here, we aimed to i- map the expression of NA receptors onto the different subclasses of cortical neurons and ii- elucidate the function of NA receptors in reinforcement encoding by the cortex. To achieve this, we analyzed multiple single-cell RNAseq datasets of the mouse motor cortex. We found that GABAergic interneurons express more transcripts for NA receptors than glutamatergic neurons. Within interneuron subtypes, the NDNF+ neurons expressed the highest level of NA receptor transcript. Next, we investigated how NA receptor expression affects NDNF+ reinforcement encoding. Our data showed that knocking out alpha-1A receptors in NDNF+ interneurons increased their response amplitude to both reward and punishment. We also showed that, through alpha-1A and 1B receptors, NA desynchronized evoked NDNF+ activity and enhanced valence decoding by NDNF+ neurons. Finally, bilateral KO of both alpha-1A and 1B receptors in the motor cortex slowed learning in a forelimb lever-press task, which requires associating lever activation with reward delivery. These data support a model in which NA shapes reinforcement encoding and sensorimotor learning by regulating L1 NDNF inhibition in the motor cortex.

P2-D-445 *Oculomotor behaviour during free viewing of dynamic video in non-human primates: Translating to human clinical application*

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The visual system utilizes external visual stimuli, together with cortical and subcortical inputs that dynamically shape oculomotor behaviours such as saccades, blinks, and pupil responses. Dysfunction within these networks produces disease-specific abnormalities in psychiatric and neurodegenerative disorders. To better understand how these metrics may serve as biomarkers of brain dysfunction, we study non-human primates (NHPs), which share anatomical and functional homologies with the human visuo-oculomotor system. While saccade, blink, and pupil behaviours are well characterized in structured tasks, oculomotor behaviour during unstructured viewing remains poorly understood in NHPs. In this study, we quantitatively contrast NHP and human oculomotor behaviour under identical experimental conditions. NHPs freely viewed dynamic video clips on a computer screen while eye movements were recorded using an Eyelink 1000. NHPs viewed 10 minutes of videos daily, consisting of short clips (3-5 s) depicting naturalistic scenes, including animals, buildings, and people. Frequent clip changes caused visual perturbations that influenced ongoing saccade, pupil, and blink behaviour. We observed both similarities and differences between species. Saccade rates were comparable between humans and NHPs, blink durations were shorter in NHPs, and pupillary responses were highly similar across species. As eye tracking is increasingly used to diagnose disease, understanding the neural circuits underlying these behaviours is critical for linking abnormal oculomotor patterns to brain dysfunction.

P2-D-446 *Oculomotor dance learning task: Implications for audio-visual cued spatial learning*

Michael Petrovski [1]

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This study aims to address whether a sequence-based learning paradigm centered on the visual-motor system can feasibly be measured while listening to music. It aims to develop a new visual-motor-based learning paradigm with music, potentially promoting neuroplasticity and creating new interventional tools. Eye movements of 10 participants (8 female, 2 male) were tracked using the Eyelink 1000 Plus system during a 68-second eye-dance sequence. The experiment consisted of a learning phase, where participants observed the sequence five times with 30-second breaks, and a performance phase, where they performed the sequence five times from memory on a grey screen without visual cues. Data was analyzed using R4.3.1, MATLAB, and Experiment Builder: Data Viewer software. Results showed a significant improvement in performance accuracy between the first session (g1; M = 40%, SD = 7.2%) and the last session (g5; M = 69.7%, SD = 22.8%). A repeated-measures ANOVA revealed a significant main effect of session on performance accuracy, $F(4, 36) = 6.99$, $p < 0.001$, $\eta^2G = 0.26$, indicating that accuracy significantly improved over sessions. Post-hoc Bonferroni comparisons showed that accuracy in later sessions was significantly higher than earlier sessions, suggesting a defined learning curve and consolidation of performance pattern across repeated practice. These findings suggest that visual-motor-based interventions have the potential to enhance motor and non-motor symptoms like depression and anxiety for neurodegenerative diseases.

P2-D-447 *Opioids do not inhibit spinal oxygen sensors during hypoxia*

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BACKGROUND: The opioid crisis in Canada is characterized by 17 deaths per day. The main cause of death by opioids is respiratory depression: this includes hypoventilation, sustained apnea, and subsequent cardiorespiratory arrest. Canonically, opioids inhibit brainstem mechanisms of breathing resulting in a reduced drive to breath and inhibit central and peripheral chemoreceptors resulting in impaired hypoxic ventilatory responses. Recently, we discovered that spinal sympathetic preganglionic neurons are spinal oxygen sensors and increase sympathetic activity in response to hypoxia. Whether opioids inhibit oxygen sensing at the level of the spinal cord remains unknown. HYPOTHESIS: Opioids reduce spinal oxygen sensing. METHODS AND RESULTS: We recorded sympathetic nerve activity in a novel in situ artificially perfused spinal cord preparation from male rats (n = 6). Hypoxic challenges were applied before and after administration of DAMGO, a selective μ-opioid receptor agonist that does not cross the blood–brain barrier. Despite five of six preparations exhibited a reduction in hypoxic response magnitude following DAMGO administration, overall there was no significant difference. CONCLUSIONS: These findings indicate that activation of opioid receptors does not eliminate spinal oxygen sensing during hypoxia. Preservation of spinal hypoxic responses in the presence of opioids suggests that spinal oxygen sensors may contribute to residual cardiorespiratory reflexes during opioid exposure, highlighting a previously underappreciated site of opioid-resistant hypoxic signaling.

P2-D-448 *Opposite effects of CB2 receptor activation on visual cortical dynamics*

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The role of the cannabinoid receptor type 2 (CB2R) in cortical visual processing remains poorly characterized. We investigated the effects of bidirectional pharmacological modulation of CB2R on neuronal activity in the primary visual cortex (V1) of mice. Intracortical electrophysiological recordings were performed during the presentation of sinusoidal gratings with varying contrast and spatial frequency, as well as during spontaneous activity. The inverse agonist AM630 and the selective agonist HU308 were compared to a vehicle control condition. Blockade of CB2R with AM630 induced a significant decrease in spontaneous neuronal

activity, reduced contrast sensitivity at low spatial frequencies, and markedly decreased gamma-band oscillation power. In contrast, activation of CB2R with HU308 increased baseline neuronal excitability and enhanced gamma synchronization. These findings indicate that CB2R finely modulates cortical network dynamics and visual responses. Our results suggest that CB2R plays an active role in regulating excitation–inhibition balance in V1 and in controlling neuronal synchronization processes involved in sensory processing. Subvention: Réseau vision, NSERC,

P2-D-449 *Perineuronal nets in a vocal motor nucleus regulate vocal development*

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Communicative behaviors, including human speech and birdsong, are important for survival and reproduction and are learned during critical periods (CPs) in development. Therefore, understanding the neural mechanisms shaping the development and plasticity of communication is crucial. Perineuronal nets (PNNs) are extracellular matrices that surround neurons regulating plasticity, including neurons in sensorimotor circuits for vocal motor learning and performance in songbirds ("song system"), and are thought to limit plasticity. In the song system, PNN expression increases over development, and degrading PNNs in the vocal motor nucleus HVC of adult birds affects song performance. However, little is known about how manipulating PNNs earlier in development affects song development and learning. To this end, we bilaterally degraded PNNs in the HVC of juvenile male zebra finches and tested the hypothesis that degrading PNNs would (a) increase the rate or extent of natural song development and (b) enhance the ability of juveniles to learn new song elements. In our analysis of natural song development, we found that songs changed significantly more quickly following PNN degradation, though not necessarily towards the tutor's (father's) song. We are currently investigating the degree to which degrading PNN in the HVC of juvenile birds extends or re-opens CPs and allows for the learning and incorporation of new vocal elements. These data highlight a causal role of PNNs in motor circuitry in developmental vocal plasticity and support their potential role in CP regulation.

P2-D-450 *Pose-estimation reveals behavioral signatures of social recognition and neuromodulation in sensory circuitry*

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Recognizing others is essential for social functioning and relies on the ability to learn and discriminate sensory signals. An individual's vocalizations can communicate identity and elicit distinct familiarity-dependent behavioural responses. Previous behavioral assays of social recognition often rely on manual scoring with limited temporal and spatial resolution, whereas automated pose estimation offers greater scope and precision. Like humans, songbirds learn to identify one another through their vocalizations (songs) and exhibit different behavioral responses to familiar vs. novel songs. Across species, norepinephrine (NE)-synthesizing neurons in the locus coeruleus (LC) project to auditory regions and respond differently to familiar and novel stimuli. But the causal role of NE in auditory circuitry to auditory learning remains unclear. Here, we tested how NE contributes to social recognition in the zebra finch by ablating NE neurons projecting from the LC to auditory areas and using a machine learning (ML) pose estimation software (SLEAP) to measure behaviour. This approach enabled quantification of differential attention, movement, and spatial use in response to novel vs. familiar songs. We have yet to detect significant effects of NE ablation on behavioral indices of recognition. Our results underscore the power of ML-based quantification of social behavior and suggest that NE signaling in auditory areas may not play a critical role in social recognition.

P2-D-451 *Prefrontal and parietal local field potentials employ different visuospatial codes for reach: A complex-valued network classification approach*

Ashkan Karimi [1], Veronica Nacher Carda [2], Jennifer Lin [2], Brando Sheldrick [2], Hongying Wang [3], Saihong Sun [2], Xiaogang Yan [2], Julio Martinez-Trujillo [4], J Douglas Crawford [2]

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Understanding how cortical oscillations coordinate spatial memory and motor planning is a central challenge in systems neuroscience. We tested whether phase–amplitude dynamics in cortical local field potentials (LFPs) encode distributed versus region-specific signals for spatial memory and planning under varying visuospatial conditions. We developed a deep Complex-Valued Neural Network (CVNN; Benevenuto & Piazza, 1992; Georgiou & Koutsougeras, 1992) to decode landmark-dependent spatial states from LFPs recorded in the posterior ventrolateral prefrontal cortex (pVLPFC, 128 channels) and intraparietal sulcus (IPS, 32 channels) of a female rhesus monkey performing memory-guided reaching tasks in which visual landmarks were stable, shifted 8° in one of eight directions, or absent (Lin et al., SfN 2025; Sheldrick et al., SfN 2025). Preprocessed LFPs were transformed into complex-valued time series using the Hilbert transform to preserve phase and amplitude information. Separate CVNNs trained on IPS or pVLPFC signals classified the three landmark conditions with >90% training accuracy and ~51% validation accuracy, significantly above chance (33%). Validation revealed regional specialization: the IPS model performed best for no-landmark trials (82%), whereas the pVLPFC model showed superior performance for shifted-landmark trials (65%). Dual-stream models combining pVLPFC with different IPS recording sites confirmed these effects via region occlusion analysis: removing pVLPFC improved no-landmark classification, while removing IPS improved shifted-landmark classification, with IPS recording location modulating these effects. These findings suggest that IPS preferentially encodes egocentric spatial representations, whereas pVLPFC is more engaged during dynamic landmark conditions, with complementary but potentially competing spatial codes emerging during integration.

P2-D-452 *Protocadherin-gamma (Pcdh-γ) impacts axon-keratinocyte interactions – A coculture model approach*

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Keratinocytes are sensory transducers involved in activating and communicating with sensory nerve endings in the skin. Disruption of sensory neuron-keratinocyte interactions such as in neuropathies, is challenging to repair. The molecular determinants of a successful skin reinnervation have yet to be elucidated and we propose that protocadherin-gamma (Pcdh-γ) is a participant in sensory neuron regrowth or reinnervation. Pcdh-γ is expressed in both sensory neurons and keratinocytes, particularly in undifferentiated keratinocytes of the stratum basale. Pcdh-γ knockdown (KD) in vitro in dorsal root ganglion (DRG) neuron cultures led to increased neurite outgrowth and crossings. Pcdh-γ KD in vivo in footpads of NaV1.8-Cre; Ai9 mice resulted in increased intraeidermal nerve fiber density (IENFD) and rendered mechanical and thermal hyperalgesia. In control coculture settings of keratinocytes and DRG, neurons preferentially extended their neurites towards and contacted differentiated rather than undifferentiated keratinocytes. This preference, however, was attenuated in cocultures treated with Pcdh-γ siRNA. Pcdh-γ KD did not impact keratinocyte size or differentiation but there was greater clumping of keratinocytes in Pcdh-γ KD aasays. Keratinocytes also exhibited greater differentiation in the presence of neurons. Interestingly, some axon-keratinocyte contacts are labelled with synaptophysin, suggesting nascent synapses. Taken together, our findings identify important interactions between keratinocytes and sensory axons, influenced by Pcdh-γ. [Supported by NSERC, Diabetes Canada]

P2-D-453 *Pulvinar-inspired skip connectivity regulates gain and decision criterion in hierarchical vision networks*

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The pulvinar is thought to regulate cortico-cortical communication through transthalamic pathways, yet the computational consequences of such modulation remain unclear. Here we test a minimal pulvinar-inspired long-range skip pathway in a hierarchical convolutional vision model, designed as a learned projection from early to late feature maps coupled to a gain-controlled gating mechanism. We evaluated the architecture in two complementary experiments. First, in CIFAR-10 categorization, the pulvinar-augmented model did not primarily act as a uniform accuracy booster; instead, it reshaped contrast-dependent response scaling and stabilized internal representations in a way consistent with gain control. Second, in a near-threshold contrast-detection paradigm with noisy backgrounds, pulvinar-like modulation systematically redistributed detection outcomes, consistent with a change in decision criterion under uncertainty, and in specific regimes supported improved discriminability. Together, these results indicate that pulvinar-inspired connectivity contributes most reliably to gain/criterion control. Thus, we suggest that the pulvinar regulates how evidence is converted into decisions, rather than to raw task accuracy." Supp: CIHR, NSERC, and RRSV

E - HOMEOSTATIC AND NEUROENDOCRINE SYSTEMS

P2-E-454 *Endothelial calcium signalling regulates capillary blood flow dynamics and vessel tone in the cerebral microvasculature*

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The brain requires constant adaptation of blood supply to fuel active neurons, but little is known about how vessel width and cerebral blood flow (CBF) are regulated in the capillary bed where smooth muscle coverage is minimal. Endothelial calcium (Ca2+) signalling is a key regulator of vascular tone, yet its in vivo role in controlling cerebral microvascular function remains incompletely understood. Using in vivo two-photon microscopy in transgenic mice expressing GCaMP8m selectively in cerebral endothelial cells, we assessed the effects of acutely elevating Ca2+ through DREADD-mediated activation. Activation of hM3Dq receptors with deschloroclozapine (DCZ) resulted in a robust and sustained elevation in endothelial Ca2+ levels compared to saline, as quantified by the peak amplitude, half-width, and area under the curve (AUC) of ΔF0/F0 signals. Importantly, EC Ca2+ activation enhances cortical perfusion, as evidenced by sustained increases in cerebral blood flow, and triggers widespread and prolonged vessel dilation. Finally, distinct temporal relationships emerge between Ca2+ dynamics and vessel behavior, where spontaneous Ca2+ events coincide with, but do not drive, diameter changes, whereas DCZ-induced Ca2+ elevations likely initiate vessel dilation. Together, these results establish endothelial Ca2+ as a rapid and powerful modulator of cerebrovascular function.

P2-E-455 *Fructose-mediated glutamatergic but not GABAergic maladaptations at NPY/AgRP neurons*

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Fructose is abundant in ultra-processed foods, and excessive fructose intake increases obesity risk. Indeed, fructose-fed mice eat more and gain more body fat than chow-fed mice. We recently showed that orexigenic Neuropeptide Y/agouti-related peptide (NPY/AgRP) neurons, which are powerful drivers of feeding, are vulnerable to dietary fructose. Fructose did not activate NPY/AgRP cells, but it acutely and persistently increased excitatory input onto NPY/AgRP cells. However, it is not known if fructose feeding also impacts inhibitory inputs to NPY/AgRP cells. Ex vivo patch-clamp recordings revealed no differences in the frequency or amplitude of inhibitory events arriving at NPY-hrGFP neurons in male or female chow- and

fructose-fed mice. Prolonged fructose feeding also did not alter GABAergic input to NPY/AgRP neurons, thus unlike glutamatergic maladaptations, GABAergic input remained resilient to fructose. To retrogradely label afferent input to NPY/AgRP neurons, we used Cre-dependent pseudorabies tracing from AgRP-cre chow- and fructose-fed mice. We found AgRP-projecting cells in the ventral part of the lateral septal nucleus; posterior part of bed nucleus of the stria terminalis; preoptic, paraventricular, dorsomedial, supraoptic, and retrochiasmatic hypothalamic nuclei; and ventral subiculum. Our ongoing work will determine if the aforementioned cells are glutamatergic, fructose-sensitive, and/or more abundant in fructose-fed mice. Together, this work will isolate neurons specifically vulnerable to fructose feeding and reveal novel targets to address diet-induced obesity.

P2-E-456 *Functional and morphological adaptations of hypothalamic tanycytes to caloric restriction*

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Hypothalamic tanycytes are glial cells that line the third ventricle and regulate the metabolic effects of hormones. Their regulatory activity is aided by unipolar projections and a barrier formation that adapts to changes in energy balance. Ghrelin is an orexigenic hormone that acts on the hypothalamus. Here we examined the possibility that ghrelin targets tanycytes by visualizing tanycytic ghrelin receptor (Ghsr) mRNA expression in mice exposed to caloric restriction (CR) in association with changes in their projection morphology. We subjected male and female mice to a 20% CR for either 3, 7, or 14 days. CR mice received daily chow allocations at 80% of their average daily food intake. We visualized Ghsr expression using in situ hybridization and used anti-vimentin labelling to visualize tanycytes. Confocal microscopy was used to determine tanycytic Ghsr expression. Tanycyte projection morphology was assessed using Neurolucida software (MBF Bioscience LLC, Williston, VT, USA). Analyses demonstrate that Ghsr is expressed in some, but not all tanycytes, and that CR may modulate the quantity of Ghsr expression. Tanycytic projection length differs depending on both sex and CR. Ventral tanycytes were longer in males, and CR caused a shortening of projections from dorsal tanycytes. Variation in these relationships may be partially explained by the degree of CR-induced weight loss. We hypothesize that tanycytes adapt to CR both through alteration of Ghsr expression and through dynamic projection morphologies, and that these may affect tanycytic regulation of hypothalamic activity.

P2-E-457 *Gustatory influences on the metabolic fate of sugar: When taste tricks the body*

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Sweetness provides an early prediction of a food's caloric value, initiating preparatory metabolic responses before nutrients are absorbed. This prediction is later evaluated against slower post-ingestive feedback, allowing expectations to be updated through learning (Dayan, 2022). In modern diets, sweetness is often decoupled from calories. Prior work has shown that diet-induced thermogenesis (DIT), the rise in energy expenditure after eating, is blunted when sweetness and calories are mismatched (Veldhuizen et al., 2017). Here, we aimed to (1) replicate this effect and (2) test whether DIT is recovered after repeated exposure to mismatched drinks. Ten participants underwent 7 sessions over 3 weeks in which they repeatedly consumed isocaloric drinks that were made (1) too sweet S+, (2) not sweet enough S-, or (3) matched for sweetness, using sucralose for sweetness and maltodextrin for calories. DIT was measured at baseline and again after participants consumed three additional bottles at home over three days. Insulin, glucose, liking and wanting were also assessed. As predicted, DIT showed a robust drink × session interaction. Specifically, DIT increased for the S-, decreased for the S+, and remained unchanged for the matched drink. DIT changes were not driven by shifts in liking, wanting, insulin or glucose. These findings (1) replicate prior work showing that sweet taste perception influences DIT to regulate the metabolic fate of sugars and (2) demonstrate gut-brain learning by showing changes in DIT to the same "mismatched" flavour following repeated exposure.

P2-E-458 *How ghrelin and its actions on the GHSR interact with chronic social stress effects in female mice*

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Social stress is a primary risk factor for depression and anxiety, disproportionately within females. Traditional social stress models primarily use male subjects; however, the novel Chronic Nondiscriminatory Social Defeat (NDSD) paradigm induces comparable stress effects in both sexes. This study investigated the metabolic impacts of chronic NDSD on female wild-type and ghrelin receptor (GHSR) knockout mice. Additionally, we assessed WT mice receiving a central GHSR antagonist, JMV2959. The 21-day NDSD paradigm involved daily 10-min exposures to an aggressive CD-1 mouse. JMV2959 was administered via a mini-pump and ICV cannula implanted seven days before stress. To evaluate palatable food preference, mice had limited daytime access to a high-fat diet (HFD). Stress significantly interfered with normal weight gain. By completion of the study, WT, saline and JMV controls increased their bodyweight over time, whereas KO controls remained stable, typical for these genotypes. Conversely, WT, saline, and JMV stressed mice showed a stunted increase in weight, while KO stressed mice lost weight during the paradigm. In terms of food intake, stressed animals across all groups consumed more HFD than controls, though KOs generally ate less HFD than WTs. Over the stress period, stressed females in all groups increased their HFD intake, whereas the intake of control groups remained consistent. In terms of energy, WT-stressed animals maintained a stable caloric intake, but KO-stressed animals increased their total calories. For our antagonists, all stressed females maintained a higher caloric intake than the control females throughout the stress period. This data highlights a differential response to social stressors, particularly in GHSR KO females, suggesting GHSR function plays a critical role in modulating metabolic outcomes under stress.

P2-E-459 Hypothalamic satiety neurons are inhibited by α2-adrenoceptor activation through direct and indirect mechanisms

Olivier Lavoie [1], Audrey Turmel [2], Axelle Khouma [2], Moein Minbashi Moeini [2], Chen Liu [3], Natalie J. Michael [4], Alexandre Caron [4]

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Hypothalamic proopiomelanocortin (POMC) neurons are key regulators of satiety and energy balance and thus represent a major target for anti-obesity drugs and metabolic hormones. Norepinephrine (NE) has been proposed to inhibit POMC neurons via α2a-adrenoceptors (ADRA2A), yet the mechanisms and physiological relevance of this pathway remain unclear. Whole-cell patch clamp electrophysiology was used to assess the effects of NE and the selective ADRA2 agonist UK 14,304 (UK) on hypothalamic POMC neurons electrical activity. Both NE and UK robustly inhibited POMC neurons, inducing hyperpolarization, reduced firing rate, and decreased input resistance. This inhibition involved activation of multiple potassium conductances and included direct and indirect components. To evaluate in vivo relevance, we generated an inducible POMC-specific Adra2a knockout mice (POMCKOA2A). Loss of Adra2a in POMC neurons had no effect on energy balance but resulted in a modest impairment in glucose tolerance in males. In POMCKOA2A::tdTomato mice, UK-induced inhibition was abolished in approximately half of POMC neurons, supporting the involvement of direct and indirect effects. Together, these findings show that ADRA2 activation robustly inhibits hypothalamic POMC neurons through direct, potassium-channel dependent, and indirect mechanisms. However, Adra2a expression in POMC neurons is largely dispensable for the regulation of energy balance in vivo, suggesting that noradrenergic control of satiety circuits involves additional cellular targets or network-level pathways beyond POMC neurons themselves.

P2-E-460 *Investigating the role of endothelial calcium transients in cerebral capillary stall recanalization*

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The brain's high metabolic demand is supported by dense capillary beds, yet 1-2% of capillaries are stalled at any given time with this percentage increasing during disease states. Prior in-vivo work has identified endothelial calcium transients which occur during spontaneous stall recanalization in healthy mice. Utilizing two-photon microscopy we can characterize cerebral endothelial calcium activity during periods of active blood flow and during spontaneous stalling/recanalization. Chronic cranial window implantation on adult mice that express Cre-dependent fluorescence reporter GCaMP8m along with plasma dye allow for real time observations. Following surgical recovery, mice are imaged once weekly for eight weeks with imaging occuring in the right hemisphere in watershed regions between the middle cerebral artery and draining venules. Preliminary findings indicate that endothelial calcium transients which occur during an active capillary stall/recanalization process express distinct characteristics compared to spontaneous calcium events recorded in flowing vessels. Futhermore, capillaries that experience longer lived stalls express distinct endothelial calcium transients. Future experiments are focused on studying calcium activity in frequently stalled capillaries and if stalled leukocytes activate distinct calcium transients. Increasing our understanding of the stalling-recanalization process and endothelial calcium transients will hopefully yield new insights for future research.

P2-E-461 *Mechanisms underlying estrogens' rapid facilitative effects on social recognition in the medial amygdala of female mice*

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Social recognition (SR), the ability to remember and distinguish conspecifics, allows for social behaviours to be modulated appropriately. Estrogens are well-established to affect SR through rapid, non-genomic mechanisms. In ovariectomized (OVX) female mice, intra-medial amygdala and intrahippocampal administration of 17β-estradiol (E2) rapidly facilitates short-term SR memory. While previous research has shown that this estrogenic effect in the dorsal hippocampus requires the activation of the extracellular signal-regulated kinase (ERK) pathway, whether this same cell signalling cascade is necessary in the medial amygdala (MeA) remains unknown. Thus, this study investigated whether the rapid facilitation of short-term SR memory by E2 in the MeA is also dependent upon ERK pathway activity. First, it was determined that 1.0μg/side of the MEK inhibitor U0126 blocked SR, suggesting that ERK pathway activity in the MeA is required for normal SR memory. Next, we assessed whether ERK pathway inhibition in the MeA would impair the rapid facilitation of SR by E2. This was tested by infusing the sub-effective dose of U0126, 0.5 ug/side, which was found not to block SR in the first experiment, followed by a dose of E2 previously found to facilitate SR in the MeA (10nM). Results indicate that the group that received the U0126/E2 infusions did not demonstrate SR, suggesting that ERK pathway inhibition in the MeA blocks the rapid facilitation of short-term SR memory by E2. Our study elucidates the cellular processes that modulate estrogens' non-genomic modulation of social cognition in females by identifying one of the intracellular pathways through which 17β-estradiol rapidly affects social recognition memory.

P2-E-462 *Vesicular transporters VNUT and VMAT1 anti-colocalize in ATP and norepinephrine 'co-releasing' PC12 cells*

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Purinergic and noradrenergic co-transmission provides modulation of neurotransmission by sympathetic nerves in tissues like blood vessels, but the underlying mechanisms of differential release are not defined. The vesicular nucleotide transporter (VNUT) and the vesicular monoamine transporter 1 (VMAT1) load

vesicles with adenosine triphosphate (ATP) and norepinephrine (NE) and identifying the vesicles that they traffic to is key to understanding differential co-transmission. ATP and NE are described as being "co-released" from the same vesicles in cells like PC12 pheochromocytoma cells, but diverse reports claim that VNUT localizes to compartments ranging from small synaptic vesicles to lysosomes. Notably, VNUT and VMAT1 relative localization has not been shown in PC12 cells. We studied VNUT and VMAT1/2 localization by immunofluorescence in adherent and non-adherent PC12 cells on collagen-I-coated coverslips, differentiated with nerve growth factor. In both PC12 lines, visual analysis showed VNUT to anti-colocalize with Synaptotagmin1 and VMAT1, while VMAT2 was not highly expressed. The majority of VNUT immunoreactivity localized to a reticular network, with a small fraction of peripheral puncta that might represent vesicular localization. Both Pearson correlation and puncta-based analyses confirmed minimal VNUT/VMAT1 colocalization. PC12 cells do not endogenously express VMAT2. These findings suggest that either VNUT loads ATP into vesicles that are distinct from VMAT1 and NE-containing vesicles, or that VNUT loads ATP into vesicle precursors that are yet to acquire VMAT1.

F - COGNITION, EMOTION AND MOTIVATION

P2-F-463 *Effect of number of training trials on olfactory learning and memory in a pavlovian conditioned odour preference task*

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Effect of Number of Training Trials on Olfactory Learning and Memory in a Pavlovian Conditioned Odour Preference TaskMohammed Ali Ahmed1 and Richard E. Brown11Department of Psychology and Neuroscience, Dalhousie University,Halifax, Nova Scotia, Canada B3H 4R2We have been developing a one-day training paradigm to assess conditioned odour preference and memory strength in mice (Mus musculus) (Brown et al., 2023, Chemical Signals in Vertebrates 15, 39–53). Using male and female Nrxn1 +/- and C57BL/6J Nrxn1 +/+ wild-type mice aged 2–4 months, we examined the effects of genotype and number of training trials (8 vs. 16) on memory strength; data were pooled across sex. The experiment was conducted in five phases: training, 24-hour memory test, 14-day memory test, extinction trials, and a spontaneous recovery test. Our hypotheses were that the Nrxn1 +/+ mice would show greater memory strength than Nrxn1 +/- mice, and that mice given 16 training trials would show greater memory strength than mice given 8 training trials. The data show a significant effect of both genotype and number of training trials, but there were significant individual differences. To analyse the individual differences, we correlated the behaviour of mice during the training trials with the scores on the memory tests. It is notable that many mice showed memory in the spontaneous recovery test 25 days after training and after five explicit extinction trials.

P2-F-464 *Enhancement of cocaine-primed reinstatement by 17ß-estradiol in ovariectomized rats is concomitant with increased activation mesolimbic brain regions*

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Background: Administration of the steroid hormone 17β-estradiol (E2) increases relapse-like behaviours in ovariectomized (OVX) female rats. An understanding of the mechanisms of this effect may permit enhancement of the efficacy of pharmacotherapies for cocaine use disorder (CUD). Methods: Female rats (N=22) were OVX, implanted with indwelling jugular catheters, and trained to self-administer cocaine intravenously on a fixed-ratio 1 schedule over 24 daily, 2h-long sessions. Cocaine was then replaced with saline, and cocaine seeking was extinguished over 22 daily sessions. Following extinction, rats were treated with systemic E2 (n=10) or vehicle (n=12) 22h and 1h before a 90-min reinstatement session under extinction conditions. Reinstatement was primed by 10mg/kg cocaine. Following reinstatement assessment, rats were perfused and the immediate early gene protein product c-Fos was quantified as a marker of neuronal activation in the cortico-striatal circuitry underlying reinstatement using immunohistochemistry. Results:

E2 replacement increased cocaine-primed reinstatement and c-Fos+ cell counts in the stria terminalis, habenula, ventral tegmental area, and nucleus accumbens shell. Functional connectivity between the ventral tegmental area and nucleus accumbens core was also enhanced by E2. Conclusions: E2 may increase relapse risk by activating mesolimbic circuitry. The effect of this hormone on the efficacy of CUD pharmacotherapies targeting this system should be considered in the development of CUD treatment strategies.

P2-F-465 *Examining network gain dynamics in the subiculum during reorientation*

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Efficient navigation depends on neural circuits that not only encode directional and spatial information, but can also rapidly reorient when cues change or conflict. The Subiculum, primary output region of the hippocampal formation, integrates directional signals from the Anterodorsal Thalamic Nuclei (ADN)–Postsubiculum pathway with spatial inputs from the hippocampus. Subiculum neurons form generalized, reference-map-like representations that support stable orientation across environments; however, how these representations respond to reorienting stimuli remains an open question. To investigate this, we recorded calcium activity from large populations of Subiculum neurons in mice using a UCLA miniscope, while animals explored an augmented-reality behavioural environment with controlled rotations of a salient visual cue that induces reorientation in the head direction (HD) system. These reorientation events correlated with fluctuations in overall population activity, which we refer to as Network Gain. We found that Subiculum population activity was strongly aligned to the head direction signal during reorientation events, and exhibited network gain dynamics similar to those observed in HD cells within the ADN. Together, these findings identify a network mechanism by which population-level gain dynamics modulate spatial memory encoding. Disruption of these dynamics may compromise the stability of directional information required for spatial memory, potentially leading to navigation-related memory deficits.

P2-F-466 *Examining the contribution of serotonin dynamics within the mesolimbic dopamine system to motivation*

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Serotonin (5-HT) plays a critical role in motivated behaviour, potentially through its ability to influence mesolimbic dopamine (DA) system function. Prior studies have examined this interaction using manipulations of 5-HT function, but 5-HT system dynamics that coordinate behaviour are unknown. To address this gap, we investigated real-time 5-HT activity within the nucleus accumbens (NAc) during motivated behaviour. In vivo fiber photometry, combined with operant responding for water in mice, was used to monitor NAc 5-HT release. Mice received stereotaxic surgery to implant a 5-HT sensor in the NAc and were trained to lever press for water. Operant behaviour was then tested under escalating reinforcement schedules. 5-HT signals were normalized, aligned to lever pressing and reward delivery, and analyzed for peri-event changes in activity using an area under the curve approach. Across reinforcement schedules, we observed a consistent pattern of serotonergic activity – an initial spike in 5-HT release at the time of lever pressing, followed by a reduction during reward consumption, and a rebound in activity upon completion of reward consumption. Notably, the amplitude of 5-HT modulation during the reward phase scaled with reinforcement uncertainty. These findings suggest that 5-HT signaling in the mesolimbic DA system is tightly coupled to motivated behaviour, particularly reward acquisition. Ongoing studies will further refine causal contributions of serotonin to motivational control, advancing our understanding of neuromodulatory regulation of goal-directed behaviour.

P2-F-467 *Experience-dependent specialization of VIP interneurons and CA1 circuit dynamics during contextual memory*

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Associating complex contexts with salient outcomes requires the hippocampus to integrate multisensory inputs and engage excitatory-inhibitory circuits to support memory encoding and recall. In CA1 hippocampus, such learning emerges from interactions between excitatory neurons and inhibitory microcircuits, yet the contribution of disinhibitory circuit motifs remains poorly defined. Vasoactive intestinal polypeptide-expressing interneurons (VIP-INs) are predominantly disinhibitory neurons that regulate local inhibition and hippocampal network flexibility during goal-directed spatial learning and novelty detection, but their role in contextual memory is unclear. Here, we examined CA1 VIP-IN activity in freely moving mice during contextual fear conditioning and recall using population and single-cell calcium imaging. During conditioning, VIP-INs were recruited by aversive cues, with responses progressively increasing across trials. Single-cell analyses revealed diverse shock-evoked responses, characterized by gradual recruitment of a majority of VIP-INs. During recall, VIP-INs showed heterogeneous engagement, with multiple functional subpopulations displaying distinct response profiles. In parallel recordings, CA1 pyramidal neuron activity closely tracked VIP-IN dynamics, whereas somatostatin interneurons exhibited weak and delayed recruitment. Together, these findings demonstrate that salient experience drives experience-dependent specialization of VIP interneurons, enabling dynamic disinhibitory control of CA1 circuits during the formation and recall of contextual associations.

P2-F-468 *Exploration drives reward-dependent long-term memory*

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In dynamic environments, we make decisions by balancing two latent states: exploiting options that maximize reward and exploring alternatives in order to learn about their value. Exploration is distinguished by an increase in reinforcement learning: the influence of rewards on future choices is enhanced during exploration (Ebitz et al, 2018). However, it remains unclear whether this happens because exploration generally improves memory encoding or specifically increases reward-dependent processing. To test these hypotheses, human participants (n=191) completed an uncertain decision-making task in which reward outcomes were paired with unique images from the Bank of Standardized Stimuli. A surprise recognition task was then used to assess how decision-making factors influenced image encoding. Consistent with prior reports, we found that reward-paired stimuli were better encoded than non-reward-paired stimuli (Miendlarzewska et al, 2016). However, images presented during exploration were no more likely to be recognized than other images, suggesting that exploration does not generally enhance encoding. Instead, we found that the increased recognition observed on rewarded trials was mostly driven by exploratory trials. Intriguingly, switches between states were linked to better recognition memory, independently of both state and reward, suggesting that state switching enhances mnemonic encoding while exploration enhances reward processing. Together these results point to a new role for latent decision-making states in shaping how we encode information into long-term memory.

P2-F-469 *Exploring Sec5/EXOC2 as a conserved regulator of sociability*

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An animal's sociability is its tendency to affiliate with conspecifics. Despite the importance of sociability for many animals, we have little understanding of its neurobiological mechanisms. While screening for sociability genes using Drosophila, we identified Sec5 as contributor to sociability (Torabi-Morashi et al., 2025, Evolution). However, it remains unclear whether the mammalian ortholog of Sec5: EXOC2, similarly impacts sociability. Sec5/EXOC2 codes for a subunit of the exocyst complex, which is involved in exocytosis

and neural function. Mutations of other exocyst subunits are associated with autism spectrum disorder in humans, which feature social difficulties as a core symptom. To experimentally determine the role of EXOC2 in mammalian sociability, we generated neuron-specific Exoc2 knockout mice using Cre-conditional gene deletion (Syn1-Cre). We found that knocking out both copies of Exoc2 in neurons (Exoc2loxp/loxp;Syn1Cre/+) was lethal–such mice perished before postnatal day 16 due to seizures (n=17/17 pups,11 litters). In contrast, knocking out only one copy of Exoc2 (Exoc2loxp/+;Syn1Cre/+) in neurons was non-lethal (n=20/20 pups,10 litters); however, it failed to reduce Exoc2 expression (RNA-scope; nKO=111 cells,3 mice; nWT=70 cells,3 mice; p=0.88). As a new strategy to generate viable mice with reduced Exoc2 expression, we are inducing Cre-conditional deletion of neuronal Exoc2 using retro-orbitally injected AAV.PHP.eB-hSyn-Cre. If successful, we will test the effect of reduced Exoc2 expression on mouse sociability using social behaviour assays.

P2-F-470 *Exploring sex differences in inhibition of prefrontal cortical dopamine during a novel context threat discrimination task*

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Identifying an environment as threatening or safe is essential for survival and depends on integrating past experiences with the present situation to guide context-appropriate behavior. Individuals with post-traumatic stress disorder (PTSD) often generalize their fear to safe environments. Importantly, PTSD is 2-3 times more prevalent in women, which suggests a sex difference in context processing. Yet, the neural mechanisms underlying these sex differences are not fully characterized. Dopamine signaling in the medial prefrontal cortex (mPFC) may mediate sex differences in context-guided behavior because mesocortical dopamine guides adaptive actions and mPFC estrogens affect dopamine release. To characterize the role of the mPFC during context threat, we used an apparatus to “teleport” mice between neutral and threatening contexts to assess fear discrimination. In TH-cre mice we expressed a cre-dependent inhibitory opsin in the ventral tegmental area (VTA) and placed optic fibers above the mPFC. We then inhibited this dopaminergic VTA-mPFC pathway during our context discrimination task and measured the immediate and prolonged effects of inhibition on discrimination ability. We found that VTA-mPFC inhibition impaired context discrimination more in females than males both immediately and 24 hours later. These results suggest a sex difference of optimal dopamine signaling to perform context discrimination. Chemogenetic studies are underway to further assess if more robust inhibition of VTA-mPFC dopamine can disrupt context fear discrimination in males. Together our findings indicate that medial prefrontal dopamine signaling may be a useful target for therapeutic interventions in people with PTSD, but there are sex-dependent factors to consider.

P2-F-471 *Flavour-nutrient and flavour caffeine conditioning*

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Many sugar-sweetened beverages contain caffeine, a stimulant that promotes dependence and higher beverage intake. Despite frequent co-consumption, how sugar and caffeine jointly strengthen learned flavour preferences remains unclear. This study investigates how sugar and caffeine, alone and in combination, shape flavour preferences through metabolic measures and fMRI. In this within-subject flavour–nutrient conditioning paradigm, participants (pilot N=10; full N=35) complete four beverage conditions: 1) non-caloric sweetener (control), 2) caloric sugar (maltodextrin), 3) non-caloric sweetener+caffeine, and 4) caloric sugar+caffeine. Each beverage is paired with a novel flavour and consumed once in-lab and four times at home. In-lab, indirect calorimetry measures and venous blood are collected pre/post-consumption to quantify energy expenditure (REE), substrate oxidation (RQ), and circulating glucose, alongside pre-conditioning flavour liking. Preliminary observations show a shift toward carbohydrate oxidation after consumption of caloric sugar, with and without caffeine, alongside increased blood glucose. Interestingly, REE increased across all conditions, with the smallest increase in control. Post-conditioning, liking increased for flavours paired with caloric sugar alone and with caffeine. Together, these early patterns are consistent

with caloric-driven metabolic shifts linked to increased flavour preference. fMRI analyses at pilot completion will test whether metabolic responses relate to conditioned liking and neural responses in reward- and nutrient-related regions.

P2-F-472 *From hardware to science communication: How Yutu became a virtual influencer*

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The recent advances in technology have been triggering the coexistence of non-human agents with human beings. This is particularly salient in cyberspace, where the emergence of virtual influencers is reconfiguring the way messages are conveyed. Interestingly, China's cyberspace has witnessed an early avatar of an artificial-agent influencer under the form of Yutu, the official Weibo persona of the Chang'e-3 mission's rover. This study explores the mechanisms that crafted Yutu's online persona, supporting its potential as a communication agent. Representationally, the Yutu Weibo account rearticulated cultural references to build a recognizably non-human persona by using a first-person interactive register and selective human cues, effectively placing it at an optimal position on the uncanny valley continuum. Interactionally, updates and exchanges cultivated attention and fostered parasocial attachment, mobilizing online users into an interactive and participatory community. Operationalizing these cognitive resources and despite its obvious artificiality, Yutu, as a personified agent, was deployed as a public diplomacy tool aligning with a soft-power strategy to translate technical milestones into accessible stories while promoting science to large audiences. In conclusion, Yutu, engineered as a virtual influencer, was successfully perceived as an effective communication partner, therefore representing an interesting model to study the new forms of computer-mediated human-machine communication enabled by the democratization of technology.

P2-F-473 *From prediction to action: Habenular control of ventral tegmental area circuits in defensive behaviors*

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The lateral habenula (LHb) sends aversive signals to the ventral tegmental area (VTA), yet how thispathway shapes learning and behavior is unclear. Combining retrograde and anterograde viral strategiesin transgenic mice, we recorded calcium activity from VTA-projecting LHb neurons and dopaminergic andGABAergic VTA neurons during behaviors. In an active avoidance task, three populations responded toshocks and predictive cues; however, their dynamics diverged across learning and around movement,indicating distinct coupling to prediction versus action. In the tail-suspension test, LHb activity increasedat movement onset, and silencing LHb→VTA transmission impaired avoidance learning, slowed escape,and reduced active coping vigor without affecting baseline locomotion. Thus, LHb→VTA projectionsprovide aversive-predicting signals needed for avoidance learning and persistent active coping.

P2-F-474 *Fronto-parietal activation supports narrative reintegration following distraction during movie-watching*

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Our brain naturally segments continuous experience into discrete events, leading to major shifts in activity across networks and changes in memory and attention. However, it is unclear how continuous experiential features constrain the changes in neural patterns at and across event boundaries. Movie-watching provides a powerful naturalistic paradigm for quantifying how cognition and brain activity change across time, place or narrative. Here, we combined three sources of data across eight films to examine how experiential reports and brain activity shift at event boundaries. First, we used multi-dimensional experience sampling (mDES) to quantify prevailing thought patterns across the films. Second, in an independent sample, we established

the moments that marked event boundaries in each film. Last, we used an open dataset where brain data was collected while participants viewed the same films. To further characterize stimulus-driven changes at event transitions, we quantified semantic, auditory, and visual features using embeddings from pre-trained neural network models. Our findings indicate that periods with fewer event transitions were associated with intrusive and distracting thoughts. Critically, this effect was attenuated when the fronto-parietal network was more active, indicating a compensatory neural mechanism that facilitates narrative reintegration following distraction. These findings highlight the value of combining mDES with neuroimaging to understand how the brain navigates state transitions during continuous, naturalistic experience.

P2-F-475 *Functional heterogeneity of hippocampal CA1 VIP interneurons in novelty-driven memory processing*

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Vasoactive intestinal polypeptide-expressing interneurons (VIP-INs) in the hippocampal CA1 coordinate mnemonic processing by mediating circuit disinhibition. To examine the subtype-specific roles of CA1 VIP-INs in novelty processing, we used single-cell imaging in freely behaving mice. Most VIP-INs were strongly activated by initial exposure to a novel environment, which diminished with familiarization, suggesting that these cells are specifically driven by novelty. Notably, the novelty-responsive VIP-INs were also highly active when mice re-entered the previously explored context, suggesting a parallel involvement of these neurons in both novelty encoding and memory recall. Distinct VIP-IN subtypes were identified based on their modulation by locomotion speed. The majority (72%) of VIP-INs showed increasing activity with higher running speed, consistent with calretinin-expressing VIP cells, whereas a smaller subgroup was suppressed during locomotion, a profile consistent with cholecystokinin-expressing basket cells and long-range projecting VIP-INs. Importantly, most novelty-responsive cells belonged to the speed-excited population. Finally, to examine how VIP-INs encode environments of different complexities, mice were exposed to a series of novel contexts with increasing memory load. We observed a trend whereby a greater fraction of VIP-INs exhibited lower activity as memory load increased. Our findings reveal a pronounced functional heterogeneity among CA1 VIP-INs, highlighting their distinct contributions to novelty detection as well as to memory encoding and recall.

P2-F-476 *Given the choice: Individual differences in concurrent intravenous cocaine and fentanyl self-administration in male and female rats*

Adiia Stone [1], Davin Peart [1], Jessica Karlovcec [1], Ana Barco [1], Anita Sikic [1], Ella Claridge [1], Rita El Azali [1], Karim Abouelnaga [1], Scott Barrett [2], Jennifer Murray [1]

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Introduction: Commonly known as ‘speedballing’, cocaine (COC) and fentanyl (FENT) polydrug use is a public health crisis contributing to high rates of overdose deaths. ‘Speedballing’ reports enhanced euphoric effects, aligning with a synergistic increase in extracellular dopamine seen in rats self-administering opioid-stimulant cocktails. Human patterns and motivations in polydrug use revealed two distinct temporal patterns: simultaneous, referring to the combination of two or more drugs in one event or sequential, referring to the consumption of one drug after the peak effect of another. Rats also express individuality in drug preference under concurrent intravenous (IV) access to stimulants and opioids that influence relapse behaviours; however, whether rats show similar temporal patterns of FENT and COC intake and associated relapse-related behaviours post forced abstinence (ABS) is still unknown. Methods: Male and female rats underwent dual jugular vein catheterization before acquiring concurrent IV self-administration of COC (0.5mg/kg/infusion) and FENT (2.5 µg/kg/infusion). After forced ABS periods, rats underwent various relapse tests (cued, uncued, and drug-primed). Results: Preliminary results indicate three distinct populations of polydrug intake that continue through ABS into relapse, in addition to drug-specific temporal intake patterns, similar to humans. Implications: Individual preferences in stimulant versus opioid availability will help to uncover neural mechanisms driving such preferences, providing invaluable insight into polydrug use

in human populations

P2-F-477 *Granularity in configural learning of abstract 2D space*

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Background: In this study, we aim to understand how animals integrate an abstract 2D auditory space. Specifically, we will look at whether rats are able to learn an integral representation of an abstract 2D auditory cognitive map, and if they are able to divide the cuemap into district predictive states. Prior work in our lab has established that with two reward zones, rats segment the space into four configural states. Objective: In this study, we will test the granularity of the configural learning the rats are exhibiting. Can rats form a higher-resolution cognitive map when the task demands the creation of more internal states?Methods: We trained 24 Long-Evans rats in a Pavlovian task. The rats were exposed to a 12x12 auditory space grid, where transitions between stimuli are limited to adjacent transitions on the grid, mimicking physical space. Three stimuli were rewarded, and learning was measured via conditioned response to the cues predictive of the reward versus non-reward. Results: Rats successfully acquired the task, and their behaviour revealed they divided the cuemap into nine distinct configural states: three that corresponded to the reward zones, and six that corresponded to the complementary non-rewarded zones. This is a more complex segmentation than what prior work has shown. Conclusion: This confirms our hypothesis that rats can perform integral learning of an abstract 2D space, and that they can adjust granularity of their internal model based on the structure of reward.

P2-F-478 *Humanized mice learn by seeking information*

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Learning can arise through different behavioral strategies, from conservative trial-and-error to active, exploratory behaviors that favor information accumulation. We show that the human-specific gene SLIT-ROBO Rho GTPase activating protein 2C (SRGAP2C) modifies the learning strategy in mice performing a sensory detection task. SRGAP2C emerged from partial duplications of the ancestral gene SRGAP2A, which regulates synaptic development. In mouse cortical pyramidal neurons, SRGAP2C induces human-like features likely associated with altered synaptic plasticity thresholds (i.e. delayed dendritic spine maturation). To investigate SRGAP2C's role in learning, mice were trained to lick a water port to obtain a reward when a whisker stimulus was present and to withhold licking in its absence. We observed strikingly different learning strategies in SRGAP2C and control mice early in training. SRGAP2C mice displayed an enhanced drive to lick, an approach that accelerates the learning of stimulus-reward associations at the cost of more punishment timeouts. We show that SRGAP2C mice are able to gather more task information in the first sessions and exhibit higher mutual information later in training. These results reveal that SRGAP2C drives a shift in behavioral strategy, favoring information accumulation over punishment avoidance, leading to an improvement in use of perception to guide action. This suggests that evolutionary changes in synaptic development induced by human-specific gene duplications may have contributed to distinct features of human learning and decision-making.

P2-F-479 *Impacts of chronic stress on cortico-accumbal and cortico-tegmental activity in goal-directed behaviours and motivation*

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Despite being the leading cause of disability worldwide, depression remains poorly understood. Prolonged exposure to stress is the main risk factor underlying anxiodepressive-like states in both humans and mouse models. The medial prefrontal cortex (mPFC) is a central hub region in chronic stress responses. A cortically-driven dysregulation of subcortical circuits, such as the cortico-accumbal (mPFC-NAc) and -tegmental

pathways (mPFC-VTA), has been associated with anxiodepressive-like behaviours in males and females. Chronic stress induces motivational dysregulations which often emerge prior to and persist beyond recovery of emotional disturbances. This project aims to assess the contribution of mPFC-NAc and mPFC-VTA pathways in goal-directed motivation and evaluate how chronic stress interferes with this process. We quantified motivated behaviours using a progressive ratio reinforcement task for water rewards in water-restricted mice. Interestingly, a motivational deficit was observed after 21 days of chronic variable stress (CVS). Calcium activity in NAc- and VTA-projecting mPFC neurons was recorded via fiber photometry during reward-seeking behaviours performed before, during, and after the CVS period. Preliminary analyses suggest that both pathways encode components of goal-directed motivation similarly at baseline, but appear to be affected by CVS differently. Globally, our results suggest that chronic stress disrupts motivation by altering the dynamics of cortico-accumbal and -tegmental circuits.

P2-F-480 *Influence of intertrial interval (ITI) duration on learning acquisition of elemental and configural discrimination tasks*

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Learning can proceed via elemental or configural processes, yet the conditions that bias learners toward one strategy over the other remain poorly understood. The present study examined whether intertrial interval (ITI) duration influences acquisition rates on elemental and configural discrimination tasks. Sixteen Long–Evans rats (n=16) were concurrently trained on an elemental discrimination task (A+/AB+/C-/CD+) and on a biconditional discrimination task. Half the subjects (n=8) were trained with short ITIs (20s) and half (n=8) with long ITIs (120s). Subjects trained with long ITIs acquired both discriminations significantly faster than those trained with short ITIs, indicating that longer ITIs broadly facilitate learning across task types. To assess associative structure in the elemental task, additional probes (B–/D–) were introduced in later sessions to test for blocking. Principal components analysis confirmed robust blocking effects in all animals, consistent with elemental learning processes. Together, these findings demonstrate that ITI duration substantially modulates learning rate in both elemental and configural discriminations, highlighting the importance of temporal parameters in shaping learning dynamics.

P2-F-481 *Inhibition of microglia in the DMS impacts goal-directed behaviors in a rat model of diet-induced obesity*

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Obesity is a growing health concern, contributing to a range of cognitive deficits including impaired goal-directed behaviour. Consumption of an obesogenic diet has been suggested to increase inflammation, microglial activity, and cause loss of dendritic spines through phagocytosis. To establish whether microglial activation is necessary for diet-induced deficits in goal-directed behaviour, this study tested whether inhibiting microglia in rats fed an obesogenic diet would reduce behavioral impairments. To do this, we administered intracerebral infusions of minocycline or saline to the dorsomedial striatum of male and female rats fed either a high fat high sugar diet (HFSD) or standard chow diet. Acquisition of an instrumental response, sensitivity to outcome devaluation, changes to microglial cell activity, and dendritic spine density were analyzed. Compared to chow-fed rats, HFSD rats displayed insensitivity to outcome devaluation [$F(1,32)= 4.55$, $p=0.041$], suggesting impaired goal-directed behaviour. Pharmacological inhibition of microglial activation via minocycline administration restored goal-directed behavior in HFSD rats with no notable effect in chow-fed rats [$F(1,32)= 4.79$, $p=0.036$]. These results indicate that inhibition of microglial activity is able to restore goal-directed behaviors in HFSD rats. Understanding the mechanisms behind impaired goal-directed eating behavior has potential to aid development of pharmaceutical interventions to assist individuals in behavioural change.

P2-F-482 *Integrating internal and external signals to optimize food decision making*

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Adaptive food decision-making depends on the integration of internal metabolic state with external food cues. While post-ingestive metabolic signals influence food reinforcement, it remains unclear whether real-time metabolic substrate utilization biases nutrient-specific food valuation. This study had two aims. First, we validated a novel MRI-compatible indirect calorimetry (IC) system enabling concurrent measurement of respiratory quotient (RQ) during fMRI acquisition. Overnight-fasted participants completed 30-minute IC measurements using both a standard protocol (pre- and post-scan) and a custom protocol (during and post-scan). Overlapping RQ distributions across protocols demonstrated reliable and consistent metabolic measurement during active scanning conditions. Second, we examined whether metabolic state predicts nutrient-specific willingness-to-pay in a food auction task. Seventeen participants bid on carbohydrate-rich, fat-rich, and mixed macronutrient foods while RQ was measured concurrently. RQ values, averaged across available pre, during, and post measurements, ranged from 0.740 to 0.867, reflecting meaningful inter-individual variability in substrate utilization. We hypothesized that higher RQ (greater carbohydrate oxidation) would be associated with increased valuation of fat-rich foods. However, correlation analyses revealed weak and non-significant relationships between RQ and macronutrient-specific bid ratings: carbohydrates ($r = -0.089$, $p = 0.733$), mixed macronutrient foods ($r = 0.125$, $p = 0.632$), and fats ($r = -0.189$, $p = 0.462$). Ongoing analyses will examine whether metabolic state modulates neural responses within striatal reward circuitry.

P2-F-483 *Integration of appetitive features in the orbitofrontal cortex during food-based choices*

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Understanding how the brain assigns value to potential rewards is central to neuropsychopharmacology, with implications for decision-making in both health and neuropsychiatric disorders. The orbitofrontal cortex (OFC) is thought to integrate sensory and contextual features of available food options to compute subjective values guiding choice. We investigated how OFC neuronal populations combine multiple appetitive features during economic decision-making. We recorded from 485 OFC neurons in rats performing a food-based choice task requiring rats to integrate information about food type and quantity. Each session (~300 trials) allowed for the precise estimation of stable preferences. Neural coding of individual features, integrated value signals, and ensemble dimensionality were assessed during offer evaluation and decision execution. OFC neurons encoded both individual features of offers (type, quantity, spatial location) and emerging value signals during offer presentation. Dimensionality analyses revealed maximal integration of these attributes before choice commitment, followed by a shift toward value-dominated coding as decisions were finalized. Our findings highlight neural computations in the OFC that transform sensory and contextual information into subjective value estimates guiding behavior. These mechanisms provide insight into the neurobiological substrates of decision-making relevant to understanding altered valuation processes in neuropsychiatric conditions.

P2-F-484 *Intraoperative functional mapping of white matter tracts: A scoping review and meta-analysis*

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Introduction: Direct electrical stimulation (DES), typically performed during awake surgery, involves applying current to the brain to induce transient deficits, thereby linking a function to the stimulated region. DES provides a unique window into brain function. However, while the cortex has been extensively studied using this method, white matter has received less attention. Methods: We synthesized the literature reporting white matter functions identified through DES in PubMed and EMBASE, following PRISMA methodology. Results: From 4,760 reported stimulation sites across 203 articles, two groups of white matter tracts were distinguished. The first included those associated with primary, non-lateralized functions: the corticospinal tract (motor function), optic radiations (visual perception), and thalamo-cortical radiations (somatosensory processing). The second involved more complex, lateralized functions: the inferior fronto-occipital fasciculus (left verbal and right non-verbal semantic processing), the superior longitudinal fasciculus and arcuate fasciculus (left phonological processing, right mentalizing), the inferior longitudinal fasciculus (left reading, right visual recognition), the frontal aslant tract (left speech production, right phonological loop), and the fronto-striatal tract (motor control bilaterally). Functional redundancy was observed for some tracts. Conclusion: This work helps consolidate functional knowledge of white matter. We anticipate that these findings will complement advances in neuronavigation and guide neurosurgical decision-making.

P2-F-485 *Inverse effects of diet and adiposity on nucleus accumbens volume in humans*

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The Nucleus Accumbens (NAc) plays a critical role in the etiology of obesity as a modulator of food-based reward. In rodents, obesity susceptibility correlates with AMPAR expression and function in this region. Likewise in humans, NAc cellularity predicts future weight gain and volume tends to be positively associated with measures of obesity. However, these studies often do not take diet into account. In the present study, we investigated if self-reported dietary fat and sugar consumption influences the relationship between body mass index (BMI) and NAc volume in 50 individuals (35 female) with overweight and obesity. Anatomical images were collected using an MPRAGE sequence on a Siemens Prisma 3T scanner, and sugar and fat consumption was measured with the Dietary Fat and Free Sugar questionnaire (DFS). BMI was not correlated with the DFS score ($p=0.89$). BMI, but not DFS was positively correlated with NAc volume ($p=0.04$). However, there was a significant interaction between BMI and DFS score, such that a higher DFS score in individuals with higher BMI was associated with lower NAc volume, and lower DFS with higher NAc volume ($p=0.04$). These findings reveal opposing effects of BMI and a high fat and sugar diet on NAc volume in this sample of individuals with overweight and obesity. This suggests that adiposity and high fat/sugar diet have distinct pathophysiological process with opposing effects on NAc volume. Results underscore the importance of considering diet in studies looking at brain health and BMI.

P2-F-486 *Investigating decision making in the hippocampus using open-source touchscreen chambers*

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The hippocampus is central to memory, but we believe it is also essential for flexible decision-making, especially when navigating uncertain environments. While previous suppression studies show that the hippocampus is involved, they haven't revealed how specific neurons actually encode and update value in real time. To address this, we are using and improving the NC4Touch system, an open-source, scalable

touchscreen setup. We have also developed a 'virtual chamber' for the system, which makes designing protocols and troubleshooting tasks much easier. These high-throughput chambers allow us to efficiently train mice on a probabilistic reversal task where they distinguish between visual stimuli with different reward odds. To visualize neural activity during this behavior, we express GCaMP6f in the dorsal CA1 and image through GRIN lenses using head-mounted UCLA Miniscopes. We then use computational analysis to pinpoint specific neural ensembles that track key moments, such as the decision point or the trial outcome and rewards.

P2-F-487 *Investigating how pre-existing anxiety levels modulate adolescent nicotine vapor-induced behavioural and neural changes*

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Adolescent nicotine use has surged globally, mainly in the form of vaping. Clinical studies show a strong relationship between anxiety- and impulsivity-related traits and nicotine use. However, little is known about how pre-existing anxiety modulates the effects of nicotine use on behavior and neurodevelopment. Moreover, most pre-clinical studies use injection models of nicotine administration that do not reflect human nicotine use. To address these knowledge gaps, adolescent male and female Sprague-Dawley rats' baseline anxiety levels were assessed using multiple behavioral tasks, and divided into groups of baseline low- and high-anxiety. Then, from postnatal day (PND) 35-44, rats were exposed to either vehicle (propylene glycol:vegetable glycerin) or nicotine vapor (NIC) (40mg/ml nicotine) for 10 minutes, 3 times a day, using the OpenVape system. Anxiety- and impulsivity-related behavioral tasks were performed after a 4-days washout period and again after PND75. In-vivo electrophysiological recordings of the Orbitofrontal Cortex (OFC) and Mediodorsal Thalamus (MDT), two key regions involved in impulsivity, were performed. Preliminary results show an anxiolytic effect of NIC on PND50 male rats. At PND75, NIC males show a decrease in OFC cell activity. NIC induced an increase in MDT cell firing frequency in baseline low-anxiety females only. Together, these results suggest that adolescent nicotine vaping has sex-specific effects on anxiety-like behavior, and that pre-existing anxiety modulates nicotine-induced neural activity changes in impulsivity-related brain regions.

P2-F-488 *Investigating the contributions of chromosomal and gonadal sex on the gut microbiome and stress resiliency through cecal transfer in a mouse model of chronic stress*

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Major Depressive Disorder (MDD) and related stress-based psychiatric conditions show a pronounced sex disparity, with females diagnosed at roughly twice the rate of males. Emerging evidence implicates the gut microbiome in MDD vulnerability through the gut–brain axis, yet females remain underrepresented in both preclinical and clinical microbiome research. This study addresses this gap by examining how sex differences in the gut microbiome contribute to stress susceptibility, with a specific focus on the distinct roles of chromosomal and gonadal sex. Cecal contents were collected from Four Core Genotype (FCG) mice to generate four donor microbiome profiles, enabling separation of chromosomal (XX vs. XY) and gonadal (ovaries vs. testes) influences. These profiles were transferred to wild-type C57Bl/6 recipients via oral gavage, followed by six weeks of Unpredictable Chronic Mild Stress (UCMS). Control males and females received microbiota from donors matching their chromosomal and gonadal sex but were not exposed to UCMS. Anxiety- and depressive-like behaviours were assessed across groups, and brains were collected for cytokine analysis to evaluate how donor sex, recipient sex, and stress interact to shape neuroinflammatory outcomes. Cecal contents were also analyzed using 16S rRNA sequencing to characterize microbial community structure. Preliminary findings suggest that certain microbial phyla are shaped primarily by donor gonadal status, whereas others are influenced by both gonadal status and sex chromosome complement. These results advance understanding of how multiple dimensions of biological sex interact with the gut microbiome to influence stress susceptibility, underscoring the need to incorporate sex as a multidimensional variable in studies of psychiatric disorder etiology and treatment.

P2-F-489 *Investigating the discriminative stimulus properties of the mu opioid receptor antagonist, naloxone, through Pavlovian associative learning*

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Introduction: Interoceptive drug stimuli can acquire conditioned modulatory properties resulting in conditioned appetitive behaviours by exteroceptive reward cues in a Pavlovian drug discrimination task. Occasion setting (OS) relies heavily on intrinsically rewarding stimuli to create strong associations, but little is known about the behavioural patterns of aversive stimuli in this task. Naloxone (NLX), a mu opioid receptor antagonist, conditions a place aversion in both opioid-dependent and naïve animals and therefore has the potential to effectively function as an OS despite being intrinsically aversive. Methods: Male and female rats underwent 32 sessions of OS under 3 training contingencies with NLX (1mg/kg) and saline: feature positive (FP), where the drug stimulus is trained to disambiguate when an exteroceptive light conditioned stimulus is followed by the unconditioned stimulus, sucrose; feature negative (FN), where the opposite contingency is true; and control (FX), where access to sucrose is random and not dependent on drug treatment. Following OS training, all animals underwent 11 sessions of NLX place conditioning (PC) Test sessions had freely roaming animals explore both sides without drug administration. Results: NLX did not effectively function as an OS at 1mg/kg and conditioned a place aversion at final test even after appetitive training with sucrose. Conclusions: The biphasic antagonistic effects of NLX likely blocked the acquisition of behaviour in OS while enhancing expression of aversive behaviours in PC.

P2-F-490 *Investigating the effects of exercise on attentional correlates in long-term concussion*

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Concussion is a mild form of traumatic brain injury which typically resolves within 10-14 days. However, concussive injury can result in long-term neurophysiological changes and cognitive deficits that persist past the point of symptom resolution. Attention is a fundamental component of cognition that is often affected by concussion and can be assessed using electroencephalography. While an acute bout of moderate exercise has been shown to alter cognitive processing in healthy individuals and is commonly used in concussion recovery, it remains unclear how exercise, particularly of varying intensities, may alter cognitive processing in long term concussion. The current study aims to investigate how moderate (MICT) and high intensity aerobic exercise (HIIT) influences attentional processing in individuals with a history of concussion. Participants that had suffered a concussion at least six months prior to participation in the study underwent both HIIT and MICT exercise interventions. A visual oddball task with novel stimuli was used to elicit N200 and P300 event related potentials, both pre and post exercise interventions (randomized 1 week apart). Preliminary analysis found that HIIT led to a decrease in N200 latency, while MICT led to an increase in N200 latency in response to non-target stimuli. These findings suggest that an acute bout of aerobic exercise can modulate attentional processing and indicate a unique effect of HIIT on early stimulus detection and response inhibition in individuals with a history of concussion.

P2-F-491 *Investigating the role of actin dynamics in the perirhinal cortex for object memory destabilization in a rodent model*

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Following retrieval, previously consolidated memories can re-enter a labile state making them susceptible to modification, whereas remote memories resist destabilization. Cofilin 1 (Cfl1) promotes actin depolymerization when unphosphorylated, while phosphorylation by LIM kinase (LIMK) inactivates Cfl1 and stabilizes spine architecture. Cellular models have shown that actin dynamics regulate glutamatergic

α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) trafficking, a process necessary for the transient exchange of calcium-impermeable (CI-) to calcium-permeable (CP-) AMPARs, which enhances synaptic plasticity. However, a strong link between actin-dependent AMPAR trafficking and object memory destabilization remains unclear. Aim 1 of the present study quantified phosphorylated (p-) Cfl1:total (t-) Cfl1 ratios in perirhinal cortex (PRh) of male and female rats following object memory reactivation (RA). Aim 2 will assess actin's role in memory destabilization through pre-RA PRh infusions of phalloidin, an actin arrest toxin. Aim 3 will assess actin dependent AMPAR exchange using a remote object memory task, with pre-RA infusions of BMS-5, a LIMK inhibitor, and post-RA quantification of CP:CI-AMPAR in the PRh. Decreased ratios of pCfl1:tCfl1 were observed in the PRh following RA. Drug manipulations of actin is expected to bidirectionally modulate memory destabilization with increased ratios of CP:CI-AMPAR when memories are labile. This project aims to establish how actin dependent processes facilitate long term memory flexibility throughout life.

P2-F-492 *Investigating the role of nucleus accumbens D1 receptor neuronal outputs to ventral midbrain in anxiodepressive behaviour elicited by diet-induced obesity*

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Obesity with metabolic dysfunction increases the risk of depression and anxiety and elicits neuroimmune responses in structures controlling mood and motivation. We showed that neuroinflammation in the nucleus accumbens (NAc) mediates anxiodepressive behaviour in diet-induced obese (DIO) male mice. We also found that DIO reduces c-FOS expression in D1 receptor medium spiny neurons (D1-MSN) and their chemogenetic activation reduces despair in male DIO mice. Targets of D1-MSN include the ventral midbrain (VM), ventral pallidum and lateral hypothalamus. Our goal here is to assess the role of the D1-MSN NAc->VM pathway in anxiodepressive behavior elicited by DIO. A double AAV approach (Flp/Cre-dependent) was used in adult male and female D1Cre mice to express excitatory DREADDs in D1NAc-VM neurons. Mice were fed a high-fat diet (HFD) or chow (control) for 12 weeks (male) or 18–24 weeks (female)(n= 8/group). Behavioral tests (EPM, open field, sociability, forced swim and sucrose preference) were carried out under chemogenetic activation (CNO). RESULTS: HFD led to significant increases in body weight, energy intake and fat mass. CNO increased c-FOS expression in Cre+ NAc D1-MSN. Preliminary findings show that D1NAc-VM activation tended to increase anxiety-like behaviour in males, whereas it was decreased in females. These preliminary results suggest that D1NAc-VM circuit activation modulates mood-related behaviours in a sex-dependent manner. Data also suggests that other NAc D1 or D2-MSN outputs mediate the anxiogenic effects of DIO. Supported by a CIHR Project Grant to SF.

P2-F-493 *Investigation into the activity of claustrum interneurons across different states*

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The claustrum is a small subcortical brain region densely and reciprocally connected with the entire cortex. Recent experiments in rodents, reptiles, and humans have highlighted the state-dependent activity pattern of claustrum neurons projecting to the cortex. Periods of non-rapid eye movement sleep and low arousal state, such as rest and 'reflexive' behaviours, are characterized by a coordinated increase in low-frequency oscillations in cortical regions, behavioural immobility and reduced pupil size. Claustrocortical neurons are specifically active during these synchronized states. Locomotion, whisking and REM sleep are associated with a desynchronized cortical state and a suppression of the activity of claustrum outputs. The underlying neuronal circuits for this state-dependent modulation of the activity of claustrum projection neurons are unknown. Inhibitory regulation of claustrocortical neurons by local GABAergic interneurons may permit a precisely timed engagement or disengagement of claustrum projection cells according to changes in state. We used fibre photometry and chemogenetic manipulation in behaving mice to investigate the in vivo contribution of local interneurons in shaping the activity of claustrum projection neurons across different states. A better understanding of how the activity of different populations of claustrum neurons relates to brain and behavioural states is essential in the investigation of the function of the claustrum.

P2-F-494 Laminar organization of medial frontal *β*-bursts during a stop signal task

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Recent studies in humans have shown that brief bursts of β-oscillations over the medial frontal cortex—known as β-bursts—may play a critical role in cognitive control. However, how these β-bursts influence stopping behavior and how they are generated remains unclear. To address these questions, it is necessary to examine the functional properties of β-bursts across the different cortical layers of the medial frontal cortex, a region strongly implicated in cognitive control. To address this, we collected intracortical local field potentials (LFP) within the SEF of four macaque monkeys and cingulate cortex of two macaque monkeys performing a saccadic stop-signal task. β-bursts were elevated during periods requiring cognitive control, including successful response inhibition, and post-error processing. Additionally, they were elevated during intertrial intervals. We observed that these intracortical β-bursts were observed across all layers of cortex. These findings will provide important constraints for biophysical and cortical circuit models of medial frontal function in relation to EEG measures and invite further considerations of β-burst function in cognitive control.

P2-F-495 *Lateral hypothalamic input engages a disinhibitory microcircuit in the dorsal raphe to promote behavioral activation*

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Behavioral activation involves coordination between hypothalamic and brainstem systems that regulate movement and internal state, but the circuit logic underlying this interaction remains poorly defined. The dorsal raphe nucleus (DRN), a major serotonergic hub, integrates diverse inputs to influence behavioral inhibition and activation. Here, we identify a disinhibitory pathway through which the lateral hypothalamus (LHA) promotes behavioral activation via DRN. Using intersectional viral tracing, electrophysiology, and single-nucleus RNA sequencing, we show that LHA inputs preferentially target GABAergic DRN neurons that locally inhibit 5-HT neurons. Silencing these DRN neurons innervated by LHA increased locomotor and repetitive behaviors, decreased local inhibition, and enhanced cFos activity in serotonergic neurons, consistent with circuit-level disinhibition. Molecular profiling revealed distinct transmitter identities and transcriptional signatures of LHA-targeted versus LHA-projecting DRN populations. Together, these findings delineate a hypothalamic–raphe circuit that transforms hypothalamic drive into serotonergic activation, revealing a mechanism by which the lateral hypothalamus promotes behavioral activation through local inhibitory control.

P2-F-496 *Learning constrains the generative capacity of the hippocampus*

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Mixed selectivity enables intelligent systems to flexibly generate novel patterns from existing dynamics, providing a reservoir of units readily adaptable to any given context. Hippocampal neurons adopt mixed selectivity to a variety of features depending on task demand, but whether this arises from task learning or reflects an intrinsic capacity of the system is unknown. We addressed this using Miniscope calcium imaging to track the behavioural selectivity profiles of hundreds of dCA1 neurons across months of learning in freely-behaving mice, from habituation to overtraining. Despite focusing entirely on activity during inter-trial-intervals (ITI)—when animals were disengaged and trajectories were random—virtually all neurons reflected an inherently mixed response profile to spatial and behavioural features from day one, with basic pre-task training driving a sparsification of these pre-existing dynamics. Task expertise sharpened rather than re-tuned behavioural features at the expense of spatial coding fidelity. Remarkably, the population did not organize to represent the animal's immediate behaviour. Instead, models trained on ITI activity increasingly decoded non-local head directions corresponding to the animal's behavioural policy for solving the task.

Thus, mixed selectivity reflects an intrinsic property of hippocampal neurons. Learning serves to constrain rather than reconstruct this high-dimensional reservoir of candidate activity patterns, generating responses aligned to relevant behavioural policy over current sensory reality.

P2-F-497 *Levonorgestrel reduces sex differences in tests of anxiety-like behaviour in Long-Evans rats*

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Levonorgestrel (LNG) is a common ingredient in many hormonal contraceptive (HC) methods, including pills and intrauterine devices, that acts as an agonist at progesterone and androgen receptors (AR). There is a knowledge gap regarding the effect of LNG use on affective behaviour, especially after adolescent use. Adolescent female and male Long-Evans rats were treated with LNG (20 µg / kg) or a vehicle (sesame oil + 5% ethanol) treatment for 17 days and anxiety-like behaviours were assessed using a behavioural battery including the elevated plus maze (EPM), social interaction test (SIT), and the light/dark box test (LDB). Composite anxiety and femininity scores were created based on z scores generated from raw data. LNG treatment in adolescent rats reduced the sex disparity typically seen in anxiety-like behaviours. Females treated with LNG demonstrated increased anxiety in the EPM and LDB tests, while their anxiety was decreased in the SIT. There was no treatment effect on overall anxiety composite scores, but analysis of composite femininity scores found that LNG masculinized behaviour in females. These results suggest the mechanism involves androgenic actions of LNG; possibly acting as an AR agonist in females and an inverse agonist in males. A follow-up study using flutamide to pharmacologically block LNG from acting at AR is currently in progress to further investigate this possible mechanism.

P2-F-498 *Activity of prefrontal Sidekick1-expressing neurons regulates behavioral adaptation to chronic stress*

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Stress is a major risk factor for depression, yet some individuals remain resilient to stress. Both environmental and genetic factors contribute to the dysregulation of neural circuits in depression and genes that regulate the formation, maintenance, and plasticity of synapses are of particular interest as potential molecular hubs for regulation of circuit function. We previously identified Sidekick1 (Sdk1) as an affective circuit hub gene in a network regulating stress resilience. Sdk1 is a cell surface molecule implicated in circuit formation in the developing retina, however little is known about its function in the adult brain. In this study we profiled the prefrontal cortex (PFC) expression of Sdk1 in both male and female mice. We found that Sdk1 is expressed in subsets of both excitatory and inhibitory neurons predominantly in deep layer 6 of the PFC and expression is conserved between mice and humans. We identify thalamic nuclei as the primary projection target of Sdk1+ PFC neurons where they synapse onto other Sdk1+ cells. Sdk1 expression was modulated by stress in a sex-specific manner. Manipulating activity of prefrontal Sdk1+ neurons during chronic stress had long term effects on Sdk1 expression, neuronal activity and resilience to stress. As a cell surface receptor, Sdk1 is a potential target for pharmacological intervention. Understanding how Sdk1 function and activity of circuitry defined by its expression confers resilience may lead to development of new mechanistically-informed treatments for depression.

P2-F-499 *Male and female rats trained on appetitive and inhibitory learning contingencies generalize the stimulus effects of morphine to other opioids*

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Background: Interoceptive effects elicited by opioids can guide behaviours through Pavlovian associations with drug-related stimuli. Following acquisition of appropriate conditioned sucrose-seeking guided by a morphine stimulus, stimulus specificity can be determined by comparing behaviour elicited by different opioid receptor agonists to baseline discrimination behaviour. Methods: Male and female rats received daily injections of either 3.2 mg/kg morphine or saline before training sessions consisting of 8 presentations of a white noise (WN) conditioned stimulus. WN was followed by sucrose delivery on morphine, but not on intermixed saline sessions for rats trained on a feature positive (FP) learning contingency. The opposite was true for rats trained on a feature negative (FN) contingency. Following stable discrimination, rats completed generalization tests as long as discrimination remained consistent. On these tests, responding to a single WN presentation was recorded after pre-treatment with one of four doses of either morphine, oxycodone, hydromorphone, fentanyl, naloxone + morphine, or saline. All rats were tested on all drugs. Results: Discrimination was more stable in FP than FN rats and clearer in males than in females. All opioids generalized to morphine at doses dependent upon learning contingency but independent of sex. Naloxone blockade of agonist-appropriate responding was clear only in FP rats. Conclusions: Our findings demonstrate that the stimulus effects evoked by morphine administration can generalize to other opioid agonists in a dose-dependent manner.

P2-F-500 *Maturational trajectory of hippocampal networks revealed by longitudinal calcium imaging in vivo*

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Episodic memories are encoded by neuronal ensembles in hippocampus. Neurons belonging to an ensemble share coactivity and functional connectivity prior to encoding experience (e.g., in experimentally-naive animals), indicating that neuronal ensembles are “preconfigured” in mature hippocampal networks. When and how this configuration arises remains unclear. To examine whether neuronal ensembles emerge in the developing hippocampus and how they evolve, we performed longitudinal two-photon microscopy in CA1 of adult (> postnatal day 60; P60) and developing (P18-25) head-fixed, transgenic Thy1-GCaMP6f mice running or resting on a treadmill. In line with previous research, we observed heightened neuronal activity in the developing CA1, that declined to adult-like levels by P24. This activity was partially characterized by an increased occurrence of synchronous activity (i.e., synchronous calcium events; SCE) that recruited more neurons than SCEs in adult CA1. Decomposition of CA1 population activity using non-negative matrix factorization (NMF) revealed neuronal ensembles in both adult and developing CA1. The size of ensembles in CA1 declined across development and were adult-like by P24, as did the selectivity of neurons that comprised ensembles. Our preliminary data indicate P24 as a critical age for maturation of CA1 networks. This study will reveal how developmental processes in the hippocampus shape mature episodic memory function, enabling future investigation of how these processes and memory dysfunction arise in neurodevelopmental disorders.

P2-F-501 *Median raphe glutamatergic and serotonergic inputs support recruitment of hippocampal CA1 VIP interneurons during novel experience*

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Vasoactive intestinal polypeptide–expressing interneurons (VIP-INs) are key regulators of hippocampal learning, gating pyramidal cell output primarily through disinhibition during novelty detection and memory

formation. How long-range neuromodulatory inputs recruit specific VIP-IN subtypes during behavior remains unclear. The median raphe nucleus (MnR) modulates hippocampal learning via serotonergic and glutamatergic projections, yet its influence over VIP-INs has not been directly examined. Here, we identified layer- and subtype-specific MnR connectivity to VIP-INs in dorsal CA1. MnR projections targeted VIP basket cells (VIP-BCs), calretinin-expressing IS-3 cells, and other VIP-IN subtypes, with perisomatic innervation producing stronger excitation in VIP-BCs. VIP-IN recruitment depended on synaptic input strength rather than intrinsic excitability, indicating a connectivity-based mechanism. Glutamatergic VGLUT3-positive inputs provided the primary excitatory drive, while serotonin engaged fast 5-HT3a and modulatory 5-HT2c receptors to enhance excitability. Importantly, MnR input was required for full VIP-IN activation during novelty exploration, identifying a brainstem–hippocampal circuit that dynamically gates disinhibition during unexpected experiences. Together, these findings reveal a dual-transmitter mechanism by which MnR recruits VIP-INs to tune hippocampal excitability during novelty-driven learning.

P2-F-502 *Median raphe VGLUT3+ neurons modulate hippocampal theta rhythm and sharp-wave ripples*

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The median raphe region (MRR) contains hippocampus-projecting glutamatergic neurons expressing the vesicular glutamate transporter type 3 (VGLUT3). The MRR is a powerful modulator of sharp-wave ripples (SWR, ~50 ms, 150-250 Hz) and theta rhythm (5 to 12 Hz), occurring during NREM sleep predominantly or wake and REM sleep, respectively. Both rhythms are essential for memory consolidation. However, the specific contribution of MRR-VGLUT3+ neurons to hippocampal rhythms is still unclear. In this study, we aim to 1) measure MRR-VGLUT3+ neuronal population activity across vigilance states in relation to hippocampal rhythms, and 2) evaluate the effects of manipulating MRR-VGLUT3+ neurons activity on SWR and theta rhythm. To target MRR-VGLUT3+ neurons, we inject Cre-dependent viral vectors in VGLUT3-Cre mice. First, we record local field potential in the hippocampus while simultaneously recording MRR-VGLUT3+ neurons activity using fiber photometry. MRR-VGLUT3+ neurons are highly active during wake and REM sleep and their activity covaries with theta properties. During NREM sleep, they are active in short bursts anticorrelated with SWR rate. Second, we optogenetically modulate MRR-VGLUT3+ neurons activity. Activation during NREM sleep powerfully suppress SWR while activation and inhibition during REM sleep disrupt theta rhythm. Taken together, our results highlight contrasted activity patterns of MRR-VGLUT3+ neurons across vigilance states and reveal a powerful modulation of hippocampal rhythms, suggesting a role of MRR-VGLUT3+ neurons in memory consolidation.

P2-F-503 *Microglia regulate memory consolidation by modulating engram neuron activity*

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Beyond their canonical role as the brain's resident immune cells, microglia are also known to actively interact with neurons and remodel synaptic connections in the healthy brain. However, whether these interactions and remodeling influence cognitive functions such as memory remains unclear. Here, we propose that microglia play a crucial role in regulating memory by modulating the activity of engram cells (i.e., neuronal ensembles activated by an experience) during post-encoding periods. Using contextual fear conditioning to study fear memory encoding, consolidation and retrieval in mice, we found that microglial depletion at training impaired subsequent memory recall one day later but spared short-term memory, suggesting a critical role for microglia in memory consolidation and/or memory retrieval. Consistent with this, engram-labeling techniques further revealed that, under microglial depletion, engram cells exhibited reduced reactivation during memory recall. One-photon in vivo calcium imaging across multiple time points before, during and after contextual fear conditioning revealed reactivation of engram neurons during

a post-encoding consolidation period, and this reactivation was disrupted by microglial depletion. By integrating 1-photon neural data with mouse freezing behavior as a memory readout, we found that engram activation was tightly coupled to freezing onset, whereas microglial depletion weakened this coupling after memory consolidation, suggesting that microglia regulate engram reactivity and behavior. These results highlight a novel function of microglia in shaping memory through modulating engram activity during consolidation.

P2-F-504 *Modelling population dynamics in cortical–basal ganglia circuits for decision-making*

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Decision-making is a process that begins with deliberation and ends with commitment to one action from a set of competing alternatives. Traditional paradigms, such as the random-dot motion task, have provided important insights into perceptual evidence accumulation, but do not capture the dynamic nature of real-world decision-making. In natural scenarios, for example, during predator–prey interactions, an agent may dynamically shift its target as perceptual evidence changes, and commitment must occur under strong time pressure. Although many computational models capture core aspects of neural decision dynamics, many are typically limited to stationary evidence and do not account for urgency signals that enable the flexible trade-off between speed and accuracy. Furthermore, recent work suggests that decision-making is not localized to a single brain region but instead emerges from distributed interactions within cortical–basal ganglia circuits. Here, we developed a biologically grounded rate-based model of distributed cortical–basal ganglia networks incorporating recurrent cortical competition, basal ganglia gating pathways, and urgency-related modulation. The model proposes a mechanistic account of flexible decision-making under dynamic conditions and reproduces experimental findings at both neural and behavioral levels. Furthermore, it generates testable predictions for population-level neural dynamics during decision-making, helping to clarify the functional contributions of cortical and basal ganglia circuits to different aspects of the decision process.

P2-F-505 *Multiplicity of error centers in the cerebral cortex*

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The brain's capacity to detect action errors is foundational for cognitive control of behavior, a capacity that is impaired in numerous neurological and psychopathological disorders. Error monitoring is indexed by a signal found in the electroencephalogram over medial frontal cortical areas known as the error-related negativity (ERN), and is found in both humans and non-human primates. Neurons rapidly responding to errors are found in both human and macaque superior frontal gyrus (SFG) and cingulate cortex (CC), but the geometry of the dipoles in the CC banks mean that neurons there would have opposing contributions to the ERN. We aim to identify, characterize and compare error neurons in the three potential areas that could contribute to ERN. Two macaques (one rhesus and one bonnet) performed a saccade-based stop signal task while we recorded simultaneously from supplementary eye fields (SEF, in SFG) and the dorsal and ventral banks of the cingulate sulcus (dCC and vCC respectively). We found neurons that are modulated by errors in all three areas in both monkeys. Error signals arise earliest, last longest, and are the most consistent in SEF. The cingulate banks differ based on the signal direction. For facilitation, vCC precedes dCC, but this is inverted for attenuation. These results demonstrate that there are three regions with differing contributions to ERN, and this knowledge will improve biophysical models of the source of ERN. Clarifying the functional distinctions within and across cortical areas will eliminate the incompleteness of current theories of cognitive control.

P2-F-506 *Multi-scale organization of hippocampal activity across CA1 and subiculum during structured locomotion*

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The hippocampus is critical for learning, memory, and navigation. Hippocampal pyramidal neurons encode for both external features of the environment and internal states of the animal, yet how different hippocampal subregions and neuronal subtypes govern these various forms of encoding is poorly understood. To address this, we used head-fixed 2-photon mesoscope calcium imaging of the dorsal hippocampus in Thy1-GCaMP6s mice, enabling simultaneous assessment of the activity of hundreds of excitatory neurons in both CA1 and subiculum regions of the hippocampus. Neuronal activity was recorded while mice traversed treadmill belts composed of distinct textures across days, allowing for the assessment of neuronal activity as a function of space, time, motor activity, and treadmill context. Our work recapitulated known feature selective properties of hippocampal neurons encoding space. Moreover, we identified distinct groups of neurons that adapted their activity over sessions, illustrating that hippocampal neurons encode aspects beyond instantaneous sensory and motor activity. These neurons were differentially present across the CA1 vs. subiculum axis, suggesting that distinct hippocampal regions are biased to encoding instantaneous vs adapting properties of behavioural states. At the population level, neural activity formed structured, low-dimensional manifolds that followed the organization of treadmill movement and exhibited within-session changes in structure. Together, we highlight how diverse single-neuron activity contributes to the formation and evolution of population-level organization across distinct subregions of the dorsal hippocampus.

P2-F-507 *Multivariate behavioural and psychological profiles predict adherence to a physical activity intervention in adults at risk for Alzheimer's disease*

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Adherence to physical activity (PA) interventions and effective intervention exposure are critical determinants of efficacy in Alzheimer's disease (AD) prevention. Although greater adherence is associated with improved outcomes, adherence varies widely and is often examined using isolated demographic factors. A multivariate approach was therefore used to identify baseline factors associated with adherence to a 4-week digital PA intervention in older adults at risk for AD. Participants were adults enrolled in the PREVENT-AD cohort (mean age 70.0 ±4.4 years; 66.7% female; n=27) and randomized to the intervention arm of a remotely delivered PA program. Baseline measures included socioemotional and motivational traits, personality, and social determinants of health, with baseline physical activity, demographic variables, and AD risk markers (genetics/plasma biomarkers) included to account for baseline heterogeneity. Partial least squares regression related baseline features to intervention adherence, defined as the number of intervention days completed over 28 days, derived from a digital platform and independently double-scored. Model performance peaked with seven latent components (cross-validated R^2=0.46). The dominant latent variable reflected a behavioural adherence phenotype, with the strongest contributions from volitional capacity (Σw^2=0.26), social support (Σw^2=0.15), self-regulation (Σw^2=0.12), and motivation/apathy (Σw^2=0.11). Area-level socioeconomic deprivation contributed modest variance, exceeding contributions from traditional demographic factors, while genetic risk and AD plasma biomarkers contributed comparatively little. Intervention adherence in adults at risk for AD was primarily associated with integrated behavioural and contextual profiles, highlighting the importance of multivariate behavioural phenotyping for optimizing prevention strategies.

P2-F-508 *Multi-voxel pattern analysis for characterizing functional connectivity underlying grit in cognitively unimpaired older adults at-risk for Alzheimer's disease*

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IntroductionAdherence to healthy lifestyle behaviours or to prescribed medication requires perseverance with stamina, and this is captured by Grit, a non-cognitive trait defined as perseverance and passion for long-term goals. Despite predicting cognitive decline and physical, emotional, and social functioning, Grit remains poorly understood and its neural substrates are unknown in cognitive aging. MethodsSixty-six cognitively unimpaired older adults with a family history of Alzheimer's disease were recruited through the PREVENT-AD longitudinal cohort. Participants completed tests that assess grit and conscientiousness and underwent resting-state functional magnetic resonance imaging (fMRI). Multivariate pattern analyses (MVPA), a rigorous data-driven whole-brain approach, were used to examine if resting-state functional connectivity of connectome-wide voxels were associated with grit scores, controlling for age, sex, pTau217 levels, education years, perceived socioeconomic status, mean framewise displacement, and conscientiousness. ResultsOur analyses identified two statistically significant (p-FDR<0.05) clusters in the right middle frontal gyrus and the left superior frontal gyrus underlying grit. ConclusionBeing the first to identify functional neural correlates supporting grit in the aging population while accounting for the variance of conscientiousness, our study provides unique insights into the construct which has important applications in adherence to clinical and empirical neurological interventions as well as in successful aging.

P2-F-509 *Network gain regulates stability and flexibility in a ring attractor network*

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The internal compass of the brain, also known as the head-direction (HD) system, forms a crucial component of the neural circuit necessary for effective spatial orientation, and includes regions such as the anterodorsal thalamic nucleus (ADN). It maintains a sense of orientation by integrating self-motion with local cues, which serve as anchors. A recent study in mice showed that network gain, a measure of population activity in the system, decreases during reorientations induced by changes in visual cues. The extent of this reduction in gain influences the dynamics of reorientation, with lower gain leading to faster resets. We hypothesize that gain can serve as a measure of the 'uncertainty' in orientation, and it reflects how confident an animal is in its orientation estimate. Thus, manipulating the degree to which a visual cue accurately predicts orientation would influence gain. We used miniscopes to perform Ca2+-recordings in the ADN of freely behaving mice while varying the separation between two identical cues in an attempt to induce uncertainty. We observed that the representation in the ADN switches between two states, which was indicative of the mice switching between anchoring to the two cues. We also observed that the gain remained low during these switch states. By introducing noise in a 1D continuous attractor network (CAN) model, we show that these switches are more prominent when gain is low, and the system maintains a stable representation when gain is high. Thus, we report the presence of unstable equilibria in the HD network, with higher values of gain leading to a robust state.

P2-F-510 *Neural circuit and behavioral signatures of stress resilience in caenorhabditis elegans*

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INTRODUCTIONStress resilience is a key property of nervous system adaptation. Previous studies show that the interneurons AIB and RIM regulate stress-related arousal and locomotor switching in C. elegans, but their role in stress resilience remains unclear. Given this, we asked whether AIB and RIM neurons causally regulate behavioral recovery after stress. METHODSA total of 240 adult C. elegans were examined under control and acute osmotic and thermal stress and classified as stress-resilient or stress-sensitive based on post-stress

recovery. Locomotion speed, reversal frequency, and recovery latency were quantified. Calcium imaging was performed by expressing GCaMP in AIB and RIM neurons, and optogenetics was used to activate or inhibit these interneurons during recovery. RESULTSStress-resilient animals (n = 118) recovered locomotion faster and maintained stable movement compared to stress-sensitive animals (n = 122). Reversal frequency normalized more rapidly in resilient animals, indicating improved sensorimotor adaptation. Optogenetic activation of AIB and RIM reduced recovery latency by ~35%, while their inhibition worsened post-stress impairment. Calcium imaging showed sustained AIB and RIM activity in resilient animals and disrupted activity in stress-sensitive animals. DISCUSSIONThese findings show that stress resilience in C. elegans depends on AIB-RIM circuit stability, providing mechanistic insight into conserved neural control of stress adaptation.

P2-F-511 *Neuronal network linking the olfactory bulb to the prefrontal cortex regulates familiarity-induced affective state transfer*

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Affective state transfer is essential for social behaviors in mice, and its degree is influenced by the familiarity between observers and demonstrators. To detect social cues and communicate, mice largely use odorant stimuli, but it remains unclear how olfaction is involved in affective state transfer or what is neuronal network that encode affective state transfer toward familiar but not unfamiliar subjects. We investigated affective state transfer toward sick conspecifics and how it is related to olfactory processing in mice. We used social preference tests coupled with in vivo Ca2+ imaging, chemogenetics, light-sheet analyses, and immunohistochemistry to show that mice spend more time with their sick cagemates than with healthy mice or sick unfamiliar mice. Light-sheet whole-brain analyses for early immediate genes revealed brain structures involved in this type of behavior, including the prefrontal cortex (PFC), and transsynaptic viral tracing showed that there are synaptic connections between the olfactory bulb (OB) and the PFC. In vivo mini-endoscopic Ca2+ imaging in the PFC revealed a specific Ca2+ signature for processing sensory signals related to sick cagemates compared to healthy mice or sick unfamiliar mice, while pharmacogenetic inhibition of neurons in the PFC abrogates the behavioral preference of mice for sick cagemates. These findings revealed that familiarity is an essential factor in affective state transfer in mice, and that the OB-PFC network is an important synaptic network underlying the interaction between mice and sick kindred.

P2-F-512 *Offspring fear conditioning and latent inhibition following cannabis smoke exposure before and during pregnancy in mice*

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Since the legalization of Cannabis sativa in Canada, cannabis use during pregnancy has increased. Cannabinoids such as Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) readily cross the placental and blood-brain barriers, where they may disrupt the fetal endocannabinoid system (eCS) signalling and development ultimately changing offspring behaviour. However, almost all people who consume cannabis during pregnancy initiate use before becoming pregnant. Therefore, in the present study, we investigated behavioural changes in mice following administration of either room air, placebo cannabis smoke, high-THC smoke , or high-CBD smoke to female mice (n=24) for seven days before breeding and during the first two weeks of pregnancy. Male and female two-month-old offspring were tested on latent inhibition (LI) in a fear conditioning paradigm to assess selective attention and learning/memory following maternal cannabis smoke exposure. Exposing mice to cannabis smoke before breeding did not alter the number of dams that delivered offspring, litter size, or offspring weight gain during the first two postnatal months. Surprisingly, cued fear memory 24 hours after conditioning was reduced in offspring from the placebo and high-CBD smoke groups. Latent inhibition was observed in air control and high-THC smoke groups; however, the

altered fear memory confounded interpretation in the placebo and high-CBD treated groups. Ongoing experiments will increase the sample size of treated dams and increase confidence in the relevance of this mouse model for typical patterns of cannabis use in pregnant people.

G - NOVEL METHODS AND TECHNOLOGY DEVELOPMENT

P2-G-513 *Can we capture resting state functional connectivity in a shorter time? A systematic comparison between the hyperband- and conventional fMRI*

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Accelerated resting-state fMRI acquisitions such as Hyperband offer the potential to reduce scan time and participant burden, but their ability to preserve clinically meaningful functional connectivity remains unclear. In this study, 108 young adults with recent alcohol and/or cannabis use completed both a 9-minute conventional resting-state scan and a 4.5-minute Hyperband scan in the same session. Default mode network (DMN) connectivity was examined using RoI-to-RoI connectivity and graph-theoretical metrics, and associations with cannabis-related measures were evaluated. Data quality metrics did not differ between acquisition types. Conventional scans showed significantly higher connectivity for select DMN connections, particularly involving lateral parietal and posterior cingulate regions, while most other connections and graph metrics showed no significant mean differences. Cross-modality agreement was generally low, especially for graph-theoretical measures. Associations between DMN metrics and cannabis use were weak and showed limited overlap between acquisition types, with several differences involving urine tetrahydrocannabinol positivity. These findings suggest that although Hyperband and conventional rs-fMRI yield comparable data quality and mean connectivity patterns, shortened acquisitions may not reliably preserve individual-level connectivity or brain–behaviour associations. Accelerated protocols should therefore be used cautiously when studying subtle clinical relationships.

P2-G-514 *Development of a head fixation protocol for awake repeated live two-photon imaging in the adult zebrafish telencephalon*

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Repeated live animal imaging is a powerful tool to visualize and analyze dynamic cellular processes in real time. While zebrafish are an excellent model for live optical imaging due to their larval transparency, smaller brains, and availability of transgenic reporter lines, reports investigating repeated live neuroimaging in the adult zebrafish remain scarce. We have developed a novel repeated imaging protocol for head fixated awake, adult zebrafish to visualize the neurovasculature in the dorsal telencephalon. This method reduces time in surgery compared to existing head fixation techniques in adult zebrafish and enables sequential non-invasive imaging of neurovascular properties via two-photon microscopy. With this method, adult fish undergo surgery to mount a headpost on the neurocranium, with adjustable arms then attached to the headposts to immobilize the head for live, unanesthetized imaging. Using the Tg(kdrl:gfp) reporter line marking endothelial cells, we demonstrate that the same vessels can be repeatedly imaged in the dorsal telencephalon for up to five days. We also show that properties of vasomotion (diameter fluctuation, frequency and amplitude) can be quantified on the same vessels in the telencephalon using our MATLAB toolbox, CHIPS (Cellular and Hemodynamic Imaging Processing Suite). We successfully validate this method through analyzing neurovasculature. However, this approach paired with the remarkable regenerative ability of zebrafish, provides future applications in fundamental neuroscience and disease modelling, such as vascular repair and stroke.

P2-G-515 *Development of reflectin as a phase-contrast marker for digital holographic microscopy — a future approach for live subcellular imaging in neuroscience*

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The ability to observe cells morphology and dynamics is necessary to understand their complex interplays as aberrations have been related to neurodegenerative diseases and psychiatric disorders. Although fluorescence has its strengths, it also has its limits. Fluorophores strategy is not ideal for morphology analysis and moreover phototoxicity and photobleaching become key consideration, especially when visualizing dynamic structures. In our lab, we developed a label-free modality known as Digital Holographic microscopy (DHM) allowing to observe dynamics and subcellular structures in live cells without causing cell damage. DHM is a really powerful technique as it can measure various parameter, such as cell's height, dry mass, morphologies and others. However, this method also has some limitations, especially regarding the discrimination between organelles such as a mitochondrion, lysosome or endoplasmic reticulum. Thus, developing a method fitting with DHM properties to discriminate subcellular structures in cells could improve its capacity. Our investigations to solve this challenge led to reflectin, an optically-active intrinsically disordered protein (IDP) protein from cephalopods that can serve as a form of camouflage or for communication. These abilities suggest that reflectin can be used in conjunction with DHM as a potential marker. Indeed, our data confirms reflectin's aggregation when transduced and that we can target reflectin to different subcellular structures. We are in the process of optimizing reflectin's performance in neurons as a marker for DHM, and we hypothesize that reflectin will be a useful addition to the DHM toolkit for future investigations into the complexity of neurons and lead to new insight that were previously not possible from existing approaches.

P2-G-516 *Drosophila melanogaster as a novel model organism to study stress and antidepressant drugs*

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Drosophila melanogaster has contributed to the understanding of genetics and, more recently, has been helpful in investigating the mechanistic basis of neuropsychopharmacology. Flies have neurotransmitters and neurobiological structures similar to vertebrates. Previous studies indicate that flies reduce locomotion and sucrose preference in response to stress, suggesting that they can be useful for developing new stress models. As in rodents, antidepressant treatments can reverse stress-induced sequelae in flies. This study aimed to evaluate the reversal of 3-day variable-stress-induced sequelae by amitriptyline, bupropion, citalopram, and fluoxetine treatment in flies. For this purpose, stressed (combination of food deprivation, cycle reversal, cold, heat) male and female flies (n = 23-36/group) were treated with 10 mM of each antidepressant or vehicle for 3 days before locomotion and sucrose preference measures in the lane-maze assay for 40 min. Data showed that locomotion was influenced by sex ($p = 0.02$), with females moving longer distances than males over 40 min. None of the antidepressants had an effect on locomotion ($p = 0.09$). Sex did not influence the sucrose preference ($p < 0.05$). Contrary to expectations, antidepressants did not reverse the stress effect on sucrose preference ($p < 0.05$). Regarding locomotion, female flies seem more sensitive to stress-conditions than males. Preference seems not be affected by these antidepressants in these conditions. However, further studies with different antidepressants and doses should be done to confirm these results.

P2-G-517 *Electrochemical biosensor for mitochondrial DNA integrity assessment as a biomarker of major depression*

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Major Depressive Disorder (MDD) is a common and severe mental illness. The underlying biological mechanisms are not fully understood, but increasing evidence shows that mitochondria play an important role. Impaired mitochondrial function leads to impaired bioenergetics, increased oxidative stress, release of circulating cell-free mtDNA (ccf-mtDNA) and activation of inflammatory and neuroimmune pathways. However, the understanding of the impact of ccf-mtDNA integrity on MDD pathological conditions is still limited. Here, we present a dual-target electrochemical DNA biosensor designed to enable fast, sensitive, and low-cost assessment of mtDNA integrity through comparative detection of two mitochondrial genes, MT-ND2 and MT-ND4. Gold electrodes with capture DNA probes were analyzed by square-wave voltammetry; triplicates were assessed by one-way ANOVA. The results show that calibration curves for MT-ND2 and MT-ND4 exhibited linear responses across a concentration range of 10 ng/µL to 100 fg/µL, with a limit of detection of 100 fg/µL for both targets (MT-ND2: $R^2 = 0.99998$; MT-ND4: $R^2 = 0.99953$, both $p < 0.001$). High target specificity was observed against non-complementary DNA sequences. The system maintained signal stability for 33 days and preserved performance across five regeneration cycles. These findings establish a sensitive electrochemical strategy for assessing mtDNA integrity, offering a versatile tool for investigating mitochondrial alterations associated with MDD.

P2-G-518 *Evaluating the repeatability of fNIRS for assessing cerebrovascular function*

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Access to timely and accurate brain imaging remains a major challenge, particularly in rural settings where advanced diagnostic tools are scarce. There is a need for portable, affordable, and reliable neuroimaging methods that can extend brain health beyond urban centres. Cerebrovascular reactivity (CVR) is a well-established physiological marker of cerebrovascular and overall brain health, yet its clinical assessment remains largely confined to advanced neuroimaging modalities that are costly and infrastructure dependent. Functional near-infrared spectroscopy (fNIRS) is a portable, affordable and non-invasive alternative for measuring CVR. However, concerns regarding repeatability of fNIRS based CVR measurements have limited its broader clinical adoption. The purpose of this study is to address existing gaps in the literature by assessing the test-retest repeatability of fNIRS based CVR measurements in a healthy adult population over a one-week interval using a fixed CO2 stimulus. Healthy adult participants completed two identical experimental sessions. Hemodynamic responses were recorded using an 8x7 optode fNIRS configuration, and CVR was quantified through changes in oxygenated and deoxygenated hemoglobin concentrations. Test-retest repeatability will be assessed using intraclass correlation coefficients (ICCs) to evaluate the consistency of CVR responses across sessions. It is hypothesized that fNIRS CVR measurements will exhibit good to excellent repeatability over a one-week period, demonstrating potential for clinical applications of fNIRS CVR measurements.

P2-G-519 *Expanding AAV diversity: An AI guided unbiased exploration of exotic viromes*

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Adeno-associated viruses (AAVs) are useful tools for gene therapy due to their cellular specificity and safety. Although new capsids can be engineered to improve the infection efficiency, they are often derived from existing sequences, and frequently from the same starting serotype, thus potentially limiting the range of improvements. To broaden the diversity of capsids available for developing new viral vectors, this project aims to build a bioinformatic pipeline to detect AAV-like sequences in fecal samples from exotic animals. We

hypothesize that these samples contain AAV capsids with novel properties, as suggested by the discovery of an AAV originating from the Mandrillus sphinx, commonly known as the mandrill. This AAV was isolated by polymerase chain reaction using primers that target conserved regions across known serotypes. However, the objective of this project is to eliminate such bias by detecting target genomes based solely on native sequences by isolating potential viruses from animal samples followed by next-generation sequencing. In parallel, an artificial intelligence model is being trained to recognize AAV genomic patterns, allowing metagenomic data to be ranked according to the likelihood of sequences being AAVs.

P2-G-520 *Fast AAV validation pipeline in rats for translational primate studies*

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Chemogenetic and optogenetic tools are increasingly being used to probe the function of neural circuits in non-human primates. A systematic pipeline to validate viral expression and effector protein function is important before high-stakes primate experiments. Here, we present a rodent-based pipeline to test the efficacy and minimize the risks associated with adeno-associated virus (AAV) use prior to translational studies. First, we refine the parameters of stereotaxic AAV injections to maximize transduction efficiency and spatial confinement in rat brains. Second, we establish a stable, sedated electrophysiology preparation in vivo using a constant-rate infusion of ketamine and xylazine to obtain stable recordings suitable for measuring even subtle optogenetic or chemogenetic modulation. We obtain quantitative readouts of neuronal population modulation using multielectrode probes with single-neuron spiking resolution. Third, we developed a standardized histological workflow to quantify AAV expression and tissue health across three dimensions: (i) cell-type specificity, (ii) transduction efficacy, and (iii) inflammation or toxicity. This anatomical investigation is interpreted alongside the neurophysiological results to characterise viral vector efficacy. Together, this pipeline yields a reproducible, quantitatively benchmark for AAV testing in vivo, including physiological tests of protein function. The results can be adapted directly to primate work, improving experimental reliability, reducing risk and cost, and minimizing animal use in downstream non-human primate studies.

P2-G-521 *Feasibility of accelerated intermittent theta burst stimulation combined with balance training in Alzheimer's disease and related dementias*

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Balance impairments are common in Alzheimer's disease (AD) and related dementias and are associated with cognitive decline and increased fall risk. Deficits in postural control and gait are evident across dementia subtypes. Accelerated intermittent theta burst stimulation (aiTBS) targeting the dorsolateral prefrontal cortex (DLPFC) has shown potential cognitive benefits in AD. Given the relationship between cognition and balance, this case series examined the feasibility of pairing aiTBS with balance training in women with AD and mixed dementia. Four women (73–88 yrs) completed a 14-day intervention. Each day aiTBS was delivered three times daily to the DLPFC using standard iTBS, followed by 10 minutes of biofeedback-based balance training. Feasibility, defined as ≥75% adherence, was the primary outcome. Cognitive function, depressive symptoms, and fall risk were assessed pre- and post-intervention. aiTBS adherence was 100% with no adverse events. Balance training adherence varied: two participants did not train due to behavioral barriers, while two completed 57–64% of sessions. Those who adhered to balance training showed improvements across more domains. Findings suggest aiTBS is feasible and well tolerated, while balance training poses adherence challenges. Preliminary patterns indicate potential benefits of combining aiTBS with physical training. Larger, placebo-controlled studies are needed to evaluate efficacy and optimize combined intervention approaches in dementia populations.

P2-G-522 *From temporal precision to delusion formation: Gamma synchrony and perceptual deficits in Schizophrenia*

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Altered gamma-band synchrony is a core neurophysiological abnormality in schizophrenia and may contribute to disruptions in the perception of brief time intervals. This study investigates whether two behavioural paradigms can help us better quantify perceptual deficits to understand the mechanisms behind the formation of delusions in schizophrenia. Participants completed the Time Perception Accuracy Test (TPAT) and an auditory interval-discrimination task based on foundational sub-second timing work in schizophrenia (Elvevåg et al., 2003), updated and reformulated as Drew's Hoots. Healthy controls (HC; n=31) and individuals with psychotic symptoms (SZ; n=32) were recruited. TPAT presents physically valid sphere collisions or collisions with artificial temporal delays. In HCs, accuracy in detecting invalid collisions increased with delay length (R^2 = 0.65, r = 0.80, p = 0.000033), with mean accuracy of 58.2% (95% CI: 52.8–63.6). Drew's Hoots tests sub-second interval judgments while minimizing reliance on working memory or counting. Consistent with Elvevåg et al. (2003), individuals with schizophrenia were expected to show reduced precision in recognizing standard durations and categorizing brief intervals as "short" or "long". Behavioural group comparisons across both tasks will be presented. Given evidence that gamma synchrony supports timing precision, we hypothesize that performance on TPAT and Drew's Hoots will index individual variability in gamma-band phase-locking. EEG data collected during both tasks will be used to explore whether behavioural timing measures track with gamma synchrony alterations in psychosis. Together, these paradigms may offer a dual behavioural–neurophysiological framework for detecting timing deficits and associated neural dysregulation in schizophrenia which may underlie the formation of delusions.

P2-G-523 *Frontal alpha asymmetry across graded sensory challenge: Investigating regulatory demands during standing balance*

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Background: Frontal alpha asymmetry (FAA), an inter-hemispheric differences in alpha wave power, has been linked to task demands and sensory states. Its relationship to real-time sensory reweighting during postural control remains unexplored. This pilot establishes methodological feasibility and generates preliminary effects to guide powered future studies. Method: Four neurotypical adults completed four 1-minute graded sensory conditions (eyes open/closed × stable/foam surface) while 13-channel EEG and physiological vibration acceleration (phybrata) sensing were recorded, resulting in concurrent EEG and biomechanical capture to cortical dynamics during balance maintenance. Results: A gradient of FAA modulation (lnF4 -lnF3) related to increasing sensory challenge is expected, where FAA is most right-lateralized when visual and proprioceptive input are challenged. Changes in FAA are also expected to correspond to increased vestibular band power, reflecting sensory reweighting when sensory cues are unavailable. Conclusion: The present work establishes a passive method for assessing whether frontal regulatory processes track graded increases in postural control demands. Proof of concept impact: Demonstrating FAA sensitivity to graded sensory demands establishes a biomarker for defining the development of sensory-motor integration in both neurotypical and neurodivergent persons.

P2-G-524 *Guided topic modeling of single-cell human prefrontal cortex methylome for cell-type deconvolution and epigenetic trajectory analysis in major depressive disorder*

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DNA methylation offers a critical window into the gene-environment interplay, revealing how external factors, such as stress, can alter gene expression. This epigenetic mechanism is relevant for understanding Major Depressive Disorder (MDD), a condition affecting people worldwide, with treatments that help only 50% of patients. Prior studies indicate that MDD-associated methylation markers are cell type-, sex-, and developmental state-specific; however, single-cell methylomics remains expensive and technically demanding, limiting its use. The objective is to adapt and validate a cell-type deconvolution framework that learns cell-specific methylation markers from single-cell references and then applies them to bulk human PFC data generated by our group. In turn, this enables recovery of sex-aware, cell–type–resolved signals across a puberty-centered age range, thereby providing valuable insights into MDD biology. We adapt GTM-decon, a guided topic model, to methylomics, where cell types are latent topics learned from single-cell PFC methylomes, and each bulk sample is a mixture of these topics. After learning signatures, we infer topic weights and cell-type–specific methylation for each bulk profile. We evaluate performance using pseudo-bulk mixtures under leave-one-donor-out testing and cross-check cell identity with available single-cell RNA-seq. In preliminary results, GTM recovers expected major neuronal and glial compositions. CpG features provide stable reconstruction, whereas CAC features improve separation of glial lineages; combining modalities improves cell-type resolution without degrading overall fit. Applied to our bulk PFC cohort (ages 8–22; both sexes; control and MDD), the model yields interpretable age- and sex-associated trajectories and candidate differentially methylated regions for downstream validation.

P2-G-525 *HeteroRC: Decoding latent information from dynamic neural responses with interpretable heterogeneous reservoir computing*

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Time-resolved decoding from EEG/MEG is essential for tracking information represented in the brain. While conventional linear decoders operating on voltage/field signals effectively capture phase-locked, evoked responses, they often fail to recover information in nonlinear, non-phase-locked dynamics. Here we introduce HeteroRC, a biologically inspired and interpretable decoding framework based on heterogeneous reservoir computing. HeteroRC projects neural signals into a high-dimensional recurrent state space with diverse intrinsic time constants mimicking neural populations' ability to integrate multi-scale dynamics. Crucially, HeteroRC operates directly on raw neural time series without the need for explicit feature engineering. Simulations show that HeteroRC outperforms conventional linear decoders for evoked responses and enables robust decoding of induced power, phase clustering, and aperiodic modulations—regimes that remain largely latent to conventional linear decoding. We then apply HeteroRC to two public EEG datasets. In a motor imagery task, HeteroRC significantly outperforms linear decoding, particularly during sustained imagery periods. In an attentional priority task, HeteroRC decodes statistically learned spatial priority information that remain hidden from conventional decoders, even in the absence of external 'pinging' stimulation. We further develop an interpretability framework that maps reservoir dynamics to virtual sources and sensor space, revealing temporal, spectral, and spatial signatures underlying decoding performance. Together, HeteroRC offers an interpretable approach to decode information from dynamic neural responses, extending beyond phase-locked activity while remaining computationally efficient, requiring no pretraining or manual feature engineering—ideal for small-sample, trial-limited electrophysiological datasets.

P2-G-526 *High SNR outperforms high diffusion weighting for OGSE-TDS axon diameter mapping precision*

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Oscillating Gradient Spin Echo (OGSE) temporal diffusion spectroscopy (TDS) is a promising technique for non-invasively estimating axon diameter (AxD) in white matter tracts. This study compares two OGSE-TDS acquisition strategies: one with a higher signal-to noise ratio with reduced diffusion weighting (DW) and another using larger DW at the cost of lower SNR to assess how these strategies affect AxD measurements for a given imaging time. A 1 mm image slice perpendicular to the genu substructure was imaged at 15.2T in two ex vivo 12-week-old male CDI mice in separate experiments. In experiment one, 9 diffusion-weighted images with OGSE were acquired per frequency (50 - 450 Hz) using apodised cosine waveforms (TE = 50 ms, TR = 800 ms, b-values up to 298 s/mm2). In experiment two, 9 DW images were acquired per frequency (50 – 450 Hz) using apodised cosine waveforms (TE = 50 ms, TR = 1250 ms, b-values up to 1500 s/mm^2). AxD was inferred by fitting the image signals to a two-compartment ActiveAx model. Experiment 1 yielded smaller AxD estimates with smaller uncertainty (1.9 ± 0.2 µm), compared to experiment 2 which produced larger AxD estimates with larger uncertainty (4 ± 2 µm). Based on the uncertainties, these experiments demonstrate that for a given imaging time, it is optimal to prioritize higher SNR with reduced DW to achieve better precision of axon diameter inferences using OGSE-TDS. Acknowledgements: Funding from NSERC and the Vanderbilt Institute of Imaging Science for use of their 15 T magnet in the experiments.

P2-G-527 *Hippocampal-claustrum coupling during sleep*

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The claustrum is a small subcortical nucleus with one of the highest density of neuronal inputs and outputs in the brain, but its function remains incompletely understood. Current mouse research suggests the claustrum is associated with delta waves and slow wave power in non-rapid eye movement sleep (NREM). However, the claustrum's relationship to other NREM related brain oscillations such as sleep spindles and hippocampal sharp wave ripples have not been characterized. To probe whether these other NREM oscillatory events are related to claustrum activity, we used a combination of in-vivo two-photon microscopy of GCaMP8m expressed in mouse claustrum axons, chronically implanted local field potential electrodes in prefrontal cortex and CA1 hippocampus, and pupillometry. We found that claustrum activity is robustly coupled to both delta waves and hippocampal ripples but weakly coupled to sleep spindles. The coordination between delta waves and claustrum activity was limited only to periods with hippocampal ripples, suggesting the hippocampus as a key modulator of claustrum activity in sleep. Such a link between cortical and hippocampal oscillations may help explain the improvements to memory when claustrum neurons are stimulated during memory consolidation. Future work will address whether the claustrum is involved in the coordination of cortical and hippocampal oscillations.

P2-G-528 *Improved sleep spindle detection using the BOSC method: A comparison with traditional approaches*

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Sleep spindles are brief bursts of 6–20 Hz local field potential (LFP/EEG) activity that occur during non-rapid eye movement sleep. Traditional spindle detection methods rely on manually set amplitude and duration thresholds, but this approach can be vulnerable to false detections and could miss low-amplitude spindles due to the inflexible nature of the thresholding technique. The Better OSCillation (BOSC) detection method offers a more robust alternative by applying frequency-specific power thresholds calibrated to the signal itself and requiring a minimum number of oscillation cycles. In this study, we compared traditional and BOSC methods for spindle detection in a variety of ways. First, we created two synthetic datasets: one with

synthetic spindles modelled on previous data and one with single wave pulses that had a period consistent with the spindle frequency band. These datasets were used to demonstrate each method's performance when given events that should be detected (synthetic spindles) and those that should not (single wave pulses). Second, we analyzed cortical local field potentials from recordings of rats during natural sleep using both methods to determine their relative effectiveness given biological LFP data. BOSC consistently outperformed the traditional approach in all situations, identifying more valid spindles while minimizing false (or likely false) detections. These findings validate BOSC as a superior method of spindle detection due to its better calibration to the actual signal.

P2-G-529 *Increasing corticospinal excitability using personalized brain stimulation: A feasibility study*

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Transcranial magnetic stimulation (TMS) is a non-invasive neuromodulation technique currently being explored as a treatment for motor disorders; however, response to TMS treatment is highly variable across individuals. This variability may arise from limited personalization of stimulation timing and delivery conditions. Recent work demonstrates that synchronizing TMS with brain activity using electroencephalography (EEG) can enhance corticospinal excitability, as reflected by increased motor evoked potentials (MEPs). The objective of this study is to investigate whether delivering TMS during pre-movement brain activity enhances corticospinal excitability compared to stimulation delivered at rest. Twenty healthy right-handed adults will participate in a single-session experiment combining EEG and TMS. A brain-computer interface (BCI) will be trained to detect EEG features of pre-movement brain activity in real time and trigger TMS prior to movement onset. The primary measure will be cortical spinal excitability as reflected by the MEP amplitude recorded from the first dorsal interosseous muscle. We hypothesized that TMS delivered pre-movement would produce significantly larger MEPs than TMS delivered at rest. Preliminary results support the hypothesis, reporting greater MEPs recorded pre-movement than at rest. Demonstrating phase-specific enhancement of corticospinal excitability would provide critical evidence for movement-informed TMS protocols and may inform more effective, individualized neuromodulation strategies.

P2-G-530 *Information-geometric classification of EEG signals with motor imagery tasks*

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In complex systems such as the brain, there is evidence that information is carried not only by the individual activations of components and their pairwise interactions, but also by higher-order interactions within the system. Promising tools for exploring these higher-order interactions in neural data come from information geometry (IG), which allows for the orthogonal decomposition of information across different orders of interaction beyond pairwise. IG methods have previously been successfully applied to the analysis of spike train data. Here, we apply them to an OpenNeuro human electroencephalography (EEG) dataset recorded during a motor imagery experiment. Participants were instructed to imagine sit-to-stand or stand-to-sit movements while sitting or standing, respectively, alongside control conditions where they imagined nothing. Using IG, we identified first-, second-, and third-order interactions among EEG channels associated with the motor imagery conditions. We then used the IG interactions from a single triplet of EEG channels as predictors in a linear discriminant analysis to classify the motor imagery and corresponding idle conditions in each of the two postures. The highest mean classification accuracy was achieved from including the entire hierarchy of interactions (73.42% across all participants and both postures) as opposed to only pairwise and lower order terms. This lends support to the idea that higher-order interactions could carry additional information not captured by pairwise and lower relations.

P2-G-536 *Molecular signatures from neuronal and oligodendrocytic extracellular vesicles isolated from blood samples in patients with ALS undergoing focused ultrasound and IVIg treatments*

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Background. The delivery of intravenous immunoglobulin (IVIg) to the brain is enhanced using focused ultrasound (FUS). This treatment aims to reduce neuroinflammation in patients with amyotrophic lateral sclerosis (ALS). To overcome the challenges of monitoring treatments responses in the brain, we developed a blood-based liquid biopsy approach to isolate extracellular vesicles (EVs) and detect their biomarkers content in a brain-cell specific manner. Methods. Plasma samples were collected from patients with ALS who receive FUS treatment targeted to the motor cortex and intravenous immunoglobulin (IVIg, 0.4 g/kg), and age-matched controls. Blood samples were collected at 8 time-points, pre and post-treatment. Total EVs were enriched from plasma and brain cell-specific EVs were isolated with antibodies to detect EVs from neurons (L1CAM), astrocytes (EAAT1), microglia (TMEM119), and oligodendrocytes (MOG). Results. Pre-treatment, the levels of TDP-43 in ALS were higher compared to control in oligodendrocytic-EVs (321 vs 29 pg/mL), and to a lesser extent in astrocytic-EVs (55 vs 33 pg/mL). Following treatment of FUS + IVIg, the levels of TDP-43 in neuronal-EVs were higher in ALS at 1 h post-FUS (Δ = 17 pg/mL). Conclusion. The enrichment of TDP-43 in ALS was striking in oligodendrocytic-EVs, corroborating prior human postmortem studies (Brettschneider et al. 2014; Nolan et al., 2020). These findings demonstrate that cell-specific, EV-brain derived liquid biopsy can capture ALS relevant molecular signatures non-invasively, thereby addressing a critical gap in ALS biomarkers monitoring.

H - HISTORY, TEACHING, PUBLIC AWARENESS AND SOCIETAL IMPACTS IN NEUROSCIENCE

P2-H-531 *Improving brain health literacy among adolescents: The maintain your brain game*

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Lifestyle changes could delay or prevent 45% of cognitive impairment, but the general public is typically not aware of this potential. An important concept associated with improving age-related outcomes is cognitive reserve. Cognitive reserve is the degree to which an individual has greater resilience to cognitive declines associated with aging and/or brain diseases. There are many evidence-based lifestyle changes individuals can make to improve cognitive reserve, which motivates improved knowledge mobilization of this important concept. Exposure to these modifiable factors begins during adolescence. We are co-developing a freely-available learning tool about cognitive reserve through game play. To date, we have run eight successful pilot events with over 200 individuals. Using a participatory action research framework, we will co-develop and evaluate the effectiveness of the “Maintain your Brain” game on teaching adolescent audiences about cognitive reserve. Via a focus group with a teacher participant-researcher, we identified many strengths of the game for adolescent audiences (e.g., the creative aspects of the game, adolescent-relevant content such as alcohol use and education). Next, we will play the game with adolescents. Through pre-and post-intervention surveys, we will assess their knowledge of cognitive impairment and cognitive reserve, as well as attitudes and behaviours regarding cognitive impairment. The game is intended to be fun and memorable, so that individuals are motivated to make lifestyle changes that improve their cognitive reserve. We will make this game freely available, and promote it to our academic and community networks. We anticipate that the game will be a useful teaching tool and ultimately will help Canadians maintain their cognition as they age and in the presence of brain diseases.

P2-H-532 *Making the brain visible: EEG-based brain–computer interfaces for education and social impact in corporate wellness*

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Mental health challenges such as chronic stress, burnout, and cognitive overload are increasingly prevalent in corporate environments across Canada, affecting employee well-being and organizational sustainability. Canadian and Quebec policy frameworks emphasize employer responsibility for psychological health and preventive, education-driven approaches, making corporate wellness a priority.Despite this shift, most wellness programs rely on dialogue-based interventions such as counselling, cognitive behavioral therapy (CBT), and mindfulness practices that depend largely on subjective self-report, offering limited insight into real-time neural processes underlying stress, attention, and self-regulation. We propose a layered framework integrating non-invasive, EEG-based brain–computer interfaces (BCIs) as an educational-training layer embedded within existing practices. BCIs provide real-time neurofeedback from scalp EEG signals during practices such as meditation or CBT exercises, targeting oscillatory activity linked to self-regulation (alpha, theta, beta bands).Further, our narrative review indicated that over 90% of Canadian programs rely exclusively on traditional methods, with fewer than 1–2% incorporating EEG-based components, despite more than 16 randomized and controlled studies globally demonstrating BCI feasibility for mental health. Thus, by making neural dynamics observable, our framework may enhance self-awareness, and strengthen engagement with existing wellness interventions, making it a non-surveillant translation of neuroscience for the society.

P2-H-533 *RetINaBox: A hands-on learning tool for experimental neuroscience*

Flavia Arias Armas [1], Erica Cianfarano [2], Brune Bettler [1], Vanessa Bordonaro [1], Megan Liu [1], Matthew Loukine [1], Mingyu Wan [1], Aude Villemain [1], Blake Richards [3], Stuart Trenholm [3]

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The way the brain encodes sensory stimuli is often far from predictable. Thus, to discover how sensory inputs are represented in the brain, neuroscientists directly record from individual neurons while delivering controlled stimulation. A challenge in neuroscience education is incorporating this experimental approach into lessons, so that instead of solely memorizing lists of facts, students get hands-on experience that captures the excitement of discovery. Laboratory classes have long been used to address this challenge, but are often limited by infrastructural, ethical, and training constraints. To this end, we developed RetINaBox (“retina in a box”), an educational tool that provides users with a hands-on system in which to discover how the visual system implements several important feature-selective computations. RetINaBox features an LED array for visual stimulation, photodiodes that acts as model photoreceptors, and two model retinal ganglion cells that integrate photoreceptor signals. RetINaBox exposes users to numerous computations in the visual system, including ON/OFF processing, center-surround receptive fields, orientation selectivity and direction selectivity. RetINaBox also features a Discovery Mode in which users must discover an unknown neuron’s preferred feature and then infer the circuitry underlying its selectivity. RetINaBox makes experimental neuroscience accessible in classrooms and outreach settings. By enabling students to generate predictions, design experiments, and interpret results, it captures the authentic process of scientific discovery.

POSTER SESSION 3

A - DEVELOPMENT

P3-A-537 *N-acetylcysteine mitigates behavioral impairments and neuronal dysregulation caused by adolescent nicotine exposure in rats*

Leandro Val Sayson [1], Marieka Devuono [1], Enzo Pérez-Valenzuela [1], Matthew John Jones [1], Marwa Idrissi [1], Jason Yeung [1], Elizabeth Osuch [2], Jean Theberge [2], Robert Hegele [3], Jibran Khokhar [1], Walter Rushlow [1], Steven Laviolette [1]

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Adolescent use of nicotine (NIC) vapes continues to rise, raising concern due to the heightened sensitivity of the developing brain to addictive substances. NIC exposure during this developmental stage has been associated with long-term neuropsychiatric effects, including mood disorders and cognitive impairments. Animal research suggests that NIC disrupts neurotransmitter systems involved in regulating emotion, behavior, and decision-making, underscoring the need for interventions that could mitigate these outcomes. N-acetylcysteine (NAC), a glutamatergic modulator shown to reduce the impact of some drugs of abuse, may offer neuroprotective benefits against NIC-induced changes. This study examined whether NAC administration during adolescence can prevent the long-lasting behavioral and electrophysiological (EPHYS) consequences of NIC exposure in male rats. Rats received NIC injections (SQ, 3 times daily) with or without NAC supplementation (drinking water) throughout adolescence. In adulthood, animals were assessed on object recognition, social motivation and memory, and depression-like behavior, followed by single-unit EPHYS recordings in the prefrontal cortex (PFC) and dorsal hippocampus (dHipp). NIC exposure resulted in significant deficits in temporal object recognition, sociability, and depression-like behavior. NAC co-treatment mostly prevented these behavioral impairments. EPHYS analyses revealed NIC-associated changes in firing frequency and bursting activity and NAC normalized the proportion of bursting neurons but did not fully restore firing frequency. These findings suggest that NAC provides partial neuroprotection against the long-term effects of adolescent NIC exposure, potentially through the modulation of PFC and dHipp neuronal activity. Future work will assess GABAergic and glutamatergic protein expressions to further elucidate underlying mechanisms.

P3-A-538 *Parental origin modulates testosterone genetic effects on the tangential growth of the cerebral cortex*

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Introduction: Androgens likely shape sex differences in brain structure. We tested if genetic variations in testosterone levels predict cortical surface area (SA) and whether these associations depend on parental genetics and offspring sex. Methods: Using the Saguenay Youth Study (1,024 adolescents; 962 parents), we calculated testosterone polygenic scores (PGS) from sex-specific UK Biobank GWAS. We tested sex-stratified associations between PGSado, PGSfather, and PGSmother on offspring SA using linear regressions. Parental PGS were adjusted for PGSado to control for direct transmission. Paternal vs. maternal differences were evaluated via permutation-based profile analysis. Results: PGSado was associated with total SA in neither males (β = -0.0691, SE = 0.0427, p = 0.33) nor females (β = 0.0657, SE = 0.0363, p = 0.2). Regarding parental effects, we observed striking sex-specific differences: (1) PGSfather adjusted for PGSado was associated with larger SA in females (β = 0.1059, SE = 0.0371, p = 0.03) but not males (β = 0.0569, SE = 0.0497, p = 0.59), while (2) PGSmother adjusted for PGSado was (trend) associated with lower SA in males (β = -0.1084, SE = 0.0516, p = 0.07) but not females (β = -0.0157, SE = 0.0361, p = 0.9876). Permutation tests revealed similar differences in parental effects in male offspring (p = 0.047) and a trend in females (p = 0.052). Conclusion: Testosterone genetics affect the cortex differently depending on parental origin. Adjusting for offspring PGS revealed possible “genetic nurture” effects of the father on his female offspring.

P3-A-539 *Perinatal Delta-9-tetrahydrocannabinol alters development of sleep and hypoxic ventilatory reflex in newborn rats*

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Perinatal exposure to cannabis has been linked to adverse neurodevelopmental outcomes, yet its impact on the maturation of sleep and respiratory control remains poorly defined. Δ^9-Tetrahydrocannabinol (THC), the principal psychoactive constituent of cannabis, readily crosses the placenta and is transferred through breast milk, exposing the developing brain to exogenous cannabinoids during critical windows of network formation. Here, we examined the effects of continuous perinatal THC exposure on maternal care, the development of postnatal sleep architecture and respiratory control. Pregnant dams received THC (1 mg/kg/day) via subcutaneous osmotic pumps from gestational day 5 to postnatal day (P)14. Maternal care behaviours, including licking, grooming, nursing, and pup retrieval, were recorded from P1–P14. Offspring underwent longitudinal assessment of sleep–wake organization using nuchal EMG, overt behaviour and EEG activity. Breathing patterns and chemoreflex responses were assessed using head-out and whole body plethysmography under normoxia, hypoxia, and hypercapnia. Our results show that maternal nursing and grooming were preserved, although THC-treated dams exhibited delayed pup retrieval. In pups, THC exposure accelerated sleep-wake maturation: the normal decline in active sleep and rise in wakefulness seen in controls at P10–11 emerged prematurely at P6. Chemoreflex testing showed that newborn pups displayed an attenuated hypoxic ventilatory responses from P0–P3, due to a smaller decrease in oxygen consumption during hypoxic challenge. Collectively, these findings demonstrate that perinatal THC exposure induces premature maturation of sleep architecture and alters early life respiratory control, underscoring a direct developmental vulnerability of sleep–breathing coordination to early-life cannabinoid exposure.

P3-A-540 *Post-natal disruption of the blood-brain barrier and abnormal brain development in an Autism model*

Celeste Laporte [1], Siyao Peng [2], Katrina Choe [3], Masha Prager-Khoutorsky [1]

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Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by social deficits and repetitive behaviours. Deficiency of the pro-social hormone oxytocin (OXT) is thought to underlie social deficits in patients and several pre-clinical models. The Cntnap2 knock-out mouse, a genetic model of ASD, has fewer OXT neurons in the hypothalamus; however, how and when this deficiency emerges during development is unknown. We hypothesize that Cntnap2 is an adhesion protein implicated in blood-brain-barrier (BBB) integrity, especially during development. Increased BBB permeability can be neurotoxic and disrupt key developmental programs such as microglial pruning. To investigate BBB permeability, we used a combination of immunohistochemistry (IHC) and super-resolution microscopy to visualize the BBB structural protein Cldn5 and quantified the extravasation of an injected tracer (Sulfo-NHS-Biotin) in the hypothalamus. Our preliminary findings show that at birth, Cntnap2 deficient mice have diminished BBB integrity. To study the implications of a leaky BBB, we used IHC to visualize OXT neurons, microglia and apoptotic cells. This revealed that neonatal Cntnap2 deficient mice have normal OXT cell numbers but increased microglial and apoptotic cell density around OXT neurons. Future work will investigate BBB and OXT system development across additional timepoints and interrogate microglial activity in Cntnap2 deficient mice. These findings will provide additional insight into the mechanisms which link genetic factors to behavioral phenotypes in patients and models of ASD.

P3-A-541 *Probing parallel changes in the synaptic proteome and transcription regulation in the MDGA2 deficient autism model mouse*

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MDGA2 is a synapse organizing protein shown to have critical roles in synapse development and function through interaction with Neuroligin (Nlgn) 1. Dysregulation of MDGA2 has been implicated in autism spectrum disorder (ASD) as demonstrated by gene linkage analysis in several human cases of autism and in mice lacking a single allele of the Mdga2 gene (Mdga2+/-), which exhibited social deficits and physiological impairments related to synaptic plasticity. Building on our previous unbiased synaptic proteomic and phosphoproteomics analyses in Mdga2+/– mice, which revealed sex- and hippocampal region-dependent alterations in synaptic signaling pathways, we now investigate whether these protein-level changes are accompanied by transcriptional alterations in genes encoding for other key synapse organizers. We performed quantitative PCR on dorsal and ventral hippocampal subregions from male and female Mdga2+/– and wildtype mice, focusing on MDGA1 and MDGA2, as well as Nlgn1, Nlgn2, and Nlgn3. This approach allows us to explore compensatory or residual expression of synapse organizers resulting from partial loss of MDGA2 and extends our understanding or transcriptional and translational processes impacted by MDGA2 reduction, thereby aiding in the identification of potential therapeutic targets associated with MDGA2 in ASD.

P3-A-542 *Regulation of inhibitory interneuron survival by the clustered Protocadherins and PTEN/PI3K signaling*

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Developmental programmed cell death by apoptosis is fundamental for shaping a functional neural architecture by eliminating excess or inappropriately integrated neurons and refining their appropriate size. Disruption of this process leads to several neurological deficits, yet the molecular mechanisms that determine survival versus death remain poorly understood. Our lab and others have identified the clustered Protocadherin gammas (Pcdhgs) as key regulators of neuronal survival in the mouse spinal cord, cortex, and retina. Conditional deletion of Pcdhg particularly affects the locally projecting interneurons (INs), suggesting a role in fine-tuning their numbers. Pcdhgs encode 22 isoforms, however, recent work has identified PcdhgC4 as the sole isoform essential for neuronal survival, with its loss phenocopying deletion of all 22 Pcdhg genes. That said, PcdhgC4 signaling remain unclear. We found PTEN to be critical for inhibitory IN survival. Pten deletion increases IN numbers and p-Akt levels, opposing the effects of Pcdhg loss. Analysis of double knockouts supports an epistatic interaction, consistent with PTEN acting upstream to negatively regulate Pcdhg-mediated survival signaling. In complementary experiments, we found that Cre-driven overexpression of PcdhgC4, but not PcdhgC3, in wild-type retina increases IN densities. Although both isoforms exhibit similar expression and localization in INs at P7, their patterns diverge by P28, with PcdhgC3 remaining enriched in INs and PcdhgC4 becoming predominantly localized to Müller glia. Western blot analysis revealed a slight, non-significant increase in Pcdhg protein levels in conditional Pten knockouts. These findings provide insight into mechanisms regulating IN survival during circuit formation and altered functions of cell adhesion molecules in brain disorders.

P3-A-543 *Selective neurotoxic effects of prenatal cannabis exposure on white matter*

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Prenatal cannabis exposure may interfere with early brain development due to the high density of cannabinoid type 1 (CB1) receptors in specific white matter pathways. We hypothesized association fibers with high CB1 receptors expression, the fornix and uncinate fasciculus, would be affected, while larger commissural and motor projection pathways, the corpus callosum and posterior limb of the internal capsule

(PLIC), would be preserved at the neonatal stage. Fifty-four newborns were included, 18 infants exposed to cannabis in utero and 36 non-exposed controls. Diffusion-weighted MRI data were acquired on a 3T scanner using diffusion tensor imaging with 25 diffusion directions, a b-value of 800 s/mm2, and 2 mm isotropic resolution. Deterministic tractography was performed to reconstruct the fornix, uncinate fasciculus, corpus callosum, and PLIC. Fractional anisotropy, mean, axial, and radial diffusivity were extracted. The tractography protocol demonstrated excellent intra- and inter-rater reproducibility (Cohen's κ = 0.91-0.99). Exposed newborns showed significantly increased mean, axial, and radial diffusivity in the fornix (p = 0.012-0.022), with a trend toward reduced fractional anisotropy. The uncinate fasciculus also exhibited higher axial and mean diffusivity in the exposed group ($p < 0.05$). No significant differences were observed in the corpus callosum or the PLIC. In conclusion, prenatal cannabis exposure is associated with selective microstructural alterations in neonatal association fibers, while major commissural and motor pathways appear preserved at birth.

P3-A-544 *Sex shapes the development of neuroinfectious virus receptors across the human lifespan*

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Neuroinvasive single-stranded RNA (ssRNA) viruses cause a wide range of neurological outcomes, from mild illness to life-threatening disease. Host factors such as age, sex, and receptor expression influence vulnerability, yet how sex and age shape ssRNA virus receptor expression in the human brain remains unclear. We applied a data-driven computational workflow to characterize sex- and age-dependent patterns of 67 host receptor genes across 10 ssRNA virus families in 11 cortical and 4 subcortical areas using a lifespan transcriptomic dataset (4 months-82 years). Lifespan trajectories were characterised for gene-area-sex (n=2010) and examined using high-dimensional analyses, machine learning, and differential expression. Most receptor genes show nonlinear developmental trajectories that differ between females and males, with the strongest sex differences in the cortex. A machine learning model trained on population-level trajectories predicted sex with 78% accuracy. Within the cortex, sex differences vary across development, with the highest frequency of differential expression in early childhood. Although virus families and cell-type associations are broadly distributed across developmental programs, select sex-by-age patterns show enrichment for specific virus families and cell-type profiles. These findings reveal complex, sex-dependent regulation of ssRNA virus receptor expression in the human brain. They highlight the importance of sex as a biological variable for understanding neuroinfectious disease vulnerability and guiding prevention and treatment across development.

P3-A-545 *Sex-dependent modulation of lateral hypothalamic–dorsal raphe and infralimbic circuits following acute stress*

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[1] *University of Calgary*

Acute stress modulates neural activity within circuits involved in emotional regulation and mood stability. Lateral hypothalamus (LH) inputs to the dorsal raphe nucleus (DRN) and prefrontal regions such as the infralimbic (IL) area, play an important role in shaping stress coping, socioemotional behaviour, and anxiety-related responses. Here, we investigated how acute stress modulates behaviour and associated neural activity within LH-modulated DRN and IL pathways in male and female C57BL/6 mice. After receiving foot-shock as a model of acute stress, mice were subsequently assessed in behavioural assays measuring anxiety-like behaviour, social interaction and stress coping. Acute stress produced measurable changes in socioemotional behaviour, with effects that differed between sexes. In vivo calcium imaging revealed a significant increase in the activity of LH axons in both DRN and IL regions following foot shock. Ex vivo optogenetic stimulation of LH terminals in the DRN revealed stress-dependent modulation of DRN serotonergic neuron activity in stressed mice compared to controls, indicating that acute stress modifies LH-mediated regulation of serotonergic circuitry. Stress-induced LH modulation of DRN and IL pathways

during socioemotional tasks differed between male and female mice. Together, these findings suggest that acute stress alters LH signaling to both the DRN and IL, with consequences for behavioural regulation in a sex dependent manner. Overall, our results shows acute stress engages hypothalamic–prefrontal–brainstem circuits that are critical for adaptive emotional regulation. Importantly, the observed sex differences further emphasize the need to consider sex-specific mechanisms when examining stress-related neural modulation for the development of strategies.

P3-A-546 *Sex-specific offspring neurodevelopmental outcomes in a rodent model of postpartum depression*

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Postpartum depression (PPD) is a serious medical condition, affecting both maternal health and increasing risk for neurodevelopmental and mental health disorders in children. One of the key physiological features of PPD in humans is persistently high levels of cortisol throughout the postpartum period. Our preclinical rodent model uses high levels of the rodent cortisol analog corticosterone across the postnatal period and faithfully recapitulates relevant depressive-like phenotypes in dams and disrupts maternal care behavior. Hippocampal neurogenesis, the process by which new neurons are produced throughout the lifespan, is involved in learning and memory, as well as regulation of stress and anxiety responses. Prior work using our PPD model found increased density of immature neurons in the hippocampus of adolescent offspring, which may reflect either increased levels of neurogenesis or delayed maturation and integration of these new neurons into functional hippocampal circuitry. In the hippocampus, signaling from parvalbumin-positive interneurons (PVI) is critical for the maturation of newly formed neurons. We found decreased PVI density and increased CD68+ microglia, indicative of an activated microglial state, in the hippocampus of adolescent offspring from corticosterone-treated dams. Given that microglia play a direct role in postnatal interneuron development, we hypothesize that maternal postnatal corticosterone exposure disrupts typical microglia-parvalbumin interneuron interactions in the offspring hippocampus. This disruption may lead to decreased PVI signaling, which in turn impairs the maturation of newly generated neurons. Ongoing work is examining microglia-PVI interactions in the developing hippocampus and using behavioral paradigms to assess functional outcomes in adolescent offspring.

P3-A-547 *Single-cell multiomics define a gradual, spatially-regulated epigenetic and transcriptional transition from embryonic to adult neural stem cells*

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Here, we ask how adult neural stem cells (NSCs) arise developmentally, focusing on murine cortical precursors that generate excitatory neurons embryonically and interneurons and glial cells postnatally. Using complementary single-cell spatial, transcriptomic, and epigenomic approaches, we show that postnatal NSC state acquisition involves a gradual transcriptional and epigenetic shift in the entire embryonic cortical precursor cell population and identify a distinct transition precursor state at E17/18 when both embryonic and the first postnatal progeny are being generated. Non-proliferative adult NSCs are also first seen at this transition timepoint, but they arise in a spatial domain distinct from that of the first postnatal progeny, indicating that NSC state acquisition is not a necessary prelude to the switch in cell genesis. These findings support a gradual epigenetically-continuous model for the transition from developing cortical precursors to NSCs and show that this is spatially separable from the transition to generating postnatal cell types.

P3-A-548 *Spatiotemporal development of sparse excitatory neuronal types within the deep mouse cortex*

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The developing brain comprises a diverse array of cell types that emerge in a tightly regulated spatiotemporal manner. Understanding the spatiotemporal organization of cell-type development is therefore critical for elucidating cortical patterning and function. Here, we integrate single-cell spatial transcriptomics to map the temporal evolution and spatial organization of cell types in the developing mouse brain. Across four developmental time points and both sexes, we profile ~1.5 million cells spanning embryonic and postnatal stages, with a focus on sparse deep cortical populations, including the subplate and claustrum. These neuronal populations are often thought to share similar developmental patterns due to overlapping molecular features in adulthood. In contrast to current thinking, we identify marked differences between the developing subplate and claustrum, including distinct cellular origins, transcriptomic and spatiotemporal maturation patterns. These findings suggest that subplate and claustrum neurons play critical yet divergent roles during cortical development. Beyond these insights, our comprehensive single-cell spatial transcriptomics dataset provides a valuable resource for investigating cell-type–specific developmental programs across the brain, enabling future studies of cellular diversity and organization during neurodevelopment.

P3-A-549 *Striatal dopamine release is region-, sex-, and age-dependent in young mice*

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During adolescence, exploratory and risk-taking behaviours increase, facilitating a transition to independence in adulthood but also coinciding with a period of heightened vulnerability to psychiatric disorders. There is significant plasticity of the striatal dopamine system during this period, which may partly underlie the behavioural change and vulnerability. Therefore, understanding how dopamine release and its regulation change across adolescence is critical. Here, we used ultrafast imaging (200 Hz) of the genetically encoded optical biosensor dLight to investigate ex vivo striatal dopamine release and its regulation by local interneurons between adolescent (P50-60) and young adult (P95-115) mice. We found that evoked dopamine release was selectively elevated in the dorsomedial striatum of young adult males, with no corresponding change in the nucleus accumbens. We also found female-specific differences across ages in response to inhibition of local glutamatergic and cholinergic signalling. Our findings suggest that striatal dopamine release changes in a sex-specific manner throughout the adolescent period, at least partly through a differential influence of cholinergic interneuron signalling. A more robust understanding of how the dopamine system develops across adolescence represents a step forward in creating interventions for high-risk psychiatric diseases during this period.

P3-A-550 *Elucidating the neurodevelopment of multisensory integration in the common marmoset*

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Multisensory integration (MSI) is a vital cognitive function typically disturbed in individuals with Autism Spectrum Disorder (ASD). However, understanding how MSI is disrupted in ASD requires an appropriate translatable animal-model for properly understanding its development and representation in the brain. The common marmoset (Callithrix jacchus), a small primate with rich social behaviors, a high reproduction rate, and the capability for genetic modification has emerged as a possible candidate for modelling ASD. To investigate MSI in marmoset models of ASD, it is first necessary to understand how this function typically develops, answering this key question: How are multiple senses encoded and combined by the marmoset brain across their development? To answer this, I am collecting behavioural data through in-cage

touchscreen system with multisensory tasks, and structural and functional (resting state and task-based) MRI data. Data are collected from 6-month-old up to two years old to uncover the neurodevelopment of MSI by correlating brain activity and structure with task performance over time. We hypothesize that a similar parieto-frontal network seen in humans will activate for MSI that is refined with age and modulated by valence and increase in myelin content. This research will have several significant societal impacts. For example, studying the neurodevelopment of primate MSI, and by extension cognition, could help characterize the development of ASD and other MSI-related disorders in humans and provide an essential step between rodent and human clinical trials.

P3-A-551 *A molecular basis of somatotopic map formation*

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Despite first being described nearly a century ago, the mechanisms governing the formation of somatotopic (ST) maps, such as the cortical homunculus described by Penfield, remain largely unknown. The mediolateral (ML) axis of the dorsal horn (DH) of the spinal cord is organised as an ST map of the proximodistal (PD) axis of the body surface. We show that this map correlates with complementary ML gradients of Teneurin-3 (Ten3) and Latrophilin-2 (Lphn2) cell surface receptors. A corresponding expression pattern is also evident in the sensory neurons of the dorsal root ganglia (DRG). Since Ten3-Lphn2 mediated repulsion in conjunction with homophilic Ten3-Ten3 mediated attraction control the wiring of hippocampal circuits, we studied the function of these proteins in DRG-DH connectivity. Towards this aim, we generated conditional knockouts (cKOs) of Ten3/Lphn2 in the DH and DRG, which revealed a range of ML miswiring phenotypes depending on the ablated gene and location, with the Ten3 DH cKO being the most severe. Furthermore, Ten3 DH cKOs also showed an abnormal distribution of Fos protein, a proxy of neuronal activity, induced by a noxious stimulus. Importantly, such mutants display an impaired ability to accurately attend to a noxious stimulus along the PD axis of the limb. We thus provide the first evidence that these molecules act in complementary gradients, are required for ST map formation, and disruption of DH ST map development is accompanied by deficits in directed somatosensory behaviours.

P3-A-552 *The cholesteryl ester transfer protein impacts HDL quantity and quality disrupting neurovascular integrity*

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Background: The cholesteryl ester transfer protein (CETP) mediates the exchange of cholesteryl esters (CE) and triglycerides (TG) between HDL and LDL, lowering HDL and raising LDL levels, thereby increasing risk for vascular dementia and Alzheimer's disease (AD). CETP polymorphisms associated with reduced activity correlate with decreased dementia incidence, suggesting CETP inhibition as a potential preventive strategy. However, the mechanisms linking CETP activity, HDL dysfunction, and neurovascular integrity remain unclear. Methods: Because mice lack endogenous CETP, we used AAV-mediated gene transfer to express wild-type (WT) CETP or three CETP mutants: active CE transfer (aCE), active TG transfer (aTG), or inactive CETP (iCETP), alongside a mock control. We assessed lipid profiles, HDL remodelling, and HDL quality by immunoassays, and evaluated neurovascular integrity through CD31 and GFAP immunofluorescence in brain tissue. Results: CETP expression remodelled HDL, altering not only its quantity but critically its quality. HDL from WT-CETP and aTG mice showed reduced APOA1 content, paraoxonase-1 activity, and cholesterol efflux compared with HDL from mock or iCETP mice. These HDL particles also failed to suppress LPS-induced NF-κB activation in b. End3 cells, indicating loss of anti-inflammatory function. Brain sections from CETP-expressing mice exhibited decreased CD31 and increased GFAP in the dentate gyrus. Only aTG-derived HDL displayed increased particle size by CN-PAGE. Conclusion: CETP-driven HDL remodelling impairs lipid distribution, immune regulation, and neurovascular integrity, underscoring the importance of HDL quality over quantity. These findings strengthen the rationale for CETP inhibition as a preventive approach for dementia and AD.

P3-A-553 *The effects of pubertal lipopolysaccharide and chronic fluoxetine treatments on anxiety-like behavior in adult male and female mice*

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Puberty is a critical developmental period, during which, exposure to immune stressors such as lipopolysaccharide (LPS) may induce enduring anxiety-like behaviors. While fluoxetine (FLX) treatment mitigates anxiety-like behaviors and reduces proinflammatory responses in other models, its efficacy in reducing sex-dependent anxiety-like behavior following pubertal LPS and its underlying mechanisms, remain unclear. Thus, we investigated whether chronic FLX treatment in adulthood attenuates anxiety-like behavior in CD1 mice, and will assess whether FLX modulates corticosterone, IL-1β, IL-10, and IL-18 concentrations in the blood. Males and females (n = 40) received LPS (1.5 mg/kg, i.p.) or saline at 6 weeks of age, a stress-sensitive pubertal period. At 10 weeks of age, mice received either FLX (~18mg/kg/day) or regular water in their bottles for four weeks. Anxiety-like behaviors were assessed using the elevated plus maze, open field test, and novelty suppressed feeding tests. Preliminary results showed that pubertal LPS increased anxiety-like behavior in males but not females in the elevated plus maze. In both sexes, FLX-treated mice consumed more chow in the home cage following food deprivation, suggesting an effect of FLX on hunger. We predict LPS will increase IL-1β and IL-18, and FLX will increase IL-10 and decrease corticosterone. These findings suggest that pubertal immune activation leads to persistent, sex-dependent behavioral changes, and that FLX treatment may modulate these effects. Further research should clarify the underlying neuroinflammatory mechanisms.

P3-A-554 *The Role of Ago1 and Ago2 in Neurodevelopment*

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Neurons are highly polarized cells relying on spatially restricted mechanisms to regulate synaptic signalling and plasticity. Local mRNA translation in dendrites enables synapse-specific protein synthesis, regulated by the RNA-induced silencing complex (RISC). Central to RISC function are Argonaute (AGO) proteins: Ago1 and Ago2, which are the predominant isoforms expressed in the brain. Despite extensive work on microRNA function, it remains unclear whether Ago1 and Ago2 are differentially regulated during neurodevelopment or occupy distinct neuronal compartments. This project aims to characterize the developmental regulation and subcellular distribution of endogenous Ago1 and Ago2 to assess potential non-redundant roles in neurodevelopment.Cultured dissociated neurons and acute hippocampal slices from mice were analyzed using immunofluorescence and Western blotting. Immunofluorescent staining was used to assess the subcellular localization of endogenous Ago1 and Ago2, including their distribution across neuronal compartments and within dendritic spines, as well as their degree of co-localization. Western blot analysis was performed at different neurodevelopmental stages to quantify endogenous Ago1 and Ago2 protein levels and determine whether they are differentially regulated over time. Preliminary results indicate that Ago1 and Ago2 localize to distinct cytoplasmic RNA-processing foci known as p-bodies. Notably, Ago2, unlike Ago1, shows prominent nuclear localization, suggesting a potential role linked to its unique endonuclease “slicer” activity. Additionally, Ago2 displays post-translational modifications not observed in Ago1, indicating differential regulation. Together, these findings suggest that Ago1 and Ago2 may fulfill distinct regulatory functions in neuronal development, advancing our understanding of RISC-mediated RNA regulation in the brain.

P3-A-555 *The role of Kirrel3 in mitral cell dendrite morphogenesis during olfactory system development and its impact on odour processing in mice*

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The formation of dendritic arbors in the nervous system relies on the dynamic outgrowth and branching of dendritic processes, followed by the pruning of exuberant branches. This process is crucial for the refinement of responses in sensory systems, such as the main olfactory system, which processes odorant signals from the environment critical for rodent survival. In this system, olfactory sensory neurons (OSNs) project axons to synaptic structures termed glomeruli in the olfactory bulb, where they form synapses with second-order neurons, called mitral cells. The cell adhesion molecule Kirrel3, is expressed on both OSN axons and in mitral cells of the olfactory bulb, suggesting it may modulate the formation of this circuit through homotypic interactions between pre- and postsynaptic terminals. Here, we investigate the role of Kirrel3 in regulating the elaboration of mitral cell dendritic arbours in the olfactory bulb. We demonstrate that Kirrel3 is differentially expressed in populations of mitral cells and that its specific ablation in these cells results in improper maturation of their dendritic arborization. Furthermore, defective dendritic pruning of mitral cells in mitral cell-specific Kirrel3 knockout mice is associated with olfactory discrimination deficits. Together, our findings identify a novel role for Kirrel3 in regulating mitral cell dendritic arborization and reveal the functional consequences of impaired mitral cell dendrite maturation on olfactory processing.

P3-A-556 *Timing-specific effects of maternal separation stress on development in protein-restricted neonatal Wistar rats*

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Early-life adversity, including maternal stress and malnutrition, plays a critical role in shaping offspring development and behavioural outcomes. Despite extensive literature investigating early-life adversity, a comprehensive understanding of the combined, timing-specific effects of maternal separation stress (MS) and protein restriction (PR) remains unclear. Here, we assess how early (EMS: postnatal day (PND)2–12) relative to late (LMS: PND10–17) maternal separation under an 8% protein restricted diet influences physical milestones including fur development, ear opening, and eye opening; motor coordination using negative geotaxis and grip strength tests; anxiety-like behaviours measured in the open-field test; ultrasonic vocalizations (USVs) analyzed for pup distress signalling and communication; and physiological stress biomarkers quantified through hippocampal BDNF, serum corticosterone, and ACTH. Our findings indicate that EMS males exhibited delayed negative geotaxis performance, transiently increased grip strength at PND14, and elevated anxiety-like behaviour in the open-field test. Distress vocalizations differed by timing, with LMS pups emitting more USVs on PND8, and EMS pups on PND16. LMS pups also produced more harmonic and simple-structured calls at PND4, while EMS pups exhibited increased harmonic calling at PND16. Together, these results underscore how the maternal environment under protein restriction can influence anxiety-like behaviours, motor development, and distress vocalization patterns, highlighting the importance of early developmental windows.

P3-A-557 *Transcriptional and splicing dysregulation in CHARGE syndrome mouse models explains the cerebellar developmental defects*

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CHARGE syndrome (CS) is a rare genetic disorder characterized by a complex pattern of congenital malformations. One poorly understood hallmark of CS is intellectual disability related to autism spectrum disorder (ASD). Pathogenic variants in CHD7, a chromatin remodeler, are the main cause of CS, while ARB2A, a co-transcriptional regulator, has also been reported as another cause of CS. Both encoded proteins play

crucial roles in transcriptional regulation and alternative splicing, which dysregulation likely contributes to all aspects of CS pathogenesis. This project is specifically focused on the neurobiological deficits. Using Arb2a^Tp/Tp and Chd7^Gt/+ mouse models, we previously found common behavioral abnormalities including hyperactivity and social deficits, which are associated with cerebellar malformations, particularly in lobules XI/X of the vermis. Histological analyses further revealed ectopic localization of granule cells and Purkinje cells, suggesting disrupted neuronal migration. To investigate the underlying molecular mechanism, we have now carefully analyzed the transcriptome of granule vs. non-granule cells that were isolated from postnatal day 7 (P7) cerebella of wild-type and mutant mice. Bulk RNA sequencing followed by differential expression and splicing analyses (DESeq2, rMATS) revealed widespread dysregulation of genes involved in cerebellar development, synaptogenesis, and neurotransmission. Several key regulators of pre- and post-synaptic signaling were commonly affected across both models, indicating convergent molecular dysfunction. Overall, these findings provide new mechanistic insights into how CHD7 and ARB2A mutations disrupt cerebellar gene expression programs, thereby contributing to the neurodevelopmental and behavioral manifestations of CHARGE syndrome.

P3-A-558 *Abnormal MYCBP2-EPHB2 signaling interplay causes neurodevelopmental defects*

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Contact-mediated cell-to-cell communication is fundamental to nervous system development and is often mediated by transmembrane receptors, such as the EPHB2 receptor. EPHB2 has been extensively involved in the specification of neuronal connections. We recently showed that EPHB2 interacts with MYCBP2, a multi-functional neuronal signaling hub. Importantly, patients with neurodevelopmental abnormalities harbor de novo mutations in the EPHB2 and MYCBP2 genes, strongly suggesting that these proteins function together during brain development. However, the mechanisms underlying this functional interaction remain unknown. Here, we model the causative impact of MYCBP2 loss of function on neural connectivity in Mycbp2 knockout mice and iPSC-derived cortical neurons. We show that MYCBP2 deficiency leads to severe structural defects in the developing brain, including agenesis of the anterior commissure and internal capsule, highlighting MYCBP2's essential role in the formation of major CNS axon tracts. Through quantitative proteomics, we demonstrate that loss of MYCBP2 profoundly alters the global neuronal proteome, including changes in KIDINS220, a downstream target of the EPHB2 receptor. Furthermore, we show that MYCBP2 depletion disrupts EPHB2-controlled protein complexes that are critical for anterior commissure morphogenesis and dendritic spine development. Together, these findings define a central role for MYCBP2-EPHB2 signaling in brain wiring and aim to provide mechanistic insight into how its disruption leads to neurodevelopmental disabilities.

P3-A-559 *Vasopressin dysregulation following transient neonatal hyperoxia in rats*

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Background: Preterm infants present elevated systemic copeptin, a blood marker of arginine vasopressin (AVP), during neonatal life and early adulthood, suggesting AVP dysregulation that may contribute to the consequences of prematurity. Neonatal hyperoxia in rats recapitulates key features of preterm birth. However, its effects on AVP regulation and further impacts remain unclear. Objective: To determine whether neonatal hyperoxia triggers AVP dysregulation. Methods: Sprague–Dawley pups were exposed to 80% O_2 from postnatal day 3–10 or room air (n=6/group/sex) and euthanized at P10 or P28. Hypothalamic expression of Avp, Crh, Fos, Bdnf, and Agtr1a was quantified by RT-qPCR, pituitary AVP storage was measured by immunofluorescence, and serum copeptin levels by ELISA. Results: At P10, males showed trends toward increased Avp and Crh (P=0.15; P=0.33), significantly reduced Bdnf (P<0.05), and elevated Agtr1a (P<0.05), suggesting altered neuroendocrine production and neuronal development. AVP storage was unchanged

in males and tended to increase in females (P=0.11). By P28, Avp, Crh, and Fos appear to shift toward downregulation (P=0.10; P=0.11; P=0.11), while Bdnf significantly increased (P<0.05), suggesting an adaptative process. AVP storage trended higher in both males and females (P=0.07; P=0.20), Agtr1a expression normalized, and serum copeptin was unchanged in males but reduced in females (P<0.05), indicating regulation at the secretion level. Conclusion: Neonatal hyperoxia potentially disrupts AVP production, storage, and secretion in a sex- and age-dependent manner.

P3-A-560 *β*-neurexin-1A knockout impairs zebrafish visual function in prey capture under low-light conditions

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Neurexin-1 (NRXN1) is a cell-adhesion protein localized to presynaptic terminals in neurons, where it can interact with different postsynaptic targets such as neuroligins and LRRTMs. Neurexin-1 plays an important role in establishing functional synapses during development. Past studies confirm that deletion or mutation in the gene is associated with neurodevelopmental disorders such as autism spectrum disorder and schizophrenia. To investigate the role of NRXN1 in establishing appropriate cortical circuits, we studied the development of the visual system in β-Neurexin-1a knockout zebrafish larvae. A paramecium prey capture experiment was performed on 6-day-postfertilization zebrafish to behaviourally assess vision under conditions of varying luminance. The predation rate of wild type fish was compared to heterozygous and homozygous mutants from the β-Neurexin-1a knockout line to determine their ability to see and capture paramecia, a behaviour which depends on proper synaptic connectivity. Our results show that under high luminance, there is no significant difference between wild-type and the mutants. However, as the luminance decreases, a reduction in predation efficiency becomes apparent in homozygous zebrafish. These findings suggest that a loss-of-function β-Neurexin-1a mutation impairs the proper formation of visual circuits required to capture prey in low-light conditions.

B - NEURAL EXCITABILITY, SYNAPSES, AND GLIA: CELLULAR MECHANISMS

P3-B-561 *Properties and activation mechanisms of membrane localized, chloride permeable Pannexin 2 channels*

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Pannexins are ion channels which can release molecules up to 1kDa. Due to the primarily intracellular localization of Pannexin 2 (Panx2), its properties are relatively unexplored compared to the extensively studied Pannexin 1 (Panx1). We now report prevalent Panx2 expression at the plasma membrane (PM) and the properties of membrane-bound Panx2. Immunocytochemistry was used to evaluate surface localization of Panx1 and Panx2, transfected in HEK293T. Cells were treated with wheat germ agglutinin (WGA, a PM marker) and an anti-calnexin antibody (an endoplasmic reticulum (ER) marker), Panx2 co-distributes with both. To explore the role and properties of Panx2 as a membrane channel, we performed whole-cell recordings in HEK293T cells expressing Panx2. Ramp-evoked currents are outward rectifying with negative reversal potential. Ion substitution experiments revealed Panx2 is primarily chloride permeable, as reported for Panx1. Due to lack of knowledge regarding Panx2 activation, we sought to examine whether Panx2 shares a mechanism with Panx1. Cell swelling due to hypotonic stimulus activates Panx1, but we show Panx2 is unaffected. Lastly, we assessed the extent to which Panx1/2 share sensitivity to pharmacological agents. Panx2 is insensitive to carbenoxolone while DCPIB inhibits both Panx1/2-mediated currents. Collectively, by studying these properties of Panx1 and Panx2, we show Panx2 distinguishes itself from Panx1. Panx2 conducts current at the PM, indicating it is functional in this subcellular location, and should be recognized as such.

P3-B-562 *PVN astrocytes regulate corticosterone secretion and stress responses*

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The stress response and basal secretion of glucocorticoids such as cortisol or corticosterone are orchestrated by corticotropin-releasing hormone (CRH) neurons in the paraventricular nucleus (PVN) of the hypothalamus, and regulated via glucocorticoid receptor (GR)-dependent negative feedback. Several afferent pathways modulate the activity of these neurons. However, their local environment of these neurons, which is composed of glial cells such as astrocytes, remains poorly explored despite the high expression of GRs and mounting evidence of their involvement in modulating neuronal activity. Here, we hypothesise that astrocytic GR signalling is critical for corticosterone regulation. One hour after in vivo activation of PVN astrocytes expressing a Gq-coupled DREADD receptor, we observed significantly elevated corticosterone levels and increased percentage of CRH neurons co-localised with c-Fos in males, suggesting a critical role for PVN astrocytes in regulating CRH activation. These results were replicated in mice with brain-wide astrocyte-specific GR deletion (GRGlastKO) and ZT2 corticosterone levels were higher in PVN astrocyte-specific GR deletion (PVN GRGfapKO) compared to controls in both sexes. To determine the consequences of astrocytic GR deletion, we analysed PVN astrocyte morphology, coverage and calcium signalling in our models. In parallel, we investigated the electrical activity of PVN CRH neurons using electrophysiology in GRGlastKO mice. This study contributes to a better understanding of the mechanisms underlying the regulation of the stress axis.

P3-B-563 *Radial astrocytes modulate the encoding of visual signals and plasticity in the developing Xenopus laevis optic tectum*

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During late stages of brain development, efficient circuit wiring relies on instructive cues from sensory experience and neural activity to drive synaptic plasticity and achieve mature functional connectivity. Initially thought to only implicate neurons, more recently astrocytes have been shown to be directly involved in the neural plasticity mechanisms that mediate structural and functional circuit refinement. Using the visual system of Xenopus laevis tadpoles, we conducted live calcium imaging of tectal neurons and glia while presenting visual stimuli. Targeted transfection of mammalian TrpV1 channels and application of capsaicin were used to elevate glial calcium. The visual stimuli presented were effective at evoking a robust response in a subset of tectal neurons, consistent with previous findings of sparse information encoding. A visual stimulation plasticity induction protocol resulted in a long-lasting decrease in both the number and amplitude of tectal neuron calcium responses. However, under conditions of chemogenetic activation of astrocytes, there was an attenuation in the decrease of the visually evoked responses caused by conditioning. Similarly, calcium signal in the neuropil, where retinal ganglion axons synapse onto tectal neurons, exhibited a significant increase in responsiveness to the stimuli after conditioning and glial activation, compared to the conditioned control group without glial activation. Our results indicate that glia modulate signal transduction and plasticity differentially in the somatic and neuropil compartments.

P3-B-564 *Region-specific synaptic adaptations in a mouse model of spinocerebellar ataxia type 6*

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Spinocerebellar ataxia type 6 (SCA6) is a neurodegenerative disease characterized by progressive cerebellar dysfunction. In both patients and a knock-in mouse model of SCA6 (SCA684Q/84Q), cerebellar degeneration occurs in a region-specific manner: Purkinje cells in anterior lobules exhibit early dysfunction and later degeneration, whereas posterior regions remain relatively preserved. We combined transcriptomic, structural, and electrophysiological approaches to examine mechanisms underlying this differential

vulnerability across regions in SCA6 cerebellum. Unexpectedly, RNA sequencing revealed many differentially expressed genes in the resilient posterior SCA6 cerebellum with changes especially in parallel fiber (PF)–Purkinje cell excitatory synapses. Consistent with this, we observed loss of PF synapses and reduced synaptic strength in the posterior SCA6 cerebellum. In contrast, the vulnerable anterior lobule III showed increased PF synaptic strength without detectable synapse loss, consistent with glutamate-mediated excitotoxicity. Together, these findings reveal divergent synaptic adaptations across cerebellar regions, suggesting that enhanced excitatory transmission may contribute to pathology in vulnerable circuits, while loss and weakening of synapses in preserved regions may represent a compensatory response that reduces glutamate excitotoxicity and cell death. Our findings demonstrate that brain regions spared from degeneration can nonetheless undergo dramatic alterations that may counteract but paradoxically also contribute to disease-related dysfunction.

P3-B-565 *Rescue of dopaminergic network stability during metabolic stress by pharmacological and genetic targeting of Panx1a*

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Pannexin-1 (Panx1) is a major ATP release channel implicated in neurodevelopmental and neurodegenerative disorders. By inducing a metabolic crisis in dopaminergic neurons with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), we had shown that global Panx1a ablation altered AMPK–mTORC1 signaling, cell death, and neuronal network connectivity. However, it is unknown whether Panx1a-dependent network instability during metabolic stress is mediated through inflammasome signaling, and which neural or glial cell populations are required for functional rescue. Pharmacological rescue experiments targeting the NLRP3 inflammasome with the small molecule INF39 alleviated MPTP-induced motor and neural connectivity deficits in both genotypes, as assessed by automated behavioral analysis, cell death detection, and in vivo dual-electrode local field potential recordings. The selective re-expression of Panx1a in global knockout larvae generated transgenic fish with cell-specific Panx1a expression in neurons, microglia, or astrocytes. In response to metabolic challenge, combined neuronal and astrocytic Panx1a re-expression conferred the greatest functional benefit. Together, pharmacological targeting of inflammatory signaling produced robust rescue across genotypes, whereas transgenic re-expression achieved partial restoration toward wild-type levels. These results support a role for Panx1a as a regulator of dopaminergic network stability during metabolic stress, acting through mechanisms involving both neuronal and astrocytic cell populations. NRSC DG RGPIN-2019-06378 (GRZ)

P3-B-566 *Rescuing the cellular and metabolic alterations underlying chemotherapy-induced cognitive impairment and fatigue*

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Introduction: Cisplatin is a chemotherapeutic agent used to treat solid tumors. However, it causes peripheral neuropathy, cognitive impairment, and fatigue, which diminish the quality of life for patients. The neurobiological consequences of cisplatin are driven by the peripheral release of the mitokine growth differentiation factor (GDF)-15 into the bloodstream. GDF15 acts on its receptor (GFRAL) in the area postrema to relay this information to the brain, ultimately resulting in cognitive impairment and fatigue. Therefore, it may be possible to protect the brain by modifying GDF15 signaling. Methods: Adult male mice received two 5-day cycles of cisplatin treatment (2.83 mg/kg/day or phosphate-buffered saline with or without concurrent GDF15-neutralizing antibody (GFRALna) (n=4-5/group). Results: Cisplatin consistently induced fatigue, measured by reductions in wheel running activity, cognitive impairment assessed through performance deficits in the puzzle box test, and body weight loss—all of which were prevented with concurrent GFRALna treatment. These behavioral changes were supported by advanced microscopy, demonstrating that cisplatin

induced a significant: (1) loss of dendritic spine density and alterations in spine morphologies; (2) loss of mitochondrial volume and morphological properties; and (3) increased cellular integrated stress response in the dorsal striatum. We anticipate that these features of cisplatin's effect in the brain will be mitigated by GFRALna treatment. Conclusions: These original findings link cisplatin-induced cognitive impairment and fatigue with the metabolic and morphological properties of dorsal striatal neurons. Thus, modifying GDF15 signaling represents a promising therapeutic approach to maintain the metabolic balance of the brain during chemotherapy and improve patient outcomes.

P3-B-567 *Restoring astrocytic metabolism potentiates cortical reorganization after stroke*

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Functional recovery after stroke is limited by incomplete cortical reorganization despite successful reperfusion and rehabilitation. Although attenuation of subacute tonic GABAergic inhibition in peri-lesional cortex increases neuronal excitability and promotes plasticity, its efficacy is constrained by persistent bioenergetic stress driven by residual inflammation and maladaptive glial reactivity. Chronic upregulation of astrocytic indoleamine-2,3-dioxygenase 1 (IDO1) contributes to this metabolic dysfunction, limiting astrocytic support of neuronal activity. Here, we show that combining extrasynaptic disinhibition with restoration of astrocytic metabolic support via IDO1 inhibition enhances peri-lesional network remapping and recovery. Using a mouse model of focal cortical ischemia, neuronal activity and astrocytic metabolic state in peri-lesional cortex were assessed longitudinally at cellular resolution using two-photon imaging of a genetically encoded calcium indicator (rCaMP) and fluorescence lifetime imaging of the NADH/NAD$^+$ redox reporter Peredox. Extrasynaptic GABAergic inhibition was titrated while astrocytic metabolism was normalized through IDO1 inhibition, restoring neuronal metabolic support. This combined intervention produced sustained elevations in peri-lesional neuronal activity without evidence of metabolic stress and enhanced cortical reorganization. At the network level, metabolic normalization combined with disinhibition improved peri-lesional cortical organization, reflected by increased electrophysiological power and superior recovery compared to disinhibition alone. These findings identify astrocytic bioenergetic support as a key constraint on activity-dependent plasticity after stroke and support a metabolism-informed neuromodulation strategy for improving recovery from ischemic stroke.

P3-B-568 *Rethinking memory consolidation: protein synthesis inhibition mimics neural shutdown*

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The de novo protein synthesis hypothesis has long dominated theories of memory consolidation, proposing that long-term memory (LTM), but not short-term memory (STM), requires new protein synthesis. Support for this view largely derives from studies showing that protein synthesis inhibitors (PSIs), such as anisomycin, disrupt LTM. However, growing evidence suggests that these effects may be confounded by the profound suppressive impact of PSIs on neural activity. The present work re-evaluates the protein synthesis hypothesis by directly comparing the behavioral effects of PSIs with those of established neural inactivators. Using Pavlovian fear conditioning, we examined the effects of anisomycin alongside muscimol and tetrodotoxin in the amygdala and hippocampus. Pre-training infusions into the amygdala impaired both STM and LTM of cued fear memory across all drugs, challenging the canonical view that STM is independent of protein synthesis. Post-training infusions of anisomycin or muscimol into the amygdala similarly disrupted the consolidation of cued and contextual fear memory. Parallel manipulations in the hippocampus yielded the same pattern of deficits, with both drugs impairing cued and contextual fear memory, contrary to the prevailing assumption that hippocampal involvement is limited primarily to contextual processing. Collectively, these findings demonstrate that the mnemonic effects of protein synthesis inhibition closely resemble those of neural inactivation. Rather than selectively preventing the synthesis of proteins required for memory consolidation, PSIs appear to impair memory by broadly suppressing neural function. This work

calls for a critical reinterpretation of PSI-based evidence and emphasizes the essential role of intact neural activity in learning and memory.

P3-B-569 *Role of astrocytes in regulation of CRH neurons and the HPA axis*

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Neuron-glia interactions are essential to regulate synaptic transmission and plasticity throughout the brain. Astrocytes are active participants in central stress responses across multiple regions, including the cortex, hippocampus, amygdala, and hypothalamus; however, their direct contribution to the modulation of stress-responsive neuronal circuits remains poorly defined. Here, we investigated astrocyte–neuron interactions in the paraventricular nucleus of the hypothalamus (PVN), a key stress-regulatory center containing corticotropin-releasing hormone (CRH) neurons that drive glucocorticoid release. Our study aims to understand the influence of astrocyte activity specifically on CRH neurons in the PVN. To address this knowledge gap, we generated a transgenic mouse line to remove glucocorticoid receptors (GR) in astrocytes by crossing GLAST-creERT with GR-flox mice. CRH^+ neurons were identified using a TdTomato-expressing viral construct, and neuronal excitability, synaptic transmission, and intrinsic membrane properties were assessed using whole-cell patch-clamp recordings in both male and female mice. Preliminary results reveal sex-dependent effects following astrocytic GR deletion. Male CRH^+ neurons exhibit a reduction in excitability, whereas female CRH^+ neurons display a distinct electrophysiological phenotype that is still under investigation. Atypical activity patterns were observed in CRH^+ neurons lacking conventional action potentials, suggesting alternative forms of neuronal activity. Future perspective will be exploring lactate as a potential factor.

P3-B-570 *Role of astrocytic N-methyl-D-aspartate (NMDA) receptors in regulating cortical neuronal function via purinergic signalling*

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IntroductionAstrocytes, a type of glial cells in the brain, bidirectionally communicate with nearby neurons via calcium signaling. These cells express N-methyl-D-aspartate receptors (NMDARs) which can cause a rise in astrocytic calcium levels. Increases in astrocyte calcium is associated with release of purines like Adenosine triphosphate (ATP), which can modulate neuronal activity. The mechanisms by which astrocytic NMDARs can modulate neuronal activity are yet to be investigated. MethodsIn this study, NMDARs in astrocytes have been selectively knocked down in mice barrel cortex (aNMDAR KD). Immunohistochemistry was performed to characterize aNMDAR KD. Awake in-vivo 2-photon calcium imaging was performed to study resultant astrocytic and neuronal changes. Texture discrimination behavior task was done to investigate sensory acuity. Acute pharmacology was done by applying ATP to barrel cortex and studying possible rescue of KD related impairments. Electrophysiology was performed to observe KD dependent changes in synaptic transmission. ResultsWe observed a KD of aNMDARs in tissue. Awake two-photon imaging showed KD dependent calcium impairments in astrocytes and neurons. There were texture discrimination deficits present. Interestingly, upon ATP application, there was a rescue of neuronal and behavioural impairments. Field recordings showed an impairment in short term and long-term plasticity in KD mice. ConclusionThis study highlights the functional relevance of aNMDARs in modulating cortical circuits. We show that aNMDARs are important for neuronal-astrocyte communication and sensory information processing. This is relevant for diseases such as schizophrenia where NMDA receptors are poorly activated and thus, can help us shed light on disease mechanisms.

P3-B-571 *Role of ELFN1 in mossy fibre to stratum lucidum interneuron information transfer*

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GABAergic interneurons within the hippocampus constitute a minority,comprising approximately 10-15% of the total cell population. Despite theirsmall number, these interneurons play a critical role in regulating both individualneuronal activity and the network-level dynamics essential for learning andmemory processes. In the CA3 region, stratum lucidum interneurons areproposed to exert feedforward inhibition, resulting in sparse activation ofpyramidal cells. Concurrently, these interneurons contribute to the generation ofdistinct firing patterns, network oscillations, and temporal constraints oninformation flow. Our findings suggest the presence of two distinct populations of interneurons. One group displays frequency-dependent facilitation, whereas the other exhibitsconsistent responses across various stimuli. We hypothesize that this dichotomymay be attributed to the differential expression of Elfn1, a transmembraneprotein known to modulate short-term plasticity at CA1 interneuron synapses. Given its widespread distribution in the CA3 region, Elfn1 likely imparts uniqueresponse properties to interneurons, whereby identical stimuli elicit disparateresponses based on Elfn1 presence. This diversification in neuronal responses not only enriches single-cellelectrophysiology and computational capacities but also enhances thecomputational capabilities of dentate gyrus (DG)-CA3 circuitry, which is pivotalfor hippocampal function in memory encoding and learning. By employingelectrophysiological recordings and morphological analyses of recorded cells,our study aims to characterize DG-interneuron-CA3 synapses, delineate thedistinct interneuron populations, and elucidate their encoding roles within thebroader context of hippocampal information processing

P3-B-572 *Role of TrkC-PTPσ–regulated Shank3 phosphorylation in synapse development and plasticity*

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Tropomyosin receptor kinase C (TrkC), a receptor for neurotrophin-3 (NT-3), also functions as a postsynaptic cell-adhesion molecule by interacting with presynaptic protein tyrosine phosphatase sigma (PTPσ) to organize excitatory synapses. To study this transsynaptic interaction in vivo, we generated mice carrying TrkC point mutations that selectively disrupt PTPσ binding while preserving NT-3 binding. We previously found that these mutant mice exhibited impaired social memory, increased anxiogenic avoidance behavior, impaired synapse maturation, and altered phosphorylation of synaptic proteins associated with neurodevelopmental disorders. However, the molecular mechanisms underlying the role of the TrkC–PTPσ interaction in the function of excitatory synapses remain unclear. To address this, we focused on Shank3, an autism-associated postsynaptic scaffold protein that is significantly hypophosphorylated in TrkC mutant mice, and we investigated how its hypophosphorylation contributes to synapse development and plasticity. Shank3 phosphorylation regulates dendritic spine density and morphology in rat primary hippocampal neurons. Furthermore, Shank3 phosphorylation is necessary for cLTP-induced increases in surface AMPA receptor expression and spine enlargement. Thus, these findings suggest that Shank3 phosphorylation, which may be regulated by the TrkC–PTPσ interaction, is a key mechanism in the development and plasticity of excitatory synapses.

P3-B-573 *Amyloid Beta protein increases dendritic spine density in stellate, but not pyramidal neurons, and causes cell type specific alterations in spine morphology in the rat medial entorhinal cortex*

Marcus Suvanto [1], Julian Gambino [1], Andrew Chapman [1]

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Soluble amyloid beta protein (Aβ) may play an important role in learning-related neuroplasticity, in part through the activation of NMDA glutamate receptors. Soluble Aβ may also contribute to aberrant NMDA-dependent synaptic strengthening early in Alzheimer's disease that may contribute to later neuronal

hyperexcitability and degeneration. We have found that brief application of Aβ1-42 causes an NMDA-dependent facilitation of excitatory synaptic responses in the medial entorhinal cortex of wildtype rats in vitro. Here we assessed the effects of central administration of Aβ1-42 on the density and morphology of dendritic spines in the rat medial entorhinal cortex. Aβ1-42 protein (n=5) or vehicle (n=3) was injected via the cisterna magna in anesthetized rats, and tissue was obtained one hour later for Golgi-staining and analysis. In layer II stellate neurons, the density of dendritic spines was significantly increased in Aβ-treated neurons (n = 27) versus control neurons (n = 20; p< 0.001), but no significant morphological changes were observed. In layer III pyramidal neurons, the density of dendritic spines did not differ significantly between Aβ-treated (n = 19) and control neurons (n = 25; p = 0.889), but measures of the size of dendritic spine heads were increased (p < 0.05). These data show differential effects of brief exposure to Aβ in stellate versus pyramidal neurons of the medial entorhinal cortex and are consistent with the idea that Aβ can have lasting effects on synaptic function by influencing dendritic spine density and morphology.

P3-B-574 *Serotonin modulation of behavioral time scale plasticity in mouse prefrontal cortex*

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Behavioral timescale synaptic plasticity (BTSP) is a recently identified non-Hebbian form of plasticity in the hippocampus and prefrontal cortex that is receiving considerable interest. A key unresolved question concerns how reinforcement signals conveyed by neuromodulators regulate BTSP, thereby solidifying their role in associative learning models. Given the increasingly recognized role of serotonin in learning, we aimed to investigate how it modulates BTSP in Layer V pyramidal neurons of mouse prefrontal cortex. We hypothesized that serotonin, acting via Gq-coupled 5-HT2A receptors (5-HT2ARs), modulates the endoplasmic reticulum (ER) calcium release dynamics, which was recently shown to enact eligibility traces that are required for the manifestation of BTSP. Two-photon calcium imaging experiments revealed that while 5-HT2AR activation had surprisingly little effects on baseline spine and dendritic calcium levels, it significantly modulated calcium dynamics in response to repeated bursts of backpropagating action potentials. Similar short-term calcium plasticity was observed upon activation of cholinergic and metabotropic glutamate receptors, suggestive of a generalized role for Gq-coupled GPCRs in L5 pyramidal neurons. Further experiments in genetically labeled 5-HT2AR-expressing pyramidal neurons confirmed these findings. Consistent with the requirement of ER calcium dynamics for BTSP, we found that 5-HT2ARs extended the coincidence detection time window for BTSP induction. This work establishes a novel dynamic framework for interactions between Gq-coupled GPCRs and calcium signaling, advancing our understanding of neuromodulatory roles in synaptic plasticity and learning.

P3-B-575 *Sex differences in endocannabinoid system gene expression in the anterior cingulate cortex and basolateral amygdala following inflammatory and neuropathic pain*

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Chronic pain is a debilitating condition affecting almost 1 of 5 adults in Canada. Despite its widespread prevalence and being a major global health concern, current treatments are not sufficient. Additionally, chronic pain is a strong risk factor for affective conditions; and people experiencing chronic pain show altered brain activity in the anterior cingulate cortex (ACC) and basolateral amygdala (BLA). People suffering from chronic pain indicate that cannabis may reduce pain symptoms. However, how the endocannabinoid system is altered in pain chronification is not well understood. Young adult (8-10 weeks old) female and male C57BL/6CR mice were used. Inflammatory pain was modeled using Complete Freund's Adjuvant (CFA) and neuropathic pain was modeled using the spared nerve injury (SNI) model. QPCR was performed for the following targets: Crn1, Crn2, Trpv1, Ppara, Pparg, Grm5, Dagla, Daglb, with Gapdh as a control. Data were compared using a two-tailed t-test. Following CFA, there were limited changes in the ACC, with males having reduced Ppara at 24 hrs but no changes in Crn1, Grm5, Dagla or Daglb. In the BLA, however, females had

increased Crn1 and Grm5 at 72 hr, whereas males had increased Grm5, Dagla, Daglb and Ppara at 72 hr. These preliminary data suggest that there are sex differences in the endocannabinoid system with inflammatory pain—which may be related to sex differences in pain chronification. Ongoing work is assessing this system with SNI. Understanding the mechanisms of chronic pain and co-morbid anxiodepressive symptoms may identify novel therapies.

P3-B-576 *Sex differences in microglial responses to cerebral microbleeds: Influence of estrogen*

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Microglia, the brain's resident immune cells, exhibit sex differences in development, gene expression, morphology, and function. These differences manifest as sex-related variations in disease prevalence, symptomatology, and treatment responses in conditions like stroke, multiple sclerosis, and Alzheimer's disease. The neuroprotective effects of sex hormones, particularly estrogen, have been linked to increased vulnerability to neurodegenerative diseases after menopause. To investigate the role of sex hormones in this phenomenon, we subjected male and female mice to gonadectomy with or without hormone replacement. Using a tamoxifen-inducible Cre mouse line, we imaged microglial motility, morphology, and phagocytic load following microbleeds in vivo. Our findings show that the percentage of mobile microglia is higher in female gonadectomized mice than in sham controls, with estradiol treatment reversing this effect. Male microglial mobility remained unaffected by these interventions. These findings directly implicate estrogen as a key signal in constraining the mobilization of microglia following injury. Given the diverse effects of estrogen signaling on cells throughout the body, current experiments are examining whether a microglia-specific knockdown of estrogen receptor alpha (ERα) is required for these sex-related differences. Collectively, these experiments shed new light on the role of sex hormones in microglial responses to injury, with the potential to promote sex-specific therapeutic strategies in the context of brain injury and neurodegenerative diseases.

P3-B-577 *Shaping synapses during development and aging: Netrin-1 regulation of hippocampal dendritic spines*

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Glutamatergic terminals primarily synapse onto dendritic spines. Changes in spine morphology correlate with synaptic strength. Maturation of thin-type spines is crucial for activity-dependent enhancement of excitatory synaptic transmission, with LTP induction increasing the volume of immature dendritic spines and promoting AMPAR trafficking into the spine head. Activation of NMDA receptors triggers netrin-1 secretion at synapses. To determine if netrin-1 contributes to regulating dendritic spine morphology, we used time-lapse confocal imaging of tertiary apical dendrites from CA1 pyramidal neurons in organotypic hippocampal slice cultures. Our findings indicate that bath application of netrin-1 rapidly increased the volume of thin-type spines, but not mushroom-type spines, providing evidence that netrin-1 selectively promotes the maturation of thin type spines. Netrin-1 is also expressed by neurons and glia in the mature brain. To investigate the consequences of the absence of netrin-1 expressed by glutamatergic neurons, we generated CaMKII-Cre/Ntn1fl/fl (cKO) mice, which we have previously demonstrated exhibit deficits in spatial memory and attenuated LTP. Preliminary findings from Golgi-Cox staining of aged cKO mice revealed altered spine density and morphology in the tertiary apical dendrites of the hippocampus. Our ongoing studies aim to determine the impact of netrin-1 on dendritic spine morphology in the hippocampus during maturation and aging.

P3-B-578 *Pharmacological study of cannabichromene and cannabigerol at the serotonin 1A receptor (5-HT1A)*

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Minor cannabinoids such as cannabichromene (CBC) and cannabigerol (CBG) show antinociceptive and anxiolytic effects that may extend beyond cannabinoid receptors. The serotonin 5-hydroxytryptamine 1A receptor (5-HT1A) is a G protein-coupled receptor (GPCR) implicated in pain and anxiety, yet direct functional characterization of CBC and CBG at 5-HT1A remains limited. We assessed 5-HT1A receptor activity using a luminescence-based Ca2+ assay and evaluated receptor engagement using radioligand binding. In Chinese hamster ovary (CHO) cells expressing human 5-HT1A receptors, CBC produced partial agonist-like Ca2+ signaling with an estimated potency (EC50) of 1.98 µM and efficacy (Emax) of 80.8% relative to the reference agonist 8-OH-DPAT (EC50 195 nM). CBG also activated 5-HT1A (EC50 73.3 nM; Emax 91.1%) and attenuated 8-OH-DPAT-evoked responses consistent with a partial agonist behaving as an antagonist. In competition binding experiments using a fixed concentration of tritiated 5-hydroxytryptamine ([3H]5-HT), both CBC and CBG displaced radioligand with estimated affinities (Ki) of 7.39 nM for CBG (95% CI 1.50–58.5 nM) and 13.9 nM for CBC (95% CI 1.86–163 nM), supporting 5-HT1A receptor binding. These data support direct modulation of 5-HT1A by CBC and CBG with distinct efficacy profiles. Ongoing work aims to extend profiling to the adenosine A2A receptor and assess pharmacology in receptor knockout mice. Determination of CBC and CBG's non-cannabinoid pharmacology may lead to novel anxiolytic and pain-relieving compounds that circumvent the intoxicating effects of cannabis.

P3-B-579 *Slice preparation matters: protective solutions shape synaptic plasticity in ex vivo brain slices*

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Introduction: Obtaining healthy brain slices is a major challenge in ex vivo electrophysiology. This can be improved by using protective cutting and recovery solutions in which NaCl from artificial cerebrospinal fluid (aCSF) is replaced with substitutes such as sucrose, choline, or N-methyl-D-glucamine (NMDG). Although these solutions are widely used for whole-cell recordings, their impact on field recordings and synaptic plasticity remains unclear. Aim: To assess whether replacing standard aCSF with protective solutions during slice preparation alters basal synaptic transmission and synaptic plasticity. Methods: Juvenile (PND 21-35) and adult (PND 140-186) Sprague-Dawley rats were assigned to four groups according to the protective solution used during slice preparation: aCSF, NMDG, sucrose, or choline. Field recordings were obtained from the dentate gyrus. Basal synaptic transmission was assessed using input-output curves, and synaptic plasticity was evaluated by inducing potentiation with theta-burst stimulation. Results: In juveniles, NMDG reduced both short- and long-term potentiation (STP and LTP), whereas sucrose and choline had no significant effect. In adults, NMDG reduced STP but not LTP. Basal synaptic transmission was also altered depending on the solution used. Conclusions: Although protective solutions improve slice viability, they may also modify physiological properties, thereby influencing interpretation and cross-study comparisons in ex vivo electrophysiology studies.

P3-B-580 *Spacing theta burst episodes improves plasticity in prefrontal cortex of socially isolated mice*

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Intermittent theta burst stimulation (iTBS) applied to the prefrontal cortex is a treatment for major depression. It is aimed at increasing the strength of excitatory synapses. Here, we use ex vivo Ca2+ imaging in mouse prefrontal cortex to measure the impact of a common treatment protocol (Clinical iTBS). We find that this pattern of electrical stimulation reliably potentiates the amplitude and spatial spread of test pulse signals in brain slices from group-housed mice. However, its reliability is jeopardized when mice are socially isolated from development. To probe the difference, we analyzed the iTBS calcium response, hypothesizing that the calcium response during induction predicts the subsequent potentiation of the test pulse signal. Indeed, prefrontal brain slices from group-housed mice show this relationship (Hsieh et al., CAN abstract), but it is dysregulated in social isolation. With the goal of constraining the calcium response during induction, we find that an alternative protocol (Spaced iTBS), with fewer episodes of iTBS and wider spacing , yields synaptic potentiation in prefrontal cortex of socially isolated mice. Taken together, the data reveal significant interactions between iTBS protocol and housing condition in their effects on synaptic potentiation. Testing generalizability, we demonstrate that Spaced iTBS is also effective in social isolation with different timing (adult-onset). Overall, strategic refinement of iTBS protocols may be useful in enhancing synaptic potentiation in the vulnerable prefrontal cortex.

P3-B-581 *Spatial learning promotes phosphorylation of CRMP2 in the hippocampus*

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Spatial navigation requires reorganization of synaptic connectivity within the hippocampus to represent new environments through emergence of cognitive maps. Individual synapses show both functional and structural rearrangement in response to spatial learning, and recent studies have suggested that post-translational modification of proteins that regulate cytoskeletal organization are critically involved in synaptic alterations underlying learning and memory formation. Collapsin response mediator protein 2 (CRMP2) is a major cytosolic phosphoprotein that forms heterotrimers with α/β tubulin to promote cellular growth and is a key regulator of axonal collapse and pathfinding during neural development. However, CRMP2 has also been associated with synapses, suggesting a potential role in synaptic transmission. Functionally, increases in phosphorylation of CRMP2 by Cdk5, GSK3β, and other kinases prevents tubulin polymerization, suggesting that increases in phosphorylated CRMP2 may facilitate structural destabilization and remodelling of hippocampal circuits that encode spatial representations. Here, we show that CRMP2 is expressed in the developing and adult hippocampus in mice. Further, we show that levels of phosphorylated CRMP2 in the hippocampus are increased following testing on a hippocampal-dependent novel object place recognition task but not a hippocampal-independent novel object recognition task in mice. Together, these findings suggest that signalling cascades that trigger increases in phosphorylation of CRMP2 can transiently destabilize the neuronal cytoskeleton to promote synaptic plasticity and structural reorganization. As such, phosphorylation of CRMP2 can act as a critical regulator of spatial learning and memory formation in the hippocampus.

P3-B-582 *Spatiotemporal dynamics of microglia in response to recurrent capillary injury in vivo*

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Cerebral microbleeds (CMBs) are small, chronic hemorrhages caused by microvascular rupture. Though often asymptomatic, they are linked to cognitive decline, likely driven by persistent neuroinflammation after injury. The brain relies on specialized cells to maintain function, with microglia serving as its resident immune sentinels. These highly dynamic cells respond to injury by migrating to damaged sites and supporting repair. Because CMBs frequently recur, understanding microglial responses to repeated injuries in vivo is critical. Here, we used two-photon microscopy to characterize microglial dynamics after successive microbleeds. Adult mice underwent chronic cranial window implantation and expressed Cre-dependent tdTomato with tamoxifen-inducible, microglia-specific Cre recombinase for real-time imaging. After recovery, cortical capillary ablation with a femtosecond laser induced microbleeds once per week over four weeks. Preliminary results show a progressive decrease in the proportion of migrating microglia with each bleed. Cells mobile after the first event exhibited reduced movement and shorter displacements in later bleeds. However, longitudinal tracking revealed that initially mobile microglia were more likely to remain mobile across injuries, while stable cells rarely became mobile. Ongoing work examines migration, phagocytic activity, and morphological changes to determine how repeated CMBs shape microglial behavior and neuroinflammatory adaptation.

P3-B-583 *Spatiotemporal maturation of astrocyte calcium dynamics during hippocampal development*

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Astrocytes display dynamic changes in intracellular calcium transients that are critical for a variety of astrocyte functions in the developing and mature brain such as modulating behavioural output, neuronal network adaptation, and response to external stimuli. As such, intracellular calcium transients are used as a proxy for astrocyte functions. However, while astrocytes undergo significant morphological and transcriptomic maturation in the first three weeks of mouse postnatal development, whether astrocytes are also subject to a functional maturation in the developing brain is not known. Here, we used a modified stereotaxic neonatal viral delivery of a membrane-tethered genetically encoded calcium indicator, GCaMP6f, to astrocytes in P1 mice and 2-photon laser scanning microscopy in acute hippocampal slices to examine the spatiotemporal features of astrocyte calcium transients and the signals that drive them from postnatal days (P)6-P70. We found that larger, faster events characterize astrocyte calcium dynamics in young animals while slower, smaller events are typical in adult with a shift occurring at P22-26 for most features. This shift suggests that astrocytes have distinct functional outputs dependent on the periods postnatal development. To test this, we developed a comprehensive paradigm to examine how astrocytes respond to neuromodulators, including norepinephrine, dopamine, serotonin, histamine, and acetylcholine throughout development and find that neuromodulator systems induce unique calcium transients in hippocampal astrocytes. Additionally, we observe a shift in the EC50 of some neuromodulators in neurodevelopment, suggesting that astrocytes refine their response to neuromodulators throughout circuit development

P3-B-584 *Spontaneous and miniature excitatory postsynaptic currents in medium spiny neurons of the dorsomedial striatum in BMAL1 knock-out mice*

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Disruption of circadian rhythms has been consistently associated with altered alcohol consumption and increased susceptibility to alcohol abuse. Emerging evidence implicates core clock genes such as Bmal1 as key regulators of alcohol-drinking behavior in both humans and animal models. Our behavioral results

indicate that conditional deletion of Bmal1 from medium spiny neurons (MSNs) in the dorsomedial striatum (DMS) significantly decreases voluntary alcohol consumption in female mice versus controls, but not in male mice. Bmal1 expression in the DMS therefore influences alcohol consumption in a sex-specific manner. To study the underlying mechanisms, we investigated the electrophysiological characteristics of MSNs in the DMS of female Bmal1-knockout mice using whole-cell recordings. Effects of intermittent alcohol exposure on recordings were assessed because long-term alcohol intake can increase mEPSC amplitude and frequency in MSNs. Chronic alcohol exposure alone did not significantly alter the amplitude, frequency, or decay time of spontaneous EPSCs, but it selectively reduced the amplitude and frequency of miniature EPSCs. Notably, the effects of Bmal1 deletion on spontaneous EPSCs were dependent on prior alcohol exposure, and Bmal1 knockout increased the decay time of spontaneous EPSCs in alcohol-naïve animals, but decreased decay time in animals with a history of intermittent alcohol consumption. Results point to synaptic alterations in the DSM associated with disruption of the striatal circadian clock which may be associated with alterations in alcohol consumption.

P3-B-585 *Sublayer-specific inhibitory and disinhibitory control of hippocampal CA1 pyramidal cells by VIP interneurons*

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Sublayer-specific inhibitory and disinhibitory control of hippocampal CA1 pyramidal cells by VIP interneuronsIloun Parisa, Grenier Jordan, Veillette Félix, Topolnik LisaHippocampal CA1 pyramidal neurons are organized into superficial (sPCs) and deep (dPCs) sublayers with distinct properties, connectivity and function. Their activity is regulated by inhibitory interneurons, including vasoactive intestinal peptide–expressing interneurons (VIP-INs), which predominantly mediate disinhibition but can also directly inhibit pyramidal cells. How these dual actions shape synaptic integration across CA1 sublayers and input pathways remains unclear. We combined optogenetics and pathway-specific electrophysiology in transgenic mice to examine VIP-IN control of excitation–inhibition balance in two PC subtypes. Optogenetic activation of VIP-INs produced similar direct inhibition in sPCs and dPCs, with no differences in response probability or synaptic strength. Despite this, VIP-mediated synapses differed molecularly: sPCs were preferentially innervated by cannabinoid receptor 1 (CBR1)–positive VIP boutons, whereas dPCs received more CBR1-negative boutons, indicating subtype-specific targeting. To assess functional relevance, we pharmacogenetically silenced VIP-INs while measuring Schaffer collateral and lateral entorhinal cortex–evoked responses. VIP-IN silencing did not alter excitatory input–output relationships but selectively increased inhibitory drive at maximal stimulation in a depth- and pathway-dependent manner. These results show that distinct VIP-IN subpopulations provide sublayer- and pathway-specific disinhibitory control, shaping CA1 output during high-activity network states relevant for hippocampal computation and memory.

P3-B-586 *Synaptic transmission onto somatostatin interneurons is enhanced under acidic conditions in an Elfn1-dependant manner*

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Healthy brain function relies on a balance between excitation and inhibition. Activation of inhibitory somatostatin (SOM) interneurons is regulated by the synaptic proteins, Elfn1 and mGluR7, and their loss results in epilepsy. These proteins regulate excitation of SOM interneurons, creating an inhibitory “emergency brake” during high excitability. Accordingly, Elfn1 knockout (KO) mice experience seizures. Increased excitability and seizures can alter extracellular pH. Noting that mGluRs are acid-sensitive, we hypothesized that acidic conditions would act on the Elfn1/mGluR7 complex to increase synaptic transmission. This would mimic prior findings that an mGluR7 antagonist increases excitatory post-synaptic current (EPSC) amplitude and enhances activation of SOM interneurons. Our results show that acidic conditions increase EPSC amplitude in whole-cell patch clamp recordings taken from labelled SOM interneurons from transgenic mice. We confirm that these effects are Elfn1-dependent as they are absent

in our Elfn1 KO mice. We also observed a significant decrease in paired-pulse ratio in acidified conditions, consistent with previous findings. These results indicate that acidification inhibits mGluR7 to enhance synaptic transmission and increase SOM interneuron activity. Future experiments will continue to explore how disturbances to brain homeostasis can interact with genetics to increase risk of epilepsy. This study describes how these synaptic proteins influence neurotransmission in acidic environments, with implications for understanding epilepsy.

P3-B-587 *Synthetic synapses: Testing biomimetic electrode coatings for enhanced neural integration*

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Synaptic differentiation does not require a cellular target. Hemi-synaptic specializations form rapidly at sites of neurite adhesion to microbeads coated with a synaptogenic protein or a synthetic cationic polypeptide like poly-lysine (PL). Engineering functional hemi-synaptic connections has the potential to improve information transfer and implanted electrode biocompatibility. However, studies examining the stability of synaptic specializations formed in brain onto PL coated beads found they degraded within a few weeks after implantation. We reported that microbeads coated with dendritic polyglycerol amine (dPGA), a non-protein macromolecular biomimetic of PL, promote enhanced synaptogenesis and synapse stability in cell culture. We show that dPGA is stable, resisting proteolysis, and that dPGA coated beads cluster neurexin, which is sufficient to direct presynaptic terminal formation. Bead curvature was thought to contribute to the formation of hemi-synaptic specializations, preventing the modification of electrodes with flat contact points. Testing this, we used cubic micro-hydrogels and coated glass surfaces to provide evidence that hemi-synaptic specializations readily form onto flat dPGA-coated surfaces. Current studies are investigating the synaptogenic potency of dPGA in vivo. We propose that synthetic synaptogenic extracellular matrices that resist proteolysis could be used to engineer electrodes with enhanced neural-biocompatibility and support bi-directional communication with neurons by directing the formation of stable synaptic specializations.

P3-B-588 *Frequency-dependent regulation of serotonin signaling in prefrontal cortex is expanded by chronic SSRI treatment*

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Serotonin signaling within the prefrontal cortex plays a central role in regulating mood and flexibility. Selective serotonin reuptake inhibitors (SSRIs) are thought to strengthen serotonin signaling in prefrontal cortex to treat mood disorders. However, how serotonin release is regulated within this region remains poorly understood. Adding further complexity, serotonergic axons can release transmitter across a broad range of firing frequencies, yet transmission differences between tonic (low-frequency) and phasic (higher-frequency) activity are unknown. To address these unknowns, we combined optogenetic stimulation and whole cell recording in brain slices from transgenic mice to directly assess electrophysiological responses to endogenous serotonin release in the prefrontal cortex. We found that optogenetically evoked serotonergic responses exhibit pronounced frequency dependence, with tight regulation evident at higher frequencies, including 20 Hz, a frequency commonly used in behavioural studies. We identified key frequency-dependent regulatory mechanisms and examined how these mechanisms are modified by chronic SSRI treatment. Notably, chronic SSRI exposure expanded the dynamic range of serotonergic regulation, recruiting de novo control by 5-HT1B and 5-HT2A receptors over responses to lower frequency stimulation. Together, these findings reveal fundamental mechanisms governing serotonergic signaling in the prefrontal cortex, demonstrate their sensitivity to chronic SSRI treatment, and highlight novel targets to enhance prefrontal serotonergic function.

P3-B-589 *The brain on cannabis: How THC affects brain rhythms during sleep-like states*

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Sleep is essential for our well-being, as poor sleep is linked to a range of health problems. With the widespread availability of cannabis products, self-medication is becoming a common approach to managing sleep disorders. Tetrahydrocannabinol (THC)—the main psychoactive compound in cannabis—is often used to promote sleep. However, THC may interfere with sleep quality by disrupting brain rhythms. The two main stages of sleep, Rapid Eye Movement (REM) and Non-REM, are characterized by distinct brain rhythms. Theta waves (4-8Hz) are present in the hippocampus during REM, while slow waves (<1Hz) appear in both the hippocampus and neocortex during Non-REM. These rhythms are thought to mediate memory consolidation. We have previously found an overall increase in slow wave power in the cortex, and a decrease in theta power following THC administration. Here we investigate how THC disrupts network dynamics within and between regions by recording and analyzing the contributions of neuronal populations across laminae in both structures. We conducted multisite laminar field recordings in the hippocampus and cortex of rats during a sleep-like state using a 14 channel linear multiprobe. Rats were anesthetized with urethane, a drug used to model sleep, which produces stereotyped cycling and improves analysis precision. This technique allows us to observe how oscillations change at different layers, including input and output regions across the hippocampus and cortex after THC, and therefore pinpoint changes to hippocampo-cortical communication after THC. Here we found distinct changes to the oscillations in particular layers, indicating differential effects of THC within structures. This research may provide a network explanation for how cannabis interferes with memory consolidation.

P3-B-590 *The effect of high salt intake on RhoA–mDia1 signaling and the cytoskeleton in vasopressin neurons*

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High dietary salt (HDS) is a major contributor to hypertension. However, the underlying molecular mechanisms linking HDS to hypertension remain unclear. Plasma sodium and osmolality changes are detected by specialized osmosensory neurons in the hypothalamic supraoptic and paraventricular nuclei (SON and PVN). Increased plasma osmolality activates SON and PVN magnocellular neurons, promoting VP release to regulate fluid balance. Salt loading (SL) causes excessive activation of VP neurons and sustained elevation of blood pressure, yet the mechanisms underlying excessive VP secretion in SL remain unknown. Our previous studies revealed that magnocellular VP neurons harbor unique cytoskeletal networks comprised of a subcortical actin layer, an array of actin comet-like structures, and a somatic scaffold of interweaved microtubules. VP neuron excitability is proportional to the density of these cytoskeletons. Moreover, SL increases actin and microtubule density in magnocellular VP neurons. mDia1, a RhoA effector in the formin family, regulates cytoskeletal polymerization and stability. We have shown that SL activates the RhoA-mDia1 pathway in the magnocellular VP neurons. Moreover, both pharmacological inhibition and Cre-dependent genetic knockdown of mDia1 in magnocellular VP neurons hinder SL-induced increases in cytoskeletal density. We hypothesize chronic HDS exposure activates the RhoA-mDia1 pathway to increase the cytoskeletal density and osmosensitivity of magnocellular VP neurons, leading to excessive VP secretion, volume expansion, elevated blood pressure, and hypertension.

P3-B-591 *The effect of serotonin modulation on lateral parabrachial nucleus inputs in pain conditions*

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The area postrema (AP) is a circumventricular structure in the medulla known for sensing circulating signals and modulating autonomic and homeostatic responses. The external lateral parabrachial nucleus (elPBN) integrates nociceptive and visceral inputs and relays them to higher-order brain regions involved in sensory perception and pain. While anatomical proximity suggests potential connectivity between the AP and elPBN, the existence, neurochemical identity, and functional relevance of this pathway remain poorly defined. Using viral tracing, CLARITY-based whole-brain clearing, and light-sheet imaging, we identified a direct projection from the AP to the elPBN. RNAscope in situ hybridization and Cre-dependent viral strategies revealed that a subset of AP→elPBN neurons express TPH2, suggesting a partial serotonergic component. Manipulating this circuit with chemogenetics revealed a bidirectional role in pain modulation: activation of AP→elPBN neurons enhanced mechanical, cold, and formalin-evoked nociceptive responses, while inhibition significantly reduced pain behavior across all assays, including Von Frey, acetone, hot plate, and formalin tests. Under chronic pain conditions (CFA model), AP activity was significantly reduced, as assessed using TRAP2 reporter mice. TRAP2-labeled neurons in the AP, captured under baseline (non-pain) conditions, were found to project to the elPBN, indicating that this pathway is active under normal physiological states. These neurons lacked co-expression of catecholaminergic (TH), cholinergic (ChAT), or glutamatergic (VGLUT2/3) markers, suggesting they belong to a unique neurochemical class. Together, these findings characterize a previously undescribed AP→elPBN pathway with a functional role in pain regulation. This circuit may represent a key interface between blood-borne signals and central affective pain networks.

P3-B-592 *The effect of systemic injections of CBD on sleep-like brain state alternation during urethane anesthesia*

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Alongside recreational use, the therapeutic use of cannabis has increased significantly, particularly as a sleep aid. THC and CBD are the two most represented phyto-cannabinoids derived from Cannabis sativa. While THC produces psychoactive effects associated with a “high,” CBD induces a sedative and relaxing state and demonstrates therapeutic effects in treating inflammation, pain, anxiety, and epilepsy. Interestingly however, research remains inconclusive regarding whether CBD promotes sleep and if so, and how. During sleep, two principal stages an organism cycles through are Non-Rapid Eye Movement (NREM) and Rapid Eye Movement (REM), which alternate rhythmically. REM sleep is characterized by theta waves in the hippocampus, whereas NREM sleep, also known as slow-wave sleep (SWS), shows slow oscillation in the hippocampus and neocortex. Male Sprague Dawley rats were anesthetized with urethane, which models brain states occurring during sleep. Bipolar electrodes were implanted to record local field potentials from the neocortex and hippocampus. Alternations between NREM and REM were recorded as baseline. CBD was then administered intravenously (IV), and changes in brain state alternations were compared to baseline. At 10 mg/kg, no consistent changes were observed, with some rats showing increased REM and others increased NREM. At 20 mg/kg, REM duration and theta wave amplitude decreased, while time spent in NREM and slow-wave amplitude increased. These findings help clarify how individual cannabinoids may influence sleep in beneficial or detrimental ways.

P3-B-593 *Investigating the cellular functions of rhomboid-related protease 3*

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Rhomboid proteases are an ancient protein superfamily, spanning a wide range of life forms. Because these proteins have persisted in living organisms for so long, they likely execute fundamental functions in the cell, otherwise they would have been eliminated. Nevertheless, we are only just beginning to understand their role in the brain. Rhomboid-3, a member of the rhomboid protease superfamily, is found in the central nervous system. Recent evidence suggests that this protein is highly expressed in cerebellar neurons associated with motor coordination. However, the cellular interaction network of rhomboid-3 remains unknown. As a secretase-A rhomboid, rhomboid-3 contains seven transmembrane domains (TMDs). Its catalytic dyad occupies the fourth and sixth TMDs, allowing the enzyme to cleave substrates via intramembrane proteolysis. Interestingly, rhomboid-3 contains cytosolic calcium-binding EF-hands, suggesting a role in calcium dynamics and neuronal firing. Our project investigates the cellular functions of rhomboid-3, allowing us to better understand its role in neurons. To this effect, we designed neuronal BioID experiments to reveal the intracellular interaction partners of rhomboid-3 in response to changes in calcium levels; these findings will be validated using proximity ligation assays. Furthermore, we will corroborate the interactors in mouse cerebellar tissue from both wild-type and rhomboid-3 knockout animals. By exploring the calcium-dependent activity of rhomboid-3, we further our understanding of cerebellar neuron function.

P3-B-594 *The mechanistic role of extracellular matrix proteins, growth factors, and peptide hormones in synapse formation and function*

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Synapse number and function decline in aging, leading to memory loss and neurodegeneration. Age-related synapse loss and cognitive decline may be catalyzed by brain-intrinsic factors or by extrinsic, secreted factors in the blood. Heterochronic parabiosis experiments in mice showed introduction of young serum into aged mice reversed cognitive deficits. Changes in the systemic levels of extracellular matrix proteins, growth factors, and peptide hormones result in improved learning and memory in vivo. These experiments do not address whether changes in synapse formation and properties underlie these pro-cognitive effects. To explore these questions, we treated primary cortical neurons with the factors and quantified synapse number by immunostaining and confocal imaging. We found osteonectin, TIMP1, and TIMP2 increased excitatory synapses, GDF11 decreased excitatory synapses, and irisin increased total synapse number, all in the absence of changes in neuronal growth and maturity. Osteonectin, TIMP1-2, and irisin exhibited differential increases in calcium spike frequency and amplitude, suggesting the factors act by distinct mechanisms. We pulled down cell surface receptors from neuronal membrane fractions and will use mass spectrometry to identify candidates. Future work will include receptor knockouts and identification of downstream signaling cascades.

P3-B-595 *The role of glial ferritin and transferrin 1 in regulating drosophila motor behavior*

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Glial cells play essential roles in the development and function of the central nervous system (CNS), and glial dysfunction has been associated with numerous CNS pathologies. How glial cells regulate neuronal circuitry and physiology is not completely understood. The Drosophila CNS contains three main glial cell types that interact with neurons - astrocytes, ensheathing glia (ENS), and cortex glia (CTX). From single-cell RNA sequencing data we created an inventory of genes enriched in these glial cell types, and conducted an RNAi-based loss-of-function screen for genes that influence motor behaviors, which identified several genes related to iron storage and transport. Knockdown of transferrin 1 (Tsf1) from ENS caused bang-sensitive paralysis. Tsf1 transports iron into cells by a mechanism not currently understood. After entering cells, iron

can either be stored in its non-toxic form through the secretory pathway, a process mediated by Zinc/iron regulated transporter-related protein 99C (Zip99C) and the ferritin storage complex, which is composed of the subunits Fer1HCH and Fer2LCH. CTX-specific knockdown of Zip99C, Fer1HCH, and Fer2LCH each reduced climbing ability and caused profound effects on overall brain morphology. Ongoing experiments will test 1) whether loss of these factors leads to neurodegeneration and cell death by ferroptosis, 2) whether post-developmental knockdown of these factors causes the same effects, and 3) the localization of GFP-tagged versions these factors in the brain. Overall, these experiments will lead to an improved understanding of the dynamics of glial iron metabolism and how it affects motor behavior.

P3-B-596 *The role of neuronal primary cilia in regulating dendritic spines*

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In the mouse cerebral cortex, pyramidal neurons form elaborate dendritic arbors studded with thousands of dendritic spines that receive excitatory synaptic inputs. The density, morphology, and dynamics of these spines are critical determinants of how neurons integrate and encode information within neural circuits. However, the mechanisms governing dendritic spine development and plasticity remain incompletely understood. Here, we report an unexpected role for neuronal primary cilia as centralized signaling hubs that regulate dendritic spine morphogenesis and synaptic function. Using conditional genetic approaches, we selectively disrupted ciliary genes in glutamatergic excitatory neurons. Loss of neuronal cilia resulted in pronounced alterations in dendritic spine structure accompanied by defects in synaptic transmission. Moreover, acute induction of ciliary dysfunction during adolescence or adulthood led to measurable changes in motor and cognitive behaviors. Together, these findings identify neuronal primary cilia as a previously unrecognized, extra-synaptic mechanism for modulating dendritic spines and synaptic function. This work reveals a novel layer of regulation essential for the proper wiring and function of cortical circuits and provides new insights into the pathophysiology of cilia-related neurodevelopmental disorders, including ciliopathies, autism spectrum disorders, and intellectual disabilities.

P3-B-597 *The role of non-ionotropic NMDA receptor signaling in synaptic depotentiation in the hippocampus*

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Long-term potentiation (LTP), or the long-lasting strengthening of synaptic connections, underlies memory and learning, which is essential to survival. The reversal of LTP, or depotentiation (DEP), underlies forgetting and memory modification, and may be leveraged as a method to treat memory-related conditions such as post-traumatic stress disorder (PTSD). The N-methyl-D-Aspartate receptor (NMDAR) has long been established to have a critical role in learning and memory, but recently, non-ionotropic, or ion-flux-independent NMDAR (NI-NMDAR) signaling has been discovered to mediate activity-dependent synaptic DEP in the hippocampus and spinal cord. We observed divergent molecular mechanisms enabling depotentiation of LTP induced using either a temporally spaced or compressed stimulation pattern on murine hippocampal slices. Applying glycine-site NMDAR antagonists 7-CK and L689, drugs that promote NI-NMDAR signaling, during electrophysiology experiments revealed that NI-NMDAR can mediate depotentiation of compressed but not spaced LTP. These findings provide a better understanding of the molecular mechanisms underlying destabilization and may subsequently reveal novel therapeutic targets for the treatment of various memory-related conditions.

P3-B-598 *The role of oligodendrocyte precursor cells (OPCs) in memory consolidation*

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While oligodendrocyte precursor cells (OPCs) differentiate into myelinating oligodendrocytes in response to synaptic inputs, accumulating evidence suggests that OPCs also play active roles in regulating neural circuit function independent of myelin. For example, a recent study shows that OPCs form contacts via their processes on neuronal somata in a neuronal activity-dependent manner. Based on these observations, we hypothesized that neuronal activity can be modified in an experience-dependent manner via OPCs. Using in vivo calcium imaging, we found that learning (tail shock) robustly activates OPC Ca2+ transients. Using contextual fear conditioning (CFC), we found that OPC activation during learning induced pronounced remodeling of process architecture, with OPC processes preferentially contacting engram neurons (cFos$^+$ cells) in CFC mice compared to home cage control mice. Selective chemogenetic inhibition of OPCs during learning impaired memory consolidation, at both recent and remote time points. Conversely, chemogenetic or optogenetic activation of OPCs during learning facilitated memory consolidation. Temporal specificity analyses demonstrated that OPC activation is critical during the consolidation window: photostimulation alone or OPC activation during memory retrieval did not alter behavior, whereas OPC activation during consolidation significantly enhanced freezing responses. Together, these findings identify OPC activation during learning as a key regulatory mechanism underlying fear memory consolidation.

P3-B-599 *The role of oxysterol-binding protein in synaptic vesicle cycling and development*

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Cholesterol is essential for synaptic development and neurotransmission, yet the underlying mechanisms of cholesterol trafficking at synapses and how disruptions in cholesterol trafficking affect synaptic structure and function remain unclear. Oxysterol-Binding Protein (OSBP) is a lipid transporter involved in cholesterol regulation, but its roles in synaptic development and function have not been studied. This study examines the effects of OSBP at the Drosophila melanogaster larval neuromuscular junction (NMJ), a well-established model to study synapses. FM1-43 imaging was performed on Osbp1 loss-of-function mutants and genetic controls to determine if OSBP is required for synaptic vesicle exocytosis and endocytosis. Our data did not reveal any differences in synaptic vesicle exocytosis and endocytosis between Osbp1 mutants and controls. To determine if OSBP is required for synaptic development, NMJs of control and Osbp1 mutants were stained with a marker of presynaptic terminals (HRP) and a marker of active zones (BRP). We found that Osbp1 mutants displayed a significant reduction in the number of presynaptic bouton number compared to the control larvae, indicating that OSBP negatively regulates synaptic growth. We are currently testing whether OSBP is involved in activity-dependent synaptic growth. In addition, we are using a genetically encoded cholesterol biosensor expressed in motor neurons to assess presynaptic cholesterol levels in control larvae and Osbp1 mutants. Collectively, this study aims to determine how OSBP-mediated cholesterol trafficking contributes to synaptic development and plasticity.

P3-B-600 *The role of RIM1/2 proteins in dopamine release*

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Dopamine (DA) is a critical regulator of movement, motivation, and learning, but how one neurotransmitter can regulate such disparate functions is unknown. One hypothesis suggests that timing and patterns of neurotransmitter release may dissociate DA as a teaching signal from DA as a movement signal. Recent work indicates that RIM1/2 proteins are critical for phasic DA release, which could provide a unique opportunity to test how discrete patterns of DA signaling contribute to discrete behaviours. We trained mice lacking RIM1/2 protein in DA neurons (RIMKO-DA) on a battery of learning and motivational tasks while using fiber photometry to record striatal DA. We found that, contrary to previous reports, phasic DA release is present

in RIMKO-DA mice, but with altered release kinetics. We sought to parameterize this alteration by measuring striatal DA with fiber photometry while optogenetically stimulating midbrain DA neurons at different frequencies and durations. We found that in vivo RIMKO-DA desynchronizes neurotransmitter release resulting in lower amplitude DA transients and a delayed return to baseline DA but that these alterations do not affect learning or motivation. Moreover, the effect of RIMKO on DA release is regionally dependent, where amplitude is blunted primarily in the dorsal striatum, while the return to baseline is delayed primarily in the nucleus accumbens. This work demonstrates that RIM1/2 are important for enabling proper timing of stimulus-evoked DA release but not critical for release in general or for facilitating normal behaviour.

P3-B-601 *The sigma-1 receptor: a molecular hub for psychostimulant drugs in the nucleus accumbens*

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The psychoactive effects of psychostimulants such as cocaine and methamphetamine are classically attributed to enhanced dopamine (DA) signaling. We recently showed that cocaine induces a long-lasting depression of neuronal firing (hypoactivity) in nucleus accumbens shell (NAcSh) medium spiny neurons (MSNs), a key reward-related brain region. This neuroadaptation promotes behavioural sensitization to cocaine and occurs independently of DA signaling, but requires the endoplasmic reticulum chaperone sigma-1 receptor (S1R). Here, we demonstrate that in vivo methamphetamine, despite distinct pharmacological properties, similarly depresses NAcSh MSN firing. Like cocaine, this effect is DA-independent but depends on S1R binding to Kv1.2 potassium channels, resulting in increased Kv1.2 surface expression. Using site-directed mutagenesis of the methamphetamine binding site on S1R in HEK293T cells, we show that methamphetamine binding to S1R is required for Kv1.2 membrane upregulation. Together, our findings provide direct evidence that besides actions mediated through conventionally studied mechanisms, psychostimulants engage a shared, DA-independent but S1R-dependent mechanism contributing to behavioural responses to cocaine. Importantly, our data suggest that psychostimulant-induced NAcSh MSN hypoactivity may represent a core process of stimulant addiction, offering new avenues for pharmacological interventions targeting multiple psychostimulants.

P3-B-602 *Theta burst calcium signals to optimize synaptic plasticity in mouse prefrontal cortex*

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Prefrontal cortex dysfunction is a hallmark of major depression that is relevant to its symptoms. An emerging treatment delivers intermittent theta burst stimulation (iTBS), to the prefrontal cortex via transcranial magnetic stimulation. The goal is to strengthen the excitatory synapses which activate this region. We hypothesize that investigation in the mouse prefrontal cortex may be useful to refine iTBS. The current clinical iTBS protocol is adapted from research that induces long-term potentiation (LTP) in rodent hippocampus. However, there has been less examination of iTBS protocols in rodent prefrontal cortex. We use wide-field imaging in brain slices from adult Thy1-GCaMP6f mice to probe calcium signals during clinical iTBS. This stimulation is given electrically in the superficial cortex. We then measure the amplitude and spatial spread of clinical iTBS calcium responses in the apical dendritic and somatic compartments of the major output neurons of the prefrontal cortex. The 20-epsiode clinical iTBS generates a complex induction calcium profile across time and space within the mouse prefrontal cortex. Response to the first TBS episode is restrained in amplitude and spatial spread but climbs in subsequent episodes before a gradual decline. Interestingly, the peak episode response predicts the subsequent level of LTP observed. Brain slices of adult mouse prefrontal cortex provide an opportunity to test the outcomes and mechanisms of the clinical iTBS

protocol. Our results identify modifications to further enhance synaptic plasticity in this understudied brain region.

P3-B-603 *Time course development of synaptic plasticity deficits following adolescent repetitive mild traumatic brain injuries*

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Adolescence represents a period of significant maturation, yet increased vulnerability to mild traumatic brain injuries (mTBI) may disrupt this process. Despite this, few studies have examined the effects of repetitive mTBI (r-mTBI) on dentate gyrus synaptic plasticity across sexes, with most work focused on the CA1 subregion and male animals. In this study we investigated the temporal nature of hippocampal synaptic plasticity deficits following adolescent r-mTBI. Female and male adolescent (P35) Sprague-Dawley rats received three r-mTBI or sham injuries spaced 72 hours apart. Long term potentiation (LTP; 4 x 100 Hz) was assessed in the dentate gyrus (DG) on post-injury day (PID) 1, PID7 and PID30. In parallel, tissue was collected from the DG and CA1 for western blot analysis of GluN2 NMDA receptor expression. Here we found that r-mTBI produced LTP deficits at PID1, 7, and 30. When we analysed GluN2 receptor expression, we noted only decreased expression at PID30, with no significant changes at PID1 or PID7. This may indicate that acute synaptic dysfunction occurs independently of NMDA receptor downregulation. As a potential mediator, we further examined endocrine and neuroimmune mechanisms by assessing levels of serum growth hormone and IGF-1 as well as microglial reactivity with Iba1 immunohistochemistry at PID7 and PID30. Together these findings demonstrate r-mTBI induces impairments in hippocampal synaptic plasticity and we hypothesize that endocrine-immune signalling may contribute to long-term dysfunction.

P3-B-604 *TNFA role in homeostatic synaptic plasticity in HD*

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Huntington's Disease (HD) is a neurodegenerative genetic disease. It manifests usually in mid-life (40-50 years of age), and the most prominent phenotype is degeneration of the Striatum. This causes the first and main symptoms to be movement involved. In our research we are using the zQ175 mouse model of HD, and analyzing males and females separately. Behavior analysis of OFT and rotarod asses the progression of the symptoms, followed with qPCR to verify TNFa molecularly in different brain regions. Parallel to that, cell cultures using P0 mice are used to make cell culture, giving us the opportunity to treat the cells for longer periods of time with TNFa and TTX. This is followed by electrophysiological recording of mEPSP. Previous studies in our lab showed a different response from MSN in the striatum compared to the cortex, as well as different outcomes in the YAC128 mouse model. Our preliminary results in the zQ175 mouse show that body weight isn't reduced in zQ175 mice up to 20 weeks. Their locomotion is lower that WT as early as 4 months. Electrophysiology is inconclusive at this point. qPCR will be done at the end of the study when the animals will be sacrificed.

P3-B-605 *Top-down modulation of the dorsal peduncular cortex in anxiety-like and fear behaviour*

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Recent work has identified the dorsal peduncular cortex (DP), located within the ventral limit of the medial prefrontal cortex (mPFC), as a key brain region modulating stress responsivity, flight, fear and affective behavior. The DP receives input projections for several regions, including the insula and amygdala, yet their contribution to DP-mediated behaviour is unknown. Here we examined synaptic connectivity of DP projections stemming from the anterior (aIC) and posterior (pIC) insular cortex, and basolateral amygdala (BLA), as well as their role in anxiety-like behaviors and auditory fear conditioning. We found that while

insula inputs to DP spans layers 2/3 and 5, BLA inputs are restricted to layer 2/3. Elevated plus maze (EPM) testing led to increased activation of both IC and BLA-projecting DP neurons compared to homecage controls. Optogenetic activation of the pIC-DP pathway is anxiolytic in animals with high baseline anxiety-like behavior, observed by significant increase in time spent in the open arms. Whereas aIC-DP optogenetic activation increased locomotion in the open field test (OFT) and mimicked the effect of pIC-DP activation in the EPM. Optogenetic manipulation of the pIC-DP (but not aIC-DP) pathway bidirectionally modulated freezing during fear retrieval in a sex dependent manner without affecting extinction learning. Finally, chemogenetic inhibition of the BLA-DP pathway did not alter anxiety-like behavior. Ongoing experiments are evaluating the effects of BLA-DP and pIC-DP inhibition in anxiety and fear. Together, these experiments uncover novel brain pathways modulating DP-driven regulation of anxiety-like and fear behaviour.

P3-B-606 *Transsynaptic organization underlying a cerebellar gateway*

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Postsynaptic adhesion molecules are critical for synapse development, with certain members implicated in neurodevelopmental disorders. We identified an understudied, broadly expressed postsynaptic organizer whose in vivo function remains poorly understood. Using CRISPR-Cas9, we generated HA-tagged in frame knock-in and knockout (KO) mouse models. Immunocytochemistry of brain sections revealed that this protein is predominantly expressed in cerebral cortex, striatum, hippocampus, and cerebellum, colocalizing with excitatory postsynaptic markers. Hippocampal expression begins at postnatal day 12 (P12, becomes restricted to the dentate gyrus outer molecular layer by P21, and cerebellar expression initiates at P8 in the granule layer. Using super-resolution imaging, we show that it redistributes within cerebellar glomeruli during development, enriching at postsynaptic sites by P30. In KO mice, related family members showed no compensatory changes. Expansion microscopy revealed that its deletion disrupts transsynaptic nanocolumn alignment within excitatory circuits of cerebellar glomeruli. Further, transmission electron microscopy revealed ultrastructural alterations in cerebellar glomeruli of KO mice. Our findings establish this protein as exhibiting spatiotemporal expression dynamics during synaptogenesis in brain regions governing cognition and motor control. The absence of compensatory changes highlights its unique functional role. Future studies will employ electrophysiology and network assays to determine its contribution to synaptic transmission and circuit function.

P3-B-607 *TRPA1 channels drive pericyte dysfunction during oxidative stress*

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Pericytes are mural cells which line brain capillaries and have been shown to regulate capillary blood flow, the blood brain barrier, and the structural integrity of capillaries. The loss of pericytes is a common early feature of vascular dysfunction in a number of brain disorders, including stroke and Alzheimer's disease. As such, preventing pericyte loss is a promising strategy for intervening early to preserve vascular function and ultimately neuronal integrity in brain disorders. Unfortunately, the mechanisms underlying pericyte loss are not well characterized. To address this, we characterized the mechanism underlying pericyte degeneration during the induction of oxidative stress- a major player in vascular pathology. Ox-stress was induced in acute rodent brain slices and pericyte dysfunction was assessed with two-photon microscopy to measure propidium iodide (PI) uptake and cell morphological dystrophy. We hypothesized that the activation of reactive oxygen species (ROS)-sensitive TRPA1 ion channels contribute to pericyte dysfunction through aberrant Ca2+ signaling. This was tested by pre-treating brain tissue with the TRPA1 antagonists A967079 or HC-030031. Interestingly, both antagonists strongly attenuated pericyte PI uptake and cell dystrophy. By contrast, TRPA1 had no effect on the dysfunction of neighboring non-vascular cells, suggesting that this pathway is specific to pericytes. In conclusion, our data highlights TRPA1 as a major target for preventing pericyte dysfunction and loss in brain disorders associated with ox-stress, such as Alzheimer's disease.

P3-B-608 *Tyrosine kinase inhibition gates a non-selective cation channel in Aplysia bag cell neurons*

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It is well-established that ion channels can be regulated by phosphorylation of serine, threonine, or tyrosine residues. In the sea snail, Aplysia californica, the neuroendocrine bag cell neurons prompt egg-laying via a period of persistent firing termed the afterdischarge, which is driven by non-selective cation channels. Prior immunostaining experiments showed a drop in phosphotyrosine levels following an afterdischarge, while single-channel recordings confirmed tyrosine dephosphorylation promotes cation channel opening. To determine the role of tyrosine phosphorylation on a macroscopic level, cultured bag cell neurons were whole-cell voltage-clamped and treated with the tyrosine kinase inhibitors, PP1 or SU6656, evoking currents of ~-1 nA and ~-500 pA, respectively. These currents were largely linear, associated with a 2-5-fold increase in membrane conductance, reversed at ~-30 mV, and sensitive to the cation channel blocker, clemizole. Collectively, this suggested the opening of a voltage-independent non-selective cation channel. In addition, HEK-293 cells expressing the Aplysia Transient Receptor Potential Canonical 5 channel presented with inward currents of ~-700 pA and ~-300 pA in response to PP1 and SU6656, respectively, suggesting this channel may contribute to the current. Lastly, under current-clamp, PP1 provoked an ~40 mV depolarization and action potential firing from a resting potential of -60 mV. Thus, tyrosine dephosphorylation may gate a cation channel that, in part, underlies the afterdischarge and ultimately reproductive behaviour.

P3-B-609 *Unlocking the regenerative potential of the mammalian retina*

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Currently, there are no available treatments to restore vision after retinal degeneration. In fish and frogs, a specialized type of glial cells in the retina called “Müller cells” can respond to injury and proliferate to replace lost cell types, acting as bona fide adult retinal stem cells. However, in mammals, Müller glia remain quiescent and lack this regenerative capacity. Our goal is to understand why mammalian Müller glia have lost this ability and explore ways to reactivate them for retina regeneration. Here, we report that the transcription factor CASZ1, a temporal identity factor that governs late-born cell type production during development, is upregulated in Müller glia following retinal injury in mammals, but not fish. We hypothesized that Müller glia-specific expression of CASZ1 triggers chromatin remodeling events that enforce a late temporal identity, preventing reprogramming into a progenitor-like state and inhibiting regeneration in mammals. Consistently, we find that Müller glia-specific conditional knockout (cKO) of CASZ1 exhibit a decrease in chromocenter number, a reduction in laminar chromocenters, and an increase in total heterochromatin area in Müller cells. Strikingly, scRNAseq and in vivo genetic lineage tracing reveal that CASZ1 cKO Müller glia transdifferentiate into progenitor-like and neuron-like cells. These results indicate that CASZ1 acts as a barrier to natural regeneration in mammals. Ultimately, by identifying the molecular mechanisms underlying Müller glia reprogramming, we aim to develop gene therapies to regenerate the retina and restore vision.

P3-B-610 *Unveiling glial contributions to Parkinson’s pathology by mitochondrial NDUFA13 knockout in dopaminergic neurons*

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Parkinson’s Disease (PD) is a neurodegenerative disorder characterized by motor symptoms such as resting tremors, bradykinesia, and postural instability. These symptoms result from dopamine deficiency in the nigrostriatal pathway due to the progressive loss of dopaminergic (DA) neurons in the substantia nigra pars compacta (SNc). A pathological hallmark of PD is mitochondrial dysfunction, as mitochondrial complex I (MCI) activity in the SNc is decreased in the brains of patients with PD. Neuroinflammation contributes to both early and advanced stages of PD. Pathological alterations in microglia and astrocytes

disrupt their homeostatic functions, shifting them towards maladaptive states that actively contribute to neurodegeneration. Here, we aim to elucidate the consequences on glial cells resulting from MCI inactivation in DA neurons after crossing DAT-Cre with NDUFA13 conditional knockout (cKO) mice. We found that animals with the cKO showed decreased levels of tyrosine hydroxylase (TH) positive DA neurons starting at 4 weeks of age. These animals also showed a marked increase in Sox9-positive astrocytes in the SNc at 4 weeks and in other regions of the midbrain (i.e. ventral tegmental area (VTA), and substantia nigra pars reticulata) at 6 weeks. We also observed an increase in glial fibrillary acidic protein (GFAP) fluorescence in the SNc and VTA at both ages, which may indicate astrocytic reactivity. We observed no change in microglial density or fluorescence. Future studies will investigate the mechanistic pathways linking mitochondrial dysfunction and glial cells in neurodegeneration.

P3-B-611 *Value coding features of serotonin neurons*

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Adaptive behaviour requires animals to continually re-evaluate the appetitive or aversive quality of their surroundings. Dorsal raphe serotonin neurons, the main source of serotonergic input to the forebrain, have been implicated in both signaling the quality of an animal's environment and regulating reward-seeking and punishment-avoiding behaviour, but the precise quantity signaled by these neurons has remained unclear, as well as how these neurons relate with behaviour. Using open-access recordings of serotonergic neurons of the dorsal raphe nucleus while animals perform a dynamic Pavlovian task, we compare firing rate and behavioral data with a model that considers reward history accumulated over a tunable timescale. Our Bayesian parameter estimation supports that serotonin neuron activity reflects reward history being estimated over a timescale of about a hundred trials on average, with a heterogeneity across individual neurons spanning 30 to 300 trials. This timescale is significantly longer and more variable than the timescale of changes in anticipatory behaviour thought to be driven by dopamine. These results provide a precise picture of the dynamics of serotonin neuron activity during conditioning and hint that dopamine and serotonin might be neither twins nor enemies in reward learning.

P3-B-612 *Viral silencing of glutamatergic PreBötzinger Complex neurons induces apneas in mice*

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The preBötzinger complex (preBötC) is a brainstem network essential for generating the inspiratory rhythm. Disruption of preBötC function leads to breathing abnormalities, including apneas (breathing pauses), which are clinically relevant due to their cardiovascular and neurological consequences. Because excitatory (glutamatergic) neurons in the preBötC are critical for respiratory rhythmogenesis, we hypothesized that their transient inhibition would disrupt breathing and increase the incidence of apneas in mice. To test this hypothesis, a Cre-dependent virus encoding a pharmacologically selective actuator module coupled to a glycine receptor chloride channel (AAV-SYN-flex-PSAM4-GlyR-IRES-eGFP) was bilaterally injected into the preBötC of VGluT2-Cre mice, enabling selective chemogenetic inhibition of glutamatergic neurons. Four weeks later, breathing pattern and metabolic rate were assessed using whole-body plethysmography following intraperitoneal injection of vehicle or the PSAM agonist uPSEM817 tartrate (1 mg/kg).Agonist administration resulted in a significant increase in minute ventilation (volume of air exchanged per minute), driven by an increase in tidal volume (volume of each breath), with no change in breathing frequency. Notably, chemogenetic inhibition also significantly increased the incidence of apneas in mice. These results demonstrate that transient silencing of preBötC glutamatergic neurons alters respiratory patterning and promotes apnea generation, highlighting their essential role in maintaining stable breathing.

P3-C-613 *Non-invasive profiling reveals heterogenous mitochondrial respiration profiles in Autism and ADHD without clear genomic stratification*

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Mitochondrial involvement has been proposed in neurodevelopmental conditions, yet mitochondrial functional and genomic variability across diagnoses remains incompletely characterized. This exploratory study assessed mitochondrial respiration and mitochondrial DNA (mtDNA) variation in autistic children, children with attention-deficit/hyperactivity disorder (ADHD), and typically developing (TD) controls using non-invasive biospecimens. Buccal epithelial cells and urine samples were collected from 30 children aged 3–17 years for high-resolution respirometry and long-read mtDNA sequencing. High-resolution mitochondrial respiration measured in buccal epithelial cells revealed modest group-level differences, with higher combined Complex I + II–linked respiration and a trend towards maximal electron transport capacity in clinical groups compared with TD controls. More prevalent hypo- (≤ −2 standard deviation, SD) and hyper-respiratory (≥ +2 SD) profiles were observed in 61% of ADHD, 31% of autistic and 3% for TD participants. No distinct mtDNA variant signatures were observed between groups with specific variant hotspots in some individuals. These findings indicate that mitochondrial features vary substantially across individuals and are not strongly stratified by diagnosis, and do not support the claim for uniform respiratory deficits or distinct mtDNA variant burdens in autism or ADHD. Collectively, these findings suggest that mitochondrial phenotypes may provide a more informative basis for stratifying neurodevelopmental variability than categorical diagnoses alone.

P3-C-614 *Novel mTOR-independent mechanisms underlying GABAergic synapse dysfunction in epilepsy*

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Epilepsy affects over 70 million people worldwide, including ~1% of Canadians, with one-third refractory to current antiepileptic drugs. Loss-of-function mutations in DEPDC5 account for 12–37% of focal seizures; while some disrupt mTOR signaling, many occur in conserved domains with unknown, mTOR-independent functions. Our lab previously found reduced GABAergic synapses in 6 dpf depdc5 mutant zebrafish, revealing novel mTOR-independent role of depdc5 in inhibitory synapse development. In my postdoctoral work, I observed a transient increase of GABAergic synapses at 5 dpf and no change at 4 dpf, suggesting stage-dependent dysregulation with transient compensatory increases followed by impaired maintenance. RNA-seq in depdc5 mutants revealed significant reduction of NAPB, which recruits NSF to SNARE complexes, essential for vesicle recycling and neurotransmission. DPYSL2, an epilepsy-associated gene regulating synapse formation, is a potential DEPDC5 interactor; previous studies show reduced NSF in Dpysl2 -/- mice. CRISPANT dpysl2 knockout zebrafish recapitulate depdc5 phenotypes, including high seizure susceptibility, reduced locomotion, and stunted growth. Currently, I am evaluating if they also have GABAergic synaptic defect. Overall, we hypothesize and currently testing if DPYSL2 interacts with DEPDC5—either directly or within a shared complex—to regulate synaptic vesicle recycling thereby controlling GABAergic synapse development. This work has the potential to identify a novel, mTOR-independent mechanism that can offer new molecular targets for epilepsy therapeutics.

P3-C-615 *Optic nerve blood barrier disruption precedes axon loss and is restored through tight-junction gene therapy*

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The optic nerve head (ONH) is highly vascularized CNS tissue and a critical site of glaucoma pathogenesis. We recently showed that ocular hypertension (OHT), a major risk factor, causes retinal blood-retinal barrier leakage, contributing to retinal ganglion cell (RGC) death and vision loss. Here, we ask whether OHT triggers ONH barrier disruption and whether reinforcing tight junctions to restore endothelial integrity protects RGCs and visual function. Adult C57BL/6 mice received intracameral magnetic microbeads to induce OHT. ONH barrier integrity was assessed using systemic Sulfo-NHS-LC-Biotin and high-resolution confocal imaging. Leakage was quantified (ImageJ), and endothelial density measured by CD31 staining. Tight junctions were strengthened by Claudin-5 (CLDN5) upregulation using AAV9 with the Ple32 minipromoter. RBPMS-positive RGC soma densities were assessed by stereology, and visual acuity by optomotor response. OHT caused significant tracer leakage into retinal parenchyma compared to sham. Endothelial density was unchanged, indicating barrier dusfunction independent of microvascular dropout. Notably, barrier breakdown occurred before measurable RGC axon loss. Furthermore, endothelial CLDN5 supplementation: (i) restored vascular integrity, (ii) reduced leakage to cham-like levels, (iii) preserved RGC density, and (iv) improved visual acuity relative to control AAV. These findings place early neurovascular barrier breakdown upstream of neuronal loss and support endothelial tight-junction reinforcement as a promising neuroprotective strategy for glaucoma.

P3-C-616 *Oxytocin modulates social salience network connectivity in ASD, scaling with social trait expression*

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Autism spectrum disorder (ASD) is a prevalent neurodevelopmental condition featuring marked social difficulties. Oxytocin (OXT) is a key modulator of social behavior and a promising drug target for ASD; yet insufficient understanding of OXT modulation of brain networks underlying social behavior limits its therapeutic development. Mice lacking the ASD risk gene Cntnap2 exhibit reduced sociability and weaker functional connectivity (FC) across the social salience network (SSN), a rodent-derived framework supporting socio-sensory integration; both are rescued by OXT (Choe et al., 2022). To test whether a human SSN-like network might also underlie sociability traits in ASD and its modulation by OXT, we re-examined a resting-state functional connectivity (FC) dataset (Alaerts et al., 2019) of adult males with ASD receiving intranasal OXT (n=8; 24 IU) or placebo (n=12). We found a positive correlation between basal intra-SSN FC and salivary OXT, suggesting sensitivity to endogenous OXT. Furthermore, ASD sociability trait expression was negatively correlated with ventromedial prefrontal cortical (vmPFC) FC with amygdala and somatosensory cortex. Intranasal OXT did not alter global SSN FC but increased pairwise FC between select SSN subregions. Interestingly, OXT-induced change in vmPFC-paraventricular nucleus FC was positively correlated with ASD sociability trait expression, suggesting individuals with lower sociability exhibited larger FC increases. Together, these findings suggest SSN as a potential neural substrate of sociability in ASD that is responsive to OXT modulation.

P3-C-617 *Parkinson's disease pathogenesis influences human microglia transcriptional identity and contributes to inflammatory responses in microglia containing midbrain organoids*

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Microglia are the resident immune cells of the brain and changes in microglial states play a critical role in Parkinson's disease (PD) pathology, contributing to inflammatory responses and to the spread of toxic alpha-synuclein aggregates. However, animal and 2D microglial models have been shown to have drastic transcriptional differences compared to their in vivo human counterparts, proving problematic when used to model in vivo systems in PD research. In recent years, new technology has allowed for the generation of 3D human-derived midbrain organoids (hMOs) from induced pluripotent stem cells (iPSCs). However, most current protocols for hMO generation are targeted towards neuroectodermal induction of iPSCs, excluding cell types derived from mesodermal lineage, including microglia. To overcome this limitation, we have developed an optimized protocol for integrating microglia into hMOs. Here, our objective is to investigate microglia induced inflammatory pathology in PD using our optimized hMO-microglia model. For this we will assess microglia inflammatory responses in our PD hMO model through single cell RNA sequencing (scRNAseq) expression of cytokines/chemokines, with preliminary data showing increased inflammatory response in PD microglia. We will then determine how microglial inflammatory responses affect PD pathology in hMOs by looking at expression of toxic synuclein aggregates and dopaminergic cell loss through immunofluorescent analysis. Lastly, to gain an in depth understanding of how our PD hMO model induces inflammatory responses in microglia, we will assess microglial transcriptional states in PD hMOs through scRNAseq. Together, the results of these experiments will reveal possible mechanisms of microglia dependent PD progression.

P3-C-618 *Personalized biomarkers of multiscale functional alterations in temporal lobe epilepsy*

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Temporal lobe epilepsy (TLE) is the most common pharmacoresistant focal epilepsy in adults. Although TLE is often surgically treatable, many patients do not reach curative intervention, largely because diagnostic and prognostic decision-making is complicated by substantial inter-patient heterogeneity in clinical profiles and neuroimaging findings. We analyzed multimodal MRI and clinical data from 645 participants (282 TLE patients, 45 disease controls, and 298 healthy controls). Using normative modeling, we quantified patient-specific deviations in intrinsic brain function relative to typical lifespan trajectories. Functional alterations were spatially heterogeneous across individuals yet showed the greatest convergence in mesiotemporal regions. Connectome-informed simulations indicated that functional abnormality propagation follows the structural connectome, implicating the hippocampus and paralimbic/medial default-mode territories as key epicenters. Multimodal integration further identified superficial white-matter microstructural alterations as a key contributor to functional disruption. Supervised machine learning models achieved AUCs of 0.77 for distinguishing TLE from disease controls, 0.74 for lateralizing seizure focus, and 0.64 for predicting postsurgical outcomes, with greater contralateral temporal deviations associated with poorer outcomes. Collectively, these findings clarify pathophysiological heterogeneity in TLE and support individualized functional biomarkers to enable precision diagnostics and presurgical decision-making in focal epilepsy.

P3-C-619 *Pharmacological study of allosteric mechanisms at the type 1 cannabinoid receptor and their application in a mouse model of acute pain*

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Introduction: Positive allosteric modulators (PAM) of the type 1 cannabinoid receptor (CB1R) can reduce pain without the psychoactivity effects of phytocannabinoids such as Δ9-tetrahydrocannabinol. GAT211 has shown dual agonist-PAM properties in vitro, alongside antinociceptive and anti-epileptic effects in vivo. While GAT211 showed promise, it suffers poor pharmacokinetics (PK). This project investigates the GAT2500 series of compounds, structural derivatives of GAT211 designed to resolve and optimize CB1R PAM pharmacodynamics (PD) and PK. The goal of the present research was to determine the PD of these novel CB1R ago-PAMs to modulate cAMP inhibition and their physiological effects in a mouse model of pain. Methods: Chinese hamster ovary (CHO-K1) cells expressing CB1R were treated with increasing concentrations of CP55,940 (positive control), GAT2500 compounds (agonism), or combinations therein (allosterism). C57BL/6 mice were treated with a subset of compounds ± CP55,940 and then assessed for nociception, as well as movement and body temperature. Results: Two compounds - GAT2513 and GAT2515 - were efficacious PAMs that shifted the potency of concentration-response curves to sub-nanomolar levels when tested in vitro. When tested in mice, they were successful in reducing cataleptic effects with mixed anti-nociceptive properties. Conclusions: The GAT2500 series of compounds show strong preclinical potential based on their high potency and efficacy as CB1R AMs with minimal psychoactivity. Planned future experiments will assess the PK of these ligands in both acute and chronic treatment models.

P3-C-620 *Pleiotrophin induces changes in the gene expression of mice cerebral cortices following ischemic strokes*

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An emerging approach in ischemic stroke research involves modulating neuroplasticity to heighten the central nervous system's (CNS) ability to recover after an injury. One method to achieve this involves counteracting the inhibition induced by chondroitin sulfate proteoglycans (CSPGs) in the CNS's extracellular matrix. A growth factor called pleiotrophin (PTN) has been shown to interact with CSPGs to promote growth processes without degrading CSPGs. Previous studies have shown PTN's neurotrophic effects; however, its role and downstream effectors post-stroke have yet to be fully explored. In this study, we used RNA sequencing to characterize the changes in gene expression with PTN administration in mice cortices post-stroke and when anaplastic lymphoma kinase (ALK), a downstream effector of PTN, is blocked by alectinib. Photothrombosis was used to induce strokes on the right sensorimotor cortex of adult C57BL6/J mice, which were then given cortical PTN microinjections the next day. Mice in the experimental alectinib group were fed a daily diet of an alectinib/jelly mixture. The brains were extracted one week post-stroke, and RNA was isolated for sequencing. We found that PTN causes differential expression in stroke animals specifically, with an overrepresentation of developmental and proteoglycan ECM components among the upregulated genes – such as igf2, vcan, and sdc3 – and a downregulation in genes related to synaptic integrity – such as psd95, camk2a, and shank1. These findings show that PTN may be beneficial post-stroke by promoting processes tied to neuroplasticity.

P3-C-621 *Proprioceptive impairment mediates the relationship between white matter disconnection and motor impairment after stroke*

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Stroke is a leading cause of death and disability, affecting +108,000 Canadians annually. After stroke, ~64% of patients experience proprioceptive impairments and ~80% exhibit motor impairments from disruptions in the brain's white matter (WM) network. Despite their frequent co-occurrence, the WM pathways through which disrupted proprioception contributes to motor deficits remain poorly understood. We used voxel-wise mediation to test whether WM disconnection influences motor impairment indirectly via proprioceptive impairment in 38 chronic stroke patients. WM disconnection (predictor) was derived from individual lesion masks relative to a normative structural connectome. Proprioceptive (mediator) and motor impairment (outcome) were quantified using robotic KINARM assessments (arm position matching; visually guided reaching). Voxel-wise indirect effects were estimated (bootstrap inference, controlling for age & sex). Significant indirect mediation effects (β=0.11-0.38, FDR $p<.05$) were observed in the arcuate, middle and superior longitudinal fascicles, aligning with previously identified pathways implicated in proprioceptive impairment; and in superficial WM connecting sensorimotor cortices. Together, these findings indicate that post-stroke motor impairment reflects network-level effects propagated through disrupted proprioceptive connections beyond classical motor pathway damage. Identifying proprioception-mediated effects provides mechanistic insight into stroke-related disability and highlights proprioception as a potential target for individualized rehabilitation.

P3-C-622 *Valproic Acid Modulates Seizure-Like Network Dynamics in Neonatal Hippocampal Slices Recorded on 3D Microelectrode Arrays*

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Epilepsy is a neurological disorder affecting about 1 in 100 Canadians and over 50 million people worldwide. While antiseizure medications can reduce seizure burden, valproic acid (VPA) remains a major concern because prenatal exposure is linked to teratogenic risk and adverse neurodevelopmental outcomes, yet the neural mechanisms underlying these toxic effects remain poorly defined. Neonates and infants are especially vulnerable because developing hippocampal circuits show distinct excitatory-inhibitory balance and synchronization that can shape how seizure-like activity (SLA) emerges and resolves. However, how VPA modulates SLA dynamics in early age tissue remains difficult to study due to the technical challenges of preparing and maintaining neonatal slices and capturing network-level activity with sufficient resolution. To address this gap, we optimized a protocol for recording neonatal slices on 3D microelectrode arrays (MEAs) to quantify network activity and VPA-dependent modulation under controlled conditions. SLA was induced using magnesium-free aCSF to promote hyperexcitability and contrasted with magnesium-containing conditions to probe state-dependent network stability. We then applied VPA and quantified changes in activity, burst structure, synchronization, and recovery dynamics alongside comparative antiseizure modulation. By pairing a neonatal slice-on-chip MEA preparation with systematic SLA induction, this work provides a platform to define VPA-sensitive, age-dependent seizure signatures and to inform safer, developmentally tailored antiseizure strategies.

P3-C-623 *Purinergic receptor P2Y2 regulates neurogenesis and functional recovery following spinal cord injury in zebrafish*

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In contrast to mammals, adult zebrafish (Danio rerio) undergo successful neuronal regeneration following spinal cord injury (SCI), thereby allowing successful functional recovery. The adaptive regenerative response to SCI in zebrafish includes injury-induced proliferation of ependymal radial glial cells (ERGs) and neurogenesis. The molecular mechanisms underlying injury-induced neurogenesis in 'regenerative' species, such as zebrafish, have not been fully elucidated and are an area of great interest. In mammals, the purinergic receptor P2Y2 has been shown to mediate NSC proliferation and neurogenesis but its potential role in facilitating these components of successful regeneration in zebrafish SCI is unknown. Here, we found that P2Y2 is dysregulated following SCI in adult zebrafish, and pharmacological inhibition decreased swim capacity two weeks after injury. While P2Y2 was expressed on actively proliferating ERGs, antagonism of this receptor did not affect their proliferation levels. However, P2Y2 inhibition did attenuate SCI-induced neurogenesis, and is strongly expressed by immature and mature neurons in adult zebrafish. Overall, P2Y2 serves as a pro-neurogenic factor during injury-induced neurogenesis and contributes to the recovery of swimming behaviour in adult zebrafish.

P3-C-624 *Recovery of cortical and subcortical signatures of pain in trigeminal neuralgia following surgical pain relief*

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Intro: Trigeminal neuralgia (TN) is a debilitating neuropathic facial pain condition that can be effectively treated with surgery. After pain-relieving surgery, brain abnormalities in TN can normalize, but the scale and dynamics of this recovery process are unclear. Machine learning (ML) can identify brain imaging biomarkers to explain the neural underpinnings of TN. We hypothesized that TN patients will have a pain signature that can distinguish them from healthy counterparts and adopt a healthier phenotype after surgical pain relief. Methods: We optimized a machine learning ensemble of classifiers on brain MRIs of 146 TN patients before and after surgery and 1068 healthy controls from external databases, and further validated it on an external set of TN patients. Results: Before surgery, the ensemble differentiated TN from age- and sex-matched HC with 99% accuracy. After surgery, 29 TN, a significant proportion ($q < 0.001$), were reclassified as HC. Prediction probabilities showed that 122/146 TN (84%) shifted towards a healthier brain profile after pain relief. Data decomposition illustrated that this normalization process is nonlinear in nature. SHAP values showed that the pain signature was comprised of insular, cognitive, and ventricular regions, with the left accumbens area being the most important feature for differentiating TN from HC. Conclusions: Our multi-site longitudinal study identified a novel, reversible TN pain signature. We illustrated that brain structure alone is sufficient for ML to distinguish between TN and being pain-free, and that recovery from neuropathic pain may be detectable within a year of pain-relieving surgery. ML holds potential to substantially augment clinicians and patient care.

P3-C-625 *Re-discovering a reaching task for mice: assessing recovery in a mouse model of intracerebral hemorrhage (ICH) using the tray reaching task*

Sierra Hedges [1], Katie Klein [1], Emily Wu [1], Kaiden Breton [1], John Gillis [1], Marly Mikhail [1], Saeid Kholghi [1], Angela Auriat [1], Gergely Silasi [1]

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Intracerebral hemorrhage (ICH) is a subtype of stroke, resulting in high mortality and disability, with only 20% of survivors regaining functional independence after 6 months1, Animal models of ICH are needed that accurately model the motor impairments that are observed following hemorrhagic injury in the basal ganglia. Striatal ICH is commonly induced in both rats and mice using the intrastriatal collagenase injection

model, however there is a need to characterize lasting impairments of forelimb function in mice. The tray-reaching task is a novel test for mice that can be sensitive to quantifying motor impairments following ICH. Mice were trained on this task daily for 3–4-weeks before receiving striatal ICH in the contralateral hemisphere. Our measure of reaching success showed transient deficits on day 3 post-ICH, however we also observed long-term compensatory behaviors with the non-injured, ipsi-lesional paw. Specifically, the number of reach attempts with the ipsi-lesional paw increased from day 3 to day 35, while use of the injured paw remained dominant. Paw use returned to baseline levels by 3-5 weeks post-ICH. Mice were assessed on a battery of sensorimotor tests of forelimb asymmetry, limb coordination, and locomotor ability. This study is one of few that include a combination of skilled (tray reaching) and gross motor tests to determine the severity of deficits and recovery longitudinally after ICH in mice. Understanding the long-term impact of ICH on sensorimotor function in mice will help identify future targets for therapeutic strategies. References:1. Øie, L. R. et al. Functional outcome and survival following spontaneous intracerebral hemorrhage: A retrospective population-based study. Brain and Behavior 8, e01113 (2018).

P3-C-626 *Electrophysiological mapping of the subthalamic nucleus in Parkinson's disease: Towards improved functional characterization for deep brain stimulation*

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Introduction: Recent advances in neurostimulation for Parkinson's disease enable simultaneous deep brain stimulation and local field potential (LFP) recording. Increased beta-band activity in subthalamic nucleus (STN) LFP is associated with motor symptom severity, while its suppression correlates with improvement in bradykinesia and rigidity. However, the exact spatial organization of STN LFP activity remains poorly characterized. This study investigates the spatial distribution of STN LFP and how stimulation modulates this organization. Methods: LFP were recorded from 20 STN using the Percept PC neurostimulator (Medtronic), without and during stimulation. Electrode contact coordinates were reconstructed in MNI space using Lead-DBS. Frequency-specific STN heatmaps were generated using spatial interpolation and gaussian smoothing. Spatial distributions were analyzed using generalized linear models and power centroids. Results: Beta-band activity was significantly higher at lateral coordinates ($p = 0.006$), with a laterally confined power centroid. During stimulation, beta activity was more strongly reduced in lateral regions ($p = 0.0015$). Alpha-band activity showed spatially differential modulation, increasing posteriorly and decreasing anteriorly with stimulation ($p < 0.001$). Discussion/Conclusion: STN neuronal oscillations exhibit a spatial organization, with lateral beta band predominance and differential antero-posterior alpha modulation. Incorporating spatial information from LFP recordings may help optimize stimulation parameters, particularly with directional electrodes.

P3-C-627 *Reduced presence of spinal inhibitory neurons in a mouse model of fragile x syndrome*

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Fragile X syndrome (FXS) is a neurodevelopmental disorder associated with autism spectrum disorder, caused by silencing of the Fmr1 gene and the resulting loss of fragile X mental retardation protein (FMRP). Individuals with FXS exhibit sensory processing abnormalities, including pronounced tactile hypersensitivity. Consistent with this clinical feature, the Fmr1 knockout (KO) mouse model also displays heightened sensitivity to touch. Despite this behavioral evidence, the molecular mechanisms underlying this tactile hypersensitivity remain poorly understood. Parvalbumin (PV)-expressing inhibitory interneurons in the dorsal horn of the spinal cord regulate tactile processing and mechanical pain. We find reduced PV protein expression in Fmr1 KO mice at both the mRNA and protein levels, with less PV interneurons across postnatal development, suggesting impaired development. To test whether this deficit is cell-intrinsic, we selectively

deleted Fmr1 in PV interneurons (Pv-Cre, Fmr1fl/fl; Fmr1 cKO). Unlike global Fmr1 KO mice, these PV-specific cKO mice show no differences in PV neuron number or Pvalb mRNA expression, indicating that PV deficits arise from extrinsic mechanisms. Ongoing work aims to identify such extrinsic cell types that regulate PV interneuron development. These results will help identify regulators of PV interneuron maturation within spinal touch-processing circuits and advance our understanding of the cellular mechanisms underlying FXS.

P3-C-628 *Age- and Sex-dependent effects of immune challenges on motor function in mice*

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Exposure to stress during puberty can lead to long-lasting consequences on brain function, as the brain is undergoing remodelling and reorganizing during this critical period of development. For example, pubertal exposure to lipopolysaccharide (LPS), a bacterial endotoxin, induces enduring motor deficits in male mice. However, it is unclear whether pubertal exposure to other immune challenges, like polyinosinic:polycytidylic acid (Poly (I:C)), a viral mimetic, during puberty could have similar sex-dependent long-term effects. Therefore, this study compared the effects of two immune challenges, LPS and Poly (I:C) in pubertal and adult male and female mice. At 6 (pubescent) or 10 (adult) weeks of age, the mice received an intraperitoneal injection of either LPS (1.5 mg/kg), Poly (I:C) (12 mg/kg), or sterile saline vehicle (0.9%). Sickness symptoms were monitored and scored up to 48 hours post-injection and body weights were measured throughout the study. Four weeks later, the mice were exposed to a series of behavioral tests, such as the open field, forepaw stride length, reverse grid hang, and rotarod. We found that pubescent females performed better than pubescent males on the reverse grid hang test, regardless of treatment. We also found that adult females treated with LPS displayed better motor coordination on the rotarod test compared to male counterparts. Taken together, our findings show that immune challenge induces age and sex-dependent alterations in muscle strength and motor coordination. This study contributes to a better understanding of the mechanisms underlying the sex-dependent development of motor deficits involved in neurodegenerative disorders, like Parkinson.

P3-C-629 *Regional and temporal dynamics of early amyloid pathology and lysosomal co-localization in 5XFAD mice*

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While extracellular amyloid plaques have been extensively studied in Alzheimer's disease, the early intracellular phase of amyloid-beta accumulation and its relationship to lysosomal dysfunction remains poorly characterized. This gap is critical, as lysosomes are the primary degradation pathway for intracellular amyloid-beta, and their failure may drive the transition from intracellular to extracellular pathology.
To investigate this early pathogenic window, we mapped the spatiotemporal progression of amyloid accumulation and lysosomal involvement in 5XFAD mice across development. Using immunohistochemistry with MOAB-2 antibody for amyloid labelling, we examined the dorsal subiculum and CA1 hippocampal regions at 4, 6, 8, and 10 weeks, plus 6 months of age. We discovered that the dorsal subiculum accumulates intracellular amyloid significantly earlier than CA1, with a critical transition to extracellular plaque formation occurring between 6 and 8 weeks. Female mice showed accelerated intracellular amyloid-beta accumulation compared to male littermates, suggesting sex-dependent vulnerability in this early phase. Critically, Cathepsin D immunostaining revealed that intracellular MOAB-2 signal strongly co-localized with lysosomes across timepoints, with lysosome density correlating with intracellular amyloid-beta burden. These findings demonstrate that lysosomal accumulation of amyloid-beta both precedes and coincides with extracellular plaque formation and identifies the 6-week to 8-week transition period in the dorsal subiculum as pivotal for understanding modelled disease progression, specifically the transition from intracellular lysosomal dysfunction to extracellular amyloid deposition.

P3-C-630 *Region-specific deletion of STEP in the hippocampal region CA2: Consequences for social and spatial memory*

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Deficits in social memory and social behavior are common features of several neurogical and neuropsychiatric disorders, including Alzheimer's disease, schizophrenia, and autism spectrum disorders. The hippocampal CA2 subregion has emerged as a critical node for social memory processing; however, the molecular mechanisms governing its function remain poorly understood. Post-mortem analyses of brains from patients with Alzheimer's disease reveal elevated levels of the striatal-enriched protein tyrosine phosphatase (STEP), a negative regulator of synaptic plasticity whose degradation is required for memory formation and synaptogenesis. STEP is highly expressed in the CA2 region, yet its specific contribution to CA2-dependent memory remains unknown. In this study, we investigate the role of STEP in the hippocampal CA2 region using a targeted genetic approach combining CRISPR-Cas9 and Cre-loxP technologies to selectively suppress STEP expression in mice. Behavioral outcomes are assessed using a comprehensive battery of tests evaluating social memory, episodic and spatial memory, anxiety-like behavior, locomotor activity, and olfaction. Molecular analyses examine changes in the expression and phosphorylation of known STEP substrates involved in glutamatergic signaling and intracellular kinase pathways. We hypothesize that selective deletion of STEP in CA2 will lead to a specific impairment in social memory while sparing other cognitive and behavioral domains. By identifying STEP as a key molecular regulator of CA2 function, this work aims to advance our understanding of the cellular mechanisms underlying social cognition and their dysregulation in diseases of the nervous system. Ultimately, these findings may inform the development of novel therapeutic strategies targeting synaptic dysfunction in neurological disorders.

P3-C-631 *Regulation of the intracellular accumulation of Tau by Numb and its role in tauopathies*

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Tauopathies are a large family of neurodegenerative diseases characterized by dysregulation of the microtubule binding protein Tau, which becomes hyperphosphorylated, disassociating from microtubules, elevating intracellular Tau levels and formation of aggregates called neurofibrillary tangles. These tangles are known to be toxic to neurons and therefore understanding how Tau is regulated in health and disease is an important step in better understanding the pathogenesis of tauopathies. Recently, our lab has shown that the long isoform of the endocytic adaptor protein, Numb72, functions as a negative regulator of intracellular Tau levels (Lacomme et al., Sci. Adv., 2022). We found that overexpressing Numb72 in retinal neurons of mouse models of tauopathy significantly reduces Tau accumulation and increases neuronal survival, but whether Numb72 can also function as a neuroprotective agent in neurons outside the retina remains unknown. To address this question we conditionally inactivated Numb in the brain using the CamKIIa-CreERT2 mouse line, and overexpressed Numb72 by AAV infection in cultured hippocampal neurons or in the hippocampus in vivo. Preliminary data show that overexpression of Numb72 reduces intraneuronal accumulation of Tau in hippocampal neurons, while inactivation of Numb in the hippocampus accelerates learning and memory deficits. Moreover, overexpression of the human ortholog Numb1 in human iPSC-derived neurons similarly regulates Tau levels. Overall, this work provides support for the development of Numb72 as a therapeutic target for tauopathies.

P3-C-632 *Regulatory roles of Parkinson's disease-associated microRNAs in alpha-synuclein expression*

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MicroRNAs (miRs) are small RNAs that are critical regulators of gene expression. In the nervous system, miRs are enriched in neurons and are essential for maintaining neuronal identity, function, and resilience. Dysregulation of miR expression and processing has been implicated in neurodegenerative diseases, including Parkinson's disease (PD). Aberrant miR activity is hypothesized to contribute to the accumulation of α-synuclein (α-syn), a key player in PD. Recent evidence suggests that miRs targeting α-syn mRNA are regulated by RNA-binding proteins (RBPs), which modulate their maturation. We hypothesize that specific RBPs interact with immature forms of α-syn, targeting miRs, thereby modulating their maturation and controlling α-syn expression in neurons. To test this hypothesis, we aim to: (1) validate miRNA-mediated regulation of α-syn in human and murine models, (2) identify RBPs associated with α-syn-targeting miRs using riboproteomics approaches, and (3) functionally characterize selected RBPs in cell models. To date, we have identified several miRs that modulate α-syn expression in both mouse and human models, notably miR-7-5p and miR-153-3p, and have uncovered multiple RBP candidates for functional validation. Focusing on miR-153-3p, we validated specific RBPs, such as Adar and MIF, that regulate its expression in human cells. Together, these findings reveal and RBP-miRNA regulatory axis controlling α-syn expression, with implications for RNA-based mechanisms, biomarkers and therapeutic strategies for PD.

P3-C-633 *Reinstating GDNF-RET response to achieve dopaminergic cell rescue in a rat model of alpha-synuclein pathology*

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Glial cell line-derived neurotrophic factor (GDNF) is a key neurotrophic factor with roles in differentiation and survival of dopaminergic (DA) neurons, making it a therapeutic target of interest for Parkinson's disease (PD). In addition, downregulation of one of GDNF's main target receptors, rearranged during transfection (RET), has been previously reported from post-mortem studies on human PD patient brains. As such, reinstatement of RET-mediated GDNF-signaling may be key to achieving protection of DA neurons. Therefore, we investigated the cell rescue potential of reinstating GDNF-RET-signaling in a rat in-vivo model of alpha-synuclein (α-syn) overexpression. We observed increased numbers of tyrosine hydroxylase (TH) and vesicular monoamine transporter 2 (VMAT2)-positive neurons in response to combined overexpression of GDNF and RET in animals overexpressing α-syn. Additionally, we noted increased levels of cells expressing phosphorylated ribosomal protein S6 (pRPS6), a previously established marker of GDNF-activity, in response to GDNF-overexpression. However, only in animals overexpressing both GDNF and RET did we observe a significant rescue of TH-positive neurons. This indicates that pRPS6 alone does not drive the DA-cell rescue response in this setting. These findings demonstrate a partial rescue response of combined overexpression of GDNF and RET in a rat α-syn lesion model, and encourages further investigation of precise downstream mechanisms driving protection of DA-neurons in models of α-syn pathology.

P3-C-634 *Repeated injury impacts immune and neural stem cell-mediated repair in the zebrafish forebrain*

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Neural stem cells (NSCs) are critical for brain repair following injury. Among vertebrates, adult zebrafish exhibit remarkable regenerative capacity, driven by NSC-mediated repair in the forebrain. Radial glial cells (RGCs), a key NSC population, produce new neurons to replace lost lineages through tightly regulated molecular and immune-mediated mechanisms. Whether RGCs can sustain long-term neuronal production

following repeated damage remains poorly understood. This study examines the impact of recurrent injury on RGC function, neuronal output, and the injury environment. Adult zebrafish were subjected to weekly forebrain injuries for up to four consecutive weeks. Histological analysis using H&E staining at 1-day post-injury revealed enlarged lesion and increased blood clotting with successive injuries. Behavioral study validating the injury paradigm showed no significant change in total distance traveled between the 1X and 4X injuries, while Click-iT TUNEL analysis revealed increased cell death after 4X injuries. Immune profiling using Tg(mpx:GFP) combined with 4C4 immunostaining revealed diminished neutrophil activity alongside a sustained microglial response. Using the Tg(GFAP:gfp)×Tg(Her4.1:mCherry) reporter line, preliminary data indicate a decline in RGC proliferation after 4X injuries. In parallel, analysis of neurogenesis using EdU/HuC/D co-labeling demonstrated reduced neuronal production. Collectively, these findings suggest that repeated injury limits zebrafish RGC-mediated regeneration through altered immune dynamics and a constrained injury microenvironment.

P3-C-635 *Repetitive transcranial magnetic stimulation paired with augmented reality to alter post-concussion dizziness*

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Introduction: Concussions impact ~1.6% of Canadians annually. One in four experience persistent post-concussion dizziness (PCD), significantly impairing quality of life. Augmented reality sensorimotor training (ARST) gamifies traditional vestibular therapy to reduce symptoms. In stroke rehabilitation, sensorimotor training is enhanced when paired with repetitive transcranial magnetic stimulation (rTMS). rTMS may have similar effects when paired with ARST, however its effects on PCD remain unexplored. We aim to determine if rTMS paired with ARST improves PCD symptoms more than ARST alone. Methods: 32 participants (aged 18-65 years) with PCD (≥3 months post-injury) will be randomized to receive REAL or SHAM (placebo) rTMS to the left primary motor cortex. rTMS will be delivered in three blocks separated by 15 minutes, with 5 minutes of ARST after each block. This intervention will be delivered for 14 days over 3 weeks. Dizziness disability will be evaluated via the Dizziness Handicap Inventory (DHI), with additional post-concussion symptoms assessed using objective and subjective measures. All outcomes will be measured at baseline (T0) and post-intervention (T1). Expected Results: We anticipate greater PCD symptom reduction in the REAL rTMS group compared to SHAM. Impact: This is the first randomized controlled trial using rTMS for PCD and the first to combine rTMS with ARST to mitigate dizziness.

P3-C-636 *Resolving variants of uncertain significance in ALS through integrated in silico and functional approaches*

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Background: The use of genetic testing for neurological disease has increased exponentially with the advent of new gene therapies and the availability of commercial genetic platforms. A frequent outcome of genetic testing is receiving a variant of uncertain significance (VUS) whose interpretation has remained a challenging problem, moreso in the presence of multiple VUS (oligogenicity). While current standards recommend against using VUS for clinical decision-making, their interpretation is dynamic and they are increasingly recognized as potential determinants of biological outcomes. Methods: We propose an approach to interpret VUS by combining predictive tools for splicing, population data, and protein pathogenicity. Findings were validated in vitro by expressing wild-type and mutant proteins in HEK293T cells and assessing subcellular localization via confocal microscopy. Results: A thorough literature review identified in silico tools and databases that could be used together to aid in variant interpretation. Utilizing this multimodal approach to VUS interpretation yielded predictions for different variants involved in amyotrophic lateral sclerosis (ALS). While these tools successfully offered predictions for some genes, a significant portion of pathogenicity is due to oligogenic inheritance that only in vitro experiments could appreciate. Conclusions: Our findings

underscore the necessity for a multimodal approach to VUS interpretation and explored limitations of the single gene approach. VUS interpretation will be necessary to a future of precision medicine.

P3-C-637 *Role of A2A purinergic receptor in glial bridge formation and cellular and functional recovery following spinal cord injury in Danio rerio*

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Zebrafish (Danio rerio) demonstrate a robust regenerative response following spinal cord injury (SCI). Zebrafish spinal ependymal radial glial cells undergo lesion-induced proliferation and migrate to form a glial bridge across the injury site. This permissive bridge aids in axonal regrowth, facilitating functional recovery. In contrast, mammalian SCI causes cellular death and neuronal degeneration. Mammalian ependymal glial cells have been shown to proliferate following injury, but do not bridge the injury site. Instead, an inhibitory glial scar is formed, preventing the regeneration of neuronal processes. Elucidating the molecular cues driving these responses would offer important insight into regenerative mechanisms unique to teleost fish. One molecular system involved in zebrafish regeneration is the evolutionarily conserved purinergic signaling. Specifically, adenosine-activated purinergic A2A receptors have been shown to regulate neural progenitor proliferation and neurite outgrowth. This project aims to evaluate the role of A2A in glial bridge formation, which is crucial for cellular and functional recovery in zebrafish following SCI. To investigate this, expression of A2A using mean intensity will be analyzed in injured larval zebrafish. In addition, exogenous manipulation of A2A following SCI will be used to assess its effects on glial bridge formation and axon regrowth. To analyze functional recovery, behavioural assessments will be evaluated. Since drugs targeting A2A are clinically available, this work has translational applications with therapeutic potential.

P3-C-638 *Role of mitochondrial dynamics in C. elegans models of Alzheimer's disease*

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Alzheimer's disease (AD) is the most common age-related neurodegenerative disease; it is characterized by the progressive degeneration of neurons initially in the hippocampus and entorhinal cortex before spreading to other regions of the brain. This leads to memory loss, cognitive decline and difficulties with problem-solving and language. In the brains of AD patients and models, it has been shown that the mitochondrial network is more fragmented than in controls due to decreased mitochondrial fusion and increased mitochondrial fission. We hypothesize that decreasing mitochondrial fragmentation will be neuroprotective in AD. To test this hypothesis, we will use a simple, genetic model organism, C. elegans, to monitor mitochondrial morphology and neuron survival using fluorescently-labelled proteins as these worms are transparent. In addition, the short lifespan of the worm will allow us to monitor whole organism phenotypes throughout aging in a rapid manner. First, we will characterize C. elegans models of AD expressing either Aβ or tau to determine which phenotypic deficits are present in these models that can be used as outcome measures. We will examine both general measures of health (lifespan, movement, fertility, resilience) as well as phenotypes related to symptoms present in AD patients (neuronal survival, neuronal morphology, learning and memory). Next, we will cross these AD worm models with C. elegans strains with increased or decreased levels of genes that affect mitochondrial dynamics, including drp-1, fzo-1, eat-3 and puf-8, and examine the resulting effect on disease-relevant outcome measures. Overall, this work will advance our understanding of the role of mitochondrial dynamics in AD pathogenesis, which may assist in the generation of treatments that can slow or halt AD onset and progression.

P3-C-640 *Seizure-sensitive neurons gate memory specificity after early life seizures*

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Memory specificity refers to the ability to recall an event with precise details, distinguishing it from experiences with similar or overlapping features. The dorsal hippocampal CA1 (dCA1) region is critical for memory specificity encoding through sparse, highly specific memory engrams, a process that relies on minimal baseline neuronal activity. Early life seizures (ELS) are known to dysregulate baseline neuronal activities. We therefore hypothesize that ELS may directly impair memory specificity, which is indeed a common and mechanistically unexplained comorbidity in early-life epilepsy. Using a c-Fos-based transgenic mouse model, we demonstrated that memory specificity, starting at P24 in mice, assessed through contextual fear memory testing, is associated with minimal baseline activation and a small, specific engram. ELS at P10 preferentially activated and enhanced the excitability of a distinct neuronal population in dCA1. This resulted in a sustained elevation of baseline activities in dCA1 pyramidal neurons by P24, which correlated with impaired contextual discrimination and a significantly enlarged engram in mice with ELS compared to control mice. Importantly, selective chemogenetic silencing of ELS-activated neurons immediately after the seizures normalized dCA1 baseline activation and fully rescued ELS-induced deficits in memory specificity. Our results identify a precise circuit mechanism underlying ELS-induced impairments in memory specificity, offering a new strategy for treating memory deficits following early-life seizures.

P3-C-641 *Selective resistance and vulnerability of extra-motor circuits in ALS revealed by eye tracking*

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Amyotrophic lateral sclerosis (ALS) is increasingly recognized as a multisystem disorder with early and frequent disruptions to energy homeostasis and autonomic control. However, these extra-motor deficits remain poorly understood and difficult to measure. Eye tracking is a non-invasive means to probe widespread, dissociable neural circuits, providing a unique opportunity to assess extra-motor pathology in ALS. In this study, 21 patients with ALS and 34 healthy controls completed an unstructured eye-tracking task involving free viewing of dynamic video clips with abrupt scene transitions every 2-5 seconds. Saccade, pupil, and blink responses were quantified, with a particular focus on visual perturbations caused by clip changes. Plasma lipids were also collected from the ALS group for exploratory metabolic associations. Compared to healthy controls, the ALS cohort exhibited intact saccadic orienting to clip changes, but attenuated pupil responses and prolonged eyeblinks. Exploratory analyses revealed associations between pupil dynamics and metabolic biomarkers of ALS. The oculomotor profile of ALS is characterized by the resistance of saccade-generating circuitry and vulnerability of brain systems regulating pupil size and eyelid position. Concurrent shifts in metabolism and pupil responsivity further suggest early disruption of central energy balance, potentially involving hypothalamic pathways. As a sensitive and disability-agnostic measure of extra-motor function, eye tracking could improve patient stratification and guide targeted therapeutic strategies.

P3-C-642 *Selective seeding of human abnormal tau proteins in subiculum projecting entorhinal cells impairs temporal association memory in a mouse model of early Alzheimer's disease*

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Alzheimer's disease (AD) is characterized by memory deficits and progressive cognitive decline coinciding with the accumulation of amyloid-β and tau pathology. In the preclinical phase, navigation impairments begin to manifest alongside abnormal hyperphosphorylated tau (aTau) proteins in the entorhinal cortex (EC). As AD progresses, aTau spreads into the subiculum (Sub), a region involved in memory encoding and recall. To simulate early aTau progression along the EC-Sub pathway and its impact on memory

systems, we employed a cre-dependent viral strategy to selectively express human mutated tau proteins (AAV2/9-Flex-P301L-GFP) in subiculum-projecting layer 2/3 cells in EC. By injecting the virus into the dorsal subiculum of tg(Oxr-1cre)C14Stl/J transgenic mice, we were able to initially seed aTau within this circuit. Immunofluorescence imaging confirmed the expression of the virus and accumulation of hyperphosphorylated tau proteins (AT8) within the EC2/3-sub circuit in as few as 4 weeks post-injection. Mice were tested on anxiety (elevated plus maze), spatial memory (water maze), and temporal association/contextual memory (trace-fear conditioning) tasks. To understand the impact of aTau on hippocampal circuit health, we also performed high-density silicon probe recordings across Sub and the CA1 region of the hippocampus while head-fixed mice engaged in virtual navigation and trace-fear tasks. Compared to cre-/- littermate controls, aTau+ mice displayed a significant impairment in temporal association memory, while spatial/contextual memory and anxiety-like behaviours were not affected. Together, these data show that aTau accumulation in the EC2/3-Sub circuit impairs temporal association memory and highlight the viability of cre-dependent viral delivery of aTau as a powerful model to probe the functional impacts of tau progression within key AD circuits.

P3-C-643 *Sensory dysregulation affects brain development and behavior in a mouse model of KBG syndrome*

Yana Kibalnyk [1], Zoe Dworsky-Fried [1], Caylin Chadwick [1], Anna Taylor [1], Qiumin Tan [1], Anastassia Voronova [1]

[1] University of Alberta

KBG syndrome is a rare neurodevelopmental disorder caused by mutations or deletions in the gene ANKRD11 (Ankyrin Repeat Domain 11). KBG patients display brain abnormalities, intellectual disability, sensory deficits, and autism spectrum disorder (ASD). Dysregulation of the sensory nervous system contributes to altered brain development and behavior in several animal models of neurodevelopmental disorders and ASD. However, the cause of sensory dysregulation in neurodevelopmental disorders is not well understood. While Ankrd11 has been shown to regulate brain development in a mouse model of KBG syndrome, its role in sensory nervous system development is unknown. To answer this question, I used a mouse model with conditional knockout of Ankrd11 in developing sensory neurons (Ankrd11cKO). I found that sensory neurons of the Ankrd11cKO trigeminal ganglia, which provide sensory input from the head and face, show transcriptomic changes in receptors and ion channels important for sensitivity to touch, temperature, and painful stimuli in both males and females. Furthermore, Ankrd11cKO female mice show aberrant number of inhibitory neurons in the somatosensory cortex, a brain region that processes information from the sensory nervous system, and the anterior cingulate cortex, a brain region important for sociability, while male mice show normal cortical interneuron numbers. Therefore, Ankrd11 deficiency in sensory neurons has direct effects on sensory neuron function in males and females, but indirect effects on brain organization in females only. Finally, Ankrd11cKO females show reduced social behavior compared to control littermates or Ankrd11cKO males. These results show that Ankrd11 ablation in sensory neurons leads to behavioral and brain development abnormalities, highlighting the role of sensory dysregulation in neurodevelopmental disorders.

P3-C-644 *Purinergic Dysregulation in the Developing Fragile X Hippocampus*

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Fragile X Syndrome is the leading genetic cause of intellectual disability among children and occurs due to the loss of the FMRP protein. Those affected by the disease experience a variety of neurological symptoms, including learning and memory impairments. These impairments implicate the hippocampus, and several synaptic pathologies have been identified during hippocampal development. Microglia and astrocytes have recently been shown to contribute to these pathologies, but little is known of the molecular mechanisms behind their dysfunction. Using the Fmr1-knockout (KO) mouse model, I examined a prominent neuron-glia signalling system, purinergic signalling. During the third postnatal week, I found that P2X7 receptor expression was reduced on hippocampal granule neurons, consistent with neuronal stress, but elevated

on dentate gyrus (DG) microglia, indicating microglia activation. I also found that P2Y2 was elevated on astrocytes in the DG and CA1, which then contributed to an increased calcium response in vitro following P2Y2 stimulation. Given the involvement of three cell types, I optimized an organotypic slice culture model for growth on commercially available microelectrode array (MEA) plates. Using the MEA to measure regional field potentials during slice development, I found differences in the power of DG theta and CA1 gamma bands between WT and Fmr1-KO slices. This is the first application of slice culture MEA to Fragile X, offering a new model for studying neuron-glia systems like purinergic signalling in the disease.

P3-C-645 *Sex differences in a stress induced depressive phenotype: a time course of behavioural and central effects*

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Females show a two-fold increased prevalence of mood and anxiety disorders. Similarly, there are sex differences in cognitive and emotive behaviours following exposure to acute and chronic stressors in rodents. We have previously shown that astroglial cells respond to five weeks of chronic variable stress (CVS) by upregulating perineuronal net (PNN) components, leading to a PNN upregulation around prefrontal cortex (PFC) interneurons in male mice. However, whether sex differences occur in the timing of the onset of these changes in response to CVS is unknown. We employed a time course paradigm whereby male and female mice were exposed to CVS for one to five weeks in duration, followed by a battery of behavioural testing for emotive behaviours and histopathological analyses of their brains. Samples of dissected PFC were processed for single-nuclei sequencing to build a complete gene expression profile of every cell type in response to CVS exposure in males and females. We found sex differences in emotive behaviours over time whereby males show increases in emotive behaviours following one week of CVS whereas females show increases at two weeks. Sequencing analyses showed sex differences in almost all cell clusters with peak sex differences in astroglia after only one week of stress, closely followed by oligodendrocytes, microglia and finally, interneurons and excitatory neurons. Altogether, these data show sex differences in the behavioural and cellular responses to chronic stress over time, with glial cells potentially showing earlier phenotypic changes followed by neurons.

P3-C-646 *Sex-dependent neurovascular and network disruption following diffuse microvascular occlusion*

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Cerebral microinfarcts (MIs) are small ischemic lesions caused by microvascular occlusions and are highly prevalent in the aging brain. Present in cognitively impaired and unimpaired individuals, MIs are strongly associated with vascular cognitive impairment (VCI). Increasing MI burden has been linked to vascular dysfunction, neuroinflammation, and cognitive decline, suggesting cumulative contributions to neurodegeneration. Here, we investigated the consequences of diffuse microvascular occlusion in vivo. Male and female C57BL/6 mice were systemically transduced with the genetically encoded calcium indicator GCaMP6s via AAV.PHP.eB.Syn.GCaMP6s delivery. Diffuse MIs were induced by injection of fluorescent 45µm microspheres into the internal carotid artery, generating lesions reminiscent of small vessel disease. Longitudinal assessments included behavioral testing, retinal angiography, and transcranial imaging of resting-state activity, visually evoked responses, and cerebral blood flow in awake, head-fixed mice. Widefield calcium imaging revealed marked impairments in evoked neuronal activity and resting-state functional connectivity, accompanied by deficits in sensorimotor and cognitive performance, with females exhibiting greater vulnerability to microsphere-induced dysfunction. Laser speckle contrast imaging demonstrated redistribution of blood flow through collateral vessels, while longitudinal imaging revealed progressive microemboli migration. Retinal angiography identified transient increases in venous diameter

and tortuosity at 2 days post-induction, and light-sheet fluorescence microscopy confirmed widespread cortical microsphere distribution persisting at 14 days post-induction. These findings establish a robust model of MI that recapitulates key features of VCI and provides a platform for mechanistic studies of sex-dependent MI-driven neurodegeneration.

P3-C-647 *Sex-specific behavioural, regional and synaptic landmarks of tauopathy revealed by PET imaging and EEG*

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Microtubule associated protein tau (MAPT) pathology is associated with dementias and numerous neurodegenerative diseases. The linkage of tauopathy to neuronal and synaptic atrophy, behavioural impairments, and molecular pathways makes it a critical target for dementia modelling and biomarker development. Novel tauopathy mouse models were developed with physiological expression via knock-in of the human MAPT gene, including human wild-type tau (MAPT), and the mutant variant MAPTS305N;Int10+3G>A (S305N). PET/CT imaging was conducted with [18F]OXD-2314 for 3-repeat/4-repeat tauopathy and [18F] SynVesT-1 for synaptic density, and electroencephalography (EEG) to measure neuronal activity and sleep patterns. Both MAPT and S305N mice exhibited phosphorylated tau (p-tau) at the PHF1 epitope at 12 months. S305Ns had a robust increase in mid-stage p-tau (CP13) and 4-repeat tau. Increased [18F]OXD-2314 tau PET uptake was observed in subcortical brain regions of S305N mice primarily in the sleep-associated hypothalamus, and more widespread increases observed in females. [18F]SynVesT-1 imaging revealed loss of pre-synaptic density in female S305N mice. Aberrant synaptic reorganization occurred in S305N mice, more so in males. All S305N mice exhibited EEG slowing with robust sleep impairments in males. Our results highlight the linkage of sleep and tau using EEG and PET imaging, and the sex-specific behavioural, regional and synaptic vulnerabilities in tauopathy. These results support EEG and PET imaging with [18F]OXD-2314 and [18F]SynVesT-1 radiopharmaceuticals for tauopathies.

P3-C-648 *Sex-specific transcriptional reorganization of dopaminergic projections following chronic social stress*

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Depressive disorders are associated with impaired reward processing and dysregulation of dopaminergic circuits. Ventral tegmental area (VTA) neurons send projections to multiple brain regions, including abundant inputs to the nucleus accumbens (NAc) and medial prefrontal cortex (mPFC), that play key roles in motivation and stress-related behaviors. Still, the transcriptional profile of these pathways under chronic stress remains poorly understood. This study combined RiboTag and RNA sequencing to profile ribosome-associated mRNA from VTA dopaminergic neurons and their NAc and mPFC projections in stressed male and female mice. Differential expression analysis showed small overlap between resilient and susceptible mice (BRSM) for both sexes in VTA and projections, and rank-rank hypergeometric overlap analysis showed a notable overlap BRSM for both sexes, except for the projections to NAc in males. Gene ontology showed multiple shared biological processes related to neuron activity BRSM for males in VTA and projections, as opposed to what was observed in females. Weighted gene co-expression network analyses revealed a distinct pattern between VTA and projections. Even with moderate preservation of most gene modules, VTA modules showed higher enrichment with differentially expressed genes and association with phenotype, and fewer sex-specific modules were found in the projections. These findings suggest that chronic stress induces sex-specific transcriptional reorganization of these networks, potentially contributing to susceptibility or resilience to stress-related disorders.

P3-C-649 *Shared vulnerability of SST neuron subtypes in Schizophrenia and Alzheimer's disease*

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Schizophrenia (SCZ) and Alzheimer's disease (AD) are distinct neuropsychiatric disorders characterized by progressive cognitive deficits and structural alterations in the brain. These disorders have shared cellular pathologies, including the loss of somatostatin (SST) inhibitory neurons. Recent work found that only a subset of SST cells were vulnerable in early stages of AD. We sought to investigate these neurons in schizophrenia, with the goal of further unraveling the shared cellular vulnerabilities between SCZ and AD. We used single-nucleus RNA-sequencing from postmortem brain samples in 671 individuals (233 SCZ cases, 438 controls) across seven datasets. To characterize the physiological properties of these cells, we used publicly available patch-seq data from human neurosurgical donors. All datasets were mapped to the SEA-AD taxonomy, enabling consistent cell annotation. In SCZ, we found significant a reduction in SST_22 ($\hat{B}$=-0.36, FDR < 0.01), SST_25 ($\hat{B}$=-0.30, FDR < 0.05), and SST_2 ($\hat{B}$=-0.27, FDR < 0.01) neurons. Vulnerable SST cells were more likely located in upper cortical layers (t=-7.40, p-value=9.68e-12), had larger Sag currents (t=7.54, p-value=2.62e-12), and had greater HCN1 expression (logFC=0.97, FDR<0.01). The vulnerable SST subtypes we identified in SCZ were shared with those previously identified in early AD. These SST subtypes are found in superficial cortical layers and are functionally more active. Our findings suggest that these neurons possess intrinsic properties that make them especially vulnerable, regardless of the broader disease context.

P3-C-650 *Single-axon tracing of the subthalamic nucleus afferent projections arising from the external pallidum in cynomolgus monkeys*

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The subthalamic nucleus (STN) is the main driving force of the basal ganglia. It projects mainly to the internal (GPi) and external (GPe) pallidum, the striatum, and the substantia nigra pars reticulata, while it receives inputs from the cerebral cortex, the pedunculopontine tegmental nucleus, the raphe nuclei, the intralaminar thalamic nuclei and the GPe. The present study aims to characterize the GABAergic STN afferents arising from the GPe. To this end, microiontophoretic injections of an anterograde tracer were placed into the GPe of cynomolgus monkeys (Macaca fascicularis), and individual axons were traced across serial sagittal sections and reconstructed in 3D. GPe-STN afferents originate mainly from collaterals of long-range (up to 10 mm) axons of GPe neurons. After leaving the GPe, the thick (~2 µm) axons travel through the GPi, giving off only few collaterals within this nucleus. The main axon then pierces the internal capsule to enter the STN through its anterior or ventral aspect. Within the STN, it divides into thinner (~ 0.6 µm) branches. These STN collaterals display large axon varicosities that are often opposed to the soma and proximal dendrites of STN neurons. Altogether, they form a restricted terminal field within the STN. Abnormal firing of STN neurons occurs in Parkinson's disease and the contribution of GPe inputs remains poorly understood. The information gathered here will help to refine a computational model of STN deep brain stimulation (DBS) used to alleviate motor symptoms of Parkinson's disease.

P3-C-651 *Single-molecule fluorescence in situ hybridization analysis of immature granule neurons in the depressed human dentate gyrus*

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BACKGROUND: The neurogenic hypothesis of depression suggests that the formation of new granule cells in the dentate gyrus (DG) of the hippocampus is implicated in depression and antidepressant action. Previously, our group has demonstrated that immature granule cells persist in the adult human DG, despite low levels of neurogenesis. Here, we aim to provide new insight into the involvement of these immature cells in major depressive disorder (MDD) at the transcriptomic level. METHODS: Using post-mortem tissue

from frozen-fixed anterior DG samples of adult non-psychiatric and depressed individuals who have died by suicide, we performed multiplexed fluorescent in situ hybridization (RNAscope) to examine immature PROX1+CALB2+DCX+ neurons, testing the hypothesis that these cells are altered in MDD. RESULTS: Our preliminary findings indicate trends toward fewer DG DCX+ cells in samples from MDD patients without antidepressant treatment compared to controls and an increased number of these cells in treated MDD subjects compared to control and untreated MDD subjects. The percentage of subgranular zone PROX1+CALB2+DCX+ cells was significantly increased in treated MDD subjects compared to non-psychiatric individuals. These immature cells displayed in MDD a different distribution within the granule cell layer (GCL) compared to controls. We also observed an abnormal distribution of granule cells in MDD subjects, reflected by GCL structural changes and ectopic immature and PROX1+CALB1+DCX- granule cells. CONCLUSION: Our findings suggest that immature granule neurons are altered in MDD.

P3-C-652 *Sleep and non-motor health over six years of community dance in Parkinson's disease*

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Non-motor symptoms, including sleep disturbances, are common and debilitating features of Parkinson's disease, a progressive neurodegenerative movement condition. Insomnia and excessive daytime sleepiness are among the most prevalent sleep-related non-motor symptoms and are associated with poorer quality of life. While treatments exist, the ability to address non-motor symptoms is limited; thus, researchers have been exploring alternative forms of care, including dance, to alleviate symptom burden. Previously, we examined cognitive performance across six years (2014 – 2019) of community dance and found significant improvements among PD-dancers (Dance group; n = 43) compared to no change in a sedentary PD (Reference; n = 28) group. Building on these findings, our present work examines the influence of sustained dance engagement on sleep dysfunction and overall non-motor symptom burden within the same study population. The Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) was used to assess sleep and non-motor outcomes in both groups. Insomnia worsened significantly in the Reference group (2018-2019, p = 0.003), while daytime sleepiness remained stable across both groups. Overall non-motor symptom burden also worsened significantly in the Reference group (2018-2019; p = 0.011), compared to stabilized scores in the Dance group. Collectively, our findings demonstrate the potential benefits of dance to support non-motor health, including preserved sleep, in PD.

P3-C-653 *Spatially resolved molecular-cellular dysregulation in the subiculum of young 5xFAD mice*

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Identifying which cell types in the brain exhibit the earliest vulnerability in Alzheimer's disease is critical for defining the first targets of dysfunction. To investigate whether excitatory subiculum neurons display signatures of molecular dysregulation early in disease progression in a cell-type-specific manner, we employed single-cell spatial transcriptomics (scST) and immunohistochemistry (IHC) in young 5xFAD mice. To spatially map and molecularly characterize transcriptomic subpopulations within the subiculum and CA1, we analyzed scST data from 6- and 10-week-old mouse brain hemi-sections. We found spatially and molecularly distinct neuronal subpopulations that express unique marker genes. Using age-specific differential gene expression analyses, we identified that Fn1-enriched distal subiculum neurons display the greatest age-specific dysregulation. To determine whether Aβ42 accumulation followed this spatially biased molecular dysregulation, we performed IHC in the dorsal subiculum. Interestingly, we found that distal subiculum cells distinctly accumulate Aβ42 earlier than spatially neighboring cells. These findings support that excitatory neurons in the subiculum display spatially biased and cell-type-specific dysregulation associated with early disease neuropathology. In the future, these results can be used as a framework to understand the molecular- and region-specific temporal progression of early hippocampal neuropathology in Alzheimer's

disease, highlighting potential cell-type-specific targets for future therapeutic intervention.

P3-C-654 *SRSF3 regulates microglia immune response in Alzheimer's disease models with Abeta and Tau-mediated pathology*

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Innate immunity chronic deregulation is a key component of Alzheimer's disease (AD)pathobiology, and rebalancing or strengthening this response is considered therapeuticallyrelevant. Microglia, the main immune cells of the brain, shift during disease from initiallybeneficial to aberrant disease-associated cells that are resistant to conventionalimmunomodulatory therapies. However, the causes and molecular mechanisms underlying thistransition to microglial toxicity remain unclear. We recently identified a novel ribosome-based regulatory checkpoint controlled by the RNA-binding protein SRSF3 that regulates innate immune gene translation in acutely activatedmicroglia. Here, we investigated SRSF3 as a regulator of innate immune responses in activatedmicroglia using APPswe/PS1 and Tau P301S transgenic mouse models. Expression of SRSF3,its active phosphorylated form pSRSF3, and disease-associated microglial markers wasanalyzed at different time points. Levels of pSRSF3/SRSF3, Aβ, phagocytic, pro-inflammatory,and neuronal marker and cognition were assessed. Increased pSRSF3/SRSF3 levels correlatedwith disease progression and were restricted to IBA1-positive cells. Intranasal delivery ofantisense morpholinos targeting SRSF3 induced a 50–60% knockdown of endogenous protein. Treatment initiated at 12 months reduced Aβ levels, increased microglial marker expression,and restored recognition memory. Together, our findings suggest that targeting SRSF3 may open new avenues for therapeuticmodulation of microglial response in AD.

P3-C-655 *Stress, seizures, and hyperactivity: Machine-learning-based behavioural analysis in a GRIN1 disorder mouse model*

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Deep behavioural phenotyping in animal models of epileptic encephalopathy can help dissect links between stress, spontaneous seizures, and broader motor phenotypes. Here, we investigate mice that carry a patient-specific variant in the GluN1 NMDA receptor subunit. Since previous work has described seizures and hyperactivity in Grin1-Y647S+/- mice, we applied machine-learning-based analysis to identify behaviours related to seizure susceptibility. Pose estimation in the open field test was performed using DeepLabCut and analyzed with SimBA and MoSeq. Compared to wildtype controls, Grin1-Y647S+/- mice showed increased horizontal locomotion and rearing, together with greater center avoidance, which suggests heightened stress sensitivity. MoSeq analysis revealed more frequent behavioural transitions and increased long-range, high-speed movements in Grin1-Y647S+/- mice. Cluster analysis identified significant associations between mouse behavioural features and susceptibility to handling-evoked seizures. To probe the strength of these relationships, a separate Grin1-Y647S+/- cohort was acclimatized to handling stress over two weeks. This intervention significantly reduced seizure incidence and rearing behaviour in the subsequent open field, while horizontal locomotion and center avoidance remained elevated. Overall, this study highlights the value of unbiased machine-learning approaches for quantifying complex behavioural phenotypes and suggests that stress-reduction strategies may improve seizure management in a mouse model of GRIN1-related disorders.

P3-C-656 *Subanesthetic ketamine disrupts predictive signaling in the prefrontal cortex*

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Corollary discharge (CD) signals allow the brain to predict and suppress the sensory consequences of its own actions, providing stability to perception and thought. Disruption of these predictive mechanisms has long been hypothesized to contribute to the disorganization of experience in schizophrenia, yet direct circuit-level

evidence has been lacking. Here, we show that ketamine, a dissociative N-methyl-D-aspartate receptor (NMDAR) antagonist, at subanesthetic doses, selectively disrupts CD signaling in the lateral prefrontal cortex (LPFC)—a region thought to be the seed of mental representations and one of the most affected areas in schizophrenia. We recorded activity from 1,342 neurons in LPFC areas 8a and 9/46 of macaques performing a visuospatial working-memory task in a virtual environment, before and after subanesthetic ketamine administration. Ketamine impaired performance and increased overall firing rates but markedly suppressed saccade-related responses carrying CD signals. This led to decreased discriminability of eye movement signals. This finding links two major ideas in neuroscience research: the role of disrupted glutamate signaling and the failure of the brain's predictive models. It provides evidence for how these mechanisms may interact in the prefrontal cortex to disturb the sense of reality.

P3-C-657 *Sublethal and lethal toxicity of amyloid-beta 1-42 oligomers in human iPSC-derived neurons*

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Amyloid-beta (Aβ) plaques are key hallmarks of Alzheimer's disease. Aβ peptides are generated by cleavage of amyloid precursor protein (APP) and released into the extracellular space in various lengths. The toxicity of Aβ is thought to depend on its aggregation state and peptide size. Among these forms, amyloid-beta 1-42 oligomers (Aβo) are widely regarded as the most toxic. In vitro studies of Aβo toxicity have been conducted mainly in rodent cells or human-derived cell lines, which may limit the translation of findings to human disease. Moreover, most work has focused on the lethal effects of Aβo. Here, we study the toxicity of Aβo in human iPSC-derived neurons—a model closer to native human neurons—and explore both sublethal and lethal effects of this peptide.iPSC-derived neural progenitors were differentiated into neurons and cultured until they formed a dense network of neurites. Cells were then treated with Aβo at different concentrations for three days. Neurite retraction, cell death, and metabolic activity were assessed using confocal microscopy and an MTS assay. We observed a dose-dependent increase in neurite degeneration and cell death, with sublethal effects being more pronounced than lethal outcomes. We also observed dose-dependent accumulation of Aβ at the cell membrane.iPSC-derived neurons are sensitive to Aβo toxicity, which causes both sublethal and lethal injury. Sublethal injury appears to precede lethal injury, indicating a gradual degenerative process. This degeneration correlates with the accumulation of Aβ at the neuronal membrane.

P3-C-658 *Suicide in youth: is local microglial gene regulation implicated?*

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Microglia orchestrate synaptic plasticity by strengthening highly active synapses and weakening less active ones. In young individuals with major depressive disorder (MDD) who died by suicide, synaptic plasticity is disrupted, though the underlying mechanisms are unclear. Local gene regulation at microglial processes contributes to synaptic plasticity in rodents, raising the intriguing possibility that a similar mechanism is disrupted in MDD and suicide. We investigated post-mortem dorsolateral prefrontal cortex (dlPFC) samples (Douglas-Bell Canada Brain Bank) from young individuals (ages 9-32) with MDD who died by suicide. Specifically, we combined fluorescence in situ hybridization (FISH; RNAScope) and immunofluorescence to detect and compare RNA transcripts within human microglial processes. Preliminary observations in case samples indicate RNA present in microglial processes, consistent with previous finding from rodent glial process transcriptomes. We hypothesize more cells will present RNA in processes in dlPFC samples of cases compared to controls. This work provides evidence of local protein translation in human glial cells, opening new avenues for understanding—and ultimately intervening in—the neurobiological underpinnings of MDD and suicide.

P3-C-659 *SUMO2-based interventions reduce synuclein pathology*

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SUMOylation is a post-translational modification by which small ubiquitin-like modifiers (SUMOs) are conjugated to target proteins to regulate processes, such as protein aggregation and subcellular localization. SUMO2 protects against acute cellular stress and promotes synaptic plasticity. Dysregulation of SUMOylation has been linked to neurodegenerative diseases, including Alzheimer's (AD) and Parkinson's (PD). Interestingly, SUMO2 is conjugated to key proteins involved in neurodegeneration, including tau and alpha-synuclein (aSyn), and modulates their aggregation and toxicity. To determine SUMO2 effects on aSyn pathology, murine aSyn preformed fibrils (PFF) were injected into the hippocampi of SUMO2 over-expressing transgenics (Tg) and non-Tg littermates. SUMO2 Tg mice displayed reduced immunoreactivity of the pathological phospho-serine129 aSyn (pS129) compared to non-Tg controls, suggesting SUMO2-induced resistance to aSyn PFF propagation. A SUMO2-based therapeutic (SBT02) was also assessed in vivo and in vitro. SBT02 treatment of primary hippocampal cultures did not affect pS129 levels but reduced presynaptic marker mislocalization and aSyn aggregate release. In a prion-like spreading model using human multiple system atrophy (MSA) brain homogenates, subcutaneous administration of SBT02 reduced motor impairments and synucleinopathy. Our findings demonstrate that SUMO2 is neuroprotective in models of synucleinopathies by reducing aSyn aggregate spread and enabling synapse rescue. SUMO2-based therapies are a promising approach to target synuclein pathologies.

P3-C-660 *Synaptopodin: A novel therapeutic target for treatment of Autism spectrum disorders*

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Autism Spectrum Disorders (ASD) is a heterogeneous group of neurodevelopmental disorders accounting for 1% of the world population and currently has no cure. With over 800 genes associated with ASD, developing therapeutics for each is impossible. Therefore, identifying shared molecules in ASD is a promising approach. In 2019, Bitar et al. studied a cohort of autistic patients and found Synpo gene as a candidate gene for ASD. The Synpo gene encodes for an actin-associated protein named Synaptopodin (SP). SP is found in a subset of mature excitatory synapses in limbic brain regions. Our lab and others have previously reported that SP is required for many forms of Hebbian and homeostatic plasticity, which are altered in ASD mouse models. Interestingly, we found altered hippocampal SP levels in ASD mouse models, such as Fragile X Syndrome mouse models (Fmr1-/y) and Tuberous Sclerosis Complex mouse models (Tsc2+/-). We hypothesize that changes in SP levels during development lead to aberrant synaptic connections and consequently result in autistic traits. We investigated if the loss of SP (Synpo-/y) is sufficient to induce ASD behaviors. Using mouse behavioral studies, Synpo-/y mice exhibited core autistic traits including repetitive behaviors, social interaction and social communication deficits. In addition, Synpo-/y mice displayed certain comorbidities found in ASD such as higher levels of anxiety as well as learning and memory deficits. These findings provide evidence promoting SP as a novel therapeutic target for multiple forms of ASD.

P3-C-661 *Targeted probiotic intervention remodels the hippocampal proteome and confers seizure protection in a neonatal rat model of infantile epileptic spasms syndrome*

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Infantile epileptic spasms syndrome (IESS) is a severe type of epilepsy typically occurring within the first years of life, characterized by seizures, developmental delay, and EEG hypsarrhythmia pattern. Unfortunately, 30-50% of cases are resistant to first-line pharmacotherapy. The ketogenic diet (KD) is often used in such cases but is also known to have significant side effects. Our laboratory has shown that KD

associated gut microbiota composition changes, via targeted probiotic administration, are sufficient to replicate the seizure-protective effects of the KD. To investigate the underlying molecular mechanisms, we employed a rodent triple-hit model of IESS, administering either a probiotic of Streptococcus thermophilus and Lactococcus lactis (PRO) to mimic the microbiota composition of KD animals, or Ligilactobacillus salivarius (LSA), a negative control. We then processed hippocampal samples for quantitative proteomics by DIA LC-MS/MS. PRO but not LSA conferred seizure protection (54% seizure reduction). Compared to LSA, PRO administration resulted in pronounced upregulation of functions spanning growth and development of neurons, synaptic depression, and migration of neural cells, consistent with the observed reduction in seizure activity. PRO also induced changes to NDRG2, UBQLN1, MAPT, PARP1, MT3, and TF resulting in downregulation of the neural injury functional pathway. These results show that PRO alters the brain proteome towards an anti-epileptic phenotype in an animal model of IESS, underscoring the importance of the gut-brain axis in this condition.

P3-C-662 *Targeting the Parkinson's Disease-associated protein alpha-synuclein using microRNAs*

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Parkinson's disease (PD) is a neurodegenerative disorder characterized by progressive death of dopaminergic neurons in the substantia nigra, and abnormal accumulation of the protein alpha-synuclein (aSyn) in neurons. In fact, a duplication or a triplication of the gene encoding for aSyn, SNCA, causes early onset PD. As such, understanding factors promoting the accumulation of aSyn will help identify novel therapeutic target. One of the elements regulating protein expression in cells are microRNAs (miRs), which are produced in the nucleus and undergo different steps of maturation, to then bind to target mRNAs to block the translation and initiate mRNAs degradation. Here, we hypothesize that levels of specific mature miRs are key determinants of aSyn expression levels in neurons, and may contribute to pathology when dysregulated. We have identified five miRs (miR-7, miR-140, miR-153, miR-214 and miR-223) known, or predicted to bind to the mRNA of aSyn. Here, we present a platform to efficiently screen the impact of the depletion of those miRs on aSyn in neurons derived from induced pluripotent stem cells (iPSCs). This research will help better understand the modulation of the level of expression of aSyn by miRs and how those miRs could be modulated in the therapeutic perspective for PD by identifying RBPs involved in its maturation.

P3-C-663 *Testicular dysfunction in a murine model of Parkinson's disease*

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Background: Parkinson's disease (PD) is marked by degeneration of dopaminergic neurons within the substantia nigra. It also shows a clear sexual dimorphism, with men being 1.5 to 2 times more affected than women, suggesting a role for sex hormones. PD is also associated with non-motor symptoms, including reduced testosterone levels, reproductive alterations, and various genital disorders. In 2008, Ruffoli et al. showed in mice that a high dose of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) altered Leydig cells and reduced plasma testosterone levels. However, their study used a single high dose of MPTP (20 mg/kg). Objective: Evaluation of dose-dependent effects of MPTP on testicular tissue using doses representative of early-stage Parkinson's disease and milder toxicity. Methods: Male mice received four injections of MPTP (5.5, 7.5, or 9.5 mg/kg) or saline (control) at 2-hour intervals. Testes were collected six days later. Dopamine levels were quantified by HPLC, and histological analyses evaluated the expression of tyrosine hydroxylase and 3β-HSD as markers of dopaminergic and Leydig cell function, respectively. Results: MPTP induced a clear dose-dependent decrease in testicular dopamine, accompanied by progressive structural alterations of Leydig cells. Conclusion: Testicular tissue is sensitive to MPTP toxicity in a dose-dependent manner, potentially reflecting the progressive nature of PD. Thus, these findings highlight testicular dysfunction

among the non-motor symptoms of PD, which are often neglected despite their clinical importance.

P3-C-664 *The effect of cannabinoid receptor 2 on blood-brain barrier dysfunction in epilepsy*

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Epilepsy affects ~5.5 per 1,000 Canadians, with approximately one-third of patients failing to respond to conventional treatments. While cannabis-based therapies like Epidiolex have shown efficacy in severe seizure disorders such as Dravet syndrome, the precise mechanisms remain poorly understood. This research characterizes the interaction between the endocannabinoid system and the BBB to identify new therapeutic targets. It is long established that the BBB is compromised in epilepsy. This study uses the CB2 agonist JWH-133 in an in vivo cranial window rat model to characterize seizure like activity through electrocorticography, leakage through angiography, and marker changes through histology and western blot. My preliminary angiography data shows that agonizing cannabinoid receptor type 2 (CB2) decreases BBB leakage and histology suggests CB2 is upregulated after seizures in BBB pericytes. Further, work to date suggests that seizure-like activity is ameliorated. These results suggest that targeting CB2 receptors at the blood-brain barrier represents a promising potential therapeutic strategy for drug-resistant epilepsy.

P3-C-665 *The fate of serotonin neurons in Parkinson's disease*

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Parkinson's disease (PD) is a neurodegenerative disorder characterized by the degeneration of dopamine neurons and the accumulation of misfolded α-synuclein (α-syn) forming intracytoplasmic inclusions known as Lewy bodies. Other brainstem regions, including the raphe nuclei, are believed to be affected in PD. Serotonin (5-HT) neurons located in the raphe nuclei are thought to play an important role in dyskinesia, which are characterized by severe abnormal involuntary movements induced by levodopa, the main pharmacological treatment of PD. Using post-mortem human brains from advanced PD patients and healthy controls, we performed stereological analyses on tryptophan hydroxylase (TpH)-immunostained sections to estimate the density of 5-HT neurons in the different raphe nuclei, as well as the proportion of these neurons containing phosphorylated α-syn. Our results revealed no significant differences in TpH+ neuronal densities in either the rostral group of raphe nuclei (caudal linear, dorsal, median and pontis) or the caudal group (magnus, obscurus and pallidus) between PD and controls. In PD, the proportion of TpH+ neurons containing α-syn was lower in the rostral group than in the caudal group. In addition, a small portion of α-syn inclusions was detected outside TpH+ neurons. Overall, these findings indicate that cell bodies of serotonin neurons are relatively well preserved in PD. Studies using the same post-mortem human brains are ongoing to determine whether 5-HT axons of these neurons that innervate the subthalamic nucleus are altered in PD.

P3-C-666 *The hypothalamic supramammillary nucleus contributes to seizures in mouse models of temporal lobe epilepsy*

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Temporal lobe epilepsy (TLE) is a severe neurological disorder characterized by spontaneous recurrent seizures. Although many anti-seizure medications exist, approximately 1 in 3 patients experience drug-resistant epilepsy. Therefore, it is critical to understand the neurobiological mechanism underlying seizures so that new and more effective treatments can be developed to improve patient outcomes. In this study, we evaluated the role of a posterior hypothalamic region known as the supramammillary nucleus (SuM) in TLE using a combination of in vitro and in vivo methods. Optogenetic slice electrophysiological

recordings revealed that stimulation of ChR2+ SuM axon terminals in the hippocampus promoted seizure activity, whereas low frequency stimulation of SuM ArchT+ axon terminals protected against epileptiform activity. Next, we used dual-color fiber photometry in the SuM and the hippocampus, where we found that SuM and hippocampal activity synchronize leading up to and during ictal activity. In vivo optogenetics combined with EEG recordings revealed that activation of SuM-hippocampal circuits increased the severity of acute kainic acid induced seizures, whereas inhibition reduced severity. Chemogenetic manipulations in chronically epileptic mice also found that SuM excitation promoted seizures, whereas SuM inhibition dramatically reduced seizure burden. Lastly, viral labelling of the SuM revealed significant reorganization of SuM-hippocampal circuitry in chronic epilepsy. Overall, this data suggests that the SuM contributes to hippocampal excitability and seizures.

P3-C-667 *The importance of cleaning up: Preliminary insights into the impact of AIH and nerve injury on the phagocytic properties of macrophages*

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Acute intermittent hypoxia (AIH) is a novel, non-invasive treatment involving breathing low number of cycles of regular air at 21% oxygen (O2) alternating with reduced O2 air at 11% O2. We find AIH enhances repair in multiple sclerosis (MS) and peripheral nerve injury models. AIH induces robust clearance of myelin and axonal debris by activated microglia and macrophages by unknown mechanisms and drives them into a pro-repair state. Thus, we posit AIH treatment increases the myelin-phagocytosing capacity of macrophages critical for nerve and MS lesion repair. We performed temporal analysis of adult male Lewis rats with unilateral sciatic nerve crush + daily AIH or Normoxia (21% O2) control treatments on the 2 days post-injury to assess impact on myelin clearance by macrophages. Qualitative analysis of nerve sections processed for dual ED-1(activated macrophage)/MerTK (phagocytic receptor) immunofluorescence revealed AIH appears to increase myelin clearance and shift MerTK expression faster than Normoxia at D4 and D7 post-injury. To elucidate whether macrophages can respond in a cell autonomous manner to AIH, Lewis rat bone marrow-derived macrophages (BMDMs) are treated in vitro with AIH or Normoxia control, then incubated with fluorescent myelin for 4hrs; experiments are stopped either immediately or 1 day later. Myelin phagocytosis and MerTK expression are being quantitatively assessed and compared to the in vivo results. Elucidating the impact of AIH on the activity of macrophages will give insight into how it promotes nervous system repair. Funded by CIHR and MS Canada.

P3-C-668 *The integrated stress response pathway in depression*

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Major depressive disorder (MDD) is one of the most common psychiatric diseases worldwide, with an average lifetime prevalence of 14.6%. Nearly two-thirds of patients with this debilitating condition are treatment resistant to currently available antidepressants. Recent studies have shown that protein synthesis in the brain is reduced in MDD, and that alleviation of depressive symptoms can be achieved by increasing protein synthesis. A single sub-anesthetic dose of ketamine alleviates depression within 1–2 hours of administration and its effects can last for up to 21 days, in part, through enhanced protein synthesis. However, ketamine's clinical use is limited due to its potential for abuse and narrow therapeutic window. Given that increased protein synthesis alleviates depressive symptoms, we propose to target one of the central cellular pathways regulating protein synthesis, the integrated stress response (ISR) pathway. Activation of the ISR during cellular stress inhibits protein synthesis, whereas inhibition of the ISR increases protein synthesis. A small-molecule ISR inhibitor, 2BAct, suppresses ISR activity without toxicity or adverse effects in animal models, even with prolonged administration, and is currently in clinical trials for several neurodegenerative conditions. Based on our promising preliminary data in mice, we hypothesize that 2BAct can alleviate depression-like phenotypes by enhancing protein synthesis. In this project, we will test the ability of 2BAct to prevent and reverse depressive symptoms in mice and investigate the underlying mechanisms. Our work has

the potential to establish a novel therapeutic approach for depression and bring hope to people living with this debilitating disorder.

P3-C-669 *The PD-associated LRRK2 G2019S mutation alters antigen presentation in human iPSC-derived macrophages*

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A significant proportion of familial Parkinson's disease (PD) cases are due to mutations in the LRRK2 gene, including G2019S and R1441C. LRRK2 is highly expressed in immune cells like macrophages, suggesting a potential link between LRRK2 and the immune response. Recent reports suggest a link between LRRK2 and antigen presentation in mouse models. However, how PD-associated mutations in LRRK2 impact antigen presentation in human immune cells has yet to be studied. Here, we investigate how LRRK2 regulates antigen presentation in human macrophages. Human induced pluripotent stem cells (iPSCs) expressing the LRRK2 G2019S mutation as well as the isogenic control line were differentiated into monocytes, then into macrophages. After stimulation with LPS, immunopeptidomics analysis was performed on the human macrophages to identify the differentially expressed peptides on the MHC-I molecules. Immunopeptidomics analysis reveals that stimulated LRRK2 G2019S macrophages differentially present 168 peptides on their MHC-I molecules, with three major clusters associated with the immune response, the mitochondria, and antigen presentation. We are currently working on establishing a multicellular model to study the impact of this aberrant antigen presentation on CD8+ T cell activation, and the downstream effects on dopaminergic neurodegeneration.

P3-C-670 *The role of m6A-mediated chaperone expression in Drosophila brain*

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N6-methyladenosine (m6A) is one of the most well-studied post-transcriptional modifications in eukaryotic mRNA, regulating various stress responses. In the brain, stress responses are crucial to maintain neuronal and cognitive function short and long-term. Thus, understanding how m6A facilitates cellular homeostasis in the brain in response to stress may provide valuable insights to stress-induced neurodegenerative phenotypes. Here we investigate the role of m6A in regulating the response of heat stress in fly brain. We show that m6A levels in the brain increase upon heat stress. Through immunoblotting, we show sex-specific chaperone expression patterns and functionally link these to METTL3, the core enzyme that deposits m6A. METTL3 knockout female mutants have increased levels of Hsp70 expression in the brain and higher resilience to heat stress. Interestingly, Hsp90 showed delayed response in METTL3 KO females but not in males upon heat shock, demonstrating sex-specific response. Overall, our data suggest m6A modification in Drosophila regulates stress response in the brain in a sex-specific manner.

P3-C-671 *The roles of astrocytic GR and ESR1 in the regulation of chronic stress-induced emotive behaviour*

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Background: Depression is a psychiatric disorder characterized by impaired neuroplasticity and well-established sex differences in prevalence. Chronic stress, the leading risk factor for depression, reduces cortical plasticity by increasing the formation of perineuronal nets (PNNs). Previous work from our lab has identified astrocytic estrogen receptor alpha (ESR1) as a key upstream regulator of this stress-induced upregulation of PNNs. However, the factor that initiates changes in ESR1 itself remains unknown. We hypothesize that this is driven by the astrocytic glucocorticoid receptor (GR), which suppresses ESR1 when activated by chronic stress. This suppression, in turn, increases astrocyte-derived PNN components, thereby

restricting plasticity and increasing emotive behaviour. Methods: To test the causal role of astroglial GR and ESR1 in regulating affective behaviour and associated neuroplasticity in the mPFC we conducted two studies. 1) We used an adeno-associated virus (AAV) to knockdown astrocytic GR (astroGR-KD) in the mPFC and 2) we employed an AAV to knockdown astrocytic ESR1 (astroESR1-KD) following one week of chronic variable stress (CVS). All mice then underwent tests of anxiety- and depressive-like behaviour, followed by immunohistochemical analyses for various markers, including PNNs. Results: Under basal conditions, astroGR-KD modestly reduced anxiety-like behaviour in both sexes without altering depressive-like measures. Conversely, astroESR1-KD exacerbated stress-induced emotionality in mice exposed to CVS in a sex-specific manner, where it increased anxiety-like behaviour in males and depressive-like behaviour in females. Conclusion: Together, these findings support a relationship between astrocytic GR and ESR1 in the regulation of mPFC plasticity and emotive behaviour following chronic stress.

P3-C-672 *Therapeutic effects of zuranolone in a murine model of Parkinson's disease*

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BACKGROUND. Parkinson's disease (PD), a neurodegenerative disorder with a higher prevalence in males, may be influenced by sex hormones. Our previous works demonstrated the neuroprotective effects of estradiol and progesterone in a murine model of PD induced by the neurotoxin MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine). In addition, allopregnanolone, a progesterone metabolite whose levels fluctuate during PD progression, may exert neuroprotective effects. However, its unfavorable pharmacokinetic profile limits its therapeutic use, in contrast to its synthetic analogue, zuranolone. HYPOTHESIS. In a murine model of PD, zuranolone would exhibit neuroprotective activity against MPTP-induced toxicity. MethODS. Male mice treated with MPTP (6 mg/kg) received zuranolone (0.5 mg/kg) for 10 days. Striatal dopamine levels were quantified by HPLC. Markers of striatal dopaminergic neurodegeneration were assessed by tyrosine hydroxylase (TH) immunofluorescence, in parallel with the analysis of neuroinflammatory (GFAP). ReSULTS. Zuranolone exerted a neuroprotective effect on striatal dopamine levels. Ongoing analyses of markers of striatal dopaminergic neurodegeneration and neuroinflammation will further characterize its neuroprotective effects. ConCLUSION. These findings suggest a therapeutic potential for zuranolone in PD. Further studies on its mechanisms of action are required before considering clinical trials.

P3-C-673 *Transcriptional and activity-dependent regulation of social dominance by prefrontal inhibitory interneurons*

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Retinoic acid–induced 1 (RAI1) is a transcriptional regulator that controls the expression of genes involved in circuit assembly, neurotransmission, synaptic plasticity, and circadian rhythm. Loss of Rai1 function is strongly implicated in autism spectrum disorder (ASD), specifically in the syndromic form Smith–Magenis syndrome (SMS). As a monogenic disorder, SMS provides a tractable model to study mechanisms underlying social impairment. We used Visium HD spatial transcriptomics to determine how loss of Rai1 alters gene expression programs within the medial prefrontal cortex (mPFC), a region critical for social behavior. We observed widespread, spatially organized transcriptional dysregulation in SMS mPFC relative to control tissue, including reduced expression of activity-dependent genes. Cell-type–resolved analyses revealed subtype-specific molecular signatures within inhibitory interneurons (INs), with more extensive transcriptional changes observed in somatostatin (SST) INs. To relate these molecular alterations to circuit function and behavior, we assessed social dominance using the tube test in mice with IN subtype–specific deletion of Rai1. Vasoactive intestinal peptide (VIP) conditional knockout (cKO) mice were more dominant, whereas parvalbumin (PV) and SST cKO mice were more frequently subordinate. These behavioral differences were accompanied by increased Fos expression in interneurons lacking Rai1 following social competition in VIP and PV cKO mice, but not in SST cKO mice. Chemogenetic inhibition of prefrontal VIP or PV interneurons normalized tube test winning rates, indicating that excessive inhibitory circuit activity

contributes to dominance alterations. Together, these findings indicate that coordinated activity-dependent and transcriptional alterations within prefrontal inhibitory circuits underlie changes in social dominance behavior.

P3-C-674 *Understanding sensory dysfunction in Christianson Syndrome*

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Children diagnosed with Christianson syndrome (CS), a rare neurodevelopmental disorder, exhibit hyposensitivity to pain and aversion to touch. This syndrome is caused by loss-of-function mutations in the SLC9A6 gene, which encodes the sodium/proton exchanger NHE6. This exchanger is expressed predominantly in the nervous system, with high expression in nociceptors of the dorsal root ganglia. How this loss in function of NHE6 results in distortions of sensory perception is poorly understood. We have demonstrated that, as in CS children, an NHE6 knockout (KO) mouse model displays similar elevated pain thresholds and aversion to touch, but the underlying mechanisms of this touch aversion are yet to be established. Our central hypothesis is that during the postnatal maturation of the spinal cord, absence of NHE6 in nociceptors reduces their excitability and interferes with the maturation process of touch and pain circuits. This is supported by previous literature showing that if nociceptors are chemically ablated in neonatal mice, touch fibers remain in an immature state in regions of the spinal cord involved in the transmission of pain signals. To determine whether the loss of NHE6 function perturbs the maturation process of spinal circuits, I will characterize the pain experience of CS children, identify how a loss in NHE6 function results in pain hyposensitivity and touch aversion in NHE6 KO mice with the anatomical tracing of pain and touch fibers in the spinal cord, and whether these somatosensory deficits can be rescued by gene complementation through the use of a rescuable NHE6 KO mouse model.

P3-C-675 *Understanding the role of rfc1 loss of function in the context of CANVAS pathogenicity using the zebrafish model*

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The Cerebellar Ataxia Neuropathy Vestibular Areflexia Syndrome (CANVAS) is a rare adult-onset ataxia. In 2019, the intronic and biallelic repeat expansion (AAGGG)>400 in the Replication Factor C1 gene (RFC1) was identified as a cause of CANVAS. However, the mechanisms by which this intronic repeat expansion in this gene causes this neurological disorder are unknown. Recent papers identified frameshift mutations in RFC1, suggesting that a loss-of-function could drive pathogenicity. Since knocking-out RFC1 in mammals leads to embryonic lethality, we generated a zebrafish loss-of-function model of rfc1 using CRISPR/Cas9. We found that the cerebellar development of the rfc1-/- larvae is severely affected, with disorganized Purkinje cell organization and a severe reduction in the number of granule cells. Using scRNAseq, we demonstrated that rfc1 is expressed in early neural progenitors and that its loss-of-function leads to defects in DNA replication processes. Ultimately, defective RFC1 signalling leads to massive apoptosis among this cell population, affecting subsequent neurogenesis, particularly of cerebellar neurons. This work is the first to investigate the function of RFC1 in vivo. By showing its role in cerebellar development, this suggests that CANVAS could be, at least partially, caused by RFC1 loss-of-function mechanisms. However, CANVAS is a late-onset disease, so we wonder if RFC1 could also play a role in a mature cerebellum...Thus, we will focus on two main areas: studying the consequences of late loss of expression of RFC1 in a mouse model and understanding the role of expansions using patient cells to correlate our observations with a more clinical aspect.

P3-C-676 *Using living human brain tissue to model and causally interpret Alzheimer's disease*

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Translation of pre-clinical Alzheimer's disease (AD) research has been critically limited by the lack of human-based models that recapitulate the brain microenvironment and its pathological processes. To address this, we leveraged living human brain tissue from temporal lobe epilepsy surgical resections in a slice culture model to examine early neuronal responses to amyloid-beta (Aβ) in their preserved brain cytoarchitecture. To begin, we determined that human cortical slices could be maintained viable in culture for up to 23 days after surgical resection, enabling long-term experimentation with chronic Aβ exposure in a living tissue model. To assess the effect of Aβ on neural activity on living human brain tissue, adjacent slices were either left untreated or exposed to Aβ oligomers, with all tissue loaded with a calcium indicator for two-photon imaging to examine neuronal activity. We identified emerging patterns of altered calcium signaling in Aβ-treated slices relative to untreated controls. Fluorescent immunohistochemistry of Aβ-treated slices revealed robust intraneuronal Aβ accumulation in the cytoplasm, with punctate concentrations suggestive of lysosomal uptake. These findings validate the utility of cultured human brain tissue for studying AD mechanisms, and suggest early cell-intrinsic changes in neuronal activity that may underlie vulnerability to intracellular Aβ accumulation, a critical early stage of AD pathogenesis.

P3-C-677 *Voluntary exercise rescues motor coordination deficits in a mouse model of ARSACS*

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Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) is an early-onset neurodegenerative disorder characterized by progressive motor dysfunction and cerebellar degeneration. The cellular alterations giving rise to ataxia in ARSACS are still incompletely understood. Brain derived neurotrophic factor (BDNF) is implicated in neuronal health and cell survival. Prior work has asserted that a reduction in cerebellar BDNF is observed in several other forms of ataxia, so we chose to investigate whether BDNF contributes to ARSACS using a knock-out mouse model, Sacs-/-. We found that Sacs-/- mice showed decreased BDNF expression in Purkinje cell somas as the disease progresses (postnatal day (P) 90; $p < 0.0001$) but not at disease onset (P40; $p > 0.05$) compared to litter-matched wild-type (WT) controls. Since previous studies found voluntary exercise to elevate BDNF expression in several brain regions, including the cerebellum, we provided WT and Sacs-/- mice with one month of voluntary exercise (free access to running wheels) starting at an early disease stage (P50), matched with sedentary controls. Using rotarod as a measure of motor coordination, we observed that motor coordination was restored to WT-like levels in Sacs-/- mice exposed to exercise, compared to sedentary Sacs-/- mice. Our findings suggest that exercise, likely acting through BDNF signaling, ameliorates motor coordination in a mouse model of ARSACS, and suggests that ARSACS patients may benefit from exercise-based intervention early in disease progression.

P3-C-678 *Human mutations in EPHB2 uncover its novel role in callosal axon growth*

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The corpus callosum (CC) is the largest bundle of axons connecting the left and right hemispheres of the human brain, enabling interhemispheric communication essential for higher-order cognitive functions. Agenesis of CC (ACC), a condition characterized by the partial or complete absence of CC, is frequently observed in individuals with neurodevelopmental disorders. EphB2, a receptor tyrosine kinase involved in neural circuit development and function, is among the many molecular effectors of normal CC development in mice. However, the precise mechanisms through which EphB2 regulates CC formation remain unclear as does its role in the developing human brain. We identified nine different mutations in EPHB2, carried by eight human patients, all exhibiting varying degrees of ACC and other neurological symptoms. Structure modelling and functional analyses revealed that these mutations disrupt distinct modes of EPHB2 signalling, aligning with the extent of ACC exhibited by the different patients. We also found a genetic association between

EPHB2 rare variants and CC structural abnormalities among UK Biobank participants who report a mental illness. Experiments in mice reveal that EphB2 protein is enriched in callosal axons during CC development, and in vivo EphB2 loss or overexpression in cortical neurons decreases or increases, respectively, the number of axons in the CC. Experiments in primary callosal neurons suggest that EphB2 functions in axonal extension. Together, these findings argue that human EPHB2 mutations result in ACC, and reveal a novel role for EphB2 in promoting the formation of the CC.

P3-C-679 *Cell-type-specific mechanisms implicated in mRNA translation and memory in aging and Alzheimer's disease*

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mRNA translation in the brain is necessary for long-term memory consolidation, and its dysregulation is implicated in memory loss in Alzheimer's disease. Pathological features of Alzheimer's disease include the accumulation of amyloid-beta peptides and hyperphosphorylated tau proteins. The accumulation of these proteins results in many stressors that trigger the integrated stress response, which phosphorylates the α subunit of eukaryotic initiation factor 2 (p-eIF2α), inhibiting general protein synthesis. Prolonged integrated stress response activation in Alzheimer's disease increases p-eIF2α levels, downregulates general protein synthesis, and impairments long-term memory consolidation. p-eIF2α is a key translational control mechanism to bidirectionally control long-term memory in health and disease. Learning stimulates general protein synthesis in a healthy brain by dephosphorylation of p-eIF2α. Cell-type-specific suppression of the integrated stress response in mice models of translation rescued memory deficit. However, the cell-type-specific translation regulation mechanisms are less understood in aging and Alzheimer's disease. Therefore, we introduced a non-phosphorylatable eIF2α into the Alzheimer's disease mice astrocytes and observed that stimulating translation in astrocytes can rescue memory deficits. Dissecting cell-type-specific translational control mechanisms in Alzheimer's can aid in developing therapeutics to target specific cell populations, potentially leading to better treatment outcomes.

D - SENSORY AND MOTOR SYSTEMS

P3-D-680 *Neuronal dynamics in the cortex of a mouse engaged in a virtual reality environment*

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Fluorescent calcium (Ca2+) imaging helps to unveil neuronal activity dynamics, such as how attention affects the brain. Combined with virtual reality (VR), it enables the investigation of complex information processing in a controlled environment. This work showcases spatiotemporal neuronal dynamics in head-fixed Thy1-gGCaMP6s mice exposed to a moving VR scene. Ca2+ activity was recorded using mesoscopic fluorescence imaging, while 20 s videos simulating a journey in the mouse cage with shelters and stimuli were displayed on two front monitors. A salient stimulus (horizontal sinusoidal grating over 20° in the binocular visual field) was presented for 7 s during a stationary phase. Four simulations were shown: with or without the salient stimulus in a normal environment (stim and sham), and with or without it in a dimmed environment (grey filter; stim/fg and sham/fg). Using umIToolbox in MATLAB, fluorescence variation (ΔF/F) was extracted and analyzed across cortical areas: primary visual cortex, extrastriate AM, LM, PM, AL, posterior parietal cortex (RL), retrosplenial, and anterior cingulate cortices. Results showed increased Ca2+ activity upon the appearance of large or contrasting objects during movement compared to the stationary phase, in both stim and sham across most visual areas. The salient stimulus also evokes activity in visual cortices, absent in sham group. An acetylcholinesterase inhibitor (donepezil, 1mg/kg) did not affect Ca2+ dynamics. These findings suggest that dynamic VR evokes distinct neuronal activity across cortical regions.

P3-D-681 *Regeneration of descending brainstem locomotor pathways after complete spinal cord injury in salamanders*

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Salamanders regenerate their nervous system and recover locomotion after spinal cord injury, yet the circuits involved are poorly defined. In vertebrates, the mesencephalic locomotor region (MLR) initiates locomotion via the reticular formation, which activates spinal central pattern generators. In salamanders, the pathways downstream the MLR are unclear, and whether they regenerate is not known. Here, we investigated how the MLR controls spinal circuits in intact and spinally transected animals. Using patch-clamp in brainstem-spinal cord preparations from intact animals, we found that electrical MLR stimulation evoked synaptic responses in reticular neurons that scaled with stimulation intensity. Trains of MLR stimulation elicited rhythmic bursting in reticular and spinal neurons of forelimb-innervating segments, together with rhythmic ventral root bursting. After spinal transection, kinematic analysis showed gradual locomotor recovery, improving between 5–10 weeks and plateauing by 17 weeks. Tracer injections below lesion showed reticulospinal axon regrowth as soon as 5 weeks post-injury. Using 2-photon calcium imaging in salamanders expressing a calcium indicator in neurons (hSyn:GCaMP6s), we found that at 5–10 weeks post-injury, MLR stimulation induced calcium responses below lesion in hindlimb-innervating segments. Blocking glutamatergic transmission in the reticular formation abolished these MLR-induced spinal responses. Our study indicates that the pathways downstream the MLR regenerate and can re-engage spinal circuits below lesion early during locomotor recovery.

P3-D-682 *Reinstatement of default mode network manifold structure underlies motor memory retrieval*

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Motor learning induces alterations in neural activity that can persist long after the effects of such learning have faded. These persistent neural alterations are thought to manifest behaviorally as ‘savings’, or faster relearning, via access to a latent motor memory. How the human brain forms and retrieves these latent memories, and the specific neural systems involved, remains unresolved. Here, using human functional MRI and a two-day sensorimotor adaptation paradigm, we show that savings is associated with the reinstatement of a large-scale cortical manifold structure formed during initial learning. Notably, this neural reinstatement effect was not observed across sensorimotor systems but was localized to regions of the default mode network (DMN). Moreover, the specific dynamics of DMN activity were linked to inter-subject differences in patterns of learning and relearning across days. These results suggest that motor savings arises from the re-expression of DMN activity patterns associated with initial learning, establishing a key role for this network in motor memory formation and retrieval. This finding, paralleling reinstatement principles from other memory domains (episodic memory, fear conditioning) and anticipated by recent computational models of motor learning, suggests a common mechanism for the flexible recall and reuse of stored memories across diverse behavioral contexts.

P3-D-683 *Relationship between corticospinal excitability and inhibition and fractionated reaction time of the first dorsal interosseous muscle*

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The purpose of this study was to assess the relationship between corticospinal excitability and inhibition and fractionated reaction time (FRT) of the first dorsal interosseous (FDI) muscle, as well as any sex-related differences. Twenty-three healthy males (24.8 ± 2.8 years) and 23 healthy females (24.1 ± 3.6 years) completed 30 trials of a simple reaction time test, in which they abducted their index finger of their dominant hand as hard as possible in response to a visual stimulus. Premotor time (duration between stimulus onset and start of muscle activity), motor time (duration between muscle onset and force production), and total reaction time (duration between stimulus onset and force production) were determined for each trial. Corticospinal excitability and inhibition of the FDI were assessed through the amplitude of the motor evoked potential normalized to Mmax (MEP/Mmax), and duration of the cortical silent period (CSP), respectively. Corticospinal excitability was similar between sexes ($p=0.21$), while corticospinal inhibition was greater in males compared to females ($p=0.02$). Motor time was longer in females than males ($p<0.01$), with no differences between sexes in premotor time ($p=0.36$), or total response time ($p=0.08$). There were no significant correlations between MEP/Mmax and FRT ($r\leq0.24$; $p\geq0.06$) or CSP duration and FRT ($r\leq0.26$; $p\geq0.24$), within males, females, or with sexes combined. The relationship between corticospinal communication and FRT remains unclear. Males may be able to produce force faster than females, despite similar premotor times.

P3-D-684 *Reorganisation of dopaminergic innervation to the motor cortex following cortical lesion*

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Loss of motor function is one of the major physical challenges faced by patients recovering from stroke. Motor skills can be learned (or re-learned after a stroke) through practice and repetition. Dopamine, a neurotransmitter typically associated with rewards, pleasure, and addiction, could play a critical role in motor skill learning and synaptic plasticity in the motor cortex. The motor cortex receives dopaminergic inputs from the Ventral Tegmental Area (VTA). We hypothesise that during re-learning of motor skills after a stroke, dopamine signals could guide synaptic plasticity and reshape neural circuits in the perilesional area to promote motor recovery. Further, we hypothesise that structural changes in motor cortical dopaminergic innervation will accompany the cortical lesion. In rats, we modelled a stroke using Endothelin-1 injections in the forelimb area of the motor cortex. We used the Montoya staircase and Cylinder tests to assess forelimb motor function before and after the stroke. We used immunohistochemistry to label Tyrosine Hydroxylase and Dopamine Beta-Hydroxylase proteins to evaluate potential changes in dopaminergic innervation to the ipsilesional and contralesional motor cortices. Early results suggest axonal sprouting in the perilesional area and a faster motor recovery following VTA stimulation during rehabilitation exercises. Our preliminary results support the importance of considering reward-related circuits in promoting recovery after stroke

P3-D-685 *Role of large somatosensory afferents in speed modulation during treadmill locomotion following pyridoxine intoxication in cats*

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Somatosensory feedback from large-diameter proprioceptive and tactile afferents is crucial for posture and limb coordination. While its role in maintaining basic walking is well-documented, how these somatosensory signals contribute to the dynamic modulation of locomotor speed remains to be identified. In this study, we investigated the effects of large-diameter somatosensory afferent loss using pyridoxine intoxication (350 mg/kg i.p. administered daily for three consecutive days) in three cats. Animals performed quadrupedal locomotion on a treadmill at speeds of 0.4 to 0.8 m/s in 0.1 m/s increments. EMG and kinematic data were

recorded before and weekly post-intoxication for 10 weeks. During the first week post-intoxication, all cats lost the ability to stand and walk. Although they recovered independent walking 2 to 3 weeks later, this early locomotion was highly unstable with poor paw placement, postural instability, and hindlimb hyperflexion. All cats walked at 0.4 m/s at weeks 2-3, but their maximal speed was limited to 0.5-0.7 m/s. Two cats reached 0.8 m/s starting at week 4, with the aforementioned deficits gradually attenuating weekly. The third cat remained limited to a maximal speed of 0.6 m/s, even at week 10. These results demonstrate that large somatosensory afferents are critical for the dynamic control of speed modulation. We are currently analyzing EMG and kinematic data to determine how the neuromechanical system is reorganized to adjust to the loss of somatosensory feedback in relation to speed modulation.

P3-D-686 *Role of NCK in the development of locomotor circuit*

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Nck1 and Nck2 are adaptor proteins that mediate signaling pathways critical for cytoskeletal dynamics and synapse formation. Although their roles have been studied in general neuronal development, their contribution to the formation of locomotor control circuits remains unclear. Here, we investigated how Nck1 and Nck2 influence the development of neural circuits underlying locomotion. We hypothesized that Nck1 and/or Nck2 are necessary for the normal development of locomotor circuits. To test this, we used Cre-lox technology to generate mutants with conditional deletions of Nck1 and/or Nck2 in all neurons or in genetically identified neuronal subpopulations.Kinematic analyses were performed during locomotion in adult mice at different treadmill speeds. Compared to control mice, double Nck1/Nck2 mutants exhibited a hopping gait. Interestingly, Nck1 mutant mice displayed more severe locomotor impairments than Nck2 mutants. Furthermore, mice lacking Nck1 in genetically identified commissural interneuronal subpopulations also exhibited a hopping-like gait, in contrast to mice lacking Nck1 in genetically identified ipsilateral interneurons. In summary, Nck1 appears to play a stronger role than Nck2 in the development of commissural interneurons critical for left-right coordination during locomotion.

P3-D-687 *Role of the potassium channel TREK1 in mechanotransduction in peripheral sensory neurons*

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TREK1 is a leak potassium channel which contributes to the tuning of cell membrane potential and neuronal excitability. TREK1 has been identified as a contributor to pain perception, including pain triggered by mechanical stimuli. We aimed to better understand the mechanisms involving TREK1 in mechanical pain. First, we studied the mechanosensitivity of TREK1-positive sensory neurons in vitro, using calcium imaging and thanks to the development of a TREK1-Cre mouse that allows conditional expression of an inhibitory DREADD receptor. The decreased reponse to mechanical stress following chemogenetic inhibition of TREK1-positive neurons showed that this population contribute, at least in part, to mechanotransduction. Using a reporter gene in TREK1+ neurons, we then performed electrophysiological recordings of mechanoactivated ionic currents in TREK1-positive cells. Surprisingly, we found TREK1-positive neurons to be predominantly non-mechanosensitive, which could suggest that TREK1 opposes mechanosensitive currents. We next used TREK1 knock-out (KO) mice to study the contribution of this channel to mechanotransduction, and showed in vitro that TREK1 KO induces an increased activation of peripheral sensory neurons in response to mechanical stimulation. Finally, we observed in vivo that TREK1 KO mice have an increased sensitivity to light touch, involving peripheral TREK1 in the transduction of both nocive and non-nocive mechanical stimuli. Further experiments are needed to determine if TREK1 is responsible for the lack of mechanosensitivity of neurons in which it is expressed.

P3-D-688 *Roles of the subthalamic nucleus and zona incerta in locomotion before and after spinal cord injury*

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The subthalamic nucleus (STN) and the zona incerta (ZI) are two nuclei located beneath the thalamus whose electrical stimulation can induce locomotion in various animal species. Previous studies have shown that optogenetic stimulation of glutamatergic neurons in the STN can modulate the locomotor rhythm, whereas stimulation of GABAergic neurons in the ZI induces exploratory locomotion. Given their potential role in locomotion, we hypothesized that selective activation of these neuronal populations could not only initiate but also modulate locomotor activity before and after spinal cord injury (SCI). To test this, viral vectors were injected into adult transgenic mice to conditionally express the photoactivator Channelrhodopsin-2 in either glutamatergic neurons of the STN or GABAergic neurons of the ZI. Locomotor behavior was assessed using kinematic analyses in response to optogenetic stimulation at rest in an open arena and during treadmill locomotion at steady speeds before and at 1, 3, and 7 weeks after SCI.Stimulation of glutamatergic STN neurons before and after SCI failed to initiate locomotion in resting mice and instead induced a deceleration during ongoing locomotion. Similarly, stimulation of GABAergic ZI neurons did not initiate locomotion at rest but caused a complete arrest of locomotor activity during treadmill walking before and after SCI. In summary, our results show that glutamatergic STN neurons do not initiate locomotion but instead slow ongoing locomotion, whereas GABAergic ZI neurons strongly inhibit locomotor activity.

P3-D-689 *Sex-dependent analgesic effects of MDMA in mouse models of acute, inflammatory and neuropathic pain*

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The drug 3,4-methylenedioxymethamphetamine (MDMA), also known as ecstasy, is a psychedelic drug with empathogenic properties. More recently, studies in humans have demonstrated the effect of MDMA in modulating pain and touch perception. MDMA has also previously been shown to exert analgesic effects in assays measuring acute thermal nociception, but little work has been done to examine its effects on mechanical hypersensitivity and allodynia in multiple pain conditions. We sought out to investigate the effect of low doses of MDMA on modulating tactile hypersensitivity in several pain models in mice. Intraplantar injections of capsaicin or Complete Freund's Adjuvant (CFA) were used to induce acute and inflammatory pain, respectively, and a spared nerve injury model was used to induce neuropathic pain. Von Frey filaments were used to quantify mechanical sensitivity. Mechanical thresholds for paw withdrawal were significantly increased in males given MDMA for acute and inflammatory pain. MDMA did not alter mechanical sensitivity in neuropathic pain for either sex. Additional characterization of the effects of MDMA on thermal nociception and locomotor activity using the Hargreaves assay and open field test. These findings reveal the potential use of MDMA for acute analgesia. The surprising finding of sex-dependent effects prompt investigation into potential sex differences in the sites of action and mechanisms by which MDMA exerts its analgesic effect.

P3-D-690 *Sex-specific development of plasticity mechanisms in the human visual cortex*

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Experience-dependent plasticity shapes the development and function of the visual cortex, yet most studies have focused on male mice, leaving critical gaps in our understanding of how this process unfolds in humans and whether it differs between sexes. Here, we analyzed the expression of 95 proteins involved in synaptic plasticity and neuroimmune function in human primary visual cortex (V1) across the lifespan, using post-mortem tissue from individuals aged 20 days to 80 years. Our results reveal that females and males exhibited strikingly different molecular development, with the largest differences emerging in early childhood (<5 years), a key period for cortical plasticity. Many proteins showed sex-specific peaks, offsets

or undulating patterns across development, particularly among immune-related markers. Synaptic and neuroimmune proteins were organized into distinct developmental “taxonomies” in each sex, indicating divergent coordination among plasticity mechanisms. Random forest models trained on population-level trajectories predicted the sex of individual cases with 83% accuracy, indicating that these trajectories are robust and biologically meaningful. Disease enrichment analyses identified sex-specific links to neurodevelopmental, psychiatric, and inflammatory conditions, suggesting different developmental routes to vulnerability and resilience. These findings suggest that females and males use different molecular programs to regulate experience-dependent plasticity in V1, underscoring the need for a more diverse approach to visual neuroscience research.

P3-D-691 *Shared and separate cortical manifold structure supports error- and reinforcement-based learning*

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Humans adapt motor behaviors using sensory feedback, ranging from precise sensory errors to scalar reward outcomes. While computational models distinguish between these error-based (EL) and reinforcement-based (RL) processes, the extent to which they recruit shared versus distinct neural architectures remains unresolved. Here, we characterized the evolution of whole-brain functional connectivity manifolds in the same human participants as they performed separate EL and RL tasks. By projecting task-based connectivity into a low-dimensional space, we disentangled learning-related manifold reconfigurations that were task-specific from those that were task-independent. We show that while both forms of learning induced robust alterations in the manifold structure of higher-order transmodal cortex—specifically within the default mode network (DMN)—the posterior cingulate cortex (PCC) emerged as a critical nexus, exhibiting a unique functional geometry that multiplexed both task-specific and -independent connectivity changes. We leveraged the repeated-measures design to identify learners who exhibited better performance across both domains. We found that individual differences in learning were not linked to activity of motor networks, but predicted by manifold changes in limbic regions. Together, our findings reveal the shared and distinct low-dimensional neural dynamics supporting different forms of motor learning, highlighting the PCC as a site of integration for diverse learning and establishing a critical link between limbic network dynamics and generalized learning ability.

P3-D-692 *Single-cell transcriptomic diversity of projection neurons of the spinal cord dorsal horn*

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The dorsal horn of the spinal cord is the first waystation in the central nervous system for pain and touch processing. Here, incoming sensory information is filtered and sent via projection neurons to the brain where it is consciously perceived. These neurons are a necessary bottleneck in the transmission of pain and are thus an attractive therapeutic target for pain disorders; however there is very little information on specifically-expressed molecules which might be leveraged for therapies. Our prior work identified spinal projection neurons as those expressing Phox2a arising from the spinal “dI5” lineage, though there appeared to be several subtypes of Phox2a+ projection neurons as well as other dI5 neurons that do not express Phox2a. Recent advances in single-cell transcriptomics combined with a proliferation of published datasets have allowed us to clarify the molecular diversity of these projection neurons. To do this, we sorted dI5 neuron single-cell transcriptomes from a number of published datasets and integrated these profiles together to reveal a comprehensive landscape of spinal projection neuron diversity. Here we contextualize this diversity with the known roles of projection neurons and speculate on which sub-types might most effectively be therapeutically blocked to alleviate pain.

P3-D-693 *A bipartite analysis of the drosophila synapse-level connectome uncovers organizational principles in the visual system*

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Vision enables animals to extract rich information from their environment and is essential for guiding higher-order behaviour. In the fly, vision is the dominant sensory modality, with visual regions occupying over half of the brain. The recently completed, fully annotated synaptic-resolution Drosophila central nervous system connectome offers a unique opportunity to explore the neural architecture underlying the fly visual system. Conventional studies view connection strength primarily from the perspective of the integrating postsynaptic cell, overlooking the role of the presynaptic partner. We have developed a bipartite approach that characterizes synaptic connectivity in the optic lobe connectome by considering both the output proportion from a pre-synaptic neuron and the input proportion to its post-synaptic partner. When both neurons invest heavily in the same connection, we term the connection a Handshake Pair. We applied this framework to most ~270 cell types in the fly optic lobe. Preliminary results reveal bipartite motifs and reciprocal Handshake Pairs among cell types whose functions are known (motion detection circuits) or unknown. Overall, the bipartite framework established in this study offers a novel perspective on synaptic organization in the fly visual system and provides a foundation for generating testable hypotheses about cell-type-specific communication to reveal new insights into how neural circuits give rise to visual behaviour and higher-order functions.

P3-D-694 *Structural changes in the lateral geniculate nucleus following perinatal auditory deprivation*

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The brain exhibits a remarkable capacity to structurally and functionally reorganize following abnormal sensory experience. It remains unclear how intact visual areas such as the lateral geniculate nucleus (LGN) develop and compensate for lost auditory input following deafness. Exuberant retinal projections to the LGN visualized with the antibody SMI-32 are pruned across development and are thought to be preserved following deafness. Y cells in the LGN relay motion information and are a promising substrate for investigating thalamic plasticity. Systematic random sampling was employed to quantify Y cell morphology in the LGN of hearing (N=5), perinatally deafened (N=4), and unilaterally deafened cats (N=1). Differences between hearing and deaf subjects were assessed using Mann-Whitney U tests. Within conditions, differences across layers were assessed using Kruskal-Wallis tests. In both conditions, neurons in A and A1 layers revealed an increase in dendrite number and length compared to the C-Complex. Dendrites were significantly longer in deaf subjects in layers A and A1. Deaf subjects exhibited increased higher-order branches in layers A and A1. In both conditions, neurons exhibited a higher branch order in layers A and A1. Deaf subjects revealed an increase in Y cell density in layers A and A1 compared to hearing subjects. Following unilateral deafness, there was an increase in Y cell density in layers corresponding to the contralaterally deafened ear. Overall, the present study reveals that the visual thalamus responds to the absence of auditory input to the brain.

P3-D-695 *Studying the function of long-range projecting VIP-expressing neurons in the facial motor nucleus*

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The vestibular system is critical for regulating balance maintenance. The medial vestibular nuclei (MVN) in the brainstem are known to work as a sensory hub that is important for vestibular functions. Little is known about MVN and its connections with other brainstem nuclei that are critical for fine-tuning balance. We identified a population of vasoactive intestinal peptide (VIP)-expressing neurons in the facial motor nucleus (FMN) of the brainstem that provides long-range inputs to MVN. Lower motor neurons in FMN have been shown to mediate specific orofacial and vibrissal muscle movements, but these FMN-VIP neurons have never been described. We employed in vivo fiber photometry, and cell-type specific ablation and chemogenetic manipulations to study whether and how FMN-VIP neurons contribute to vestibular-mediated balance maintenance. We found that these FMN-VIP neurons are cholinergic neurons. Ablating or acutely silencing FMN-VIP neurons altered the animals' balance performance. Using anterograde monosynaptic labeling, we further identified that the major postsynaptic targets of FMN-VIP neurons are the GABAergic neurons in MVN. In vivo Ca^{2+} and ACh sensor recordings demonstrated that FMN-VIP neurons are activated only when the animal's balance is challenged, releasing ACh to modulate MVN activity and fine-tune body posture for balance maintenance. Lastly, cell-type specific rabies tracing revealed that the major input regions to FMN-VIP neurons are from reticular formation, a phylogenetically old brain structure that is known to regulate balance. Altogether, the work from this project unveils a new downstream circuit pathway in the brainstem that regulates balance and postural maintenance.

P3-D-696 *Sub-anesthetic ketamine impairs auditory deviance detection across cellular, population, and mesoscale levels*

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Detecting unexpected sensory events is crucial for adaptive behavior. In the neocortex, repetitive stimuli elicit reduced responses, while deviant stimuli trigger enhanced activity. This phenomenon is reflected in the mismatch negativity (MMN), an EEG biomarker of deviance detection that depends on NMDA receptor function. Despite its importance, the cellular and network mechanisms involved remain understood. We used multi-electrode array recordings in awake mice to investigate how sub-anesthetic ketamine, a partial NMDA receptor antagonist, affects auditory deviance detection. In primary auditory cortex (A1), a subset of neurons exhibited a biphasic spiking response to deviant sounds. The second peak of this response was abolished after ketamine administration, highlighting NMDA receptor-dependent signaling. We also recorded from the posterior parietal cortex (PPC), a hub for multisensory integration. PPC neurons responded selectively to deviant, but not repetitive, sounds, and this response required intact NMDA receptor function. Functional connectivity analysis using Weighted Phase Lag Index revealed signaling from A1 to PPC during deviant detection. Ketamine disrupted this inter-regional communication, indicating impaired prediction error signal propagation. These results show that sub-anesthetic ketamine weakens both local neuronal responses and long-range cortical coordination during auditory deviance detection. Our findings, under review in the European Journal of Neuro., provide new insights into how NMDA receptor hypofunction alters predictive auditory processing.

P3-D-697 *Subcellular synaptic connectivity patterns and motor control in C. elegans*

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Coordinated movement relies on predictive mechanisms and mechanosensory feedback to maintain gait, correct errors, and adapt to or integrate sensory stimuli during ongoing behavior. RIA interneurons have previously been shown to regulate stimulus-directed orientation behaviors by integrating estimated head movements with sensory input. Here, we show that in the absence of sensory cues, RIA is essential for maintaining gait and restricting locomotory head movements to the dorsal-ventral plane through feedback inhibition onto head motor neurons. When signaling between RIA and SMD neurons is blocked in either direction, animals frequently lift their heads off the agar surface. This appears to be caused by a failure to properly transition between dorsal and ventral head bends. We explore this novel phenotype using RIA-specific knockouts of genes involved in calcium regulation and synaptic function, automated quantification of head lifts, and calcium imaging of neurons and muscles. We show that this feedback relies on the spatiotemporal features of local calcium events in the RIA axon. It is independent of UNC-2-mediated transmitter release and involves peptidergic transmission from RIA. We propose that this circuit motif is analogous to recurrent inhibition in the vertebrate spinal cord and functions as a proportional control mechanism to maintain gait and regulate transitions between dorsal and ventral bends.

P3-D-698 *Task-dependent modulation of hindlimb cutaneous reflexes during forward and backward walking before and after cervical spinal cord injury in cats*

Rasha Al Arab [1], Sirine Yassine [1], Johannie Audet [1], Stéphanie Gabriella Tonleu Dongmo [2], Jonathan Harnie [2], Khaled Ashkar [2], Félix Maheux [2], Alain Frigon [2], Charlène Nadeau [2]

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During locomotion, spinal networks integrate supraspinal commands with cutaneous inputs to coordinate muscle activity in response to external perturbations. Spinal cord injury (SCI) disrupts this integration, as shown after incomplete thoracic SCI, but how cutaneous reflexes are modulated after cervical SCI (cSCI) during forward (FW) and backward (BW) walking remains unknown. Here, cutaneous reflexes were evoked by stimulating the right and left superficial peroneal (SP) nerves, and electromyographic responses were recorded from five ipsilateral and contralateral muscles during FW and BW hindlimb-only treadmill locomotion at 0.2 m/s in eight cats, before and after a right cervical hemisection at C2–C3. Preliminary data from one cat show that specific reflex responses emerged or disappeared after cSCI. For example, before cSCI, right SP stimulation evoked short-latency inhibitory responses during FW in contralateral sartorius and long-latency excitatory responses during BW in ipsilateral soleus and vastus lateralis, which were absent after cSCI. Conversely, after cSCI, stimulation evoked long-latency inhibitory responses in ipsilateral semitendinosus during FW and short-latency excitatory responses in contralateral vastus lateralis during BW, not present in the intact state. Left SP stimulation during BW resulted in the loss of several mid- and long-latency responses in all contralateral muscles. These preliminary findings indicate that cSCI alters the distribution of cutaneous inputs according to task. Analyses of the remaining animals and additional muscles are ongoing.

P3-D-699 *Thalamic integration of basal ganglia and cerebellar circuits during motor learning*

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The ability to control movement and learn new motor skills is one of the fundamental functions of the brain. The basal ganglia (BG) and the cerebellum (CB) are two key brain regions involved in controlling movement, and neuronal plasticity within these two regions is crucial for acquiring new motor skills. However, how these regions interact to produce a cohesive unified motor output remains elusive. Here, we discovered that a subset of neurons in the motor thalamus receive converging synaptic inputs from both BG and CB.

By recording circuit-specific neuronal activity in mice learning motor tasks, we found that motor thalamus neurons integrate BG and CB signals and show distinct movement-related activity. Lastly, we found a critical role of these thalamic neurons and their BG and CB inputs in motor learning and control. These results identify the thalamic convergence of BG and CB and its crucial role in integrating movement signals.

P3-D-700 *Thalamocortical-like circuits hierarchically process sensory information in topographically organized regions in the Zebrafish forebrain*

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In the mammalian cortex, distinct first-order thalamic nuclei contribute to the regionalization of the cortex by transmitting topographically selective sensory information to specific cortical regions. In the cortex, this sensory information is further hierarchically processed along the caudal-rostral axis of the brain. Yet, it is still unknown whether similar thalamocortical and hierarchical computations are conserved in more distant vertebrate species. In zebrafish, the dorsal telencephalon (or pallium) is considered homologous to the mammalian cortex, but it is still unclear as to how sensory information is transmitted to the zebrafish pallium and whether it is architecturally similar to other vertebrates. Using a combination of anatomical tracing, electrophysiological circuit mapping, and in vivo Ca2+ imaging, we revealed a thalamocortical-like pathway in the zebrafish brain. Our results show that the preglomerular nucleus (PG) is the primary diencephalic input to the zebrafish pallium. Furthermore, we found that distinct PG neurons encode different sensory modalities (light vs mechanical vibrations) and they distribute this information to topographically distinct zones in the zebrafish pallium. In contrast, pallial neurons exhibited sensory responses that were organized in multiple layers of topographically organized hierarchies, ranging from sensory-specific responses to mixed-selective and coincidence-detecting nonlinear responses. Interestingly, we found that this increase in sensory computation complexity was spatially organized along the posterior-anterior axis of the pallium mirroring its mammalian counterpart. Thus, our results suggest that hierarchical sensory processing across topographically organized pallial regions is a highly important functional feature that evolved millions of years ago and can be generalized across all vertebrates.

P3-D-701 *The Drosophila central complex and navigation in three dimensions*

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We tested how two different cell populations in the Drosophila central complex—a region that calculates navigational angles and vectors—function in the context of flies walking right-side up versus upside down. We found that the angular variable signalled by EPG neurons rotates in a consistent direction in the brain when Drosophila turn in a given egocentric direction (i.e., to their left or right), independent of whether flies are right-side up or upside down. We further found that asymmetrically stimulating the neurons that convert the EPG signal into a steering signal, called PFL3 cells, causes flies to turn in a fixed egocentric direction independently of the flies' angle to gravity. These results speak against the central complex signalling the fly's heading direction in a single external reference frame during three-dimensional maneuvers. We are considering two alternatives: navigational variables may be referenced to multiple locally consistent reference frames, or they may be referenced to a globally consistent compass direction projected into the fly's egocentric frame.

P3-D-702 *The effects of cervical spinal cord injury on cutaneous reflexes from forelimb afferents to muscles of all four limbs during locomotion in adult cats*

Sirine Yassine [1], Rasha Al Arab [1], Johannie Audet [1], Charlène Nadeau [1], Stéphanie Gabriella Tonleu Dongmo [1], Félix Maheux [1], Jonathan Harnie [1], Alain Frigon [1]

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During locomotion, cutaneous afferents continuously inform the nervous system about the body's interactions with the external environment. For example, when the foot dorsum contacts an obstacle during the swing phase, cutaneous mechanoreceptors activate spinal circuits that elicit a coordinated whole-body response, adjusting the trajectory of the perturbed limb while maintaining balance. Spinal cord injury disrupts the integration of this sensory feedback and alters cutaneous reflex modulation. However, how cervical injuries affect the distribution of cutaneous inputs, particularly those arising from the forelimbs, to motor pools controlling all four limbs remains unexplored. Here, we evoked cutaneous reflexes in muscles of all four limbs by stimulating the right and left superficial radial (SR) nerves during treadmill locomotion at 0.4 m/s in eight cats, before and after a right cervical hemisection at C2-C4. Following cervical hemisection, marked changes were observed in the ipsilesional forelimb with right SR stimulation. Specifically, short-latency excitatory homonymous responses showed increased occurrence, reduced onset latency, and altered phase-dependent modulation, suggesting enhanced excitability of these pathways. In contrast, contralesional homonymous reflexes, as well as bilateral crossed, homolateral, and diagonal pathways, were less affected. Together, these findings demonstrate that cervical hemisection primarily alters reflex modulation in the ipsilesional forelimb by enhancing homonymous reflex excitability while largely preserving other reflex pathways.

P3-D-703 *The role of claustro-cortical projections in sleep-mediated motor learning consolidation*

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Motor memory formation involves two distinct stages – the acquisition stage that involves trial-to-trial practice within a single session, and a consolidation stage that often refers to the offline processes occurring during sleep which stabilize motor memory. However, the neural mechanisms driving sleep-dependent motor skill consolidation remain poorly understood. Here, we reveal that the claustrum – a subcortical nucleus located between the striatum and insular cortex with established roles in sleep – projects to the motor cortex. Using in vivo two-photon axonal Ca2+ imaging, we found that during motor training, which consists of alternating running and stationary phases, a specific subset of M1-projecting claustral axons exhibits selectively enhanced activity during the stationary phase, suggesting a potential role in motor learning. Further analysis of c-Fos expression in the claustrum revealed that mice underwent motor training exhibited a greater number of c-Fos$^+$ neurons during subsequent sleep compared to immediately following training, indicating elevated claustral activity during post-training sleep. Overall, our results show a potential contribution of the claustrum–motor cortex pathway in sleep-mediated motor learning consolidation.

P3-D-704 *The role of microRNAs in drosophila nociception*

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MicroRNAs (miRNAs) are small, non-coding RNA molecules that contribute to the regulation of nearly all biological processes by controlling post-transcriptional gene expression. Increasing evidence suggests miRNAs are important modulators in pain, with specific miRNAs being upregulated or downregulated following acute tissue injury and in patients with disorders like fibromyalgia and complex regional pain syndrome. Targeting miRNAs in pain research has demonstrated significant potential as biomarkers for diagnosis of pain disorders, and even therapeutic targets for treatment of chronic pain. Despite this acknowledged potential, a functional screen of all available miRNAs for their involvement in pain does

not exist. The objective of this study is to identify and characterize specific miRNAs contributing to the nociceptive response. This will be accomplished by behaviourally screening 130 Drosophila melanogaster lines in which individual miRNAs will be targeted in nociceptors using miRNA sponges that sequester and inhibit miRNA function. Each line is tested using a Drosophila larval thermal nociception assay to determine altered sensitivity to stimuli. Our current results have found that the expression of some miRNA sponges in nociceptors results in hypersensitivity, whereas expression of others result in hyposensitivity relative to controls. The full collection of available miRNA sponges is currently being tested, and miRNAs found to be involved in nociception will be further characterized using molecular approaches and potential targets will be identified.

P3-D-705 *The role of the lumbar spinal network in hindlimb locomotor recovery after incomplete spinal cord injury depends on lesion level in adult cats*

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Hindlimb locomotor recovery after complete thoracic (T) spinal cord injury (SCI) is due to the presence of a lumbar network that interacts with somatosensory feedback. In cats that recovered locomotion following an incomplete thoracic SCI, hindlimb locomotion is expressed the day after spinal transection, which normally takes 2-3 weeks (Barrière et al. 2008, Audet et al. 2023). This indicates that the lumbar network becomes more independent after an incomplete thoracic SCI. However, the role of the lumbar network following an incomplete cervical (C) SCI remains unexplored. 14 cats were assigned to two paradigms. Group C underwent a right C2 hemisection followed 15–18 wks later by a complete T12 transection. Group CT underwent a right C2 hemisection followed 17–22 wks later by a left T10 hemisection, and 12–13 wks later by a T12 transection. Kinematic and EMG data were recorded one day after transection, with/without perineal stimulation (PS), which facilitates locomotion in spinal-transected animals. Without PS, none of the 14 cats in either group expressed locomotion after spinal transection. With PS, three cats of Group C showed weak alternating movements without weight bearing, one cat generated weak unilateral movements of the right hindlimb, and four cats showed no locomotion. With PS, two of six cats of Group CT performed weak alternating movements. These results indicate that hindlimb locomotor recovery after incomplete cervical SCI depends on descending cervical inputs and less on intrinsic lumbar mechanisms than after incomplete thoracic SCI.

P3-D-706 *The role of V3 spinal interneurons in the vestibular control of posture in mice*

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Proper control of movement and posture relies on descending projections from the vestibular nuclei to spinal motor circuits, yet the interneuronal organization of the vestibulospinal tract remains poorly defined. V3 neurons are excitatory commissural interneurons essential for regulating locomotion, gait transitions, and sit-to-stand movements, making them promising candidates for mediating vestibulospinal inputs. This study assessed the functional organization of vestibulospinal connectivity to spinal V3s. Using neonatal brainstem-spinal cord preparations of Sim1cre/+;Igs7GCaMP8s mice, we recorded V3 responses, via calcium imaging, in the L2 spinal cord evoked by electrical stimulation of cranial nerve VIII. Preliminary results showed responding V3s to be primarily ipsilateral and ventrally located, with a mean shortest latency of ~133 ms. Blocking glycine activity with 0.5uM strychnine significantly shortened the response latency to ~83 ms, suggesting a modulatory role for glycinergic inhibition in vestibular drive to V3s. Similar experiments in the L5 spinal cord are ongoing. To assess functional relevance, postural stability was evaluated using an elevated beam task. Adult mice lacking functional V3s, via genetic silencing, exhibited impaired performance on narrow beams (≤ 2 cm), adopting compensatory strategies, and required increased traversal time (≤ 1.5 cm) compared to wildtype controls ($p \leq 0.05$). Together, these findings define key features of vestibulospinal input to V3 interneurons and support their role in postural control under balance-challenged conditions.

P3-D-707 *The structure-function relationship of the oscillatory pacemaker nucleus network in weakly electric fish*

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The Pacemaker Nucleus (Pn) of weakly electric fish Apteronotus albifrons is an oscillating neural network comprising ~150 synchronized neurons that controls an electric organ discharge (EOD). Both the Pn and EOD fire continuously at frequencies near 1000 Hz, and with sub-microsecond variation in cycle length, they are the most precise biological oscillators known. Yet these fish also transiently desynchronize the Pn network on millisecond timescales to produce communication signals, thus balancing network flexibility with extreme temporal precision. Previous work has shown that the Pn is a sparse and weakly coupled network with no clear anatomical organization, but the mechanism behind its nimble function is unclear. We hypothesize that the Pn is structured as a "small-world" network, which balances stability and flexibility through clustered and efficient connectivity. We predict that small-world network features will be consistent across individuals, and thus provide a framework for understanding network function as well as baseline variability in network structure. To test this hypothesis, we use whole-mount samples to characterize the intact 3-dimensional network structure of the Pn across individuals. The structure-function relationship within the Pn network may provide insights into other oscillatory networks such as those underlying Alzheimer's and Parkinson's.

P3-D-708 *Theta-specific dual-brain stimulation of the right temporo-parietal junction modulates the sense of joint agency during alternating tapping*

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We often experience a sense of joint agency during interaction, described as the shared feeling that "we are acting together". Studies using Electroencephalogram (EEG) hyperscanning—a technique that simultaneously records brain activity from multiple individuals—have revealed that joint agency is associated with inter-brain connectivity. However, its causal role in joint agency remains unclear. In this study, we administered dual-Transcranial Alternating Current Stimulation (dual-tACS) over the right temporo-parietal junction (rTPJ) in 13 dyads performing an alternating tapping task (reference ITI = 0.5 s; 180° relative phase). The stimulation involved modulating in-phase and anti-phase coupling across theta (6 Hz), alpha (10 Hz), and beta (20 Hz) frequencies. The results showed that tapping speed in the theta anti-phase condition was significantly slower than the reference ITI, whereas no reliable deviation from the target inter-tap interval was observed in other conditions. However, the relative phase remained stable at approximately 180° across all conditions. Crucially, within the theta band, anti-phase stimulation resulted in significantly lower reported joint agency compared to in-phase stimulation. A mediation analysis indicated that the inter-tap interval might partially mediate this effect, although the indirect pathway was not statistically robust. These findings imply that anti-phase theta stimulation over the rTPJ diminishes joint agency by impairing coordination efficiency—without disrupting timing stability—providing causal evidence that rTPJ-mediated inter-brain synchrony is essential for the experience of joint agency.

P3-D-709 *Timing-related activity in the supplementary eye field of macaques*

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Medial frontal cortex (MFC) supports adaptive behaviour by representing durations between key events. Within MFC, the Supplementary Eye Field (SEF) has been associated with proactive aspects of gaze control before actions are executed, yet the neural mechanisms underlying this function remain unclear. We recorded single-unit activity from SEF in two bonnet macaques and two rhesus macaques performing a stop-signal task. Monkeys were rewarded for making a saccade to a target and for inhibiting it when a stop signal

appeared. Each trial began with fixation, followed by a variable delay before target presentation, allowing assessment of neural activity related to the temporal structure of the task. We describe distinct functional groups of SEF neurons whose firing patterns were related to the timing of task events. Neurons in these groups showed gradual increases or decreases in firing rate prior to target presentation. These ramping patterns varied with the duration of the delay, indicating sensitivity to elapsed time within the trial. Together, these results characterize timing-related activity in SEF during a task requiring response execution and inhibition and provide further description of how SEF activity relates to task structure during performance monitoring and executive control.

P3-D-710 *TMS reveals causal contributions of egocentric and allocentric functional connectivity hubs to reach behaviour*

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Introduction: Goal-directed reaching relies on egocentric (EGO; body-centered) and allocentric (ALLO; landmark-centered) reference frames. Musa et al. (2025) identified two cortical hubs within the visual peripheral (VP) network (Schaefer et al., 2018): a superior hub, ExstrSup-2 (dorsal stream), linked to both EGO and ALLO processing, and an inferior hub, ExstrInf-2 (ventral stream), selectively associated with ALLO. Here, we used transcranial magnetic stimulation (TMS) to test the causal role of these hubs in reaching. We hypothesized that TMS to ExstrSup-2 would disrupt EGO reaching, while stimulation of either hub would affect ALLO reaching due to the transformation of allocentric into egocentric coordinates for action (Chen et al., 2018). We further tested whether individual VP network modularity modulates susceptibility to TMS effects. Methods: Participants (n=16) completed a delayed reach-to-touch task under EGO & ALLO instructions, matched for sensory and motor demands (Musa et al., 2024). Resting-state fMRI localized individual TMS targets and quantified VP modularity. Triple-pulse TMS (1 Hz, 110% motor threshold) was applied during the memory delay to ExstrSup-2, ExstrInf-2, or a no-stimulation control. Accuracy, precision, and reaction time were analyzed. Results: TMS to ExstrSup-2 impaired both EGO & ALLO precision and lengthened reaction time. In contrast, ExstrInf-2 stimulation selectively worsened ALLO task accuracy & precision. Higher VP modularity was associated with smaller TMS-induced performance decrements, particularly following ExstrSup-2 stimulation. Conclusion: These findings provide causal evidence that dorsal stream hubs support both EGO and ALLO reaching, ventral stream hubs are specialized for landmark-based actions, and greater VP network modularity confers resilience to neural disruption.

P3-D-711 *Too much of a good thing: How the spinal cord responds to oxygen excess*

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We discovered that preganglionic intermediolateral nuclei (IML) neurons in the thoracic spinal cord are oxygen sensors, increasing sympathetic activity in response to hypoxia. We hypothesize that the Spinal Oxygen Sensor (SOS) is also sensitive to hyperoxia because the hypoxic sensing mechanism involves reactive oxygen species (ROS), long associated with oxygen excess. Specifically, the SOS proposed mechanism involves two cytosolic enzymes, nitric oxide synthase (NOS1) and NADPH oxidase (NOX2), the generation of ROS and activation of membrane Transient Potential Receptors (TRP), causing influx of Ca2+ and neuronal excitation. Using a novel rat in situ artificially-perfused spinal cord preparation, we show that sympathetic activity in hyperoxia is 2-fold higher than in normoxia. Blockade of the hypoxia sensing components, NOS1 and NOS2, does not abolish the hyperoxic sympathetic excitation. Moreover, when blocked independently the response was exacerbated. Inhibition of TRP channels abolishes the hyperoxic response. TRP channels are activated by post-translation modifications such as formation of disulfide bonds. We showed that dithiothreitol, a compound that reverses disulfide bonds, also eliminates the hyperoxic response. We conclude that the SOS increase sympathetic activity under hyperoxia via activation of TRP channels, likely by a direct effect of excess oxygen inducing disulfide bonds. This result adds to growing evidence that prolonged exposure to hyperoxia can be detrimental and should be used cautiously as a therapeutic

intervention for treatment of hypoxemia.

P3-D-712 *Transformation of vestibular signals in the interposed versus rostral fastigial nuclei of the cerebellum*

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Daily tasks such as postural control and reaching require estimates of body motion and orientation. Vestibular signals are essential for such estimates but to contribute appropriately two key computations are required. First, ambiguous otolith organ signals must be combined with spatially transformed rotational signals (e.g., from the canals) to distinguish translation from tilt. Second, these estimates must be transformed from a head- to a body-centered reference frame. Prior work showed that deep cerebellar rostral fastigial nucleus (rFN) cells reflect both computations, consistent with a role in body postural control. However, less is known about motion coding in the adjacent interposed nuclei (IPN). Because the IPN play a role in reaching, we hypothesized that, like rFN cells, many IPN cells should reflect the vestibular transformations to estimate body motion. To test this, we recorded in the IPN of a macaque monkey as he was passively moved in 3D space for different translation and tilt stimuli. To distinguish head- from body-centered coding cell tuning was characterised across different static head orientations relative to the body. Similar to rFN cells, IPN cells responded to translation and tilt in unequal proportions, consistent with a partial solution to the problem of distinguishing these motions. Furthermore, many IPN cells reflected at least a partial transformation of vestibular signals toward body-centered coordinates. These preliminary results suggest that IPN cells, like rFN cells, reflect the vestibular transformations necessary to estimate body motion.

P3-D-713 *Ultrasonic noise in the housing colony affects behaviour and physiology of adult rats*

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Perception is dictated by our sensory capabilities which vary widely across species. Hearing in humans is confined to a relatively narrow range, thus the presence of ultrasonic noise, sound with a frequency >20 kHz, is often overlooked. Concerningly, it has been determined that the laboratory is rife with ultrasounds which may be a stressor for rats not only due to their extended hearing range but also their use of ultrasonic vocalizations to communicate. To understand the significance of ultrasonic noise in the laboratory, rats were exposed to no noise, white noise (2-20 kHz, 70 dB), or ultrasonic noise (40 kHz, 70 dB) for a 2-week period, based upon previous screening of facility background noise. Both behavioral and physiological parameters were subsequently investigated to assess the effects of noise exposure on animal welfare. Results indicated various differences: rats exposed to ultrasonic noise spent significantly more time in the center of the open field and less time in the open arms of the elevated plus maze compared to animals exposed to no noise and white noise; rats exposed to ultrasonic noise had elevated fecal corticosterone levels; rats exposed to ultrasonic noise and no noise had significantly lower daily anal infrared temperatures and increased adrenal gland weights as compared to animals exposed to white noise. These findings bring attention to the presence of ultrasonic noise and its ability to significantly alter rat behavior and physiology in unexpected ways. Acknowledgment of ultrasonic noise as a confounding variable will not only lead to improved validity of rodent research but also improve animal welfare.

P3-D-714 *Uncovering distinct NPAS4-expressing SST-IN ensembles during the acquisition of different motor movements*

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The primary motor cortex (M1) is essential for the initiation of voluntary movement and plays a critical role in motor learning. While motor-learning research has largely focused on excitatory neurons, the contribution

of inhibitory neurons in shaping learning-related plasticity remains poorly understood. Recent work from our lab has shown that, during motor learning, a subpopulation of somatostatin-expressing inhibitory neurons (SST-INs) in M1 contributes to motor memory formation through the activity-dependent transcription factor, NPAS4. We aim to determine whether learning different motor movements recruits distinct ensembles of NPAS4-expressing SST-INs. To address this, we use the NPAS4-Robust Activity Marking (NRAM) reporter system, which enables labeling of movement-specific NPAS4 ensembles. By training animals with different motor tasks, we found 40% overlap in NPAS4+ SST-IN ensembles, with the remaining 60% being movement-specific. To further probe circuit changes during this process, we employed in vivo two-photon imaging in awake mice to chronically monitor spine re-organizations on movement-specific dendritic branches during the acquisition of two distinct motor behaviors. Ongoing analyses are assessing whether movement-specific NPAS4+ SST-IN ensembles directly regulate spine remodeling on their corresponding movement-specific dendritic branches. Overall, this work seeks to uncover the cellular mechanisms on how inhibitory neurons contribute to differential motor movement memory formation.

P3-D-715 *Uncovering the role of Podxl in photoreceptor cell polarity and function*

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In the mammalian retina, vision begins when light is detected by rod and cone photoreceptors (PR) and converted into electrical signals. This process depends on precise cellular polarity, with the apical domain of PRs organized into inner and outer segments, and the basal domain containing the cell body and synapse, each maintaining distinct protein compositions. While this organization is essential for photoreceptor function and survival, the mechanisms that establish and maintain this polarity remain poorly understood. Podocalyxin-like protein (Podxl) represents a compelling candidate to regulate PR polarity. Initially characterized in the kidney as a key determinant of protein localization, cell morphology, and epithelial polarization, we recently found Podxl expression in rod and cone inner segments and synapses. To determine Podxl function in PRs, we generated Podxl conditional knockout (cKO) mice in both rods and cones using the Cre-loxP system. Our data revealed striking disorganization of the photosensitive compartments and significant visual dysfunction in these cKO mice. To uncover the molecular basis of these defects, we used in vivo IP-MS to identify Podxl interacting partners. We identified proteins involved in intracellular trafficking, cytoskeletal organization, and synaptic structure, which will help to uncover the mechanism of Podxl function in PR biology. Because the role of Podxl in the CNS remains poorly characterized, this work will provide fundamental insights into the mechanisms underlying neuronal polarity and how these mechanisms fail in disease.

P3-D-716 *Unraveling the impact of aging on neural barrier integrity in mice*

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The nervous system is protected by layers of neural barriers: blood-brain barrier (BBB), blood spinal-cord barrier (BSCB), and blood nerve barrier (BNB), each playing pivotal roles in maintaining homeostasis of the nervous system. Our previous studies show that nerve injury-induced neuropathic pain is associated with impaired BNB and BSCB integrity, which is essentially mediated by the inflammation process. While aging is characterized by a chronic, low-grade inflammatory status (aka. Inflammaging), it remains elusive whether these barriers remain intact across the lifespan of healthy individuals. It is, therefore, important to understand whether and how normal aging process impacts the integrity of neural barriers in healthy aging mice, and in aging mice with nerve injury. Using young (2-4 months) and aged (>20 months) mice of both sexes, we observed that neural barrier integrity is compromised under normal aging condition, with reduced tight junction protein expression across all three barriers and a specific upregulation of ICAM1 in BSCB. No sex differences were detected in age-related changes in barrier function and structure. Interestingly, in nerve injury condition, while BNB breakdown in female aging mice remains significant at day 30 post-injury which is similar to their young counterparts, in male aging mice, nerve injury-associated BNB disruption is

already abolished. At one-month post-injury, fluorescent dye extravasation around BNB is significantly lower in male aging mice than those observed in male young mice. Our findings provide a better understanding of potential neural barrier impairment during normal aging, suggesting that a leaky neural barrier could be a contributor to the age-related diseases, including chronic pain in the aging population.

P3-D-717 *Using combined TMS-EEG to investigate cortical changes in response to acute muscle pain*

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During acute pain, motor control is reduced, presumably to prevent movements that could provoke further injury. To examine cortical mechanisms underlying these motor changes, we combined transcranial magnetic stimulation (TMS) and electroencephalography (EEG) to record TMS-evoked potentials (TEPs) in participants receiving acute experimental muscle pain. Thirty participants receive either a 0.2mL bolus injection of isotonic saline (0.9% NaCl) into the right first dorsal interosseous (FDI) muscle which produces no pain, or hypertonic saline (5% NaCl) injection which produces moderate pain over 20 minutes. Single-pulse TMS is delivered over the left motor cortex targeting the right FDI muscle, with 64-channel EEG concurrently recorded before, during, and after pain resolution. TEP peaks' amplitude is compared across time and between groups. We hypothesize that the amplitude of the TEP peaks at 45ms (indexing GABAergic neurotransmission) will increase in response to pain. Preliminary results (hypertonic n=10, isotonic n=12) suggests a dissociable trend between groups, as Bayesian linear mixed models revealed a robust Group×Time interaction during pain, with the hypertonic group showing increased TEP amplitude (β=0.65, 95% CI [0.24,1.05]) while the isotonic group showing a decrease (β=-0.56, 95% CI [-0.95,-0.16]) compared to baseline. These preliminary findings suggest a distinct neurophysiology underlying pain processing. This is the first study to apply simultaneous TMS-EEG in acute muscle pain, providing new insights into pain mechanisms.

P3-D-718 *Vision loss triggers transient changes in motor-related cortical states in the adult mouse visual cortex*

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Loss of visual input in adulthood profoundly reshapes cortical function, yet the dynamics of this adaptation remain elusive. Homeostatic plasticity mechanisms are known to restore excitatory activity levels in the primary visual cortex (V1) within a few days, but how activity evolves beyond that timescale is unknown. Using longitudinal mesoscopic calcium imaging across the dorsal cortex of adult mice, we tracked large-scale activity before and after bilateral enucleation (BE) during head-fixed spontaneous behaviour. We reveal that BE not only alters V1 activity but also disrupts its modulation by behavioural state—a fundamental organising principle of cortical processing. Strikingly, locomotion-driven enhancement of V1 activity collapsed within 24 hours, while quiescent periods became dominated by slow oscillations within 1 week. These opposing, state-dependent changes followed distinct recovery trajectories, converging only at ~10 weeks. Thus, beyond the rapid homeostatic stabilisation of excitatory activity, the restoration of behavioural-state modulation of large-scale cortical dynamics unfolds over a much longer timescale. This could reflect slow rewiring of cortical circuitry, temporarily disrupting basic functions to achieve long-term stability. This study describes long-term changes in activity following an abrupt decrease in cortical excitation, but the underlying mechanisms remain unknown. Further research into this ten-week window will deepen our understanding of the brain's ability to adapt.

P3-D-719 *Visual attention in peripersonal space: Hand vision and proprioception differentially modulate V2 feature selectivity*

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Bringing the hand near a visual stimulus enhances visual processing. This effect is linked to peripersonal space (PPS), the body-centered region where visual and proprioceptive information interact. Despite extensive behavioral evidence, the neural basis of this interaction in early visual cortex remains unclear. In this study, we investigated how hand proximity modulates orientation selectivity in area V2 by recording single-neuron responses from two rhesus monkeys. The monkeys performed a fixation task while their hand was positioned near a visual stimulus while either being visible or occluded, and compared with when the hand was away from the stimulus. When the near hand was visible, neural firing rates in V2 were significantly higher, accompanied by sharper orientation tuning. In contrast, occluding the hand broadened orientation tuning compared to when the hand was away. These effects emerged rapidly after stimulus onset and were coherent across the population, demonstrating that PPS is actively prioritized during visual processing. Together, the findings reveal two complementary (feedback) signals in V2: a congruence-driven enhancement when visual and proprioceptive inputs align, and a mismatch-driven suppression when they conflict, indicating that V2 integrates multisensory cues to encode PPS and support action-relevant visual processing.

P3-D-720 *Visuospatial context and task performance are encoded in Ventrolateral Prefrontal Cortex LFP activity during a head-unrestrained, memory-guided reach task*

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The purpose of this study was to understand how prefrontal local field potential (LFP) signals encode visual landmark information during a memory-guided reach task, and how this is modulated by performance and spatial variables. We implanted a 128-channel Plexon Array over the ventrolateral prefrontal cortex (vLPFC). Single unit activity, LFPs and behavioral signals were recorded simultaneously in a Rhesus monkey. The task began with central gaze fixation, after which a landmark (four dots forming a virtual square) was presented. A visual target then appeared transiently, followed by a visual mask. After the mask, the landmark either reappeared at the same location (stable landmark condition) or shifted (landmark shift condition). The fixation light then extinguished, signaling a reach to the target. Controls were the same, but without the landmark. Preliminary time-frequency analyses revealed frequency-specific decreases in LFP power during the memory delay, followed by increases peaking near movement onset across all conditions. Correct stable landmark trials and landmark shift trials showed a second power increase between acquisition and reward. These landmark-related modulations were reduced during error trials. Low-frequency LFP power also exhibited spatial tuning, with stronger modulation for targets located ipsilateral to the recording site, whereas initial hand position had a more uniform effect. These preliminary findings suggest that vLPFC LFP signals reflect task-relevant spatial information and performance-dependent modulation during memory-guided reaching.

P3-D-721 *Acute effect of VTA stimulation on M1 neuronal activity*

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The primary motor cortex (M1) is responsible for fine motor execution and motor learning. Learning is known to be associated with neuronal plasticity. Dopaminergic signaling in M1 is necessary for motor learning and is thought to modulate M1 neuronal plasticity. The ventral tegmental area (VTA) sends dopaminergic signals to M1 either from direct or indirect pathways, as well as GABAergic and glutamatergic projections. The functional role of these complex VTA-M1 pathways remains poorly understood. Our objective here is to characterize the influence of the VTA-M1 pathways on M1 neuronal activity under different conditions.

To this end, we used intracortical multielectrode arrays in rats to record M1 responses to VTA optogenetic stimulation. Using different viral vectors in TH::Cre rats, we were able to target VTA dopamine neurons, either selectively or along with glutamatergic and GABAergic neurons. We assessed the immediate impact of their activation on the activity of individual M1 neurons and the neuron population under different conditions: anesthesia, free-behaving or motor learning. We found a clear modulation of M1 activity during and after VTA stimulation. This effect of VTA stimulation on individual M1 neurons was diverse and varied with respect to labeled neuron types and different behavioral conditions. Neuronal population responses were analyzed using dimensionality reduction. A clear trajectory representing neural population dynamics was observed. Immunohistochemistry was performed for the clarification of neuron types in the VTA. The results suggest that VTA-M1 projections could reshape neuronal activity in M1 and may facilitate fine motor learning and neuronal plasticity.

P3-D-722 *Examining the relationship of interocular delays, depth perception, and suppression in amblyopia*

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Many visual tasks rely on binocular vision, which requires precise timing of signals from both eyes. In amblyopia, this integration is often disrupted suppression of the amblyopic eye and delayed processing. Understanding interocular delays could guide binocular treatments. This study compares measures of interocular delay with perceptual depth measures, examines their stability, and evaluates their relationships with suppression in adults with amblyopia and controls. Participants completed three tests assessing interocular timing, depth perception, and suppression. Interocular delay was measured with a monocular tracking task with one eye occluded. Depth perception was evaluated with a structure-from-motion cylinder with varying disparity. Participants with amblyopia showed slower processing in the amblyopic eye, poorer stereoscopic depth perception, and stronger suppression than controls. Interestingly, interocular timing was significantly associated with suppression strength ($r = 0.62$, $p < 0.001$), whereas stereoscopic depth perception showed no reliable relationship with either timing (($r = 0.01$, $p = 0.98$) or suppression ($r = -0.28$, $p = 0.4$). These findings indicate a dissociation between stereoscopic depth perception and interocular timing in amblyopia and suggest that delayed processing and suppression reflect a shared binocular imbalance not directly captured by standard depth-perception measures.

E - HOMEOSTATIC AND NEUROENDOCRINE SYSTEMS

P3-E-723 *MTBI suppresses water intake without impairing the thirst circuit in mice*

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Of all traumatic brain injuries (TBI), mild traumatic brain injuries (mTBIs) are the most common, affecting millions of individuals globally every year. mTBIs lead to characteristic autonomic dysfunctions that are believed to involve the hypothalamus. While the hypothalamus is known to mediate acute hypothermia after mTBI, its role in regulating thirst following injury remains unclear. Here, we investigate whether mTBI alters spontaneous daily water intake and the thirst response induced by a systemic hypertonic stimulus. The first experiment assessed daily water intake in mice under basal conditions and up to three days post-mTBI. Preliminary data show a significant suppression of water intake lasting 24h post-mTBI ($F(1, 12) = 42.71$, $p < .001$). To determine if the thirst network is still functional post mTBI, we administered a hypertonic solution 3h post-TBI and assessed water intake following injection. Hypertonic saline robustly stimulated water intake to a similar extent in both mTBI and sham mice (between-groups comparison, $p = 1.00$), indicating that the thirst circuit remains functional following injury. To determine whether reduced water intake following mTBI is caused by decreased activation of thirst promoting neurons, we will quantify cFos expression in the organum vasculosum of the lamina terminalis (OVLT) and the subfornical organ (SFO). Together, these

findings suggest water intake is suppressed following mTBI without altering the thirst circuit providing insight into hypothalamic dysfunction post mTBI, which could have clinical implications for mTBI patients.

P3-E-724 *Neurometabolic remodelling in hypothalamic appetite neurons in high-fat diet induced obesity*

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Obesity is a metabolic disease that can result from impairments in appetite neurons in the hypothalamus. A key driver of appetite neuron dysfunction is poor diet. For example, mice fed a high-fat diet have flawed circuit architecture in the hypothalamus and reduced hormone sensitivity in appetite neurons, which together cause weight gain that is disproportionate to caloric intake. Preventing these outcomes is a key target for anti-obesity therapeutics, but our limited understanding of appetite neuron diversity and spatial heterogeneity has stalled efforts to target these cells. Here, we applied single-cell spatial transcriptomics to brains from mice fed a high-fat diet to test the hypothesis that spatial context is an important factor in determining which appetite-regulating neurons are dysregulated in obesity. High-fat diet altered the expression of hormone resistance mRNAs in hunger (Agrp+) neurons depending on their spatial context. Agrp+ neurons closest to the median eminence showed increased insulin-like growth factor binding protein 5 mRNA and decreased leptin receptor mRNA. Conversely, Agrp+ neurons near the third ventricle had increased somatostatin and Rims3 mRNA, which may contribute to leptin resistance through increased inhibitory tone in Agrp+ neurons. Taken together, our data suggest that anatomically defined transcriptional patterns underlie endocrine receptivity and appetitive tone in obesity. We hope that this work will help inform new therapeutic strategies for the management of obesity to reduce comorbidities including type 2 diabetes.

P3-E-725 *Persistent sensitization of osmoresponsiveness by chronic salt loading: A potential role for nax channels as mediators of homeostatic memory in rat vasopressin neurons*

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Arginine vasopressin (AVP) secreting neurons in the supraoptic nucleus (SON) are excited by acute hyperosmolality and hypernatremia to promote water reabsorption by the kidney and essential for fluid homeostasis. Previous work has shown that chronic salt loading (SL) in rats (2% NaCl drinking water for 7 days) enhances the osmoresponsiveness of AVP neurones to acute stimuli. This study aimed to characterize the temporal window of this functional hypersensitivity and investigate the potential role of sodium-level sensitive channels (NaX) in this process. NaX channels act as atypical sodium sensors that modulate neuronal excitability. Using whole cell recordings in vitro, we found that the inward current mediated by NaX in response to an acute sodium stimulus was significantly greater in slices from SL animals compared to euhydrated animals. This finding indicated that an upregulation of Nax channels contributes to the hypersensitivity of AVP neurons after SL. Using Neuropixels probes in vivo, we recorded SON neuronal activity in SL rats and during subsequent rehydration periods of 1, 3, and 7 days. To evaluate functional sensitivity, an intravenous challenge of 2 M NaCl (30 uL/min) was administered. Our results revealed that the responsiveness to the acute challenge was significantly potentiated in animals previously exposed to SL. This state of hypersensitivity persisted for at least 3 days after SL was terminated, with neuronal responsiveness returning to control levels only after 7 days. These findings demonstrate that chronic salt intake induces a persistent state of homeostatic memory that may be physiologically adaptive. This state is mediated by a persistent sensitization of AVP neurons that may reflect an upregulated expression of NaX channels.

P3-E-726 *Regulation of vasopressin neuron activity and fluid balance in pregnancy*

Olena Makashova [1], Jieyi Yang [1], Masha Prager-Khoutorsky [1]

[1] McGill University

Olena Makashova1olena. Makashova@mcgill.ca Jieyi Yang1jieyi.yang@mcgill.caMasha Prager-Khoutorsky1*masha.prager-khoutorsky@mcgill.ca1Department of Physiology, McIntyre Medical Sciences Building, McGill University, Montreal, QC, Canada Regulation of Vasopressin Neuron Activity and Fluid Balance in Pregnancy AbstractPregnancy involves multiple adaptive physiological changes that are essential for maternal health and the proper development of the fetus. One of the critical changes is increased water retention of up to 50%, which elevates total circulating blood volume to ensure adequate perfusion of maternal organs, the fetus, and the placenta, to prepare for blood loss during childbirth, and to enable lactation. These dramatic shifts in fluid balance during pregnancy are mediated by vasopressin (VP, antidiuretic hormone) that plays a primary role in fluid homeostasis by controlling water retention, vascular resistance, and blood pressure. Increased VP secretion minimizes water loss and protects the organism against dehydration. However, exaggerated VP release causes excessive water retention, elevated vascular resistance, and can lead to hypertension. VP is produced in hypothalamic neurons located in the supraoptic and paraventricular nuclei. This system undergoes structural remodeling during pregnancy, a reduction in astrocytic coverage in the supraoptic and paraventricular nuclei, which facilitates hormone release. Although the mechanisms driving astrocytic remodeling during pregnancy remain unclear, our recent work suggests that microglia might be involved. Using an animal model, we examine how VP release is regulated during normal pregnancy to meet the cardiovascular demands of fetal development, compensate for blood loss during labor, and support milk production during lactation.

P3-E-727 Absence of TNF-α exacerbates hedonic feeding, weight gain, and behavioral alterations during chronic high-fat high-sugar diet exposure

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Weight gain is a major factor in the development of obesity, with high-fat, high-sugar diets (HFHS) playing a critical role. HFHS not only drives chronic inflammation but also disrupts reward-driven circuit, reducing preference for low-fat foods and impairing feeding behavior. Tumor necrosis factor-alpha (TNF), a pro-inflammatory cytokine recently identified adipokine, appears to mediate these effects. TNF is mainly produced by glial cells in the brain and adipose tissue in the periphery. Elevated TNF levels in obesity highlight the inflammatory basis of metabolic dysfunction. This study investigates how TNF contributes to diet-induced weight gain and related metabolic and behavioral changes. We hypothesize that microglial TNF deficiency contributes to weight gain and behavioral alterations under chronic HFHS exposure. To investigate it, WT, global TNF-α knockout (KO), and TNF conditional knockout (cKO) mice were fed HFHS for 8-9 weeks. At week 8, animals underwent behavioral testing using the light dark box (LDB), open field test (OFT) and novel object recognition (NOR) task to evaluate the anxiety level and memory capacity. To assess metabolic status, Insulin, leptin and adiponectin were measured by qPCR. WT mice exposed to HFD showed increased anxiety-like behavior and impaired recognition memory in the OFT and NOR tests, respectively. In contrast, both KO and cKO mice showed no significant behavioral impairments under the same dietary conditions. Under normal diet, KO mice had lower baseline body weight, while feeding HFD, they exhibited significantly greater weight gain compared to WT controls. TNF deficiency disrupts reward processing and promotes hedonic feeding and excessive weight gain, supporting its therapeutic relevance in diet-induced obesity and cognitive dysfunction.

P3-E-728 *Tanycytes in the central regulation of cardiovascular and hydromineral homeostasis*

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Circumventricular organs (CVOs) are brain regions characterized by the presence of fenestrated capillaries and thus have an incomplete blood–brain barrier. In addition, CVOs harbor tanycytes, specialized glial cells. Tanycytes feature a unique morphology, with cell bodies forming the ventricular wall of the CVOs, their processes extending into the brain parenchyma, and endfeet contacting fenestrated vessels. Therefore, tanycytes can directly link peripheral circulation and cerebrospinal fluid and thus are thought to act as gatekeepers, regulating body-to-brain communication at the CVOs. However, the functional role of tanycytes remains largely unknown. The organum vasculosum of the lamina terminalis (OVLT) and subfornical organ (SFO) are CVOs that regulate cardiovascular and hydromineral balance. Angiotensin II (ANGII), the effector of the renin–angiotensin system, acts via peripheral and central mechanisms to modulate blood pressure, stimulate thirst, and promote salt appetite. Because circulating ANGII cannot cross the blood-brain barrier, its central actions are mediated via the OVLT and SFO, where neurons are activated by systemic ANGII. Our results suggest that the ANGII type 1 receptor (AT1R) is expressed not only by neurons but also by OVLT and SFO tanycytes. Using a combination of calcium imaging with GCaMP6 and electrophysiology in mice with AT1R ablated in tanycytes, we examine the role of tanycytes in mediating systemic ANGII signals to local neurons. We test the hypothesis that OVLT and SFO tanycytes are involved in ANGII signaling to modulate neuronal activity and regulate thirst and cardiovascular and hydromineral homeostasis.

P3-E-729 *The effects of oxytocin signalling on anxiety-like behaviour and TNF expression in a mouse model of PTSD*

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In patients with Post Traumatic Stress Disorder (PTSD), early social intervention is a key predictor of successful recovery. Early social intervention produces an effect called social buffering, in which closeness to peers reduces both stress and inflammation. However, social buffering has a narrow therapeutic window in both humans and mice alike, and it is poorly understood why. Here we test the effects of oxytocin on hippocampal Tumor Necrosis Factor Alpha (TNF) and anxiety-like behavior in group housed and isolated mice after the Single Prolonged Stressor (SPS) model of PTSD. Oxytocin is released during social bonding and creates the experience of social reward. These experiments will provide insights into the potential mechanisms of social buffering and its therapeutic window to help develop PTSD treatments outside this critical time window. Male and female C57BL/6 mice were tested in isolated and grouped housing conditions after SPS. First, we assessed oxytocin neuron activation in the paraventricular nucleus and oxytocin expression in the ventral hippocampus and amygdala. Next, we tested the behavioral effects of oxytocin agonism and antagonism in isolated and group-housed mice respectively, after SPS. Finally, we quantified TNF mRNA levels in the ventral hippocampus and amygdala of mice from our behavioral experiments. Initial behavioral evidence suggests that oxytocin antagonism elevates anxiety-like behavior in group-housed mice after trauma. These results support the hypothesis that social buffering reduces stress through oxytocin signaling.

P3-E-730 *Traumatic brain injury activates vasopressin and oxytocin neurons of the supraoptic nucleus, causing hyponatremia*

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After a traumatic brain injury (TBI), one in three people experience hyponatremia. This electrolyte disorder characterized by low serum sodium causes water to move into tissues, leading to swelling that is particularly dangerous for the brain. However, the mechanisms by which TBI leads to hyponatremia are unknown.

Because supraoptic vasopressin (VP) neurons lie in a mechanically vulnerable area, we investigated the hypothesis that TBI inappropriately excites VP neurons, causing excessive VP release, renal water retention and hyponatremia. We also tested if excessive oxytocin (OT) release participates in TBI-induced hyponatremia. Using a preclinical closed head TBI model, we found that TBI lowered serum sodium in male and female mice versus sham injury. This effect was mimicked by pharmacologically activating peripheral VP or OT receptors, and partially rescued by antagonists.c-Fos analysis showed that TBI activates VP and OT neurons of the supraoptic nucleus. Accordingly, patch clamp recordings revealed an increased firing rate in supraoptic VP neurons from TBI mice, with increased intrinsic excitability and facilitated excitatory inputs. We are currently investigating the mechanisms leading to inappropriate activation of supraoptic neurons. Our c-Fos data indicated that supraoptic astrocytes are also acutely activated by TBI, and ex vivo calcium imaging showed that TBI increases astrocytic calcium event duration. We propose that TBI acutely activates supraoptic astrocytes, causing neuronal excitation and inappropriate VP and OT release, which results in hyponatremia.

P3-E-731 *Mechanistic insights into neurotensin-mediated control of body temperature and hypotension*

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Neurotensin (NT) is an endogenous tridecapeptide that induces a prolonged, dose-dependent decrease in core body temperature via activation of the two G-protein coupled receptors, NTS1 and NTS2. Harnessing NT's hypothermic properties may offer a therapeutic strategy for inducing protective hypothermia in clinical settings like cardiac arrest or ischemic stroke. However, the concurrent induction of hypotension by NT and its analogs has limited their therapeutic application. Elucidating the mechanisms that differentially mediate NT-induced hypothermia and hypotension is therefore critical for therapeutic advancement. Here, we hypothesized that histamine selectively contributes to NT-induced hypotension but not to hypothermia. Using implemented telemetry probes in rats, we simultaneously monitored blood pressure and core body temperature, following administration of the NT receptor agonist HPI-363. Pharmacological modulation of histamine signaling was achieved using the H1 receptor antagonist cetirizine and the mast cell activator compound 48/80. Peripheral manipulation of histamine signaling did not alter HPI-363-induced hypothermia, supporting a central mechanism underlying NT-mediated thermoregulation. Ongoing studies will further delineate central versus peripheral contributions by measuring physiological responses to intracerebroventricular HPI-363 in the presence of peripheral or central cetirizine. Together, these findings advance our understanding of the distinct pathways governing NT's physiological effects and support the feasibility of selectively engaging NT-driven hypothermia while minimizing hypotension. This mechanistic insight will inform the development of safer more targeted NT-based therapeutics for neuroprotection.

F - COGNITION, EMOTION AND MOTIVATION

P3-F-732 *Opioid receptor distribution in the claustrum-dorsal endopiriform complex*

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The claustrum is a thin subcortical structure that coordinates cortical network activity through its abundant reciprocal projections with most of the neocortex. The claustrum is enriched in opioid receptors, and recent work has implicated the claustrum in opioid-related behaviours including pain, reward, and negative affect. However, the precise distribution of these receptors within the claustrum is unknown. Using multiplex in situ hybridization (mFISH) we visualized expression of the expression of mu (Oprm), delta (Oprd), kappa (Oprk), and ORL1 (Oprl) opioid receptor genes at single-cell resolution in the mouse claustrum-dorsal endopiriform. Our data found that the claustrum was particularly enriched with Oprk, although Oprm, Oprd and Oprl were also present as well. Notably, Oprk exhibited a unique pattern of expression restricted to a specific

population of excitatory projections. Through spatial mapping we found these Oprk+ cells were localized to the claustrum core. Meanwhile, the other opioid receptors exhibited a broader expression pattern across both excitatory and inhibitory populations. Through the analysis of a publicly available single cell sequencing dataset from the macaque claustrum we were able to confirm a shared pattern of expression of claustrum opioid receptors between species. Together, these findings demonstrate an evolutionarily conserved, cell-type-specific organization of opioid receptor expression in the claustrum-dorsal endopiriform. These results indicate that Oprk expression is a defining molecular feature of claustrum-core excitatory projections and suggest the other opioid receptors have more nuanced roles in modulating local claustrum activity.

P3-F-733 *Pannexin-2 modulates glutamatergic-dependent habituation memory and cellular stress responses*

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Pannexin-2 (Panx2) is an ion channel enriched at ER-mitochondria contact sites, intracellular domains critical for calcium homeostasis and metabolic signaling. Despite its abundance in neurons and glia, the role of Panx2 in learning and memory remains poorly understood. To examine how Panx2 contributes to adaptive neural plasticity, we focused on habituation, a conserved form of non-associative learning that enables organisms to suppress responses to repetitive, non-salient stimuli. Here, we investigated the role of Panx2 using a visual habituation paradigm in 6-day-old zebrafish larvae. Behavioral analyses revealed that Panx2 knockout larvae (Panx2Δ11) displayed impaired retention of habituation memory 24 hours after training. Pharmacological manipulation revealed that this impairment was specific to glutamatergic signaling, with knockout larvae exhibiting increased sensitivity to glutamatergic receptor antagonism. At the molecular level, under metabolic stress conditions, Panx2 loss showed transcriptional changes indicative of disrupted calcium regulation and cell stress responses, including upregulation of ER calcium channels and intrinsic apoptotic pathways. Additionally, Panx2Δ11 showed altered ATP dynamics, suggesting impaired bioenergetic adaptation. Together, these findings identify Panx2 as a regulator of glutamatergic-dependent habituation memory and cell stress responses. Given its localization at ER-mitochondria junctions, Panx2 may provide a link between neuronal bioenergetics and memory consolidation.Funded by NSERC-DG RGPIN-2019-06378 (GRZ).

P3-F-734 *Passive versus active waiting paradigms differentially affect trial-to-trial dependencies impacting impulsive action*

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Impulsivity is evident when an individual acts with limited forethought of the consequences, a behavioural trait with links to their emotions. Although prior research has examined the general influence of emotion on impulsivity, the impact of transient emotional states on impulsive actions remains underexplored. In considering this relationship, we reasoned that because tasks probing impulsive actions typically withhold reward following a premature response during the waiting period, this momentary negative outcome could influence behaviour on the subsequent trial. Thus, we hypothesized that premature responses would show trial-to-trial dependency, such that a premature response would be more likely to follow a previous premature response than a previous successful trial. We were also interested in whether the level of task engagement during the waiting period (i.e., active versus passive waiting) modulates impulsive action and these trial-to-trial dependencies. Using a rat model, we compared behaviour across two tasks that differed in waiting demands: a modified two-choice serial reaction time task requiring passive waiting, and a modified lever-based reaction time task requiring active waiting. Our results revealed clear behavioural differences between the tasks, demonstrating that both premature responding and trial-to-trial dependencies are strongly influenced by the waiting paradigm. Together, these findings provide an important first step toward using these behavioural models to investigate the neural mechanisms linking transient emotional states to

impulsive actions.

P3-F-735 *Planning mechanisms assessed with sequence unblocking*

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The Successor Representation family of algorithms has become a popular conceptualization of reinforcement learning in biological organisms. By representing state transitions in terms of probabilistic temporally discounted future state occupancies, these algorithms forgo the intensive planning of model-based reinforcement learning approaches. When paired with a replay mechanism as in SR-replay, Successor Representation algorithms maintain a similar level of flexibility to model-based learning. However, information related to transition sequences is unavailable because of the lack of a planning mechanism. In the present study, rats underwent a novel sequence-unblocking procedure. In training, a blocked stimulus is presented before a neutral stimulus, which predicts a rewarded stimulus. The stochastic control group disperses the blocked stimulus across trials such that the blocked stimulus is a worse predictor of the neutral stimulus. After the training phase, rodents are probed with the blocked stimulus in extinction and magazine entry is recorded to measure expectation of the saccharine-solution reward. Experimental rodents respond to the blocked stimulus significantly more than control rodents during the extinction test. Because the blocked stimulus cannot be used to directly predict the reward at test, a sequential planning process could be used to predict the absent neutral stimulus and then the absent rewarded stimulus. SR-Replay cannot generate a reward prediction from the predicted neutral stimulus and thus does not satisfy this requirement.

P3-F-736 *Population structure of reward-induced remapping in the hippocampal CA1*

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Hippocampal CA1 cells encode both task structure and environment to support a cognitive map. When task parameters change, place cells remap to support a goal-referenced representation. However, it remains unclear how single-unit remapping of non-place cells affects the population geometry. Here, we ask whether the larger population of non-place neurons remaps in a structured, behaviorally relevant way. To address this, we re-analyze two-photon recordings of CA1 neurons recorded in virtual track with intra-session reward-zone switches. We isolate non-place cells via a Skaggs information criterion and study the population similarity kernel across space, which characterizes the representational geometry. We show that: 1) the population code exhibits a pronounced orthogonalization of peri-reward locations and remaps to maintain that orthogonalization when reward zone changes. 2) A cross-similarity kernel between pre- and post- reward-switch maps reveals strong shared structure, indicating a reward-relative code. 3) When both reward and environment change, reward-centric constraints persist at the population level but shared structure decreases at the single neuron level. 4) Tensor component analysis applied to trial-wise kernels quantifies the speed of remapping (<10 trials). 5) Finally, stronger peri-reward orthogonalization predicts higher lick ratio. Together, these findings identify a structured, reward-relative, and adaptable geometry of the population code in non-place CA1 neurons, emphasizing the need of a population geometry perspective to understand hippocampal coding.

P3-F-737 *Predicting learning outcomes by manipulating mushroom body neurophysiology in Drosophila melanogaster*

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Associative memory has been found in most animal species, including Drosophila melanogaster. Current theory is that associative memory is stored as a synaptic depression between mushroom body neurons (MBN) and mushroom body output neurons (MBON) pre- and post-training. Unpublished data from our lab show socially isolated flies that had impaired learning compared to the grouped flies, had a significantly

lower pre-training odor response in the MB, but unaltered post-training odor response, leading to a decreased magnitude of the synaptic depression. Thus, we hypothesize that it is the reduced pre-training odour responses that dictate their poor behavioural memory performance. This brings us to the question of my project: Can we predict behavioural learning performance based on the pre-training odour responses? Previously, it was reported that activity of dopaminergic neurons (DAN) was necessary for maintaining odour responses in the MB. By using the temperature sensitive cation channel trpA1 to hyperactivate DAN, we found that this manipulation leads to an increased pre-training odor response in the MB, and that flies have improved learning. Conversely, expressing the genetically modified K+ channel EKO to moderately inhibit the activity of DAN, we found that flies showed lower pre-training odor response in the MB, and impaired learning. Currently, we are dissecting the roles of specific clusters of DAN to identify which control learning. The findings from this study could provide key insights into the mechanisms of learning and memory.

P3-F-738 *Prenatal alcohol exposure alters social reward behaviour and dopamine receptor expression in male and female rats*

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Prenatal alcohol exposure (PAE) negatively impacts cognitive, physiological, and social development. Adolescence is a period marked by increased social exploration which may be exacerbated by PAE. We assessed how PAE affects social reward behaviour across sex and development using a social operant conditioning task at postnatal day (P) 30, P40, P50 and P70. Rats completed three days of training on a fixed ratio of 1:1 (one nose poke = one social reward), a progressive ratio test (PRT) of 5, and two days of extinction sessions (1:1 ratio with social stimulus removed). PAE rats showed greater social preference than control rats on training and PRT. During extinction, PAE males continued responding for the previously social stimulus, resisting the control typical shift toward a non-social preference. Western blotting revealed increased D2 receptor expression in the nucleus accumbens (NAcc), of PAE males and females at P30 and P50. In contrast D3 receptor expression was reduced in the NAcc of P30 males and in the medial amygdala of PAE males (P30 and P50), and females (P40 and P70). The observed increases in D2 expression, coupled with decreases in the inhibitory D3 receptor, may contribute to the heightened social motivation in PAE rats by shifting the balance of dopamine signalling toward increased reward sensitivity and reduced behavioural inhibition.

P3-F-739 *Psilocybin enhances reward-based learning by reshaping attractor dynamics in decision making*

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Reward-based learning is central to adaptive behavior and is disrupted in psychiatric disorders, including depression. Accumulating evidence suggests that acute treatment with serotonergic psychedelics, such as psilocybin, can exert enduring antidepressant effects. We hypothesized that psilocybin induces lasting changes in reward-based learning. To test this, we combined behavioral modeling with a discrete dynamical systems framework to quantify how psilocybin alters decision-making dynamics in mice performing probabilistic reversal learning (PRL) in a two-arm bandit task. Animals with differing levels of task experience (novice vs. expert) received a single injection of psilocybin or saline to assess sustained effects on behavior. Choice behavior was fit using multiple behavioral models to estimate latent variables governing learning and decision-making. The fitted models were then interpreted as discrete dynamical systems, and their phase portraits were analyzed to characterize the underlying landscape of decision dynamics. Across models, phase portraits revealed two attractor states for each input condition, corresponding to high-value choice biases for each bandit arm. Psilocybin systematically altered the geometry of these attractors in a manner dependent on reward contingency, task experience, and sex. These geometric changes paralleled increases in the log-likelihood ratio, reflecting stronger evidence accumulation favoring one choice over the other. Together, these findings suggest that psilocybin enhances reward-based learning by reshaping the attractor landscape of decision dynamics, providing a principled interpretation of subtle but persistent changes in

adaptive behavior.

P3-F-740 *Region-specific constraints on neuronal allocation during visual fear memory encoding*

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Memories are encoded by widely distributed, sparse ensembles of neurons active during memory acquisition, known as engram neurons. In the lateral amygdala (LA), neurons with higher intrinsic excitability at the time of learning become preferentially allocated to part of an engram, a process termed neuronal allocation. However, whether competitive allocation is a universal feature of memory circuits or a specialized property of associative hubs remains unknown. Using visual fear conditioning in mice, we used a “dual-optogenetic” strategy to investigate excitability-based allocation across the visual fear circuit. By optogenetically increasing the excitability of a random, sparse population of neurons during training and subsequently inhibiting those same neurons during a memory test, we could determine if they were functionally integrated into the engram. Our results show a striking regional dissociation in allocation flexibility. While we successfully biased engram allocation in the LA and the lateral posterior nucleus (LP) of the thalamus, this competitive process failed to occur in the basal amygdala or primary visual input structures, including the lateral geniculate nucleus (LGN), primary visual cortex (V1), and superior colliculus (SC). These findings reveal that excitability-based allocation is not a universal principle of neural encoding. Instead, we propose that recruitment flexibility is a specialized feature of associative regions, whereas primary sensory and motor-related structures possess “hard-coded” circuitry that lacks the plastic capacity to support competitive neuronal allocation.

P3-F-741 *Resilience as a moderator of discrimination-related cortical thinning: A neuroimaging investigation of social determinants of health*

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Background: Social determinants of health (SDOH), particularly perceived discrimination, profoundly affect brain structure. Perceived racial discrimination is associated with reduced cortical thickness in the anterior cingulate cortex (ACC). Resilience increases cortical thickness in right hemisphere regions. Despite evidence linking discrimination to brain harm and resilience to protection, no studies assess if resilience buffers discrimination-related cortical thickness changes. Method: Parents and youth (n=34) completed questionnaires assessing discrimination, resilience, and mental health. Cortical thickness was obtained through FreeSurfer 6.0 and CBRAIN. Recruitment is ongoing Data will be analyzed using linear regression models to examine discrimination, resilience, and their interactions. Results: We expect that more discrimination relates to a thinner cortex, while more resilience relates to a thicker cortex. Conclusion: This study will demonstrate whether resilience serves as a neurobiological protective factor that buffers discrimination-related cortical thickness reductions in the anterior cingulate cortex among youth. Action/Impact: Resilience may offset cortical thinning linked to discrimination. This research shows the neuroprotective role of resilience and could have implications for interventions to protect brain health in youth facing discrimination.

P3-F-742 *Resolving deliberation under threat: implications for anxiety*

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Anxiety arises when uncertain outcomes force a conflict between motivations to approach potential benefit and to avoid possible harm. Resolving such conflicts often occurs through deliberation, evaluating alternative futures. While deliberation under conflict between positive outcomes has been well-studied, how deliberation under threat is translated into approach or avoidance remains unknown. We address this

question using a “Gauntlet” task in which a robotic predator guards a food source, forcing animals to forage under threat. During this task, animals often hesitate along the journey out, providing a discrete window into deliberation (reminiscent of vicarious trial and error, seen when deliberating between positive outcomes). On this task, abortive and continued trajectories are behaviourally matched, allowing the decision process itself to be isolated from reactive defense. We find that decisions to abort are associated with enhanced representation of future threat relative to decisions to continue, despite both behavioural deliberative windows preserving representations of safety. Comparisons with attack-triggered retreats further reveal that abortive decisions are not attenuated escape responses but instead retain goal-directed structure, emphasizing safety and navigational goals during withdrawal. Together, these findings identify threat weighting at the moment of commitment as a key decision variable governing behaviour under threat and provide a mechanistic framework for understanding how deliberative decisions give rise to anxiety-like behaviour.

P3-F-743 *Rôle du pulvinar dans les réponses défensives et la réaction à la nouveauté sociale chez la souris*

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Bien que la voie thalamo-corticale soit principalement associée à la perception consciente, le pulvinar pourrait contribuer au traitement rapide de stimuli visuels saillants impliqués dans les réponses défensives. Par ailleurs, la survie des mammifères sociaux repose sur une interprétation adéquate des signaux sociaux, tels que l’identité, la familiarité ou la nouveauté d’un congénère. Des altérations de cette interprétation sont observées dans plusieurs conditions neuropsychiatriques, où des indices sociaux peuvent être perçus comme menaçants et déclencher des réponses défensives inadaptées. Toutefois, les mécanismes neuronaux permettant de coordonner le traitement des menaces et des signaux sociaux demeurent mal compris. Cette étude vise à examiner le rôle du pulvinar dans cette articulation, en évaluant son implication à la fois dans les réponses aux menaces visuelles et dans les comportements sociaux.

P3-F-744 *Role of Cajal-Retzius neuron-derived PD-L1 in hippocampal-dependent behavior*

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Cajal-Retzius (CR) cells are transient neurons crucial for brain development and function. After birth, the number of CR neurons is reduced drastically, with a proportion persisting in the hippocampus, a brain region important for learning and memory. The function of this subset of neurons remains largely unknown. We recently found that CR neurons uniquely express programmed death-ligand 1 (PD-L1) in the hippocampus under physiological conditions. Although this signaling molecule is mainly known for regulating auto-tolerance peripherally, new evidence points to a role in hippocampal-dependent behaviors. Interestingly, we found that CR neuron-derived PD-L1 is significantly reduced in mice after training in the Morris water maze (MWM) test, suggesting that PD-L1 might be involved in learning and/or memory. Here, using a conditional knockout (cKO) of PD-L1 in CR neurons, we investigate the role of this protein in learning and memory. We found that cKO mice have enhanced memory recall in the MWM. This memory improvement was accompanied by increased phosphorylation of the extracellular signal-regulated kinase (ERK) in CR neurons, suggesting that selective loss of PD-L1 boosts memory recall by changing CR neuron activity. Our study identifies CR neurons as a previously unrecognized source of PD-L1 in the hippocampus, emphasizing the function of this signaling molecule as a regulatory mechanism for memory formation. Future studies will investigate the molecular mechanism by which PD-L1 in CR neurons modulates memory and its potential use to rescue age-related memory decline.

P3-F-745 *Role of hypocretin/orexin neurons in social behavior and social stress*

Matthew Dawson [1], Mio Tsutsui [1], Naila F Jamani [1], Osman Sinen [2], Derya Sargin [1]

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Social stress disrupts normal social behaviour and is a risk factor for anxiety and depression. Yet, our knowledge of which brain regions and circuits are affected by social stressors remains incomplete. Based on our previous work, the activity of hypocretin (Hcrt) neurons—a cluster endemic to the lateral hypothalamus governing arousal and motivation—is essential for normative social behaviour. Here, we expand our findings to test the hypothesis that acute and chronic social stress produces deficits in social interaction by disrupting the activity of Hcrt neurons and projection regions. We first performed fiber photometry recordings from Hcrt neurons in control (group-housed) and isolated (single-housed from weaning onwards) mice to examine population activity differences during social interaction. Different modalities of social behaviour were quantified with machine learning. Here, we show Hcrt activity increases in both female and male control and isolated mice upon initial interaction with a same-sex stranger but isolated mice show blunted activity. Isolated mice also show deficits in social interaction. Next, we measured Hcrt neuron axonal calcium activity to examine how Hcrt signaling changes in projection regions during social interaction and in response to social fear. Our results show how experiences of social fear alter both behavioural responses and Hcrt activity during subsequent social interactions. Finally, by modulating subgroups of Hcrt neurons, we demonstrate that specific modalities of social behaviour are encoded by distinct Hcrt projection subpopulations.

P3-F-746 *Role of the lateral periaqueductal grey in flexible defensive strategies*

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Generating context-appropriate defensive responses to threat is essential for survival. While defensive behaviour is often operationalized as freezing, animals express a repertoire of behavioural strategies, including avoidance and risk assessment. The periaqueductal gray (PAG) organizes expression of defensive behaviour along its dorsal-ventral axis, but the specific contribution of the lateral PAG (lPAG) to threat-related behaviour is less understood. To understand the role of lPAG, we systematically varied threat intensity experience in a context fear avoidance task. We used deep learning–based pose estimation approaches to characterize defensive behaviour patterns beyond the traditional freeze/no-freeze binary. We observed a range of defensive phenotypes across experimental groups and found that behaviour expressed during the conditioning phase of the task predicted freezing and avoidance strategies during the test phase. We then performed calcium imaging in the lPAG with fiber photometry during our task. lPAG activity dynamically tracked defensive responses, including entry and exits into the threatening context. To test causality, we chemogenetically inhibited lPAG neurons with DREADDs and observed differential effects on freezing and avoidance. Together, these data identify the lPAG as a potential node for flexible defensive behaviour selection across individuals.

P3-F-747 *Septal interneuron inhibition reveals time-course of spatial memory consolidation into hippocampus-independent form*

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Hippocampal place cells support spatial and episodic memory. Their activity is coordinated by theta oscillations and shows phase precession, which may support sequence learning and depends on a functional medial septum (MS). We inhibited MS interneurons using inhibitory DREADDs, providing a reversible disruption of septo-hippocampal function. Mice were trained on an 8-choice spatial reference memory task in which the rewarded arm changed daily. Each session included two forced-choice information trials followed by five free-choice trials. After learning, saline and deschloroclozapine (DCZ; 0.5 mg/kg) were given orally on alternating days. DCZ reduced performance to near chance for ~1 h, whereas saline had no

effect. Control mice lacking DREADD expression showed no impairment. The same mice were then trained with the reward in the same arm each day. Group 1 received alternating DCZ/saline; Group 2 received DCZ daily. In Group 1, performance rapidly became independent of DCZ, whereas Group 2 remained impaired. This supports consolidation theory: with repetition, memories become less hippocampus-dependent and more cortical. In two mice, silicon-probe recordings during virtual-reality treadmill running showed that DCZ markedly reduced hippocampal theta for ~1 h while overall unit activity and firing rates were largely preserved. Preliminary data suggest limited change in place field properties despite theta suppression. These findings show that DREADD-mediated MS inhibition reliably suppresses hippocampal theta and impairs spatial memory without broadly suppressing firing, offering a powerful approach to study the time course of systems consolidation.

P3-F-748 *Serotonergic modulation of identified ventral hippocampus output pathways in anxiety*

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The hippocampus functions as a cognitive hub, with the ventral hippocampus (vHP) encoding and relaying distinct behavior-contingent information to selective downstream targets. Moreover, the vHP receives dense serotonergic inputs from the raphe nuclei and expresses a diverse repertoire of serotonergic (5-HT) receptors. Our laboratory demonstrated that optogenetiv activation of 5-HT neurons projecting to the vHP (5-HTvHP) selectively increases anxiety-like behavior in female mice, revealing a sex-specific role for this pathway. However, the neural mechanisms underlying these differences remain unclear. We hypothesize that sex-specific emotional responses arise from physiological differences in 5-HT modulation at both presynaptic and postsynaptic levels. To address presynaptic mechanisms, we performed in vitro whole-cell patch-clamp recordings on 5-HTvHP neurons of adult male and female mice and analyzed their electrophysiological properties. Female median raphe region 5-HTvHP neurons shown a uniquely hyperexcitability compared to male neurons and other raphe subregions, suggesting their key role in sex-specific modulation of anxiety. To address postsynaptic mechanisms, we combined retrograde AAV labeling and fluorescent in situ hybridization to map the expression of hey 5-HT receptors (Htr1a, Htr2a, Htrc, Htr4, Htr5b) across vHP projections to PFC, NAc, LS, LH, and BLA. We hypothesize that 5-HT release in the vHP selectively activated and suppresses distinct pathways, fine-tuning emotional behavior. Our work revealed pathway- and sex-specifc differences in the expression pattern of excitatory and inhibitory Htrs. Together, this project defines how 5-HT signalling engages distinct vHP circuits to shape emotion-related behaviors differently in male and female mice.

P3-F-749 *Sex dependent effects of dopaminergic and endocannabinoid tone on fear expression in DAT heterozygous mice*

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Elevated dopamine (DA) signalling and altered endocannabinoid (eCB) tone are implicated in stress related psychopathology. We examined dopamine transporter heterozygous (DAT-HET) mice, which exhibit a stable elevation in extracellular DA and modest alterations in eCB signaling, as a mechanistic model of dopaminergic bias and vulnerability. Using fear conditioning paradigms, we observed intact cued fear acquisition and recall across genotype and sex, with no differences during tone or post tone periods, indicating preserved cue driven fear learning. In contrast, during contextual fear conditioning, a genotype by sex interaction emerged at 24-hour recall, driven by reduced freezing in DAT-HET females relative to wild type (WT) females, with no genotype differences in males. This indicates a selective alteration in contextual fear expression at recall rather than a global learning deficit. To probe eCB modulation, we administered a selective monoacylglycerol lipase (MAGL) inhibitor to elevate 2-arachidonoylglycerol (2-AG). DAT-HET mice

displayed increased locomotor responses relative to WT controls, consistent with enhanced sensitivity to 2-AG driven DA modulation. In exploratory analyses of cued fear under MAGL inhibition, time resolved assessment revealed prolonged post tone freezing in DAT-HET mice, suggesting delayed disengagement from conditioned threat without changes in peak fear expression. Together, these results show that elevated tonic DA shapes fear related behaviour in a task and sex dependent manner and interacts with eCB signaling to influence threat responding.

P3-F-750 *Sex-specific cortico-accumbal transcriptional remodeling links fetal growth restriction to attention-deficit/hyperactivity disorder (ADHD)-like behaviors*

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Fetal growth restriction (FR) is associated with increased risk for attention-deficit/hyperactivity disorder (ADHD), a neurodevelopmental condition with higher prevalence in males, yet the molecular basis of this sex-specific vulnerability remains unclear. We examined the impact of FR on ADHD-like behaviors in adulthood and the associated transcriptomic alterations within the medial prefrontal cortex (mPFC) and nucleus accumbens (NAcc), regions involved in executive function and locomotion/motivation. Sprague Dawley dams were assigned to control or food restriction (FR) groups on gestational day 10. Adult offspring were assessed using the open field (OF) and attentional set-shifting task (ASST; n=10–12/group), and another cohort was used for bulk RNA-sequencing (n=9–10/group/sex/region). FR males, but not females, exhibited hyperactivity in the OF, reflected by increased mobility. In contrast, FR females showed initial rule discrimination impairments in the ASST, with no deficits in strategy shifting. Transcriptomic analyses revealed marked sex- and region-specific effects of FR. In the mPFC, FR induced 355 differentially expressed genes (DEGs) in females and 309 in males, with minimal overlap. In the NAcc, 300 DEGs were identified in females and 417 in males (24 overlapping). Pathway analyses identified WNT/β-catenin signaling as a common FR-affected pathway across sexes and regions. In contrast, lipid metabolism pathways were uniquely altered in the female mPFC, while male-specific NAcc changes were enriched for neurophysiological processes, including opioid receptor signaling and intrinsic membrane excitability. Together, these findings show that FR induces sex-specific ADHD-like phenotypes linked to distinct cortico-accumbal transcriptomic signatures. Funding: NSERC, CIHR, and CanNRT Platform.

P3-F-751 *Sex-specific effects of oral lactate on hippocampal neurogenesis and memory in young mice*

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Adult hippocampal neurogenesis supports memory processes such as pattern separation and is regulated in a sex-specific manner, with sex hormones (e.g., estrogen) enhancing BDNF signalling to promote stem cell proliferation and neuronal maturation. Exercise enhances neurogenesis in part through lactate, a metabolic substrate that also acts as a signalling molecule, crossing the blood–brain barrier and accumulating in the hippocampus. However, the extent to which circulating lactate directly modulates neurogenesis and hippocampal function, and whether these effects differ between sexes, remains unclear. To address this, young adult male and female mice received oral sodium L-lactate or an equimolar sodium chloride control for two months to model exercise-induced elevations in circulating lactate while isolating lactate-specific effects. Adult hippocampal neurogenesis was assessed using BrdU labeling combined with immunofluorescent staining for markers of neural stem cells (doublecortin) and mature neurons (neuronal nuclei). In addition, western blot analysis was performed to assess synaptic plasticity (post-synaptic density 95) and neurotrophic support (brain-derived neurotrophic factor) levels. Pattern separation was evaluated using the Spontaneous Location Recognition task, while hippocampal-dependent spatial memory and cognitive flexibility were assessed using the Morris Water Maze. Anxiety-like behaviour was measured using the Elevated Plus Maze. Lactate treatment revealed sex-specific differences in markers of adult hippocampal

neurogenesis. These preliminary findings identify lactate as a key metabolic mediator of exercise-induced hippocampal plasticity and memory, providing insight into sex-specific regulation of adult neurogenesis with potential implications for cognitive health interventions.

P3-F-752 *Shared and individualized representations in vision and mental imagery*

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Mental imagery is often described as perception in the absence of sensory input. However, the extent to which visual perception and visual mental imagery share a similar representational structure remains poorly understood. A behavioral similarity-judgment task was completed by forty-two participants. Subjects arranged the same set of thirty stimuli from the Natural Scenes Dataset in a multidimensional plane: one while viewing the images and one while imagining them from textual descriptions they had previously generated. Results revealed a strongly shared representational geometry in visual perception, with higher inter-subject similarity ($r = .33$) relative to mental imagery ($r = .29$ paired $t(41) = 4.66$, $p = 0.00003$). While imagery exhibited a coherent structure across participants, inter-subject similarity was weaker, indicating greater inter-individual variability. Cross-modal self-specificity analyses demonstrated that each participant's imagined representations were more strongly aligned with their own visual structure ($r = .49$) than with those of others ($r = .31$, paired $t(41) = 7.67$, $p < 0.000001$), revealing a consistent subject-specific correspondence between conditions. These results indicate that visual perception evokes higher shared representations across individuals, while mental imagery expresses more individualized ones. This supports that mental imagery relies on more personal transformations than perception, and the importance of understanding individual-specific internal profiles in the study of representations between these two processes.

P3-F-753 *Sigma-1 receptor signaling in D1 neurons shapes cocaine-induced plasticity of intrinsic excitability and cocaine-seeking behavior*

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Persistent reductions in intrinsic excitability of nucleus accumbens shell (NAcSh) medium spiny neurons (MSNs) is a key cellular adaptation to cocaine exposure and contribute to addiction-related processes. Our ongoing work in mice shows that firing rate depression is more persistent after intravenous cocaine self-administration than non-contingent exposure, lasting up to 90 days in an incubation-of-craving protocol. These adaptations are restricted to dopamine D1 receptor–expressing (D1R) MSNs and are prevented by pharmacological blockade of the sigma-1 receptor (S1R), an endoplasmic reticulum chaperone protein, without altering natural reward seeking. While these findings identify S1R as a key regulator of cocaine-induced neuronal hypoactivity in NAcSh D1R-MSNs, its cell-type–specific role and behavioral relevance remain unclear. To address this, we selectively deleted S1R from D1-MSNs using a conditional knockout mouse model. Preliminary whole-cell patch-clamp recordings indicate that S1R deletion alters synaptic transmission and intrinsic excitability in a sex-dependent manner. Consistently, male D1-S1R cKO mice exhibit enhanced cocaine reward in a conditioned place preference task and altered cocaine self-administration, particularly during extinction. Together, these results demonstrate that S1R within D1-MSNs acts as a sex-dependent modulator of neuronal excitability and cocaine-related behaviors. Ultimately, our objective is to determine whether S1R's differential ability to control neuronal activity is a contributor of sex differences in drug addiction.

P3-F-754 *Sport-related concussion history is associated with persistent neural noise and altered attentional context processing*

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A history of sport-related concussion (SRC) is associated with an increased risk of subsequent musculoskeletal injury despite clinical recovery. This elevated risk may reflect persistent alterations in sensorimotor efficiency that become evident under high cognitive demand. The present study used electroencephalography (EEG) to examine neural efficiency and compensatory control following SRC. Both stimulus-evoked activity (P300 event-related potential amplitude) and background neural noise (aperiodic 1/f spectral slope of the EEG power spectrum) were assessed while young adults with and without a history of SRC performed an n-back working memory task under varying cognitive load. Load was manipulated by requiring participants to indicate whether the current probe letter matched (33% probability) or did not match (66% probability) the letter presented 0-, 1-, 2-, or 3-trials back. Preliminary results (8 SRC history, 7 controls) showed that neural noise increased with cognitive load in both groups; however, the SRC history group exhibited persistently greater neural noise across all conditions, regardless of trial type. In contrast, P300 amplitude differed between groups only on non-match trials. Together, these findings suggest that SRC history is associated with a persistent elevation in neural noise that alters baseline attentional allocation and context maintenance, rather than selectively impairing updating to rare, behaviourally salient events.

P3-F-755 *Structural and functional plasticity across changing social environments*

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Primates are innately social creatures, and the richness of their social environment is a critical determinant of mental health, longevity, and reproductive success. While it is established that the primate brain must adapt to the demands of social living, the specific neural mechanisms that track dynamic changes in social environment, and the timescale over which they occur, remain poorly understood. We performed a longitudinal, multi-modal MRI study in 13 male macaques undergoing controlled, reversible transitions between single-living and social housing. Using an A-B-A experimental design (Single Living-Pairwise Living-Single Living) over 15 months, we collected longitudinal voxel-based morphometry (VBM) and resting-state functional MRI (rsfMRI) data to map structural and functional plasticity across cortical and subcortical networks. VBM revealed state-dependent increases in grey matter volume during Pairwise Living in the right temporal cortex (STS) and subcortical regions, including the thalamus, striatum, and medulla. These volumetric gains were transient, reversing upon the return to Single Living. Network-Based Statistics identified a large-scale functional reorganization associated with Pairwise Living, characterized by strengthened coupling between frontal integrative regions and temporal, parietal, and limbic structures. These findings help establish a causal link between social environment and neural reorganization, suggesting that social complexity is supported by a dynamic interplay between cortical perceptual systems and subcortical regulatory circuits.

P3-F-756 *Structuring the world drives the developmental self-organization of behavioral and neural niches*

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Brain and cognitive development are driven by a fundamental trade-off: organisms can invest expensive neural resources to adapt to a complex world, or they can actively structure the environment to match their neural representations. While this internalizing-constructing tradeoff is well-theorized, the developmental dynamics that commit organisms and their neural resources to one strategy over the other remain unclear. We present a computational model of cognitive development that optimizes a joint objective of sensory

prediction error and environmental maintenance cost. We find that the interaction between prediction and action drives a spontaneous developmental bifurcation. Rather than a mix of strategies, an initially homogeneous population splits into two distinct, stable phenotypes: “internalizers” (high neural complexity, low structuring) and “constructors” (low neural complexity, high structuring). This mirrors phylogenetic divergences seen in nature (e.g., active hunting vs. web-building in spiders) and ontogenetic trade-offs in humans (e.g., complex cognitive maps for navigation vs. cognitive offloading via GPS). We also observe strong developmental canalization: early investment in complex models reduces adaptability when the environment changes. This canalization is alleviated by pruning neurons that are not used, demonstrating neural atrophy facilitates adaptability. These results demonstrate how active structuring creates a self-reinforcing loop between behavior and neural representation, driving the emergence of stable cognitive niches.

P3-F-757 *Telling friends from foes: Contributions of the medial amygdala to social memory*

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Social memory is our ability to remember and recognize others. It is critical to guide appropriate social interactions and is impaired in numerous neuropsychiatric disorders, including autism spectrum disorder and social anxiety disorder. While the hippocampus has traditionally been regarded as a major social memory hub, the role of other brain regions received less attention. Our study identifies the medial amygdala (MeA) as another critical site which houses engrams supporting social memory. The reactivation pattern of these engrams is social subject-specific, while the strength of engram reactivation positively scales with the success of social memory recall. Importantly, these engrams appear to be engaged in both neutral and emotionally salient types of social memory. We further show that blocking oxytocin receptors (OXTR) following initial social encounter impairs social memory recall via suppression of MeA engram reactivation. Using longitudinal calcium imaging, we observed that OXTR antagonism likely disrupts engram re-engagement during the late offline consolidation period, thus perturbing memory stabilization. Together, our findings accentuate the MeA as an important player in the engram network involved in different types of social memory.

P3-F-758 *Retrosplenial Cortex encodes peer direction and coordinates social approach behavior in mice*

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Tracking and coordinating approach to conspecifics is central to social behaviors in mice and other social animals. The retrosplenial cortex encodes allocentric direction, and in addition encodes directional information to salient environmental features. We asked whether the retrosplenial cortex dynamically tracks the direction of a peer mouse during freely moving social interaction. Utilizing head-mounted miniaturized microscopy of calcium transients in ensembles of neurons, we found 5-10% of cells in the retrosplenial consistently track the dynamic position of a peer mouse relative to the subject mouse across 5-minute social exploration epochs. These egocentric peer direction cells have similar encoding properties to traditional head direction cells, but are not uniformly distributed in all directions, with peer mouse positions immediately in front and behind the subject mouse underrepresented in the ensemble. Chemogenetic inactivation of the retrosplenial cortex reduced the elevated social investigation of a stressed peer mouse, suggesting that retrosplenial cortex coordinates social approach behaviors.

P3-F-759 *The basal ganglia as a distributed reinforcement learning system computing general values*

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Dopamine modulation of striatal circuitry is a key neural system for decision-making and motor control, where dopamine release onto striatal neurons serves as a learning signal that updates learned predictions encoded in the striatal neurons. While the reward prediction error hypothesis quantitatively predicts the activity of some dopamine neurons, many studies reveal a heterogeneous view, where dopamine-modulated striatal circuitry is involved in many computations, such as goal-directed behavior and habit formation. These functions are often associated with distinct striatal subregions that receive input from different midbrain dopaminergic populations, which have been independently manipulated using optogenetic stimulation across numerous rodent behavioral studies. However, these diverse observations lack a comprehensive computational framework that reconciles these sometimes conflicting experimental observations. To tackle this, we introduce QVH, a unified computational model for dopamine-modulated learning in the ventral striatum (VS), dorsomedial striatum (DMS), and dorsolateral striatum (DLS). We leverage the framework of general value functions to assign a distinct computational role to different striatal subregions and dopaminergic projections within the reinforcement learning framework. We show that our model can explain a range of experimental observations that separately manipulated the dopaminergic projections to VS, DMS, and DLS via optogenetic stimulation. More generally, the QVH model acts as a mechanistic, anatomically referenced, and testable model that balances the three main axes of dopamine-modulated striatal computation. It can be used as an in-silico testbed to generate testable hypotheses to design future experiments that manipulate or record the activity of dopamine and striatal neurons in the basal ganglia.

P3-F-760 *The effect of chronic Δ9-THC consumption on flexible decision making*

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Flexible decision making is critical for navigating and adapting to a changing environment. Many neuropsychiatric disorders including drug addiction are associated with maladaptive patterns of decision making, including an overreliance on habitual behavior and altered sensitivity to prediction errors. Evidence suggests that this behaviour can be influenced by consumption of Δ9-THC, the primary psychoactive constituent of cannabis, however, there have been few studies conducted that demonstrate the differences between adult and adolescent consumption. In order to test this behaviour, I have had success training head-fixed mice to identify which of the two spouts positioned directly in front of them have a higher probability of delivering water reward. When the reward probabilities reverse every 20-40 trials, mice quickly adapt and perform above chance levels. I have tested a paradigm of oral Δ9-THC administration with preliminary, moderate effects on flexible decision-making patterns. I have also conducted a dose-response study to determine the effective dose and am now performing a chronic Δ9-THC administration study in a cohort of adolescent mice. I plan to test another cohort of adult mice to determine whether their decision-making processes are differently affected by Δ9-THC consumption. This work is critical for understanding the impact of cannabis exposure on decision-making processes, particularly in the most vulnerable populations.

P3-F-761 *The effects of chemogenetic activation of the anterior paraventricular nucleus of the thalamus to ventral subiculum pathway on cue-induced heroin seeking following chronic food restriction in abstinent rats*

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Relapse remains a major challenge in treating opioid use disorder, with heroin relapse rates going as high as 90%. Our research focuses on examining the underlying neuronal mechanisms of heroin relapse that is exacerbated by chronic food restriction. Our laboratory has shown a role for the anterior paraventricular nucleus of the thalamus (aPVT) in cue-induced heroin seeking following food restriction in male and female abstinent rats. The aPVT projects preferentially to the ventral subiculum (v.sub), an area critical for drug seeking. Our laboratory has found that inactivating the aPVT-v.sub pathway decreased cue-induced heroin seeking in female rats, but not male rats. To further understand the role of the aPVT-v.sub pathway, we chemogenetically activated the pathway. Here, we infused a viral vector carrying an excitatory Designer Receptor Exclusively Activated by Designer Drug (DREADD) into the aPVT and a bilateral guide cannulae aimed at the v.sub to test cue-induced heroin seeking in food-restricted and sated rats. Rats were trained to self-administer heroin (0.1 mg/kg/infusion) for 10 days, followed by 15 days of forced abstinence where rats were either sated or food restricted. On day 15 of food restriction, v.sub was infused with deschloroclozapine (DCZ: 0.1 mM/0.5 µl) or vehicle. Rats then underwent a heroin-seeking test under extinction conditions. We expect that food-restricted rats will show greater heroin-seeking than sated rats, and that activating the aPVT-v.sub pathway will increase cue-induced heroin seeking in rats.

P3-F-762 *The impairing effect of electroconvulsive shocks on retrograde memory processing, neural ensemble retention, and engram reactivation*

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Electroconvulsive therapy (ECT) induces retrograde amnesia, limiting the wide use in clinical practice. Neither the particular elements in memory processing affected by cECS, nor the underlying neural mechanisms, are clear.By treating mice with cECS at different times post-learning, we aimed to pinpoint the critical window in memory processing vulnerable to the amnesic effect of cECS. Mice treated with cECS immediately after learning, but not one week after, showed impaired recall. cECS before retrieval also impaired recall, suggesting that cECS disrupted both memory consolidation and retrieval. Contextual fear memory is well-mapped at the neural circuitry level. The same neural ensembles activated during encoding are reactivated at retrieval, forming a memory engram. Using FosTrap2A mice, neurons in the hippocampus (HPC) activated by either encoding or retrieval were labeled with different fluorophores to examine engram reactivation. cECS treatment reduced the reactivation rate.cECS has been shown to increase adult neurogenesis (ANG) in HPC, which may disrupt engram reactivation and induce forgetting. To inhibit ANG in HPC, mice were injected with temozolomide while treated with cECS. However, pharmacological inhibition of ANG did not rescue the memory impaired by cECS. To investigate the destiny of engram structure after cECS, we aim to selectively reactivate HPC engram cells during retrieval. We hypothesize that optogenetic reactivation of the engram can rescue cECS-induced amnesia, suggesting that the engram structure of impaired memory is maintained but inaccessible.

P3-F-763 *The lateral entorhinal cortex supports adaptive switching between memory encoding and retrieval*

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Although memory encoding and retrieval are often studied separately, real-life cognition requires continual switching between recalling relevant prior knowledge and integrating new information. These operations rely on bidirectional interactions between the neocortex and hippocampus, with the lateral entorhinal cortex (LEC) serving as a critical interface. However, the specific contributions of the LEC to these operations remain unresolved. We investigated the necessity of the LEC for flexibly switching between memory encoding and retrieval using a spatial learning task. Water-restricted mice collected rewards at two out of four ports in a square-shaped maze in two daily epochs. Reward locations remained constant within a day but changed across days. When the LEC excitatory cells were chemogenetically inhibited from the first epoch onward, mice were slower to learn new reward locations and failed to recall them one hour later. When the same manipulation was applied after learning, mice chose correctly during unrewarded probes but quickly abandoned them and began relearning, indicating unstable retrieval. These impairments were due to an increase in erroneous reward-seeking at unrewarded locations, rather than reduced reward-seeking at the correct locations, or changes in overall motivation or locomotor activity. These findings suggest that LEC activity is required for stabilizing behavioural states appropriate for encoding or retrieval by suppressing unnecessary exploration and promoting adaptive, memory-guided responding.

P3-F-764 *The mediating role of alcohol demand in pathways from drinking motives to hazardous drinking*

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Hazardous drinking (HD) contributes substantially to preventable morbidity and mortality. Alcohol demand (i.e., reinforcing value) is associated with HD, but whether it is influenced by drinking motives and mediates their effects on HD is unclear. This study examined structural relations among drinking motives, alcohol demand, and HD. Heavy-drinking young adults (n=1308; 56% female; Mage=22 years) completed measures of drinking motives and HD (heavy drinking days per week, alcohol consequences). Alcohol demand was assessed with an alcohol purchase task. Structural equation models modelled associations between drinking motives, alcohol demand, and HD. Higher demand was associated with greater HD for all demand indices (intensity, elasticity, Omax, breakpoint). Enhancement motives were associated with greater HD, both directly and indirectly via higher intensity (consumption at zero cost), Omax (maximum expenditure), and breakpoint (price suppressing consumption to zero), and via lower elasticity (cost sensitivity). Coping motives were associated with greater HD, both directly and indirectly via higher intensity, Omax, and breakpoint. Social motives were indirectly associated with greater HD through higher Omax and lower elasticity, whereas conformity motives were indirectly associated with less HD via lower Omax. Results suggest that associations of drinking motives with HD are in part mediated by alcohol demand, highlighting demand as a potential mechanism linking drinking motives to alcohol-related harm, particularly for enhancement- or coping-motivated drinkers.

P3-F-765 *The role of basolateral amygdala neuronal ensembles in fear discrimination*

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BLA neuronal ensembles are believed to encode single fear memories through stimulus-specific patterns of coordinated neuronal activity linking a conditioned cue to an aversive outcome. Yet, it remains unclear how BLA neuronal ensembles support fear discrimination when multiple cues predict threat. To address this, rats were trained in two conditioning paradigms: either two cues of the same sensory modality or two cues of different modalities were paired with shock. Using the Daun02 inactivation method in Fos-LacZ transgenic

rats, we deleted the ensemble activated by one of the fear eliciting CS. This disrupted fear to that cue in both designs; importantly, fear expression to the second fear-eliciting CS was also disrupted in both the same-modality and different-modality designs. These findings suggest that BLA neuronal ensembles supporting fear memories formed in close temporal proximity within the same context are not strictly modality-specific, indicating a degree of overlap or interaction between fear memory representations within the BLA. We further deleted the unconditioned stimulus (US)-activated ensemble and observed impaired CS-evoked fear expression, consistent with overlapping recruitment of CS and US ensembles. Together, these results indicate that fear memories are encoded by partially overlapping BLA ensembles, which may limit the precision of fear discrimination. These findings are discussed in terms of how BLA ensembles organize threat memories across sensory modalities.

P3-F-767 *The role of microglial GPR120 in anxiodepressive behavior, energy metabolism and microglia reactivity in response to chronic unpredictable stress*

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GPR120 (FFAR4) is a long-chain fatty acid receptor with recognized anti-inflammatory and antidepressant properties. Neuroinflammation, largely mediated by microglia, contributes to neuropsychiatric and metabolic disorders. GPR120 activation exerts anti-inflammatory effects, whereas its deficiency promotes inflammation and metabolic dysfunction. Chronic unpredictable stress induces neuroinflammation and anxiety- or depressive-like behaviors. We hypothesized that microglial GPR120 deficiency exacerbates these stress-induced alterations. Adult male and female microglia-specific GPR120 knockout and control mice underwent two weeks of daily unpredictable restraint stress or remained unstressed. Body weight, food intake, and behaviors reflecting anxiety- or depressive-like states (elevated plus maze, open field, forced swim, social interaction, sucrose preference, novel object) were assessed. Microglial morphology and phagocytic activity (IBA-1, CD68) were quantified in the medial prefrontal cortex (mPFC) and nucleus accumbens (NAc), and neuronal activity evaluated using cFos staining. Loss of microglial GPR120 increased body weight, food intake, and anxiety-like behavior under stress. GPR120 deletion elevated microglial density, reactivity, and CD68 expression in mPFC and NAc. Stressed mice (KO and control) showed reduced mPFC neuronal activity. These results highlight a critical role for GPR120 in limiting microglial activation, phagocytosis, neuroinflammation and stress-related behavioral changes. Supported by a CIHR grant to SF and TA.

P3-F-768 *The role of the orbitofrontal cortex in integral learning of a two-dimensional auditory task*

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This experiment investigates the role of the orbitofrontal cortex (OFC) in facilitating integral representation of an auditory space. To test rats' ability to learn compound stimulus dimensions, we trained 20 rats on a Pavlovian task in which 2 sets of auditory cues were configured to represent a 2-dimensional space. The stimuli consisted of 12 distinct tone frequencies and 12 distinct clicker frequencies, which were combined for 144 compound auditory stimuli. 2 of the auditory compound cues were paired with a saccharin reward. We sought to determine whether temporary DREADD-induced inactivation of the OFC across the learning phase (days 1-16) of the task would impair learning between the compound stimuli and saccharin. We injected the experimental AAV8-CaMKIIa-hM4Di-mCherry (n=11) or control AAV8-CaMKIIa-mCherry (n=9) into the OFC prior to the experiment. To learn the stimulus set, rats were exposed to 'random walk' paths through the auditory space, such that they would listen to a progression of compound cues in which each transition consisted of an incremental change in frequency in one of the auditory dimensions. To assess the role of the OFC in learning these compound cues, rats received injections of a DREADD agonist (Agonist 21) or saline throughout the first 16 days of the 34-day experiment. Learning was assessed through reward anticipation and performance on 2 extinction tests (days 17 and 34). OFC-inactivation inhibited the rats' ability to respond in anticipation of the reward based on the particular compound cue configurations, indicating that OFC is required for integral learning in a reward setting.

P3-F-769 *Time cells in the human brain support working memory maintenance*

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Working memory (WM), the active retention of information over short periods, is a fundamental cognitive function, yet its underlying neural mechanisms remain little understood. A potential mechanism for maintaining WM are spiking sequences of 'time cells', activated after a cue to-be-remembered, encoding its identity and time since its presentation. However, it is unknown whether such a temporal code exists in the human brain. Here, we found time cells in single neuron recordings from medial frontal and temporal lobes of patients performing a WM task. Time cells consistently fired at distinct time points during WM maintenance, collectively forming spiking sequences. Hippocampal time cell activation correlated with successful WM maintenance, whereas pre-motor time cell activity was mediated by WM load. We also identified cue-specific time cells that responded selectively after a given cue, encoding both memorandum identity and maintenance time. Together, these findings demonstrate that time cell sequences in both medial frontal and temporal regions support WM, highlighting the role of temporal coding in memory processes.

P3-F-770 *Transcranial magnetic stimulation over the cerebellum promotes attentional performance in ADHD*

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Attention Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder characterized by symptoms of functional impairment and inattention. Individuals with ADHD also exhibit deficits in higher-level cognitive functions essential for goal-oriented behavior, including attention selection and cognitive control. Neuroimaging and neuromodulation studies have implicated fronto-parieto-cerebellar networks in ADHD, with reduced volume in the right cerebellar hemisphere. This work aimed to investigate the role of the right cerebellum in attentional modulation in individuals with ADHD. We hypothesized that excitatory neuromodulation over the right cerebellum would improve attentional performance in individuals with ADHD compared to healthy controls. Twelve participants were recruited, including six diagnosed with ADHD and six controls. Participants completed a cross-modal attentional blink task pre- and post-intermittent theta burst stimulation (iTBS) applied over the right lateral cerebellum. Preliminary results demonstrate an increase in the ability to extract the tactile target from the mask in baseline conditions and in the experimental conditions post-iTBS within the ADHD population. Comparatively no change in performance in either condition is observed in the controls indicating that attentional processing in healthy individuals may be operating at a performance ceiling, whereas individuals with ADHD show greater capacity for modulation. These findings suggest a cerebellar role in regulating cross-modal attention and represents a viable neuromodulation target in ADHD.

P3-F-771 *TRAPing neurons involved in contextual fear learning and memory*

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Engram neurons are ensembles of cells that are thought to represent the physical basis of a memory following a learning event. In the present study, we sought to study engram cells involved in contextual fear learning and memory. We used Targeted Recombination in Active Population (TRAP2) mice crossed with tdTomato (Ai9) reporter mice to conditionally and permanently label engram neurons with 4-hydroxytamoxifen immediately following contextual fear learning. A subset of mice underwent fear memory retrieval 14 days later and were euthanized 90 minutes later to evaluate immediate early gene activity in engram neurons following memory retrieval via cFos immunohistochemistry. We quantified Ai9+ engram neurons and their reactivation rates (Ai9+cFos+) across brain regions, including the hippocampus, amygdala, prefrontal cortex, septum, cingulate and claustrum. We found that male and female mice that received footshocks showed greater freezing during fear learning and memory tests compared to no-shock controls. We also found that mice that received footshocks had a significantly greater number of Ai9+ and

Ai9+cFos+ neurons across numerous brain regions, relative to no-shock controls. A separate subset of mice underwent brain slice electrophysiology 3 days after fear conditioning. Whole cell patch clamp recordings of dentate granule cells and CA1 pyramidal revealed differences in Ai9+ vs Ai9- neurons on measures of spontaneous activity and intrinsic firing properties. Overall, these findings advance our understanding of how engram neurons contribute to fear learning and memory.

P3-F-772 *Ultrasonic vocalizations as markers of Anxiety and Depression in rats after spinal cord injury*

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Spinal cord injury (SCI) often leads to chronic anxiety and depression, but research and treatment tend to focus primarily on motor deficits. In rodents, many paradigms of anxiety- and depression-like behaviour typically depend on locomotion, which is inherently confounded in SCI models. Since motor impairment could mimic or mask affective behaviour after SCI, this motivates a need for new complementary, motor-independent measures. We tested whether rat ultrasonic vocalizations (USVs) can serve as markers of anxiety and depression after cervical SCI, including socially transmitted changes in uninjured conspecifics. Adult rats were recorded in their home cage before and after SCI during baseline and reward contexts. USVs were detected and quantified via deep-learning (DeepSqueak) to extract acoustic features and classify USVs by frequency patterns linked to negative versus positive affect. Behavioural assays were performed in parallel, and multivariate feature reduction with group comparisons identified the most informative acoustic features. Preliminary analyses indicate post-SCI shifts in USV patterns consistent with reduced positive-affect calling and increased negative-affect calling. Mean call frequency and call sinusoidality emerged as prominent distinguishing features, and early recordings of uninjured rats showed increased negative-affect calls after neighbouring rats received SCI. These results support USVs as a promising readout of affect after SCI, proposing evidence for potential feature-based markers and vocal-affective social contagion. Ongoing work will complete behavioural and USV analyses and test convergence with injury severity and limbic neuroanatomical measures for marker specificity to anxiety- and depression-like states.

P3-F-773 *Understanding the mechanisms of psilocybin-enhanced fear extinction in the lateral amygdala*

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The inability to form safe associations following an emotionally salient event, reflected by impaired fear extinction, is a core feature of post-traumatic stress disorder (PTSD). Although exposure-based psychotherapy is the first-line treatment, a substantial subset of patients are unresponsive, underscoring the need for approaches that enhance extinction learning. Pavlovian fear extinction consists of repeated, unreinforced conditioned stimulus exposures, which allows researchers to explore the neural mechanisms underlying exposure-based therapies. Serotonergic psychedelics, including psilocybin, have shown promise in facilitating fear extinction, yet the neurobiological basis of this effect remains poorly understood. Our study investigates the mechanisms of psilocybin-facilitated fear extinction in the lateral amygdala, a critical locus of emotional memory processing. We demonstrate that psilocybin enhances the extinction of a fearful memory by significantly reducing the cued fear response, and that this effect is specific to psilocybin administration prior to the extinction learning event. Using activity-dependent neuronal tagging, we show that psilocybin reduces reactivation of the engram encoding the original fear memory following extinction training. Finally, using a chemogenetic approach, we identify parvalbumin-expressing interneurons as a candidate cell population contributing to the observed behavioural effects. These findings provide insight into the neurobiological underpinnings of psychedelic-facilitated fear extinction in the context of engram dynamics in the lateral amygdala.

P3-F-774 *Unravelling non-canonical subicular circuits: Projecting somatostatin cells anatomy and function in memory*

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Connectomic studies of hippocampal circuits have traditionally focused on excitatory long-range projections, with inhibitory neurons often assumed to act locally. While most inhibitory neurons in this structure are indeed interneurons, here we uncover a dense, long-range projection from subicular somatostatin (Sst) expressing neurons to CA1. Using the Synaptag system to label presynaptic sites of Cre-expressing neurons. We found that Sst neurons with soma in the dorsal subiculum heavily innervate the stratum lacunosum-moleculare of CA1, with projection density increasing toward rostral dorsal CA1. To map monosynaptic inputs to subicular Sst neurons, we performed cell-type–specific rabies tracing in Sst-Cre mice. This revealed that the primary input to subicular Sst neurons arises from CA1 pyramidal cells at rostro-caudal levels matching their projection targets. To assess functional connectivity, we combined high-density silicon probe recordings across the subiculum and CA1 with optogenetic manipulation using the bidirectional opsin BiPOLE. Activation of subicular Sst cells strongly inhibited CA1 pyramidal cells and putative inhibitory neurons in the stratum oriens. Together, these findings reveal a reciprocal inhibitory–excitatory loop between CA1 and the subiculum, mediated by Sst neuron projections. Ongoing work leverages this experimental framework to investigate the activity patterns of projecting subicular Sst neurons and their influence on CA1 oscillations and pyramidal cell representations during learning in virtual navigation and trace-fear conditioning tasks.

P3-F-775 *Unreinforced spatial learning and memory using massed and spaced training in juvenile and adult rats*

Klara Doelle [1], Katie Stewart [1], Hannah Mckillop [1], Sebastien Church [1], Thomas Keiller [1], Altan Erman [1], Matthew Holahan [1]

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The hippocampus (HPC) and anterior cingulate cortex (ACC) both play a significant role in the formation and retention of spatial memory. It's hypothesized that encoding occurs in the HPC and is integrated into the ACC to create lasting memories. HPC maturation occurs late in development. This has functional implications for spatial memory. Research has examined the effect of spaced training (ST) on recent and remote spatial memory using various tasks. ST was generally beneficial, but most spatial memory tasks involve reinforcement to encourage learning. This may create confounding variables. We examined ST on the open field task in juvenile and adult rats to elucidate developmental differences in unreinforced spatial learning and memory. Male and female rats were grouped into massed (MT) or ST, trained for two consecutive days (P21-22 or P45-46) and tested after 3 weeks (P43 or P67). Analysis of behaviour focused on path length and time in the center. Counts of c-Fos positive cells in the ACC and the CA1 region of the HPC will be used as a measure of neural activity in these regions. There was a significant effect of age across all path length comparisons. P21-43 rats explored significantly less than P45-67 rats. On day 2, there was a significant effect of group on path length ($p<0.05$), with ST rats exploring more than MT rats. ST rats also appeared to explore more on day 2 than day 1 ($p=0.067$). These findings were conserved across sex and age. Analysis of c-Fos expression in the CA1 and ACC will clarify the association between exploration and spatial memory of the arena.

P3-F-776 *Using naturalistic stimuli and EEG-fMRI to uncover the neural activity associated with emotion*

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A key objective of emotion research is to determine the neural activity that underlies a natural emotional experience. Prior studies use group-averaged behavioural ratings to link neural activity to a subject's emotional state. This method identifies common, stimulus-driven neural responses; however, this approach obscures meaningful individual differences in emotional interpretation. The current study addresses this

limitation by emphasizing individualized ratings, allowing for the identification of brain regions that reflect subject-specific emotional appraisal of naturalistic stimuli. In this study, naturalistic stimuli and functional magnetic resonance imaging (fMRI) were used to explore the neural activation of 7 (mean age = 26.1, SD = 6.3, 3 females) healthy subjects while viewing film clips that range in emotional salience, where neutral clips are used as controls. General linear model analysis reveals the Middle Frontal Gyrus (Cohen's d = 1.01, p = 0.037) as preferentially active in individualized emotional processing, compared to the Inferior Parietal Lobule (Cohen's d = 1.04, p = 0.034) which is preferentially activated in the group-averaged contrast. This highlights how individualized valence ratings engage higher-level cognitive regions involved in emotional regulation, while group-averaged ratings engage sensory regions responsible for perceiving emotions. These results emphasize the need to consider the method of subjective rating integration when analyzing naturalistic fMRI data.

P3-F-777 *Using overexpectation and pavlovian instrumental transfer (PIT) to understand the mechanisms of behavioural change*

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Understanding the behavioural and neural processes that support behavioural change is crucial, as these processes underlie adaptive behaviour and when dysregulated, lead to maladaptive function. Reduction in established behaviour can occur through overexpectation, which arises when two separately conditioned stimuli (e.g., tone A and light B, each predicting reward) are presented together, generating an expectation of greater reward than is delivered. Violation of this expectation reduces responding to the compound and subsequently to the individual cues. This reduction in conditioned responding may reflect inhibitory stimulus–stimulus (S–S) or stimulus–response (S–R) associations. Which inhibitory association drives behavioural reduction after overexpectation remains unknown. To address this gap, we used a Pavlovian-to-Instrumental Transfer (PIT) test. In PIT, conditioned stimuli associated with a specific outcome elevate instrumental responding associated with the same outcome. Critically, outcome-specific PIT provides evidence that S-S association guides behaviour. If inhibitory S-S associations are learned during overexpectation, then PIT would be eliminated. Alternatively, if inhibitory S-R associations are learned during overexpectation then PIT would be preserved. Our data showed intact outcome-specific PIT for both control and overexpectation cues, indicating that inhibitory S–R associations underlie behavioural reduction after overexpectation training. These findings inform the associative mechanisms regulated by brain regions implicated in overexpectation.

P3-F-778 *Valence encoding in molecularly and spatially defined cell types of the nucleus accumbens*

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Valence, the quality by which something is perceived as good or bad, appetitive or aversive, is a fundamental building block of emotional experience and a primary driver of adaptive behavior. Stimuli with positive valence elicit approach and stimuli with negative valence are avoided. The nucleus accumbens (NAc) is crucial for valence processing, but it remains unclear how different cell types in the NAc contribute to this integration. Recent findings challenge the traditional view that D1-receptor-expressing medium spiny neurons (D1-MSNs) mediate responses to appetitive stimuli, while D2-receptor-expressing MSNs (D2-MSNs) respond to aversive stimuli. Moreover, there is significant molecular, spatial and functional heterogeneity within D1- and D2-MSNs that must be integrated to accurately map the identity of cells recruited to valence ensembles. To uncover the molecular logic of valence representation in the NAc, we used single-nucleus RNA sequencing in mice trained in a mixed-valence Pavlovian conditioning task. Using acute signatures of recent neural activity, we examine cell-type specific responsiveness to appetitive and aversive stimuli and use long-term learning signatures to explore the stability of valence representation. By integrating spatial

transcriptomics data, we build a spatially informed model of positive and negative valence representation across the full extent of the NAc. We further explore and integrate the role of other cell types to achieve a comprehensive understanding of accumbal principles of valence encoding. Overall, this work establishes a framework for interrogating valence across the brain.

P3-F-779 *VIP interneuronal dynamics in memory-encoding hippocampal spiking sequences*

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Episodic memory relies on the spiking sequences of pyramidal neurons in hippocampus to encode spatiotemporal contexts. Such sequences are tightly regulated by inhibitory interneurons, including parvalbumin (PV), somatostatin (SST) and vasoactive intestinal polypeptide (VIP) expressing cells. PV/SST cells provide direct somatic and dendritic inhibition on pyramidal cells respectively, while VIP cells inhibit PV/SST cells, thus 'disinhibiting' pyramidal neurons. This integrated network ensures precise spiking sequences and maintains the excitation/inhibition (E/I) balance, critical for memory encoding and temporal organization. Although PV/SST-mediated inhibition has been extensively explored, VIP-mediated disinhibition remains poorly understood, especially within the hippocampal CA1 area. Here we investigated how VIP-mediated disinhibition contributes to the memory encoding in hippocampal CA1, using in vivo voltage imaging with genetically encoded voltage indicators (GEVIs). To characterize VIP dynamics during diverse sensory inputs and locomotion outside memory activation, we first described VIP activity in CA1 of untrained VIP-Cre mice during head-fixed treadmill running and randomized delivery of olfactory cues, auditory cues and water rewards. We then described VIP membrane potentials during an odor-cued working memory task. We have previously shown increased PV/SST activation during odor cues, preceded by a sharp hyperpolarization at cue onset, with both features regulating pyramidal spiking sequences. Hence, we focused on VIP dynamics at cue delivery and particularly at cue onset, to elucidate temporal relationships between VIP activity and memory-encoding pyramidal sequences. Our findings shed light on the role of VIP-mediated disinhibition in shaping pyramidal spiking sequences and provide insights into inhibitory circuits during hippocampal memory encoding.

P3-F-780 *Viral tools to alter Blood-brain barrier gene expression and decipher its role in memory and cognition*

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Experiences linked to emotions impact memory consolidation and associated brain neuronal circuits. Posttraumatic stress disorder and major depressive disorder are examples of mental disorders where memory deficits are observed. Our lab highlighted that stress induces blood-brain barrier (BBB) alterations in a sex and brain region specific manner in mice and human depression. BBB cells can secrete growth factors and overexpress some markers to allow behavioral responses in stressful and cognitive situations. However, little is known about the relationship between emotional valence, memory encoding and BBB function. In this study, we looked at the BBB effects after an aversive memory experience: fear conditioning (FearC). Male and female mice went through acquisition on day 1, followed by context, cue and recall tests. In transcriptomes, fibroblast growth factor 2 (Fgf2), which regulates BBB integrity, was upregulated in ventral hippocampus (HC) for male and female footshocks mice. FGF2 protein in those mice seems to come from perivascular astrocytes in ventral HC. We then took opportunity of viral tool to manipulate BBB integrity via Fgf2. We injected AAV-shRNA-Fgf2 in HC to see how its downregulation from astrocytes could affect behavior. We confirmed lower FGF2 signal in the HC. Then, we injected a cohort in vHC and ran memory tests (Novel object recognition, Y-maze and FearC) few weeks after injection. AAV-shRNA-Fgf2 mice showed anxiety behaviors in NOR and Y-maze, and impairment in FearC acquisition and contextual test. In summary, Fgf2 could be an important link between memory dysfunction and vascular barrier impairment. This BBB modulator might be a key molecule of memory formation in HC, expending our knowledge on BBB integrity role in cognitive processes.

P3-F-781 *Creation of a normative database of younger adult data for telephone-based neuropsychological assessment*

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The Canadian Longitudinal Study on Aging (CLSA) has advanced understanding of aging in Canada; however, modifications to key neuropsychological measures and the exclusion of adults under 45 years of age limit comparisons with existing normative data and younger adult populations. Specifically, the CLSA uses a modified, telephone-administered version of the Rey Auditory Verbal Learning Test (RAVLT) with only one learning and one recall trial, which cannot be compared to the normative data with the typical administration of multiple learning trials. The present study aims to replicate the CLSA telephone cohort cognitive protocol in a younger adult sample to establish normative data for these modified assessments. Canadian adults aged 20–45 complete the modified RAVLT, Mental Alternation Test, and Animal Fluency Test via telephone. The target sample size is 400 participants. Preliminary analyses of the current sample (N = 53) indicate that there is a difference between the immediate (M = 6.36, SD = 2.58) and delayed (M = 5.46, SD = 2.39) recall trials of the modified RAVLT. These findings suggest measurable memory decline across a brief delay in younger adults when using the CLSA-modified protocol. Compared to published RAVLT norms for 20-29 year olds (N = 498, M = 11.3, SD = 2.3), the delayed recall in our sample (N = 26, M = 4.50, SD = 1.75) is significantly lower ($t(25) = -19.82$, $p < .001$) due to the lack of learning trials in the modified RAVLT. Data collection is ongoing, and final analyses will examine age-related patterns and associations between memory and executive functioning. This preregistered study will produce a freely available database that will improve interpretation of CLSA cognitive findings and support future neuroscience research on healthy aging and cognitive performance across the lifespan.

P3-F-782 *Win-stay and win-shift rule-coding in rat medial frontal cortex*

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To study the neural mechanisms underlying cognitive flexibility, we developed a novel rule-switching task for rats. Under the Stay Rule, the correct Side—left or right, remained the same for every trial in the block. Under the Shift Rule, rats alternated their Side choices—left and right, from trial to trial to get reward. At trial onset, rats had to maintain nose-fixation in the central port for a 1-second delay period. They would then hear an auditory signal representing the end of delay and onset of the response phase. We conducted single-unit recordings from the anterior cingulate cortex (ACC) and the secondary motor cortex (M2) while rats learned to switch between the rules. Rats improved on the number of switches achieved over days. To understand how the neurons encoded task-related factors, we performed a demixed principal component analysis (dPCA). We performed dPCA separately for neuronal activities during (1) the delay period and (2) the peri-response period. We found that neurons in both ACC and M2 responded to both Side and Side-Rule interaction. The Rule information was also present, to a weaker extent. Our novel task is well suited for the analysis of the single-neuron, population, and network-level mechanisms that support this training-related improvement in cognitive flexibility.

P3-G-783 *Intermittent synchronization between arousal and spontaneous brain activity*

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Fluctuating levels of arousal are increasingly understood as playing a key role in shaping the spatiotemporal structure of spontaneous brain activity. In particular, recent accounts of synchronization between markers of arousal and global waves of brain activity measured with fMRI in humans have suggested a model in which travelling waves that integrate ongoing arousal cycles with large-scale excitability patterns explain the topographical organization of functional connectivity. Asking if such observations could be replicated in other species with different imaging modalities, we here report the presence of global waves of infra-slow brain activity that are synchronized with arousal indicators in the mouse brain using widefield calcium imaging and pupillometry data and show that these waves can recapitulate time-averaged functional connectivity. We further observe that although oscillations in regional calcium activity and pupil diameter are mostly coherent, the temporal phase relationship between the two is scattered with phase slips, which are sudden changes in phase difference. Hypothesizing that arousal-related neuromodulators play a key role in synchronizing pupil diameter with spontaneous brain rhythms, we predict that such phase slips are more likely to occur when arousal is low and go on to demonstrate an inverse relationship between phase slip frequency and pupil diameter. Our results support a model in which neuromodulatory centers help synchronize arousal levels with a global traveling wave that explains the spatiotemporal organization of spontaneous brain activity.

P3-G-784 *Investigating multizonal convergence in the cerebellar nuclei through input-specific viral labelling*

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Although traditionally known for its role in motor coordination, the cerebellum is also involved in cognitive, autonomic, and behavioural processes, making it an important site for integrating multimodal information in the brain. Purkinje cells integrate this multimodal information and relay it to the cerebellar nuclei (CN), the sole output of the cerebellum. Purkinje cells are organized into zones associated with specific functions, and we have previously shown that some individual CN neurons receive convergent Purkinje cell input from multiple functional zones. Existence of multizonal CN (mCN) neurons challenges the role of the CN as a simple relay center and implicates it in multimodal information integration. To understand their contribution to cerebellar processing, we designed a viral strategy to target mCN neurons. We combined a dual reporter mouse line (Ai224) that enables intersectional recombinase labelling with AAV1, an adeno-associated virus which enables anterograde transsynaptic viral transfection. Stereotaxic injections of AAV1 constructs of Flp and Cre recombinase into two functionally distinct cerebellar lobules of male and female adult(~p40) Ai224 mice, enabled nuclear localized EGFP (Flp) and tdtomato (Cre) expression in downstream CN neurons. mCN neurons receiving input from both lobules can be identified through colocalization of EGFP and tdtomato. Using this approach, we can characterize the anatomical, molecular, and electrophysiological properties of mCN neurons and unveil the organizational principles of multimodal integration in the cerebellum.

P3-G-785 *Investigating the transcriptomic profile of cells encapsulated by perineuronal nets in the human brain: Establishment of a novel protocol*

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Introduction: Perineuronal nets play a central role in maintaining healthy brain function, including the regulation of plasticity and balanced inhibitory activity of the cells they encapsulate. Yet, no study to date has managed to successfully isolate and comprehensively profile the gene expression patterns of PNN+ neurons themselves. Aiming to help fill the knowledge gap, this study optimized an entirely novel protocol designed to extract and sequence PNN-encapsulated cells from post-mortem human vmPFC tissue using a combination of laser capture microdissection, non-commercial cDNA synthesis, and high-depth next-generation sequencing. Methods: Five subjects including both sexes were included in this protocol's pilot validation run, ranging in age from 25-68. Samples were collected using a Zeiss PALM Microbeam laser capture microdissection system and stained using immunofluorescent proteins. cDNA synthesis was conducted using a non-commercial workflow designed to accommodate low-input, lower-quality RNA. Samples were sequenced on an SPrime Illumina flowcell. Results: Despite low starting RNA integrity and concentration values, all samples generated consistently strong results, indicating that the optimized protocol is compatible with high-depth sequencing platforms. Bioinformatic processing confirmed expression of key PNN-associated genes, as well as minimal contamination from either surrounding cell types or environmental impurities, indicating successful isolation of PNN+ neurons. Conclusion: Using a novel protocol, this study successfully generated the first high-depth, transcriptomic characterization of PNN+ cells. This breakthrough has the potential to not only uncover the molecular mechanisms by which these nets shape neural networks, but also how they may falter in the case of injury or disease

P3-G-786 *Mesoscale reconstruction of 3D microstructure and fibre orientation in whole brains with automated serial tilted polarization sensitive optical coherence tomography*

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A comprehensive mapping of white matter connectivity and microstructure are crucial to our ability to understand brain function and behaviour. Connectivity has traditionally been assessed through invasive tract-tracing and ex-vivo dissection or more recently through non-invasive diffusion-weighted magnetic resonance imaging (dMRI) and probabilistic tractography. However, these approaches fall short of capturing the intricacies of neural circuitry at the multi-cellular to regional scales due to poor scalability (tract tracing/dissection) on one side and poor spatial specificity on the other (dMRI). We have developed an automated serial histology tilted polarization-sensitive optical coherence tomography (as-psOCT) platform to enable rapid quantification of the structural organization supporting circuit-level brain function, extracting both estimates of tissue microstructure (OCT intensity) and in-plane fibre orientation (birefringence-dependent polarization). Using the rodent cerebellum as a model system we have characterized white- and grey-matter microstructure in 3D (up to 10x10 micrometer in-plane resolution) and are building the algorithms, tools, and pipelines to combine multiple orientation maps acquired at different tilt angles to reconstruct 3D maps of fibre orientation for psOCT anatomical tractography. This comprehensive strategy aims to overcome the limitations of existing approaches to reveal fundamental insights into the principles of anatomical organization and connectional architecture.

P3-G-788 *New in vitro and ex vivo methods for studying human dorsal root ganglia*

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Chronic pain represents a major unmet medical need, affecting millions of patients worldwide and imposing a substantial societal burden. Despite decades of intensive basic research and the identification of numerous candidate targets, very few novel analgesics have successfully translated to the clinic. A key contributor to this translational failure is the reliance on preclinical models that insufficiently capture the complexity and species-specific biology of the human nervous system. In particular, fundamental differences between rodent and human sensory neurons limit the predictive value of commonly used pain models. Human dorsal root ganglia (hDRG) neurons play a central role in pain perception, yet their study is hindered by limited tissue accessibility and by experimental approaches that alter native cellular phenotypes. Here, we present the development of complementary human-relevant platforms to investigate the functional properties of hDRG neurons ex vivo. We established long-term hDRG cultures and organotypic slice preparations that preserve neuronal heterogeneity and key aspects of native tissue organization. Neuronal activity is assessed using electrophysiological recordings and calcium imaging in response to defined stimuli, alongside histological analyses to monitor structural and molecular features over time. In addition, we evaluated a cryogenic preservation strategy that enables long-term storage of viable human sensory tissue while maintaining functional integrity. Together, these approaches provide a physiologically relevant framework for studying human sensory neuron function and support improved translational strategies for pain research.

P3-G-789 *Nonlinear interactions between slow and fast alpha rhythms predict individual differences in pain sensitivity*

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Individual differences in pain sensitivity vary widely, yet the neural mechanisms underlying this variability remain incompletely understood. Alpha-band activity (8–13 Hz), which reflects cortical inhibition and excitability, has been linked to pain perception. Alpha activity comprises two physiologically distinct components: slow alpha (8–10 Hz) and fast alpha (10–12 Hz), generated by different cortical ensembles. While peak alpha frequency (PAF) reliably predicts prolonged pain sensitivity, prior work has largely examined alpha features in isolation and using linear models. It is unclear whether interactions between slow and fast alpha rhythms better explain individual differences in pain sensitivity or whether these relationships are nonlinear. This project adopts a methods-driven approach to evaluate interaction-based alpha models using a large multi-site EEG dataset comprising nine laser-evoked pain studies (N = 678) collected with 32-, 62-, and 64-channel systems. Trial-level slow- and fast-alpha power, their ratio, and PAF are extracted. To harmonize data across EEG systems, signals are reconstructed into cortical source space and summarized within anatomically defined regions of interest. Relationships between alpha features and pain sensitivity are examined using Generalized Additive Mixed Models, which model nonlinear and subject-specific effects while accounting for repeated measures. Preliminary modelling evaluates whether nonlinear, interaction-based alpha models provide a more unified account of pain sensitivity than existing single-metric approaches.

P3-G-790 *Paired neuroimaging and transcriptomics in the same individuals reveal region-specific molecular correlates of brain structure*

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Previous imaging-transcriptomics studies have linked brain structure to gene expression using unmatched data or RNA from a single brain region. Datasets with paired structural MRI and RNA data from multiple regions per subject enable direct analysis of how transcriptomic variation across individuals relates to their brain structure. We performed association analysis on individuals with ante-mortem MRI and post-mortem bulk RNAseq from five brain regions (n=102 samples/region on average). Regional cortical thickness, surface area, volume, and curvature were estimated using FreeSurfer. We applied linear models to assess cross-sectional gene-MRI associations. We identified 6897 genes demonstrating significant associations with MRI structural features across the five examined regions (pFDR < 0.1). Imaging-transcriptomic associations were region-specific, with minimal overlap across brain regions. Comparing temporal cortex RNA to middle temporal cortical volume yielded 1873 significant genes, 1504 of them not present in gene sets for the other features and sample sites. Gene set enrichment analysis with cell type markers implicates changes at the cell type level in MRI associations. For example, greater temporal cortex volume was associated with increased excitatory neuron expression (p=1.9e-5) and decreased microglia (p=2.6e-7). Our findings help bridge the gap between macro-scale brain imaging and micro-scale omics. By linking MRI features to underlying molecular mechanisms, we can more accurately identify and interpret neuroimaging biomarkers in psychiatric disorders and aging.

P3-G-791 *Reconstruction of the corpus callosum fibers of the rat with tilt-angle polarization-sensitive optical coherence tomography*

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The white matter of the brain is composed of millions of axons that transmit information between specialized gray matter regions through a complex network. Unraveling the complexity of these connections is essential to understanding cognition and behavior in both humans and other animals. However, current approaches (i.e., invasive tract tracing; non-invasive diffusion MRI) are fit for purpose, suffering from poor scalability and limited spatial resolution respectively. This has created a significant need for mesoscale imaging techniques that can bridge the gap between these two resolutions. We utilized a custom developed automated serial histology polarization-sensitive optical coherence tomography (as-psOCT) platform and image processing pipeline to characterize, quantify, and validate structural connectivity in the rat brain. As axons passing through the plane of a section cannot be detected by standard OCT/psOCT, which severely limits our ability to estimate 3D fiber orientations, our platform was specifically designed to acquire multiple images of the same tissue from various tilt-angles (0–15°) to enable true 3D reconstructions of tissue orientation. To validate this technique, we imaged a dissected rat corpus callosum twice (at 0 and 90° rotations; 10x10um in-plane resolution; 5 tilt-angles) as a model for a large, well-characterized fiber bundle with known orientation. Our 3D reconstruction allows us to confirm the reconstruction accuracy of the 3D orientations of in-plane fibers with the proposed tilt-angle approach.

P3-G-792 *Spatial tuning reflects linear perceptual versus nonlinear memory encoding in hippocampus*

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The hippocampus is crucial for both spatial navigation and episodic memory, yet how it balances these functions remains debated. A long-standing view categorizes hippocampal neurons as either spatially or non-spatially tuned. Combining in-vivo electrophysiology in macaques with computational modeling, we

demonstrate that this classification reflects a deeper principle: a trade-off between linear encoding of the present and nonlinear integration of the past. Our results show that neurons classified as spatially tuned (STNs) primarily encode linear combinations of immediate, behaviorally-relevant variables. In contrast, non-spatially tuned neurons (nSTNs) rely on nonlinear recurrent mechanisms to integrate information over extended timescales. We further show using a task-optimized artificial recurrent neural network (ANN) that nonlinear recurrence is essential for capturing the response dynamics of nSTNs and for the emergence of non-spatially tuned units during learning. These findings reframe the role of spatial tuning, suggesting it is a marker for linear, perceptual encoding. This work provides a unified framework where a continuum of linear to nonlinear computation allows the hippocampus to bridge immediate perception and memory, supporting both navigation and the formation of complex, temporally-extended memories.

P3-G-793 *STUAART: Real-time assessment of mouse health and behaviour through its weight*

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Daily monitoring of mouse weight and behaviour is often required to assess the animal's health and wellness. However, measuring weight and evaluating the animal's behaviour, while essential, require the interaction of an experimenter, which could in turn influence the animal's behaviour by inducing stress and jeopardizing its wellbeing. Additionally, the whole process is time-consuming for the experimenter, preventing continuous data acquisition. Automated evaluation of the weight and behaviour of the animal in its home cage could provide more accurate information about its health and habits. We developed the Smart Tracking Unit for Automatic Animal Research Testing (STUAART), an automated and customizable system to continuously monitor the weight and some specific behaviour of the animal. Our system is easily adaptable to any home cage, low-cost, and user-friendly for non-experts in electronics and programming. We take advantage of load cells and 3D-printed platforms to create a mosaic of scales that cover the whole surface of a normal mouse cage. The mass time series are used to identify behaviours, such as hanging and locomotion. This automated mouse home cage could provide a better overview of a resident animal's health and behavioural changes without the need for human intervention.

P3-G-794 *Targeted gene delivery to astrocytes using intelligent phagemid-assembled gene expression (iPHAGE) technology for neuronal regeneration*

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Neurodegenerative diseases are characterized by the neuronal loss, with existing therapies limited to symptomatic management rather than neuronal regeneration. Astrocyte-to-neuron reprogramming is a promising regenerative approach; however, clinical translation remains limited by the lack of safe, efficient, and targetable gene delivery systems for the CNS. Here, we evaluate the feasibility of the Intelligent Phagemid-Assembled Gene Expression (iPhAGE) system, a bacteriophage-based, non-viral gene delivery platform, for targeted astrocyte delivery of the neuronal transcription factor NeuroD1.iPhAGE vectors derived from filamentous M13 bacteriophages were engineered to carry the NeuroD1 gene under the control of the astrocyte-specific promoter. Miniphagemids were purified, and characterized for titer, size, and bacterial backbone contamination. Gene delivery efficiency and cellular responses were assessed in resting and lipopolysaccharide-activated A7 cells using fluorescence reporters, luciferase assays, viability measurements, and neuronal marker analysis.Miniphagemid production yielded high-titer vectors with negligible bacterial DNA and minimal cytotoxicity in vitro. Gene delivery was observed in both resting and reactive A7 cells. Induction of PSA-NCAM expression suggested the emergence of early neuronal features under selected conditions. To improve vector specificity, surface ligands were evaluated for preferential targeting of reactive astrocytes. Ligand selection influenced delivery efficiency: the SFSNIAIR peptide demonstrated the strongest

preference for activated A7 cells, while IRL1620 showed a moderate increase in delivery compared to EGF. This work establishes a foundation for iPhAGE-mediated astrocyte targeting and identifies key barriers that must be addressed for effective neuronal reprogramming in regenerative neuroscience applications.

P3-G-795 *TEMPO: 4D motion distillation for unsupervised monocular 3D pose estimation*

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Longitudinal quantification of behavior, and its linkage to brain dynamics, remains a core challenge in neuroscience. Behavior is easy and cheap to record with monocular video, yet movement unfolds in 3D and over time, with kinematics shaped by growth, aging, and changing sensory context. In practice, most pipelines still rely on supervised 2D keypoint estimation, which is expensive to label, biased, brittle across setups, and discards rich information about 3D structure, context, and long-horizon dynamics. Recovering articulated 3D pose from monocular video is fundamentally ill-posed, and existing unsupervised approaches that rely on sparse 2D cues often suffer from depth ambiguity, identity swaps, and weak 4D (space–time) consistency. We introduce TEMPO (Temporal Embedding of Motion for Pose Optimization), which learns canonical 3D pose from monocular video by distilling a temporally coherent 4D motion representation. A high-capacity teacher first extracts a consistent motion embedding from raw video using motion- and geometry-sensitive features. A lightweight student then predicts per-frame parameters of a parametric body model, yielding smooth canonical 3D pose trajectories over long timescales. Preliminary results on challenging monocular animal recordings are promising, and we are expanding evaluation to quantify gains in 3D pose accuracy and downstream behavioral analysis.

P3-G-796 *Testing the efficacy of qEEG-guided TMS for the treatment of persistent post-concussion symptoms (PCS)*

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Mild traumatic brain injury (mTBI) accounts for most brain injuries and is typically followed by cognitive deficits, somatic, and affective symptoms. About 25% of mTBI patients develop persistent post-concussion symptoms (PCS) persisting past the 3-month recovery period, impairing quality of life with limited response to pharmacological treatment. This pilot study aims to evaluate the clinical efficacy and associated neuroimaging changes of qEEG-guided transcranial magnetic stimulation (TMS) treatment on adults suffering from persistent PCS following mTBI. Eligible mTBI patients with persistent PCS (>3 months) were submitted to 10 qEEG-guided TMS sessions. Clinical and functional magnetic resonance imaging (fMRI) assessments were carried out pre and post treatment to evaluate the evolution of baseline PCS severity, cognitive function (working memory in task-based fMRI), resting-state fMRI (rs-fMRI), and cerebral electrophysiological condition. Follow-up clinical assessments were performed after 1 and 3 months to evaluate post-treatment outcomes over time. Preliminary results demonstrate a decrease in PCS and improved performance on working memory tasks at both post-treatment assessments. Increases in BOLD activation were observed in the dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), caudate nucleus, and thalamus during task-based fMRI, and overall patterns approached those of healthy controls. qEEG showed increased alpha waves and decreased delta waves, suggesting improved alertness and fatigue. These results support qEEG-guided TMS as a promising treatment approach for persistent PCS in mTBI patients.

P3-G-797 *The creation of a psychedelic platform technology for future drug screening and cognitive discovery*

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Psychedelic-assisted psychotherapy shows clinical promise, but current compounds are long-lasting and have the potential for negative experiences, limiting scalability and motivating the search for safer alternatives. We hypothesize that psychedelics that produce distinct subjective experiences likely evoke distinguishable cellular homeostatic responses that can be integrated into compound-specific neurobiological “signatures” and used to screen for novel compounds. Our strategy is to expose human brain organoids to psychedelics and profile their responses using multiple homeostatic assays. These readouts will be integrated using machine learning to generate compound signatures and refined using our proprietary 90-compound library linked to detailed human experience reports to confirm accuracy. Preliminary data show long-term exposure to psilocin has no impact on calcium flux imaging; however, acute exposure shows divergence in calcium event rates, suggesting discernible compound-specific effects, although this comparison requires further validation through increased replicates. Ongoing studies seek to optimize the assays and generate signatures for psilocin and other psychedelic compounds with dimension reduction and supervised machine learning, forming the foundation of our platform.

P3-G-798 *TRACR: A novel transsynaptic tracer toolkit for in vivo visualization of mammalian circuit connectivity*

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Capturing dynamic changes in neural circuit connectivity in development and disease requires neuronal tracing strategies designed to reversibly visualize synaptic connections in vivo. However, existing tracing methods are limited by their modularity, cytotoxicity, or throughput. Thus, we developed a novel anterograde transsynaptic tracing toolkit, termed TRACR (TRanssynaptic Anterograde Circuit Readout). TRACR utilizes cell adhesion at the synapse and synthetic Notch signaling (synNotch) to report on the postsynaptic targets of a defined starting population. When a presynaptic “Sender” GFP ligand binds a postsynaptic “Receiver” receptor, an exogenous transcription factor induces “Reporter” gene expression. These TRACR components are expressed in vivo in the mouse brain and retina with AAV vectors and transgenic animals. Using known molecular markers and anatomical relationships, TRACR accurately identified the postsynaptic targets of local inner retina circuits, as well as the targets of the long-range retinal ganglion cells in the brain. To optimize TRACR labeling fidelity, a modified synNotch Receiver significantly reduced background Reporter leakiness. Further, we applied various promoters and AAV serotypes to increase TRACR expression levels and enhance Reporter labeling efficiency. Finally, we are assessing the specificity of different presynaptic motifs for Sender ligand targeting to axon terminals. The present work expands a modular and genetically-encoded transsynaptic tracing toolkit, with implications for the study of circuit assembly, degeneration, and repair.

P3-G-799 *Using multi-omics knowledge graphs to discover novel neurodevelopmental disorders mechanisms*

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Studies have identified contributing genes, their regulatory elements, transcriptomic profiles, cell-type liabilities, and neuroimaging signatures associated with neurodevelopmental disorders (NDDs). Research strategies have mainly been unimodal, but recent work in multiscale neuroscience and multi-omics has begun to recognize the importance of synergistic interactions between biological levels of observation for the etiology and progression of NDDs. However, the difficulty of integrating multiple highly compartmentalized and non-standardized data sources has complicated the development of a unified mechanistic model for NDDs across scales. We hypothesized that knowledge graphs (KGs, heterogeneous

networks connecting datatypes) and graph representational learning would allow us to shed light on relations between multiple levels of biological observation and discover novel NDDs mechanisms. We aimed to build an NDD mechanistic model spanning molecular, cellular, meso- and macro-scopic networks. Methods : We used multi-omics measures in human brain tissue of individuals with NDDs and controls from PsychEncode. Networks were constructed using multi-omics data (genetic association, differential expression, differential splicing, coexpression, chromatin-gene linking, enhancer-promoter association, etc.). Biological inferences were established using graph representational learning. We used cross-validation and independent datasets to test our predictions for novel contributing genes, as well as novel transcriptional profiles and cell types implicated in the ASD/NDDs.

P3-G-800 *Using self-supervised foundation model for confocal microscopy for microglia segmentation*

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Microglia are central regulators of adult brain homeostasis, contributing to synaptic remodeling, neuronal surveillance, and injury responses. Using RNA-seq and ATAC-seq in mice lacking Mef2 activity in microglia, we identified widespread transcriptional and chromatin alterations associated with region-specific changes in microglial density, morphology, and cellular behavior. Quantifying these structural differences is essential for linking molecular dysregulation to microglial function.However, robust segmentation of microglia remains challenging. Threshold-based and classical image-processing pipelines often struggle to balance sensitivity and specificity, increasing bias and reducing reproducibility. Given the cost and time required to generate high-quality confocal datasets, a more scalable and reliable computational strategy is needed. To address this gap, we are developing a confocal image foundation model. The model is pretrained on a large, diverse confocal dataset spanning tissue sections and cell-culture preparations, collected across multiple research teams, enabling it to learn broad, task-agnostic visual representations without annotation. The pretrained model will then be fine-tuned on a curated, pre-segmented microglia dataset, adapting it to microglial morphology and improving downstream segmentation.By integrating multi-omics findings with a confocal foundation-model pipeline, this work aims to establish a scalable, low-bias framework for characterizing how Mef2-dependent gene regulation shapes microglial structure and function across the brain.

P3-G-801 *Visualizing melanin granules in parkin-expressing neural cells using transmission electron microscopy*

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Neurodegenerative diseases often involve subtle cellular changes that are difficult to resolve using conventional light microscopy. Transmission electron microscopy (TEM) provides nanometer-scale resolution, making it a powerful tool for ultrastructural analysis in neuroscience. Using the TEM housed at the University of Ottawa enabled detailed examination of fine features in neural tissues and cell models. Here, we demonstrate the utility of TEM in a project studying Parkinson's disease (PD), a disorder characterized by progressive loss of dopaminergic neurons, in which mutations in the parkin gene cause early-onset PD. Parkin protects neurons by neutralizing reactive dopamine metabolites, becoming oxidized, and contributing to neuromelanin formation. Using a model of induced melanin formation to mimic dopamine stress and neuromelanin production in humans, we examined parkin localization and melanin ultrastructure. Indirect immunofluorescence showed no major changes in parkin distribution, although parkin-expressing cells produced more melanin than parkin-deficient cells. Since light microscopy and Mason-Fontana staining lack sufficient resolution to assess melanin granule size or organization, TEM imaging was employed. TEM revealed discrete melanin granules and enabled detailed visualization of granule morphology and cellular localization in cultured cells and brain tissue. These findings highlight the value of TEM imaging for studying ultrastructural changes in neurodegenerative disorders.

H - HISTORY, TEACHING, PUBLIC AWARENESS AND SOCIETAL IMPACTS IN NEUROSCIENCE

P3-H-802 *Teaching neuropsychology through simple and cost-effective activities: Paper cortex and case study escape room*

Nicole Vittoz [1]

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Neuropsychology is a challenging curriculum to deliver at an undergraduate level. In this poster, I will offer ideas for learning activities that help students grasp two main lessons. One is concept of functional organization through vertical (columns) vs. horizontal (layers) of cortex. The activity is simple, requiring only a few sheets of paper in different colours. The other is a game (conceptual escape room) that helps students diagnose cortical injuries through a series of simple dissociation-logic assessments. They are presented with a brief clinical case and must choose which lobe is associated with the compromised functions. They then address whether the symptoms indicate left or right hemisphere damage (or both). They also identify which level of processing is likely associated with the symptoms: primary, secondary, or tertiary. For visual system, they choose the “what” vs the “where” pathway. Once they answer each of the logical elements correctly, they will have uniquely identified the diagnosis associated with the presented case. Once all cases are completed, they will have a full set of puzzle elements. When they solve that simple puzzle, unlock the reward: a master list and diagram of the cases and how they fit into the dissociation logic, using lobes, levels and hemisphere as the major clues. Much like means, motive, and opportunity in murder mysteries, this game engages students as detectives and centers foundational concepts in clinical neuropsychology, without the overwhelm of clinical terms and symptom overlap. Demonstrations available.

P3-H-803 *The efficacy and shortcomings of spinal surgery referral systems across canada: A systematic review*

Tharushi Perera [1]

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Background Canada faces some of the longest waits for spine care in developed countries, with median waits from family physician referral to treatment rising to 30 weeks. However, a paucity of research exists concerning the efficacy of alternative referral pathways for Canadian spine surgery. This review will compare structured referral models and assess their impact on wait times, appropriateness of surgical referrals, imaging use, patient experience, and unintended harms. Methods A PRISMA systematic review was conducted evaluating referral systems (2005-2024), including MEDLINE, Embase, Web of Science, targeted grey literature, and reference chaining. Eligible studies empirically evaluated referral systems or compared models; descriptive and non-Canadian studies were excluded. Results: Across 4,244 screened abstracts and titles, 20 Canadian studies were synthesized (N=17,892). Structured pathways produced shorter Wait-1, with a mean reduction of 12.6 weeks (95% CI: -4.5, 29.7), and absolute reductions from 8.6 to 20.6 weeks. Traditional systems had high inappropriateness (e.g., 44% and 80.4%), whereas structured triage increased surgical candidacy (e.g., 59.1% and 37.6%) and reduced MRI use (e.g., 53% and 39%). Conclusion Structured spinal referral pathways improve front-end access and referral appropriateness,though downstream operative bottlenecks and heterogeneous reporting limit conclusions on totalreferral-to-surgery time. These findings support scalable investment in standardized, province-wide triage infrastructure alongside equity-stratified evaluation of outcomes.