

# Canadian Connections

Highlighting Recent  
Neuroscience Research



## **CAN-ACN**

CANADIAN ASSOCIATION FOR NEUROSCIENCE  
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# Message from the President

Dear reader,

I am very proud to bring you this collection of stories highlighting recent discoveries made by the Canadian brain research community. These stories describe research that is providing a better understanding of brain function in health and disease, and new insights into how the brain controls our emotions, memories, social interactions, mood, behaviour, and our responses to the events around us. This type of research helps us to understand what makes us who we are, teaches us how to keep the brain healthy, and provides new strategies for brain repair following disease or injury.

Neuroscience research impacts all Canadians. One in three Canadians will be affected by a neurological disorder, injury or psychiatric disease in their lifetime. Unfortunately, there are no clear causes or cures for the vast majority of conditions that affect the brain and spinal cord. Health Canada estimates the economic burden of neurological and psychiatric conditions represents 14% of the total burden of disease in this country. The cost of brain disorders exceeds those of cardiovascular disease and cancer. The cost of brain diseases will continue to increase as life expectancy increases and the population ages.

Research offers the best hope for the many Canadians affected by these debilitating nervous system disorders. Canadians are at the forefront of developing new investigative approaches and new avenues of research that allow us to delve deeper in the brain to understand its inner workings.

These rapid "made in Canada" advances, coupled with global collaborative initiatives aimed at mapping the important connections in the brain raise the prospect of genuine breakthroughs in our understanding of the healthy and diseased nervous system. Because of this, many scientists believe that we now live in the golden age of brain research.

The stories in this booklet highlight recently-published Canadian discoveries, most from the last six months. They have all been made possible by the expertise built over many years in Canadian research laboratories and research centers.

Public funding of our laboratories is what makes these breakthroughs possible, and we are thankful for this opportunity to present to you a small sampling of what this investment brings to Canadians.

We hope you enjoy reading them!



**Freda Miller, PhD**

Professor, University of Toronto  
Senior Scientist, Hospital for Sick Children  
President of the Canadian Association for Neuroscience

# CAN-ACN Advocacy Committee members



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# Can we avoid the drastic consequences of anaesthesia?

Surgery has become an integral part of modern medicine, which many of us take for granted. But as anyone who has undergone an operation knows, there are risks. Perhaps the most important – and usually the one most taken for granted – is the act of “going to sleep,” officially known as general anaesthesia.

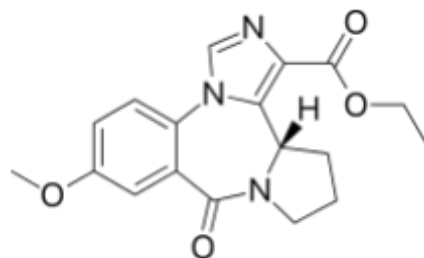
This fundamental procedure ensures that patients are motionless as the various surgical events are being performed. While this is true, most people don't realize that the patient is not actually asleep. Instead, the person has entered a drug-induced coma. Not surprisingly, this high risk state puts a significant burden on the anaesthesiologist to ensure the individual's vital signs are maintained. Thankfully, those trained in the practice of anesthesiology know how to safely support patients in this suspended drug-induced state.

Despite the best of care, there may be potentially unstoppable effects of anesthetics on the brain that contribute to post-surgery troubles. A common one is postoperative delirium, which is a state of confusion and inattention that is often accompanied by hallucinations and sometimes aggression. Another problem, which is referred to as postoperative cognitive deficits, is characterized by memory loss and deficits in problem solving. Such problems can severely hamper a person's ability to function normally in the postoperative period. Both of these conditions can lead to troubles for the patient during and after recovery. They may also add to the

already skyrocketing cost of health care in the form of extended hospital length-of-stay and the need for admission to long-term care facilities.

Some twenty years ago, a researcher from Sunnybrook Health Science Centre, Dr. Beverley Orser, decided that it was time to better understand how anesthetics affect the brain. Her compiled research tells a story unlike any other as it takes us into the depths of the brain. The results, produced over the years, have also led to some dramatic revelations and patented discoveries as well as a possible path forward to reduce the deleterious effects of anesthetic drugs on the brain.

A chemical known as L-655,708 may prevent memory loss



Back in 2009, Orser's group came up with a major modern revelation of the effects of anaesthesia on the brain. They discovered a particular piece of a protein, known as the alpha 5 subunits of the gamma-aminobutyric acid subtype A receptor (abbreviated to  $\alpha 5$ GABAAR) was a target of a prototypic general anaesthetic known as etomidate. When the chemical bound to the receptor, the brain was unable to develop

memories. The discovery was considered to be a turning point as it opened the door for continued research at the molecular level.

With this in place, Orser's team wanted to find out just how long the effects of anaesthesia last on the brain. Although convention suggested the length was only a few hours, her

researcher revealed troubles with memory that lasted for days. The reason for the memory loss was a sustained increase in the function of the memory-blocking protein. This meant the anaesthetics were sticking around in the brain for much longer than anticipated. It also suggested a treatment for reversing the effects may not be as easy as once thought.

The answer turned out to be simple in theory but harder to enact. To maintain memory function, the team had to prevent the receptor from being expressed. When they stopped production of  $\alpha 5$ GABAAR in mice, they could remember. These new results offered a potential path for possible treatment options but also made the path far more difficult. Instead of chemically stopping the effects, they had to somehow stop the process from happening altogether.

It took a year but the team found an answer in the form of chemicals known as nootropics. In the lab, the group revealed these molecules could dive into those brain cells and stop the activity of  $\alpha 5$ GABAAR. When tested in mice, the results were dramatic. Even with anesthesia, they could form memories and be able to retain them.

The results of nearly a decade of work from Orser's team have helped to demystify the workings of anaesthetics at the molecular level. Considering little advancement has been made in nearly 160 years, this is in itself remarkable. But the journey is far from over. With the mechanism in place, they can look towards attempting similar experiments in larger animals in the hopes of gaining enough evidence to support clinical trials.

The next steps may take yet another decade before the results are finally useful to anaesthesiologists around the world. However, in light of the risks due to such a necessary part of surgery, the path, while still winding, is well-worth following. After all, providing the best care for patients is not simply a matter of keeping them alive, but also ensuring they thrive and return to their full function.



About Dr. Beverley A. Orser, MD,  
PhD, FRCP

Professor of Physiology and Anesthesia,  
University of Toronto  
Canada Research Chair in Anesthesia  
Staff Anesthesiologist, Sunnybrook Health  
Sciences Centre

Dr. Orser's laboratory research focuses on understanding the molecular mechanisms of general anesthesia. She has published over 140 scientific papers and has been invited to lecture at national and international conferences. In addition, Dr. Orser is committed to training the next generation of research students and clinician-scientists.

Learn more about Dr. Orser on her website:  
<http://orserlab.com/>

# Could an antibiotic treat Alzheimer's Disease?

Alzheimer's disease is growing in Canada at an unprecedented rate. At the moment, over half a million people suffer from this debilitating condition but that number is expected to nearly double over the next generation. The effects of this illness are tragic, such as memory loss as well as changes in behaviour, judgement, and normal daily function. For this reason, understanding this disease and finding meaningful treatments are considered a priority.

As Alzheimer's progresses, a protein, known as amyloid- $\beta$ , begins to clump together, forming what is officially called a plaque. As this happens, the neurological landscape changes as neurons begin to die off. Despite decades of research, the mechanism behind this loss remains, for the most part, a mystery.

Over the years, researchers have taken a closer look at amyloid- $\beta$  and have revealed some potential warning signs. Different cell types, including neurons as well as microglia and astrocytes, appear to act differently when near a plaque. They also appear to be hyperactive, suggesting the microenvironment may be toxic. Yet, whether this contributes to the loss of neurons has yet to be shown.

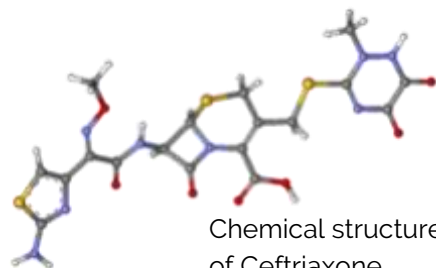
Now the proof may be at hand thanks to a group at the University of British Columbia led by Dr. Brian MacVicar. His team ventured into the area around amyloid- $\beta$  in search of mechanisms responsible for cell death. Their results, published in the journal *Nature Communications* reveal one particular molecule may act as a lynchpin. Perhaps more importantly, this

molecule, known as a glutamate transporter, or GLT-1, may be a target for treatment using already approved medications.

The team worked with a special type of mouse, known as APPPS1, which stands for amyloid precursor protein and mutant human presenilin-1. This mouse is unique as it makes the human forms of the components needed to form amyloid- $\beta$ . As the animal ages, a similar progression to Alzheimer's occurs, allowing researchers to track the molecular dynamics of disease.

The method for testing was rather straightforward. The mice were injected with a molecule called the intensity-based glutamate-sensing fluorescent reporter, more commonly called iGluSnFR. As the name implies, when the molecule encounters a neurotransmitter, known as glutamate, it glows. The mice were then observed using a specialized microscope, which was designed to track changes in glutamate levels in real time. The choice of glutamate as a marker was not a random choice. For

well over a decade, researchers have known glutamate movement in the brain is an important indicator of cellular health. It regularly moves in and out of cells and has a normal rhythm. The key to these dynamics isn't the chemical itself; rather, it's the protein that moves the molecule in and out of cells. This is GLT-1. When brain cells are healthy, GLT-1 is in ample supply. However, when it disappears, glutamate doesn't move. This is a bad sign for the cell. When this happens, death inevitably follows. For the team, the loss of GLT-1 in cells near





the amyloid- $\beta$  would confirm cells in that region are destined to die.

As expected, when the tests were run, cells around those amyloid- $\beta$  deposits had less GLT-1 activity. This meant the cells in the region were suffering from a toxic environment and neurons eventually would face an untimely death. For the researchers, this helped to prove amyloid- $\beta$  was indeed toxic and causing cell death. Yet while this evidence alone was noteworthy, for the team, it only represented the first step. The next involved trying to restore GLT-1 levels in the hopes of counteracting the effects of amyloid- $\beta$ . To do this, they relied on a decade-old approach to protect the brain. They used antibiotics.

Although most people view antibiotics solely as bacterial killers, these chemicals also have the ability to change the dynamics of our own bodily systems. One particular drug, ceftriaxone, can single-handedly increase the levels of GLT-1 in the nervous system. For MacVicar's team, this offered a perfect opportunity to see if they could reverse the effects of amyloid- $\beta$ .

When the mice were given the antibiotic, the results were remarkable. The drug did exactly as expected and began to raise the GLT-1 levels. As this happened, the toxic effects of the area decreased. Glutamate went back to its usual dynamics and the cells regained – at least for a short period of time – some respite against the toxic environment.

These results provide a real link between the formation of amyloid- $\beta$  and cell death in the surrounding region. As expected, the lynchpin in this study is GLT-1, suggesting this protein may be considered a priority in understanding disease progression. Perhaps more importantly, the identification of GLT-1 offers hope for treatment in the future.

While ceftriaxone is not currently being used for Alzheimer's treatment, the potential for its use appears to be strong. This study may invigorate researchers to find ways to use this antibiotic as part of combination therapy. While this is not a cure, new management strategies may be developed to help those hundreds of thousands of Canadians suffering to manage their symptoms.

## About Dr. Brian MacVicar, PhD, FRSC, FCAHS

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Brian MacVicar is one of the world's pioneers in describing the activity of brain cells known as glial cells, thus contributing to a new appreciation for their essential roles in brain maintenance, protection and repair. His research has shown that a class of glial cells called astrocytes regulate both dilation and constriction of blood vessels in the brain, providing new insight into how the brain intrinsically regulates its own blood supply and into the pathological changes in blood flow observed following stroke, haemorrhage and vascular dementias.

Learn more about Dr. MacVicar's research:  
<http://macvicarlab.ca/>

# Is it possible to slow the progression of Alzheimer's Disease?

Of all the neurodegenerative diseases, Alzheimer's disease (AD) stands as the most common worldwide. While the onset is complex in nature, a hallmark sign of illness is the accumulation of a particular peptide in the brain, known as amyloid beta ( $A\beta$ ). When present, the molecule can aggregate to form plaques and also interact with cells in the brain leading to altered signalling and function.

One particular devastating interaction occurs between  $A\beta$  and metabotropic glutamate receptor 5 (mGluR5). This molecule normally interacts with an amino acid, glutamate, to modulate calcium oscillations during normal cell signaling. However, the same effect can be stimulated by  $A\beta$  leading to significant loss of calcium. The end result is altered cell function. As levels of  $A\beta$  increase, so does the potential for greater damage to overall neurological function.

Potential avenues for treatment via mGluR5 have been examined for several years. One particular treatment option is 2-chloro-4-((2,5-dimethyl-1-(4-(trifluoromethoxy)phenyl)-1H-imidazol-4-yl)ethynyl)pyridine (CTEP). This molecule possesses a high affinity for the receptor and acts as an inhibitor of activity. This molecule has already been examined in mice as a possible treatment in fragile X syndrome and major depressive disorder. In both these cases, administration has shown significant benefit.

As a result of the positive results from treatment, a team of researchers led by Dr. Stephen Ferguson at the University of Ottawa wanted to find out whether CTEP could be useful in helping to treat Alzheimer's disease. They published their findings earlier this year in *Cell Reports*. Based on the results, the inhibition of the interaction between  $A\beta$  and mGluR5 may offer a possible route for treatment to slow down the disease.

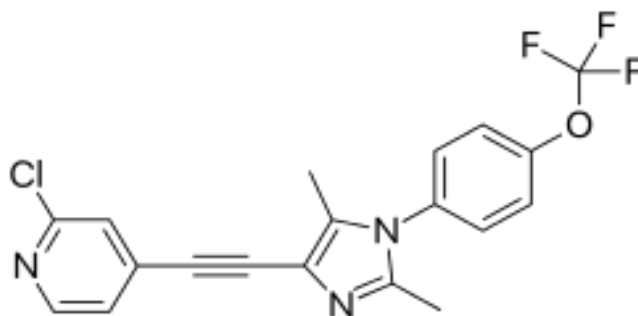
The group worked with two different mouse models possessing the capability of developing conditions similar to Alzheimer's disease. The team waited for the animals to reach nine months of age such that they would be well into the developmental phase of the disease and have significant amounts of  $A\beta$ .

The mice were given CTEP by abdominal injection every other day

over the course of 3 months and were observed in the hopes of seeing behavioural improvement. They did. The drug was working just as the group hoped. This finding suggested CTEP was most likely helping to slow the degenerative process and when used over the long term could possibly ameliorate the prognosis.

The next step was to identify exactly how CTEP was accomplishing this task at the cellular level. The authors expected to see healthier brain tissue as a result of chronic

Chemical Structure of CTEP



treatment. They did. However, what was somewhat surprising was the apparent reduction in the amount of A $\beta$  in comparison to controls. Somehow, the molecule had not only inhibited the interaction with mGluR5, but also had led to a decrease in the amount of the amyloid peptide.

The results of the study clearly show the potential benefit of CTEP in AD and offer an unexpected benefit worth investigating further. Due to the reduction of A $\beta$  in mice chronically treated with the drug, the authors suggest a possible direct involvement of mGluR5 in the formation of toxic amyloid peptides. While this may be the case, the mechanism behind this theory remains unknown and requires further study.

Although promising, this study does represent only a model and as such cannot be directly extrapolated to humans. It will be years before CTEP reaches clinical trials though the road may be less bumpy should this time come. This is because an analogue of this molecule, known as Basmiglurant, is already in phase II clinical trials. The experience with this particular drug may pave the way for CTEP to receive a smoother ride moving forward.

## About Dr. Stephen Ferguson, Ph.D.

Professor, University of Ottawa  
Brain and Mind Research  
Institute



Canada Research Chair in  
Neuroscience

Dr. Stephen Ferguson's research is focused on understanding how a specific type of receptors, called G-protein coupled receptors (GPCRs), interact with other molecules in health and disease.

This research has led to the identification of novel mechanisms contributing to disease processes involved in hypertension, anxiety, stress and depression as well as neurodegenerative diseases such as Alzheimer's and Huntington's diseases.

Furthermore, his lab is also developing small molecule and investigating the utility of repurposing existing drugs that interact with GPCRs for the treatment of neurodegenerative disease.

Learn more about Stephen Ferguson's research:  
<https://med.uottawa.ca/cellular-molecular/people/ferguson-stephen>

# How do our brains cope with stress?

It's one of the guarantees of life: stress. At the core, it's a perception of a physical or psychological threat that is designed to help us survive. But the triggers are varied and there is no single way to deal with the impending sensation of harm.

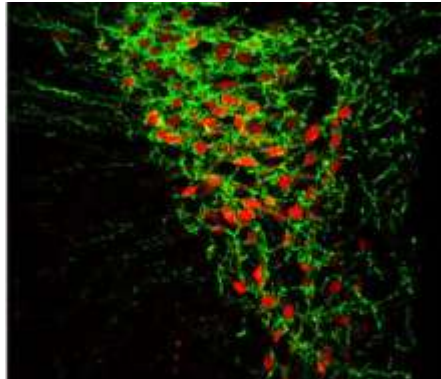
For years, researchers have studied the stress spectrum and identified numerous behavioural changes. Most are simple to understand such as heightened awareness, risk avoidance, and the fight or flight response. Other actions are self-directed and may appear to be independent of normal coping strategies. These non adaptive reactions may be indicative of pathologies requiring medical attention.

It is easy to observe these behaviours visually, yet what is missing is an understanding of the mechanism behind the development of irregular responses. Finding the location as well as the responsible cell types in the brain has remained a mystery. But there now may be some answers thanks to the laboratory of Dr. Jaideep Bains at the University of Calgary.

The team recently published an article in *Nature Communications* in which they examined complex behaviours in mice after a stressful event. The group combined visual observations of behaviour with manipulations to either activate or silence one group of cells in an area of the brain known as the paraventricular nucleus of the hypothalamus, PVN for short. Their results uncovered brain circuits which may be responsible

for controlling behavioural features after stress and, surprisingly, may be involved in altered behaviours associated with autism spectrum disorder.

Before the stress test, the mice were observed so the researchers could identify a palette of eight distinct behaviours that the mice displayed in a random fashion. To initiate stress in the mice, the group used a well-known method known as the foot shock test which elicits an immediate, useful stress response. After the event, the team expected to see a shift in the frequency of the behaviours the mice exhibited.



CRH Neurons in Action

After the stress test, the group did note immediate changes in the way the animals behaved. The stressed mice exhibited a very specific sequence of behaviours in which they progressed from a highly vigilant state of walking and exploring their environment to a state in which they exhibited long bouts of grooming. The authors hypothesized that this

switch from behaviour focused on the outside world to one that is inwardly focused is an important part of recovering from a stressful event.

Next, the authors focused on the brain circuit that may be involved in controlling this shift. They turned their attention to cells in the PVN that manufacture a well-known stress chemical signal called corticotropin-releasing hormone, or CRH.

To determine the role of CRH neurons in the stress response, the team used an optogenetic method in order to either turn on

(using blue light) or turn off (using yellow light) CRH neurons in the mice's brains, immediately after they were stressed. The team hypothesized that turning off CRH neurons would interfere with the shift from exploratory behaviours to inward focused grooming behaviour while turning them on (with blue light) would enhance the inward focused behaviour.

The results revealed that yellow light did reduce grooming, and increased rearing and walking. This confirmed one part of the hypothesis that these CRH neurons were necessary for the mice to shift their behaviour toward more self-centered activities.

Next, the authors showed that turning CRH neurons on using blue light resulted in more time spent on inward focused grooming behaviour, and a decrease in exploratory behaviour. The information suggested the CRH neurons were sufficient to drive the switch from external-focused to internal-focused behaviour.

The only question left to answer was the strength of influence of CRH neurons on overall behaviour. To do this, they exposed the mice brains to blue light while undergoing different types of stress including the introduction of new environments and new objects. As expected, the overstimulation of these CRH neurons reduced interest in the environment and again led to an increase in grooming and self-directed behaviours.

The results reveal the importance of the CRH neurons in dealing with stress. These neurons help to dampen the impact of environmental cues to help cope with different stimuli. In addition, there appears to be natural sequence of behaviours that promote the return to a baseline state.

Yet, as seen in the final experiment, if the activity of CRH neurons is elevated, the brain may not have a natural baseline state, leading to avoidance and self-centered behaviour. This complex reaction in which some individuals tune out the outside world and exhibit repetitive, self-directed and stereotyped behaviours is seen in some people with anxiety or autism spectrum disorder. The similarity may not be indicative of cause or association, yet the results of this study suggest there may indeed be a previously unknown role for CRH neurons in some autistic-like behaviours.

## About Dr. Jaideep Bains, Ph.D.

Professor,  
Physiology &  
Pharmacology



University of Calgary

Dr. Jaideep Bains studies how stress affects brain function and connections.

His team is specifically interested in studying the effects of stress at the level of the connection between nerve cells, the synapse. His research has recently provided insight into how stress is remembered at the molecular level in the brain, and how hormones interact to feedback inhibit the response to stress through direct action on the brain.

Read more about his research on his website: [stressnomics.com](http://stressnomics.com)



# Why do we have multiple memories?

Have you ever noticed when you remember something from your past, you may also recall other events from that time. This association seems even more pronounced when remembering moving events, such as the assassination of President John F. Kennedy, the demise of the space shuttle Challenger, and more recently, the tragic events of 9/11. While many of us experience these multiple memories, the mechanism behind their formation has been a biological enigma.

The first description of multiple memories came in 1908. Back then, the evolutionary biologist Richard Semon called the phenomenon an **engram**. He defined it as an "*enduring though primarily latent modification in the irritable substance produced by a stimulus*." Essentially, particular events could somehow activate the brain such that a collection of memories could be formed.

Over the years, numerous theories regarding the formation of engrams have been made, yet none have uncovered the underlying mechanisms involved. Results from a group of researchers at the Hospital for Sick Children in Toronto led by Drs. Sheena Josselyn and Paul Frankland shed light on the subject. Their work was published in the journal *Science*.

Much like many famous engram causing events – such as assassinations, natural disasters, and acts of terror – the group used a strong emotional stimulus, fear, to invoke engrams in mice. Two different types of stimulus were used so the reactions could be interpreted separately. The team also timed the fear stimulus to determine if it correlated to engram formation.

In the first experiments, the team presented a stimulus that was separated from the fear stimulus by either six hours or twenty-four hours. As they expected, the memory of the event occurring less than six hours from the fear stimulus was enhanced, but not that of the event occurring twenty-four hours away. This helps explain why we seem to recall several memories at the same time as a major occurrence.

The team then went further into the brain to identify the mechanism behind this co-allocation of memory. In these experiments, the group focused on the presence of a particular protein known to be involved in memory, called the "Cyclic adenosine monophosphate/calcium ion-Response Element Binding protein", or CREB. Josselyn's group knew that CREB plays a significant role in the development of memories in a section of the brain known as the lateral amygdala. The levels of CREB in combination with the excitability of a neuron normally dictate whether it will be allocated into a memory.

The team wanted to determine if co-allocation of memories, engrams, also depended on CREB levels and excitability levels. The group used optogenetic techniques to modify neurons in the lateral amygdala such that blue light would excite them while red light would inhibit them. As expected, excitation led to memory allocation while inhibition prevented the process. To test CREB, a virus was used to infect cells and either increase or reduce the levels of this protein. Again, higher levels led to memory while a lack of the molecule ended up in less recall ability. These results had no dependence on time as they were artificially manipulated.

While the team proved the chemical basis for the formation of multiple memories, they still needed to show how neurons connected to form a proper engram. Amid the massive number of neurons within the lateral amygdala, hundreds would presumably be ready to allocate memories. Yet, not all of them did. There were winners and losers in the competition. There had to be a controller akin to a gatekeeper working to guide the formation of these multiple memories.

Based on the anatomy of the lateral amygdala the best candidate happened to be a group of cells known as “gamma-aminobutyric-acid-releasing parvalbumin interneurons”, or PV interneurons. Despite the long name, these cells have a simple task: inhibit widespread signaling. When the team examined these cells, they were highly active around inactive cells (“losers”) within the first six hours after the initial fear event. After twenty-four hours, however, the PV cells were quiet. In the same way, if the PV cells were inhibited, “losers” could acquire memories.

The result of these experiments offers a possible mechanism for engram creation. An initial event provoking fear is memorized by a group of lateral amygdala “winner” neurons possessing high levels of CREB and excitability. Once the winners are chosen, the PV interneurons close the gates so “losers” cannot participate. This restriction lasts for a number of hours such that any other memorable events are co-allocated to the same neurons. But after a day or so, this merging of memories no longer occurs.

The unveiling of this mechanism may help to understand why that flood of memories occurs when recalling historic occasions. But the information also could be used to help develop better memorization techniques in the future, to study for exams or remember important dates. The potential to improve memory is at hand and may one day help you to remember life better.

## About Dr. Sheena Josselyn, Ph.D.

Senior Scientist,  
Neurosciences & Mental  
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Associate Professor,  
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Toronto

Canada Research Chair, Molecular and Cellular  
Cognition

The research in the Josselyn lab is dedicated to understanding memory. To unravel the molecular, cellular and circuit processes that underlie learning and memory, her team uses a multidisciplinary approach that focuses on mouse models and attempts to translate these basic findings into humans.

Previous research from her laboratory has shown memories can be manipulated in mice by selectively silencing or activating brain cells and has provided insight into why most people do not have memories from their very early life.

Read more about her research on her website:

<http://www.josselynlab.com/>



# Can we see the mental trap of PTSD?

Post-traumatic stress disorder (PTSD) is a scourge for anyone who suffers from it. The symptoms are heartbreaking – nightmares, flashbacks, poor sleep quality, irritability, and a lack of concentration. Some even feel disconnected from reality as they perceive being trapped in a mental cage from which they cannot break free.

While medical professionals can identify the outward signals of PTSD, finding the inner cause has been difficult at best. Researchers have tried for decades to determine the cause at the psychological and eventually the neurological levels of human existence. In the latter, several factors have been associated with the onset of illness ranging from serotonin and cortisol levels to altered electrochemical signalling in the brain. Some models have been developed in an attempt to explain how PTSD may come about yet none can offer an explanation as to how that trap forms and why it is so hard to break.

There may, however, be a breakthrough in understanding the PTSD “mental cage” thanks to a Defence Research and Development Canada project at the Hospital for Sick Children in Toronto, Canada. The research team, partly led by Dr. Elizabeth Pang, have taken a different approach to examining the effects focusing on the brain in real time. Their results, which were published in the *Journal of Neuroscience*, offer a novel perspective on how traumatic events constrain the mind.

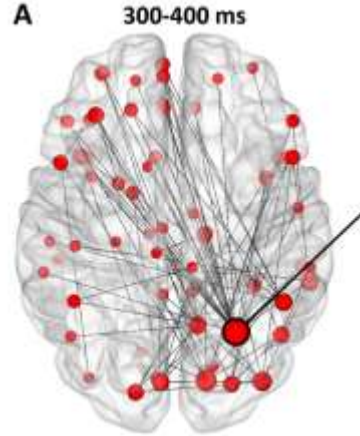
The team wanted to examine PTSD at the level of brain

processing. For Pang's group, the most effective route was magnetoencephalography, or MEG. As the name implies, the goal is to measure the neuromagnetic field in the brain and then record brain oscillatory and amplitude changes. With each reading, they could properly determine where the brain was most active and also which areas remained relatively silent.

This wasn't the first time MEG was used to examine a symptom of PTSD. Back in 2013, the technique helped to understand how trauma affects emotional processing. The results provided some perspective on why sufferers seem to be closed off. The threat detection mechanism is raised – as one might expect – and eventually a network is developed in the pre-frontal cortex to anticipate danger rather than fully process the stimuli.

A few years later, Pang's team expanded on this discovery by using MEG to provide a more comprehensive understanding of the fear factor over time. The results suggested those confirmed to have psychological PTSD had higher amplitudes of response to neutral stimuli as compared to those without the condition. This suggested the neural patterns, particularly in the first few milliseconds after a stimulus, such as a word or image, were somehow changed.

Pang's most recent study focused not on the response to stimuli but on the mechanism of processing. To do this, they invited military volunteers both with and without PTSD as well as civilians with and without mild brain traumatic injury. The



separation of these individual types could offer perspective on the difference between PTSD and brain injury. If the team were right, all four groups would end up showing distinct processing profiles.

Once the volunteers were chosen, they were monitored as they were asked to view a variety of stimuli in the form of images and words. The MEG profiles were collected and then analyzed to determine both the location of the magnetic fields and also the frequencies to assess mental function in the brain. Once this was completed, the team could then examine the differences between the four groups.

When the results came back, those suffering from PTSD appeared to be consistently engaged in a mental loop of brain activity. Based on the frequencies, the team realized these processes were associated with memory and information processing. This overabundance of one type of frequency prevented others, including those linked to conscious thought, from being used appropriately. It's why PTSD sufferers did not respond as strongly as those without the condition to the various stimuli.

The examination into the difference in frequencies also provided some perspective on how those with PTSD suffer. They are locked in a world of memories and continual processing with no apparent means for escape. This would directly impact their ability to fully experience the stimuli of the environment affecting the quality of their lives. Over time, this inability to function in the social context could eventually erode other aspects of self-esteem and self-worth leading to anger, aggression, depression, and self-harm.

The results do, however, open a door to possible future treatment options. By helping to balance out the frequencies, the effects of the trap may be lessened and a person's quality of life may improve. Although no indicated treatments are available at the moment, the use of MEG may be able to help speed up the search for the right key to that mental cage and provide these people a better quality of life.

## About Dr. Elizabeth Pang, Ph.D.



Neurophysiologist,  
Associate Scientist in  
Neurosciences &  
Mental Health  
The Hospital for Sick Children

Assistant Professor, University of Toronto

Dr. Elizabeth Pang studies sound processing in the brain in children. This approach allows her to investigate dysfunctions in children with Landau-Kleffner syndrome and autism spectrum disorder, to see if patterns of change could serve as fingerprints for various disorders. Her interests also include examining higher cognitive functions such as speech, language and math processing.

View Dr. Pang's profile at SickKids:

<http://www.sickkids.ca/AboutSickKids/Directory/People/P/Elizabeth-Pang.html>

# How does loneliness lead to depression?

*"The most terrible poverty is loneliness, and the feeling of being unloved."* -Mother Teresa

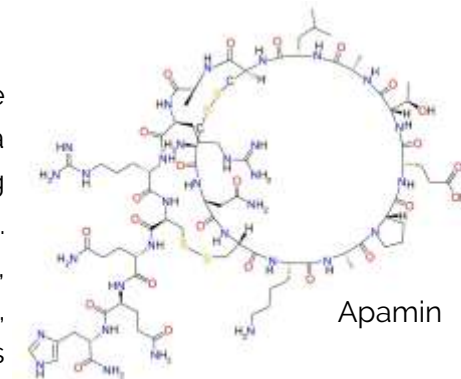
At one time or another, everyone experiences moments of social isolation, when there is no one around and the world is confined to one's own existence. In short bursts, these moments of solitude can be therapeutic and may lead to emotional regeneration or creativity. Yet when loneliness becomes chronic, the effects may be deleterious to one's emotional health.

Humans have a fundamental desire to be needed. The absence of this can lead to a variety of mental health conditions, including addiction, antisocial behaviour and depression. While from a purely psychological perspective, this consequence of isolation is well-defined, at the physiological level, the mechanisms have remained only vaguely understood. But that may now change thanks to a team of researchers from the University of Toronto, led by Dr. Evelyn Lambe. The group published a study examining the effects of social isolation on the mouse brain. The results, published in the journal, *eLife*, point to a specific mechanism and more importantly, a possible route for treatment.

The experimental procedure was relatively straightforward. Fifty-seven mice were kept either individually (29), or in small groups (28) for at least seven weeks. At this time, the mice were tested to determine any anxiety and/or depressive behaviours.

Once the testing was complete, the brains of the mice were examined to determine if there were any differences in physiological function.

The first noticeable change in socially isolated mice was an increased level of anxiety as well as propensity to eat more food. This in essence mimicked what is seen in humans when they are in similar states. The mice also appeared to have less interest in seeking pleasure either through exercise or in eating sweets. This too mirrored the symptoms seen in humans suffering from depression.



At this point, the researchers wanted to venture into the brain to find out what might be happening at the molecular level. The group focused on the reward centre of the brain, known as the dorsal raphe nucleus and the cells responsible for pleasure, 5-HT neurons. If the suspicions were correct, the neurons in socially isolated mice would react differently than those from those living in groups.

As expected, the neurons in lonely mice were less excitable and did not respond to normal levels of stimulation. Upon further analysis, this change was due to an elongated resting period between neuron firings. This condition, known as increased afterhyperpolarization, not only offered perspective on the effect of social isolation, but also pointed to a particular suspect. The state of afterhyperpolarization is partially controlled by a number of proteins known as small-



conductance  $\text{Ca}^{2+}$ -activated  $\text{K}^{+}$ , or SK channels. These proteins are found in various parts of the body including the brain. If the group's hunch was correct, then blocking these proteins from working properly would reverse the effects of isolation.

Thankfully, there was a rapid means to perform this experiment as a chemical known as apamin had been shown to block these channels and restore normal firing. When the molecule was used in the experiments, sure enough, the difference between the isolated mice and the group-housed ones disappeared. The team then went even further to identify which specific SK channels were responsible. It turned out the subtype known as SK3 was uniquely involved in the process.

At this point, it was time for the ultimate test. They attempted to restore normal behaviour in the socially isolated mice by administering apamin to the animals. In every case, when the chemical was used, the mice improved. The team had found – at least in mice – exactly how loneliness leads to depression.

For the authors, this incredibly important discovery is just the first step. With the mechanism unveiled and a possible treatment in hand, they can perform even more experiments targeting SK3 in the hopes of finding a possible therapeutic approach to depression. Should they be successful in this venture, they may be able to explore avenues for human treatment.

While this therapy remains years in the future, the team can rest easy knowing they have finally unlocked a long-standing mystery. This information also may offer those who suffer from social isolation an appreciation of what is happening at the molecular level. It may also engage them to find solutions as they now know the effects may be reversible.

## About Dr. Evelyn Lambe Ph.D.

Associate Professor,  
University of Toronto

Canada Research Chair  
in Developmental  
Cortical Physiology



The Lambe Lab research team focuses on the prefrontal cortex, a brain region critical for attention as well as the regulation of anxiety. Her studies aim to characterize circuitry in this brain region, and how it is changed during development, and by molecular, pharmacological, and behavioural manipulations.

Such information is important to identify vulnerabilities in the development of brain circuitry and to design novel therapeutic interventions for attention and anxiety disorders.

View Dr. Lambe's profile at University of Toronto:

<http://www.physiology.utoronto.ca/content/evelyn-lambe>

# Could social interaction improve language learning?

Acquiring a language is a difficult process. One of the best ways to succeed involves the use of a tutor. This one-on-one interaction allows for direct learning as well as interaction without distraction. Usually, the teacher is an expert in that specific language. But when it comes to learning a mother tongue, the most useful tutor happens to be an infant's parent.

Babies actually begin to learn speech before birth as they gain perspective on phonetics. Afterwards, they rely on their parents to provide them with a variety of lessons to improve their ability to communicate. However, not all methods are effective and several parameters such as the frequency, amplitude, and timing of speech are critical in determining how well a child will attend to speech and, ultimately, learn speech sounds.

A team of researchers at McGill University led by Dr. Jon Sakata have published a study in the *Proceedings of the National Academy of Sciences* demonstrating how and why vocal learning is heavily influenced by personalized, face-to-face tutoring. They accomplished this not with humans, however, but the zebra finch, which shows remarkable similarities to humans in terms of vocal learning.

The experimental process performed by Sakata's team was rather straightforward. Young finches around 6 weeks of age were placed into one of two situations. The first, known as social tutoring, involved placing the birds in a cage beside another cage containing an adult male finch ('tutor'). The second was passive tutoring in a soundproof box such that exposure to songs occurred using a speaker. The learning experience occurred over five days after which point the birds

were housed individually for at least two months to allow their songs to develop. The authors found that the adult songs of socially tutored juveniles were significantly more similar to their tutors' songs than those of passively tutored juveniles, indicating that socially tutored birds learned their tutors' songs better. Additionally, they found a very close relationship between attention and song learning; juveniles that were more attentive to their tutors' songs showed significantly better song learning.



There was another interesting outcome of this experiment. The tutors not only directed their songs towards juveniles but also, as might be expected, directed their songs away from the young birds. The students, in turn, seemed to discern between the two types. In particular, they paid more attention to the songs that were intended for them. The authors found

introductory notes were produced more frequently during the directed songs; in some sense, tutors could have been doing their best to get the students to pay attention. In addition, the lesson sections, known as motifs, were spaced further apart, giving the younger birds an opportunity to process and learn. In human terms, this delay matches the slower speech adults use when teaching children. The final observation was a change in the pitch of tutor zebra finches' songs, which was lower when tutors sung to students. This was quite interesting as humans also tend to change the pitch of their speech when talking to children, albeit in the opposite direction.

The group wanted to find out if their observations were unique to tutoring. They conducted the same experiment with one

difference. Instead of juveniles, adult females were the audience members. The results were fascinating. The males produced more introductory notes when singing to females, just like with the juveniles, and this could have served to increase female attention to the male. But when it came to motifs, males did not space them out when singing to females.

The authors then investigated whether social tutoring had effects at the neurobiological level. To do this, they performed the tutoring experiment but only for a few hours. The team then examined the brains of these students in the hopes of seeing a difference in one particular cellular factor known as Early Growth Response Protein 1 (EGR-1). The protein is involved in song control and learning in finches and could also be important in recognition memory in humans. For the authors, EGR-1 offered the perfect marker to follow the progress of education.

The team was particularly interested in looking at neurons in parts of the brain that mediate attention since attention and learning were closely related. As such, they examined EGR-1 expression in neurons from the locus coeruleus, which is responsible for attention, and in the ventral tegmental area, which is involved in reward. As expected, juveniles with social tutoring had a significantly higher level of EGR-1 expression in neurons in both regions compared to birds that were not tutored, or that received passive tutoring.

This study offers a reason behind the supremacy of social interaction in learning a language. By having a tutor who focuses on helping the individual student, the brain is activated in such a way that it may be able to acquire and retain more. This study suggests more can be accomplished with a tutor than simply relying on dictionaries, textbooks, and computer software.

## About Dr. Jon Sakata, Ph.D.

Associate  
Professor,  
Department of  
Biology, McGill  
University



Dr. Jon Sakata's team uses neurophysiological, immunocytochemical, and neurochemical tools to reveal mechanisms underlying vocal learning, motor control, and social behavior.

His research shows that social interactions promote and guide vocal learning in songbirds as well as humans.

He is also interested in how the structure and organization of vocal signals vary across social contexts, in birds, humans and other species.

Learn more about Dr. Jon Sakata on his website:

<https://sakatasongbirdlab.wordpress.com>

# Does sleep help us remember?

Improving memory is a quest that never seems to end. For centuries, humans have attempted to find the right combination of social actions to better retain what we've learned. Over the years, some options have shown promise such as fasting and strenuous exercise. While effective, they are not particularly popular. Then there's the odd concept of intranasal injection of insulin. It goes to show that an idea with promise might not be the best idea.

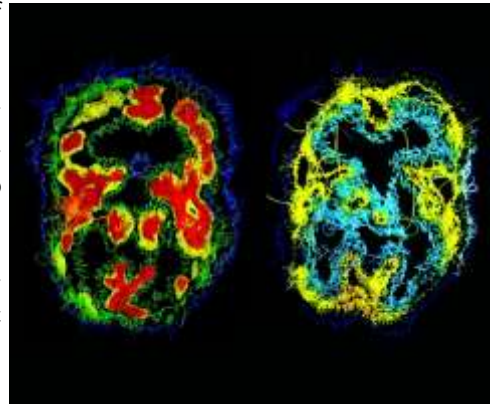
All these activities, regardless of their attractiveness, have one thing in common. They all stimulate an area of the brain responsible for catalyzing long term memory – the hippocampus. While it is not a storage house for memories – they are stored throughout the brain – this area does seem to be responsible for understanding one's place in an environment (called spatial memory), and autobiographical events (referred to as episodic memory).

There is another means to improve memory through stimulation of the hippocampus. It's sleep and in particular rapid eye movement (REM) sleep where dreams typically occur. As our bodies rest, our brains are catching up with our experiences, processing them and placing them into our neural network for use at a later time, a process named memory consolidation.

The involvement of REM sleep in memory consolidation has been suspected for several decades, yet never proven. Researchers can show sleep deprivation leads to lower

memory retention, as well as self-confidence and psychological mood, yet the underlying mechanism has yet to be elucidated.

That may now change thanks to researchers from McGill University. A team led by Dr. Sylvain Williams, has recently revealed that REM sleep is indeed causal for memory consolidation in mice. The study, which appears in the journal, *Science*, also found a part of the brain that may be the lynchpin to foster mouse memories.



Visualizing the brain during REM sleep

The group used mice for the experiments so they could examine and follow hippocampal electrical activity. But the target of the experimental manipulation was a different area of the brain known as the medial septum. Previous research had shown that neurons of this regions are connected to the hippocampus and release the neurotransmitter GABA to generate a particular type of oscillating electrical current – known as theta waves - during REM sleep.

The team theorized these waves were responsible for memory consolidation and as such, the medial septum played a causative role.

In order to prove this, the researchers used an elegant approach involving optogenetic manipulation of medial septum neurons. These neurons were modified so that a flash of yellow light would inhibit them, and consequently reduce GABA release in the hippocampus.

The first experiment involved the use of yellow light to stop GABA release during REM sleep. As expected, the size of the theta waves in the hippocampus was significantly reduced. This in itself was an achievement as it showed the medial septum was indeed responsible for the production of theta waves in the hippocampus. But this wasn't the ultimate goal.

The next experiment went to the heart of the theory. Mice were exposed to two different objects and then allowed to sleep. Some of the mice were treated with yellow light during REM sleep while others were left as controls. The next day, the mice were returned to the cage but one of the objects had moved. If the team was correct, the control mice would ignore the unmoved object – having already memorized it. In contrast, the mice treated with yellow light would explore both objects as if they were new. The mice did exactly as expected. The inhibition of medial septum neurons resulted in a lack of memory formation.

The group went on to attempt other experiments to determine which types of experiences were under this similar control. Fear and contextual memory recall experiments revealed the same outcome. However, when a cued recall test was performed, there was no change. This latter result was expected as this type of memory occurs in a different area of the brain.

For the authors, the study proved their theory, at least in mice. Yet, there are hints these results may have usefulness in the human context. By stimulating medial septum neurons that release GABA, we may be able to develop a sleep-based route to improve memory. While this may be years away, the promise is quite high thanks to a recent though unrelated study examining the use of theta wave stimulation in epileptic patients. In this study, not only does the condition improve, but the volunteers also experience an enhancement in memory consolidation.

About Dr.  
Sylvain  
Williams,  
Ph.D.

Professor, McGill  
University



Researcher,  
Douglas hospital research center

Memories are central to our personal identity. Yet, how memories are created or recalled remains incompletely understood. The hippocampus, which is the learning and memory center of the brain, contains millions of neurons that have to synchronize together seamlessly for memory to function. When neurons synchronize brain rhythms can be recorded. The Williams hippocampal rhythm laboratory aims to understand how different types of neurons synchronize and participate in rhythm and memory generation.

Learn more about Dr. Sylvain William's research on his website:

<http://sylvainwilliams.ca/>



# Does the brain have volume control?

It's an experience most of us have encountered at one time or another. We turn on the radio, stereo, television, or YouTube video and the volume is just too loud. Our reactions are almost immediate combining a mixture of frustration, helplessness, and a need to turn down the sound. Thankfully, we quickly can adjust the dial, slider, or remote to achieve a more comfortable level.

Now imagine that volume control is permanently fixed in one spot. If the levels are too high, you have to find other ways to deal with the auditory intrusion. It can lead to pain, irritability, and possibly an alteration in normal behaviour. In essence, when the sound is too loud, you suffer.

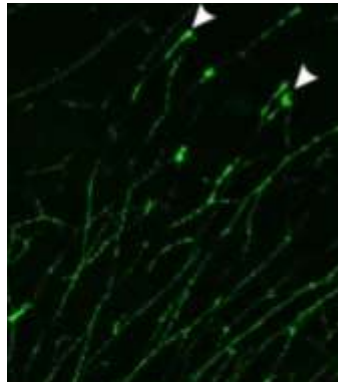
This scenario may be occurring in some individuals with autism. However, rather than sound, the culprit is the movement of chemical ions, which like a battery produce small amounts of electrical charge. These act as signals in the brain, and are known as excitatory transmissions. When there are too many of these excitations occurring at once, the smooth harmony of brain function turns into a cacophony leading to an inability to process properly. This in turn may lead to a variety of outward symptoms such as impaired memory, lack of social skills and repetition of certain actions, known as stereotypy.

Figuring out how the brain develops this fixed electrical volume control has been a challenge. Yet there may be a breakthrough thanks to a team of researchers led by Drs. Steven Connor and Ann Marie Craig at the University of British

Columbia. The group has discovered a possible volume control switch during development. Based on their research, which is published in the journal *Neuron*, the answer may lie in a single protein known quite simply as MDGA2.

In the brain, there are two specific types of synapses responsible for electrical transmission, excitatory and inhibitory. As the names imply, these structures control the levels of

MDGA2 on Neurons



signal going through the brain. In healthy individuals, there is equilibrium between the two types of signals. Yet in several cases of autism spectrum disorders, there appears to be a mismatch in which there is more excitation. For Dr. Craig's group, this imbalance provided a basis for their search.

Their efforts paid off in 2013 when they discovered a group of proteins officially called MAM

domain-containing glycosylphosphatidylinositol anchors (thus the

MDGA). They used lab cultures to show that one of these proteins, MDGA1 suppressed the inhibitory side of volume control, suggesting deletion or at least reduction of these proteins might somehow cause an imbalance. But to show this concretely, they needed to move from the lab to mice. When the shift was made, there were quite a few surprises in store.

The first was the absolute necessity of another form of MDGA, MDGA2. Without this protein, the mice died. When mice carried only one copy of the gene, rather two, as seen in normal animals, less protein was, yet, the animals lived.

Once the testing on these mice with less MDGA2 began, a second surprise emerged. Based on their 2013 results, the team expected a reduction in MDGA2 would lead to an increase in the inhibitory transmissions. This was not the case. Instead, the balance shifted heavily to excitation. When the team examined the hippocampus, they found the actual density of excitatory synapses was increased.

To be sure the results were occurring in real-time the team used fluorescent dyes that become brighter when cells are active, called voltage-sensitive dyes.

As previous results suggested, the amount of activity – the volume – in the brain was strikingly higher. There was a higher degree of functional connectivity throughout the cortical surface of the brain. This has been seen in autism patients assessed using fMRI. This showed this genetic change was leading to a dramatic, widespread shift in activity, not only in the hippocampus. The only unsurprising result was that these mice with reduced MDGA2 exhibited numerous symptoms associated with autism spectrum disorders. They had impaired cognitive performance, and social interactions and made repetitive movements.

At the most basic level, this study unveiled how one particular protein, MDGA2, may be involved in the development of autism. The authors therefore suggested this mouse model may serve well for future studies on the neurodevelopment of autism. From a larger perspective, this study also revealed how a single genetic change had a drastic effect on an individual.

The concept of a single protein having such control over the volume of electrical transmissions suggests every molecule matters in the developing brain. It's also indicative of the general fragility of brain development. Even a minor alteration, whether genetic or environmental, can have lasting impacts.

## About Dr. Ann Marie Craig

Professor of Psychiatry,  
University of British  
Columbia  
Canada Research Chair  
in Neurobiology



Specialized connections between nerve cells, called synapses, are the basic units of communication in the brain. Dr. Ann Marie Craig and her team are interested in how nerve cells in the brain make synaptic connections and modify connections with experience.

Her team studies these questions of synapse development and synapse plasticity mainly from a cellular and molecular viewpoint. This fundamental research bears directly on psychiatric disorders. Genetic variants in multiple synaptic organizing complexes are linked to autism spectrum disorders and schizophrenia. The cellular, molecular, and animal studies they are developing contribute to rational and effective therapies for these disorders.

View Ann-Marie Craig's profile at UBC Neuroscience:

<http://neuroscience.ubc.ca/people/Craig>

# How does the brain deal with motion?

Most people take motion-sensing for granted. Our eyes pick up on something moving and our brains are sent a signal to let us know something has occurred in our space-time continuum. Despite the simplicity of the task, the mechanisms underlying this ability are incredibly complex. They have been studied for over fifty years and the neural circuitry underlying motion detection is probably the best described circuitry in the brain. Yet, researchers have not discovered all the answers.

At the back of the eye is the retina, which essentially acts as the recorder and translator for higher visual centres in the brain. Light enters the pupil and through a multi-layered process, complex images are simplified and translated into an electrical code (consisting of strings of 0 and 1s, much like a computer). Specialized retinal circuits working in parallel are used to encode various aspects of the visual scenes including color, motion, form etc. To accomplish this task, a variety of cell types are needed including:

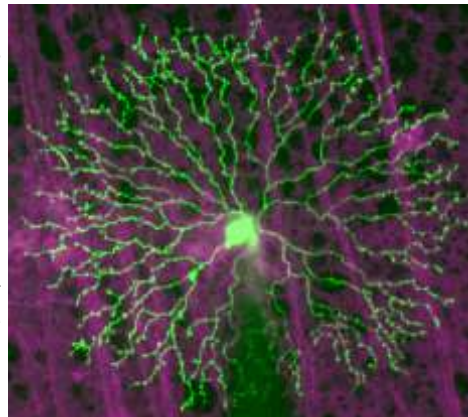
- photoreceptors, which respond to light
- bipolar cells, which connect photoreceptors to output retinal ganglion cells (RGCs);
- Inhibitory amacrine cells, which control bipolar cell signals to RGCs; and
- RGCs, which amalgamate signals from bipolar and amacrine cells to create a binary code;

The direction of moving objects is computed by specialized set of RGCs – aptly named direction sensing cells – which respond to motion only along a 'preferred' but not 'null' direction, aligned

with the cardinal axes (N,S E or W). Research into the mechanism behind direction sensing has implicated three neurotransmitters: glutamate, acetylcholine (usually called ACh) and gamma-aminobutyric acid, also known as GABA.

Much of the ability of RGCs to encode direction arises from inhibitory signals evoked in the cells during null direction motion, provided by a particular group of amacrine cells, known as starburst or SACs. However, the same SACs producing

critical inhibitory signals required for direction selectivity also send excitatory signals, through the release of ACh. The enigma of what might be best described as applying the brake and the accelerator at the same time has confused researchers for several decades. A recent study by a team led by Dr. Gautam Awatramani at the University of Victoria, may now provide an answer to this long-standing conundrum.



A starburst amacrine cell

The team worked in the lab using retinas isolated from mice, and kept alive in a dish by providing them with oxygen and other nutrients.

In these conditions, the RGCs continue to respond selectively to a particular direction. The setup provided a unique preparation for probing the properties of an intact neural circuit. They used an intricate method of measurement using finely pulled glass electrodes to measure electrical responses from single cells. They could thereby identify the physiological properties of direction coding circuits with incredible resolution.

As these experiments were performed, an interesting picture

began to develop. As expected, they found SACs provided, under natural viewing conditions, both excitatory and inhibitory signals required for RGCs to produce direction selective signals. But they could finally see how the brake and accelerator signals worked together. It turns out SACs ACh/GABA signalling had an incredibly precise timing schedule. During non-preferred directions of movement, SACs sent out ACh and GABA at the same time leading to a net inhibition of the RGCs. But when the preferred direction was recognized, ACh signals were produced a few milliseconds before GABA signals. This short but effective shift led to a strong stimulation the RGCs. This maintained the recognition of direction and also time, even if it would be imperceptible to most.

The result was not only fascinating but also controversial. The idea SACs alone could drive direction coding went against an emerging theory stating the drivers of direction selectivity were the bipolar cells. To substantiate that SACs alone could drive direction selectivity in RGCs required Awatramani's team to take their study of SACs to another level using optogenetics. This technique allowed them to directly manipulate genetically modified SACs using light and prove their results conclusively. The actual experiment involved first blocking photoreceptors and bipolar cells with drugs so they would not send any signals; under these conditions if any direction was sensed and coded, it would have had to come from the SACs, which were genetically modified to be themselves light-sensitive. When they stimulated the SAC network, the RGCs responded in a direction selective manner. The experiment was a complete success, nailing down the role for SAC ACh and GABA in the direction selective circuit.

The results of this study published in the Journal *Neuron*, provide a better understanding of the complexity of direction sensing and offer a mechanism upon which future experiments can be designed. However, on a grander scale, the results suggest co-release of GABA/ACh SACs may be a perfect model for ensuring high fidelity inhibition/excitation in other parts of the brain. By having a multi-purposed "cell" with the capability of sustaining signal integrity, high-fidelity neural computations can be maintained under diverse conditions. This may ultimately serve to help improve computer network design, internet reliability, and even the resolution of audiovisual devices.



## About Dr. Gautam Awatramani

Associate Professor, University of Victoria

Dr. Gautam Awatramani's research interests are focused on circuits involved in two sensory systems: those in the retina and the auditory brainstem. His lab uses an interdisciplinary approach to understand how various neural computations are performed at the circuit and molecular level.

Learn more about Dr. Gautam Awatramani :

<https://www.uvic.ca/science/biology/people/faculty/facpages/awatramani.php>

# What makes stationary objects look like they are moving?

Back in 1834, whilst walking along Scotland's Loch Ness, the esteemed researcher Robert Addams reported on a strange phenomenon. As he looked upon the Falls of Foyers, he seemed to notice movement in the rocks. More specifically, they were moving in the opposite direction of the water. Knowing stones were immobile, he began to wonder how his eyes had deceived him. He conceived a theory in which the eyes were trained to follow motion and improperly lead to motion perception in the inert objects.

We now know this phenomenon as a motion aftereffect (MAE). As the eyes witness motion for extended periods of time, the person becomes adapted to this occurrence and may impart motion on other objects. Over the last 50 years, several parameters involved in MAE were determined. Two of the most influential happened to be the size and contrast of the object in motion. As one might expect, increasing contrast between the object and the background led to greater MAE. Yet in terms of size, smaller objects appeared to have greater influence than larger ones. As the object grew in size and contrast, the ability to perceive its motion – and thus develop MAE – was reduced. These latter results have been confirmed using velocity tracking of the eye.

Despite an outward understanding of the effect of motion and perception, there was until recently very little information on the actual neurological mechanism. While many believed this was occurring solely at the retina of the eye, others suggested

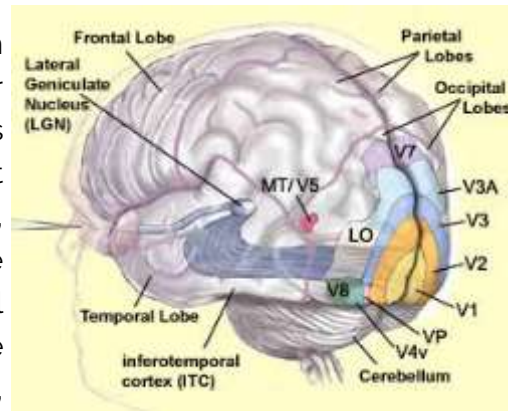
there may be a role for a part of the brain called the middle temporal region of the visual cortex, in particular visual area 5 (MT/V5). How this may occur at the level of neuronal firing has not been fully determined.

Now we may be one step closer thanks to Drs. Liu D. Liu and Christopher Pack at the Montreal Neurological Institute at McGill University. In collaboration with Dr. Ralf Haefner at the University of Rochester, they have documented a neurological

basis for visual motion perception and how it can be misinterpreted. Their results are published in the journal *eLife*.

The team performed their studies in two rhesus monkeys such that both their eye movements and brain functions could be monitored in real time using a combination of infrared eye tracking and electrophysiological recordings of the MT/V5 region. Before the experiments could begin, the animals were trained to fix their vision on specific dot in the middle of a screen. This was the control point.

For the experiments, at different intervals, the control dot would disappear as another one appeared in a different area. The monkey would follow the dot as trained and data on eye movement and neuron firing was collected. The test was conducted between 20 and 40 times to provide some statistical significance. The test was performed using a variety of dot sizes and contrasts in order to determine how these parameters affected motion perception.



The MT/V5 region



When the testing was complete, the researchers conducted a series of data analyses to correlate eye movement with firing neurons. If there was little correlation between movement and neural response, the action was considered to be noise. With this in place, they could then review the results and determine how size and contrast affect motion perception. The results from eye tracking showed larger size and greater contrast led to poor motion perception. This was no surprise. But when they examined how the brain contributed to this finding, the team found evidence for an unforeseen function.

The number of firing neurons in the MT/V5 region increased with size of the object as expected yet, the location of this increase was limited to areas associated with optical tracking of the object. The result was the production of non-selective firing, also known as noise. In contrast, neurons responsible for determining the surrounding environment did not fire as often as anticipated. As a consequence, the monkeys' ability to distinguish the object and the environment was hampered.

For the authors, the results hinted at a possible mechanism for the phenomenon. With increased size and brightness, a type of neural desensitization occurred in the MT/V5 region as a result of increased noise. To deal with this, a trade-off happened in which neurons responsible for perceiving the surrounding environment did not fire as often as needed leading to spatial suppression and poor motion perception. In essence, the animals were desensitized to the object and as a result, were unable to follow it in relation to the surrounding area.

While the research offers perspective on the possible neurological mechanism behind the inability to properly perceive motion, the authors also note this type of spatial suppression is also seen in certain populations such as the elderly and also those with schizophrenia. The authors suggest this may be an area worth investigating in the future.

The study may also offer some perspective on Robert Addam's quest to understand why he saw those moving stones. The large and highly contrasting water from the Falls of Foyers led to an imbalanced firing of neurons in the MT/V5 region akin to desensitization. With spatial suppression taking over to account for the noise, the trade-off would result in assigning movement to the surrounding area and making something he knew to be inert, seem to be in motion.



## About Dr. Christopher Pack, Ph.D.

Associate Professor, McGill University  
FRQS senior scholar

One of the goals of the research in Dr. Christopher Pack's laboratory is to develop a quantitative understanding of how different aspects of neural activity relate to memory, perception and behavior. He is particularly interested in the ways in which subjects use eye movements to scan their surroundings.

Learn more about Dr. Chris Pack on his website:

<http://packlab.mcgill.ca/>

# Why do some people have trouble playing “Freeze”?

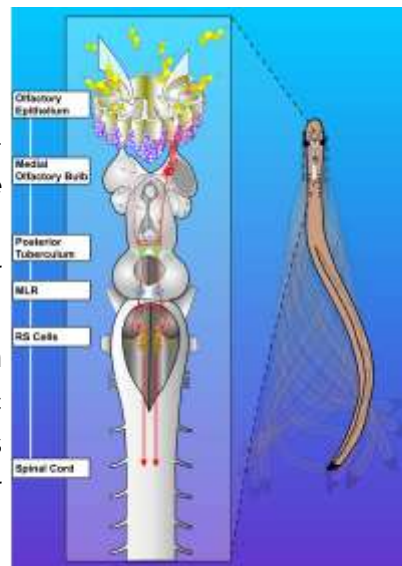
On the playground, a popular game for kids of all ages is “Freeze.” The concept is rather simple. A leader tells the participants they are free to move around until everyone is told to freeze in place. Those who don't suddenly stop are notified they are out and the game continues. It's a great way to learn how to deal with environmental stimuli and also how to better control locomotor abilities. But most of all, it's a great deal of fun.

For neuroscientists, understanding how we move in the environment – better known as locomotion – and freeze, also has been an enriching experience lasting well over half a century. Back in the 1940s, researchers learned one of the headquarters for movement was in a region of the brain stem known as the reticular (literally networked) formation. Even closer examination in the 1960s revealed a specific area within this formation devoted to making us move. It was called the mesencephalic locomotor region or MLR for short.

Finding the area was just the first step. Researchers still needed to learn how the cells in this region controlled running and walking. Unfortunately, due to the complexity of the human body, finding the answer to this question was simply not possible. To have a better idea, a much simpler nervous system was needed. Routine go-to animals such as cats, rats, and mice were also too complex for this task. Researchers needed to go even further down the evolutionary tree.

Eventually, the optimal animal was found in the form of the lamprey. It's a small, jawless fish with a fully functioning nervous system that appears to be an early ancestor of the human nerve network. It also has the MLR meaning it represented a good model for studies on locomotion.

The research took a few decades but Dr. Réjean Dubuc at the Université du Québec in Montreal reached the point where he and his colleagues could provide an understanding of how the lamprey starts to move, or in this case, swim. They found two different types of lamprey locomotion. The first, sensory-evoked locomotion, is based on a stimulus, such as touch. A sensory signal is integrated in the brainstem and then sent down to the spinal cord to produce movement. But, locomotion is often initiated in response to internal cues. This is where the MLR comes into focus. This area sends out signals to the spinal cord to initiate locomotion. As for what controls the extent of movement, this responsibility falls on a group of cells known as reticulospinal (RS) cells. As the name implies,



The lamprey nervous system

they link the reticular formation with the spinal cord. The MLR projects to these RS cells and sends them electrical signals. It's up to them to determine how to translate this into action. Dubuc has found that much like a dimmer switch, the RS cells can interpret the intensity of the MLR signal and then control the intensity of the locomotor output.

While Dr Dubuc's work provided an explanation of how we

begin locomotion and also the type of movement we may choose, there was still one unanswered question: how do we freeze? Thankfully, that answer – at least in lampreys – has now been found. Dr. Dubuc's team revealed in the journal *Cell Reports* how a specific population of RS cells are responsible for slowing down and eventually coming to a stop.

When Dubuc's team examined the population of RS cells, they realized there were three different types of activities upon MLR stimulation. These were conducted by separate groups of cells. One was activated at the start of movement in the form of a burst of discharge. Another set maintained movement continually responding to the MLR signal. Finally, there was a group activated – also in the form of a burst – to halt movement.

What intrigued Dubuc's team was the burst occurring at the end of the stimulation, which seemed to indicate a 'stop' signal. When chemicals known to stimulate these now-named 'stop cells' were used, swimming was indeed halted suggesting they were responsible for a cessation of locomotion. But when other experiments following these 'stop cells' were performed, the results revealed much more than an 'off' switch.

The 'stop cells' conducted their burst during active swimming, meaning the stop signal was not immediately obeyed by the rest of the body. Time was needed to respond appropriately. In addition, the cells were not fundamental to stopping. When they were inactivated, the lampreys still managed to stop swimming although the ability was impaired. This latter observation suggested these cells were perhaps not the only ones to control stopping; rather they offered a signal to prompt more rapid stopping action.

The results of this study reveal a rather complex set of actions required to efficiently stop in place, particularly based on environmental cues. Yet, there is enough information to help provide anyone failing at the game of freeze with an excuse. Simply blame the RS cells for not properly listening to the MLR. Granted, it may not be enough to get back into the game, but it will definitely make for an interesting discussion as you sit with the others who also forgot to stand still.

About  
Dr.  
Réjean  
Dubuc,  
Ph.D.



Professor,  
Université  
du Québec à Montréal  
Professor, Université de  
Montréal

Dr. Réjean Dubuc's research aims to understand rhythmic activities such as locomotion and breathing. By studying the simple nervous system of the lamprey, his team gains an understanding of the connections and properties of the neurons involved in movement. These discoveries help better understand changes that occur in certain disorders such as Parkinson's disease.

View Dr. Réjean Dubuc's profile:  
<http://www.sap.uqam.ca/kin/personnel/Dubuc.html>

# How does the brain deal with starvation?

If you happen to watch any survival-based reality series, such as Canada's "Survivorman", you'll come to realize starvation has a dire effect on the body. A person becomes weak, disoriented, and begins to crave protein. In humans, this is considered to be normal as we are considered omnivores. Yet, this effect also can be seen in other species, including one usually considered to be herbivorous.

The common fruit fly, *Drosophila melanogaster*, primarily feeds, as the name implies, on decaying fruit and the microorganisms inhabiting it. Yet, when this insect undergoes starvation, its tastes change. After several days with no food, they turn carnivorous and even cannibalistic. This dramatic change in food choice, while observed, still has yet to be fully understood.

One theory suggests the fly's neurological taste mechanisms change during starvation. The insect somehow is able to desensitize to non-traditional flavours of different nutrient sources. Although several different taste types exist, for the fruit fly, the main deciding factor is bitterness. If a food is bitter, it is normally avoided. However, in times of starvation, this awareness of bitter flavour may be turned off.

A team of researchers from the University of British Columbia led by Dr. Michael Gordon, investigated this theory in the hopes of finding an answer. Their work, published in the journal *Current Biology*, focused on bitter taste receptors during

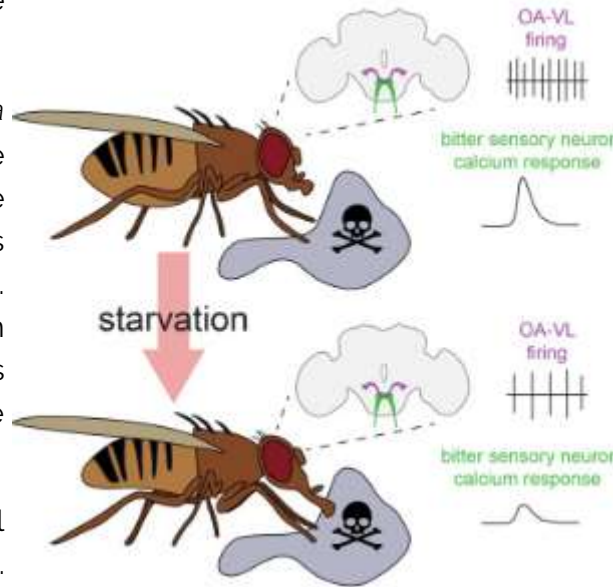
starvation. Their results confirm the theory although the actual mechanism behind this switch is far more complicated than once believed.

The team focused on a group of neurons known as gustatory receptor neurons, or GRNs. These are involved in taste and can differentiate between sweet and bitter. These neurons connect to an area of the brain called the subesophageal zone, or the SEZ. When a fly detects a flavour, the GRNs send a signal to the SEZ at which point the fly can determine whether the nutrient is worth eating.

However, during starvation, a change occurs in how taste is transmitted. Sweet GRNs are more active while bitter GRNs are suppressed. In essence, the fly becomes less likely to notice a bitter taste during starvation. This in turn, may

allow flies to consume unconventional foods.

The team first wanted to find the neurons responsible for this change in taste sensation. Using fluorescent markers, they were able to identify a group of suspect neurons lying near the bitter GRNs. This cluster, known as the OA-VLs (for ventrolateral cluster of octopaminergic neurons), produced two neurotransmitters called octopamine and tyramine. Last year, both chemicals had been implicated in fruit fly starvation / starvation resistance and appeared to be an excellent starting



point.

At this point, the group needed to find out if the OA-VLs had any effect bitter taste sensation. To accomplish this, the team altered the ability of these neurons to send signals to the GRNs. When signals were inhibited, the flies lost their aversion to bitter chemicals, just like flies that had been starved. This suggested there was indeed a link between the cluster and the GRNs.

While the experiments offered visual evidence, the team still wanted to find out whether this was an indirect or a direct effect. In other words, they wanted to find out if the lynchpins of this switch in taste were octopamine and tyramine. They did this by adding these chemicals directly to the brain to see if there would be any effect. As expected, bitter sensitivity returned during starvation. However, this did not increase sensitivity in normally fed flies. This suggested the effect of these neurotransmitters was reflective of the starvation state.

The results of this study reveal a remarkable process of bitter taste desensitization. Instead of being controlled by the GRNs themselves, the effect is governed by the OA-VLs through the secretion of octopamine and tyramine. During starvation, the effect of the neurotransmitters – bitter sensitivity – is dampened. This enables the fly to seek out any source, regardless of taste, in the hopes of gaining sufficient amounts of nutrients to survive. Once the fly has been properly fed, bitter sensitivity returns to normal.

The effects of starvation are obviously intense and this study offers perspective on how the brain attempts to deal with the condition. Depending on the severity of nutrient loss, the brain may even cause a fruit fly to eat unconventional foods. But this shouldn't come as a surprise. Whether you happen to be a human or a fly, when the situation is dire, there is every reason to believe the individual will eat just about anything to survive.

## About Dr. Michael Gordon, Ph.D.

Associate Professor,  
University of British  
Columbia



The sense of taste provides animals with critical information about the nutritional suitability of foods. The Gordon lab, uses the powerful fruit fly model system to understand how neural circuits process taste information and control feeding behaviour.

The Gordon lab also uses feeding and other motor circuits to probe the molecular control of neural development.

Learn more on the Gordon laboratory website:

<http://www.zoology.ubc.ca/~gordon/>



# Why do we need that sip of water before bed?

Have you ever noticed a tendency to drink some water right before going to bed? It's a common occurrence although the reason behind this action is not well understood. This unfortunately has led to a rather large-scale debate regarding the potential health benefits and risks of having a swig before sleep.

Over the years, some researchers have suggested the action is based on a physiological need, such as elevated body temperature or low water concentration in blood. Others have suggested this action is psychological rather than biological in nature as it increases the chances for REM sleep and dreaming. Then there are those who feel this action has no health value at all. After all, drinking immediately before sleep means you will no doubt have to disturb your regular period of rest for a quick bathroom break.

For a group of researchers at McGill University led by Dr. Charles Bourque, none of these arguments appeared to be correct. They felt there was a nascent, neurological reason for this swig before slumber. They decided to explore this trait in mice in the hopes of finding the mechanism behind the nightly thirst. Their discovery, which now published in the journal *Nature*, revealed the reason for this process may be more important than once believed.

The first step was to act as mythbusters and show thirst had nothing to do with physiological needs. They did this by restricting various components of diet and monitoring various

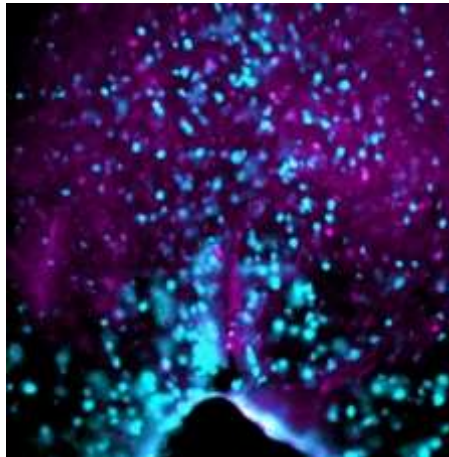
vital signs such as temperature, blood salinity, and water concentration in blood. None of these changes amounted to any difference in water intake. The animals still went for water right before bed.

To remove the second theory – psychological motivation – the team explored areas of the brain responsible for this need for hydration. This was not all that difficult as they already had one area in mind for testing. It's called the organum vasculosum lamina terminalis, or OVLT. It's a small, bead-like structure near the hypothalamus and is responsible for thirst. In addition, this area has no involvement in the production of dreams.

The team examined the activity of the OVLT during normal wakefulness, which they called the basal period; and right before bed, known as the anticipatory period. As expected, the OVLT was more active right before bedtime. This meant the urge for hydration had little to do with dreaming and instead was regulated by some other factor.

For the authors, the most likely molecule causing this sudden thirst was vasopressin.

It's long been known to be involved in water retention and acts as a neurotransmitter in the brain. They also had figured on the area of the brain responsible for this action. It's known as the SupraChiasmatic Nucleus, or SCN. This area is known to be involved in circadian rhythm and contain vasopressin neurons.



Thirst neurons

When the team examined the SCN for the electrical activity of vasopressin neurons, they saw, as expected, a rise in their activity during the anticipatory period in comparison to the basal period. This observation suggested there was a link between the SCN and the OVLT and that vasopressin was the signal between the two regions. To determine if this was indeed the route of vasopressin-based electrical activity, the team used optogenetics to modify the release of vasopressin. As expected, when vasopressin was released, the mice drank more in the anticipatory period. But when vasopressin was shut off, there was no difference in intake compared to the basal level.

With the mechanism all but determined, there was only one last experiment to perform. They had to knock out the actual receptor for vasopressin, appropriately known as vasopressin 1a receptor, or V1aR. When they did, the drinking rate stayed the same for both basal and anticipatory periods.

The study reveals exactly how, at least in mice, the urge to have that beverage before bedtime occurs. As the body begins to anticipate the sleep period, the SCN begins to send vasopressin to the OVLT. Once here, the hormone acts as a neurotransmitter with V1aR to activate the neurons in that area. When they get excited, they send signals to initiate the thirst response.

As to why this happens, the data shows that in the absence of water intake the mice become dehydrated overnight. Whether this is true for humans remains to be determined. Even so, this study offers a fascinating glimpse into the impressive spectrum of brain activities. In this case, the brain – using the clock – can predict physiological trouble and take preventative action to avoid imbalance.

This concept of foreshadowing unveiled by the authors reveals how much we still haven't uncovered amid the spectrum of brain functions. With more research such as those by Dr. Bourque, we are certain to continue to gain insight – and no doubt captivation – about the yet undiscovered wonders of the brain. We may even get a chance to enjoy a good night's sleep.

## About Dr. Charles Bourque, Ph.D.

James McGill  
Chair



(Neurobiology of hydration)

Professor, Department of Neurology-  
Neurosurgery, McGill University

Associate Member, Department of  
Physiology

Dr. Charles Bourque and his team study how the brain monitors body hydration, salt and temperature. Life-threatening defects in body fluid balance are featured in many acute clinical conditions, including drug overdose, heart failure, sepsis and traumatic brain injury. Moreover changes in fluid balance likely link dietary salt intake to many forms of hypertension.

Visit his website for more information  
<http://bourquelab.mcgill.ca/>

# What determines the fate of a stem cell?

Death is a normal part of the life cycle of cells. When death is programmed, it even has a name, apoptosis. Over the years, researchers have learned how the process happens and its importance in overall health.

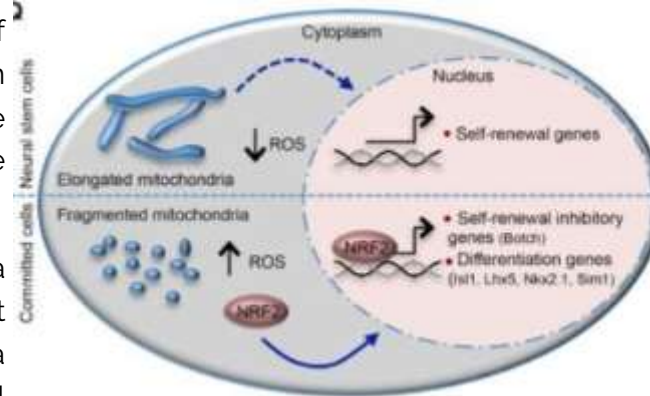
One of the first steps in apoptosis involves the mitochondrion. Mitochondria are structures inside cells that are mainly responsible for energy production. When the time comes to call it quits, the structure begins to break down into fragments. As this happens, the cell is prompted to make proteins responsible for deconstructing other cellular structures. In addition, another group of molecules, known as reactive oxygen species, or ROS, are formed. These molecules seek out proteins and damage them with incredible efficiency.

Fragmentation of the mitochondria is a telltale sign of a cell's fate. Yet it turns out the result may not always be death. For a particular group of cells known as neural stem cells, there may be another option: lead a new type of life. The revelation

comes as a result of a recent study from a University of Ottawa research team led by Dr. Ruth Slack and her postdoctoral fellow, Dr. Mireille Khacho. They recently published in the journal *Cell Stem Cell* a fascinating observation of life in the face of the signals of death. Their work brings a new understanding of how stem cells live and, how, sometimes, instead of dying they may differentiate.

Stem cells are the foundation of life, acting as the first generation for all cell types in the body. They multiply over the course of life, a process known as proliferation. But, when they are called upon, they change their identity, transforming – or differentiating – into different types of cell such as bone, skin, muscle, immunological cells, and, in the case of neural stem cells, nerves. This transformation allows for self-renewal so we never lose out on the cells we need to stay alive.

Normally, the population of proliferating stem cells is maintained. However, as we grow older, their numbers drop. As this happens, the ability of the body to renew itself decreases and the impact of damage on already living cells tends to add up. Because of the involvement of the mitochondria and ROS in cell death, they have been regarded as the main culprits in this stem cell reduction. Slack's group wanted to understand the underlying mechanism.



How Stem Cells Commit To Change

The group conducted the experiments using mice. At first, the team chose to examine the effects of mitochondrial fragmentation and ROS formation in embryos during brain development. The team could then observe how these cells reacted to the well-known signals of death.

As anticipated, proliferating stem cells had an elongated mitochondrial structure meaning they were alive and well. But stem cells with fragmented mitochondria were not dying as one

might expect. Instead, they were differentiating. To be sure this observation was real, the team used genetically altered mice only capable of forming fragmented forms of the mitochondria. Just like the normal mice, the stem cells acted in the same way by differentiating. A closer look at this mechanism revealed ROS played a major role. Levels rose only moderately but this was sufficient to signal a change of cell fate. For some reason, the programming in neural stem cells was different at the genetic level.

To get a better idea of what happened, the group searched for difference in gene expression that could lead to this shift in stem cell fate. They found the expression of one particular gene, nuclear factor (erythroid-derived 2), or Nrf2 for short, was increased. The gene is known as an oxidative stress response gene and is normally expressed to help combat elevated levels of ROS. As the levels of Nrf2 rose, so did the chance for differentiation and stem cell depletion.

While significant insight into the mechanism has been found, it was still limited to the embryo. To appreciate the effect on adults, the team had to work with fully grown animals. They did this by letting mice to grow to six weeks of age and then sparked the same type of mitochondrial fragmentation in neural stem cells. Within a few weeks, the mice began to display learning impairment. In essence, the loss of adult stem cells was having consequences at the behavioural level.

Although the experiments were conducted in mice, they outline a rather interesting perspective on aging and the brain. As increased fragmentation occurs, the stem cells continue to differentiate and deplete the population. As a result, there is less opportunity to self-renew when damage occurs. This could lead to a higher risk for neurodegenerative disorders.

The study also opens the door to possible therapeutic options as an exploration of antioxidants to reduce the levels of ROS during mitochondria fragmentation. There is already clinical evidence suggesting antioxidants reduce the risk for neurodegenerative disorders. This study supplies more reason to learn whether we can use these chemicals to preserve the stem cell population throughout our lifespan to stave off disease.

## About Dr. Ruth Slack, Ph.D.

Professor,  
University of  
Ottawa



The Ruth Slack Laboratory focuses on the field of neural regeneration.

Using both in vitro and in vivo studies, her team is examining mechanisms that regulate stem cell maintenance, neurogenesis as well as neuronal survival in the adult brain.

Over the long term, her research interests involve the identification of strategies for the treatment of acute brain injury and neurodegenerative diseases.

Learn more about Dr. Ruth Slack on her website:

<http://www.med.uottawa.ca/ruthslack/eng/index.html>



# Do stem cells have a secret language?

What convinces a stem cell to determine its fate? It's one of the most persistent questions in modern biology. Research over the last four decades has revealed there is no easy answer. For example, in the brain, stem cells in the embryo produce all of the different cell types at precise times and amounts. If stem cells are perturbed by altering their ability to make those cell types, this is thought to contribute to neuropsychiatric and developmental disorders.

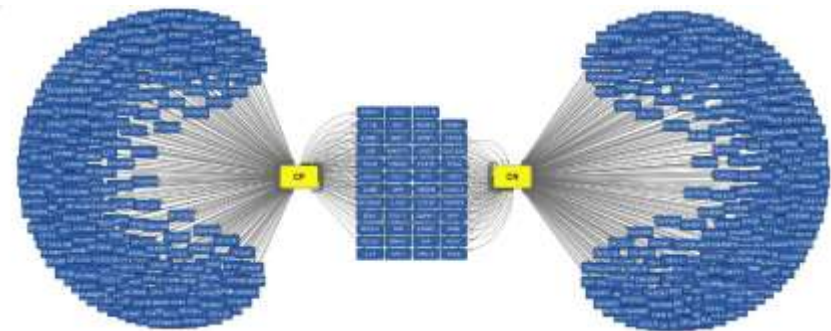
Stem cells receive signals from other cell types, blood vessels, and the cerebral spinal fluid, and even produce signals themselves. This in itself raises numerous questions. What are those signals? How many are there? How does a stem cell decide to respond to one signal and not another? More importantly, how can this all happen in a coordinated manner to ensure the proper communication in the brain?

To construct a communication network, a team of researchers at the Hospital for Sick Children led by Drs. Freda Miller and David Kaplan identified signals produced by stem cells and neurons that may influence each other's function in the mouse embryo. They used the approaches of gene expression analysis – also known as transcriptomics – as well as the protein equivalent, proteomics, to identify cell surface receptors. Then, using bioinformatics, they combined the data to construct the network and predict which signals are required for stem cells to produce neurons. The results, available in the journal *Neuron*, revealed an unexpected diversity in signals and the involvement of a particular molecule normally associated with another bodily function.

The authors first found that stem cells are exposed to hundreds of signals (also called ligands) in the developing brain, including those produced by neurons in their environment. They found, however, that stem cells had receptors for only about 32 of these ligands. After identifying these 32 proteins, they generated a communications network that enabled them to predict the ligands that potentially direct stem cells to make neurons. With this information in hand, the team returned to the lab in order to test how many of the ligand-receptor combinations might be considered, in a word, proneurogenic. They didn't test all of them as many had already been studied in other labs or were not functional during the stage of embryogenesis explored in the first experiments. This reduced the number to just eight possibilities.

The next steps were relatively straightforward. Cultures of neural precursor cells were exposed to the various factors and then examined for any changes in the ability of stem cells to generate neurons. Three factors not previously known to instruct stem cells to make neurons were identified, neurturin, glial-derived neurotrophic factor, also known as GDNF, and

Stem cell communication





interferon gamma, a modulator of immune responses.

Having reduced the number from hundreds to three, it was time to go back to the mouse model. This time, the team tested whether injection of the three ligands into the embryonic brain could promote neuron formation from stem cells. But this wasn't the only task. They also wanted to know if they could block the function of those ligands using antibodies. As expected, when the ligands were introduced into embryonic mouse brains between day 13 and 14 – a critical time in mouse brain development - more neurons were produced, and the antibodies inhibited the generation of neurons.

To reinforce this observation, the team genetically removed these receptors to see if they could prevent this effect. As expected, the rise was no longer seen. These three ligand-receptor combinations had proven to be proneurogenic.

In addition to revealing yet more information on how stem cells produce neurons, this study also offers a glimpse into the power of systems biology approaches to identify individual factors in cell biology and stem cell development. But perhaps the true value of this technique is an out-of-the-box approach to developmental neuroscience. The identification of interferon gamma is a surprise as it is primarily associated with immune responses. Yet, the molecule had a significant effect. This alone reveals the power of developing communications networks for all of the cell types in the developing and adult brain.

As we gain more information from communications networks, we may one day understand exactly what is happening at the microscopic level during development and provide insight in brain activities such as learning. Perhaps more importantly, we may finally gain a grasp on what occurs during aging as well as when the brain suffers injury or undergoes neurodegeneration allowing for the developments of treatments and other means to heal.

## About Dr. Freda Miller, Ph.D.

Professor, University of Toronto

Senior Scientist, SickKids research institute

Canada Research Chair in Developmental Neurobiology

International Research Scholar -Howard Hughes Medical Institute

Dr. Freda Miller is best known for her studies of neural and dermal stem cells and of neuronal growth, survival and programmed death. Major findings from her lab have provided evidence that adult mammalian skin contains an accessible multipotent dermal stem cell that can generate peripheral neural cells, identification of proteins that play a critical role in determining the life, death and degeneration of mammalian neurons, and that one way genetic disorders cause cognitive dysfunction is by perturbing formation of neurons during embryogenesis.

Learn more about Dr. Freda Miller at SickKids:  
<http://www.sickkids.ca/AboutSickKids/Directory/People/M/Freda-Miller.html>



# Is there a genetic cause for multiple sclerosis?

Imagine losing the ability to control your nerve function. You may encounter numbness and weakness in the limbs. Your ability to speak could decline as well as your vision. Tics and tremors might take over certain parts of your body. You even are at risk for depression. These are just a few of the symptoms of multiple sclerosis, better known as MS. This condition affects over two million people worldwide and leads to significant reductions in a person's quality of life. Yet quite possibly the worst aspect of this disease isn't the range of symptoms, but the culprit causing them.

Our immune system is our natural defense force against pathogens and toxins. Exposure to these invaders leads to a response to clear the threat. Yet, in some cases, the immune system loses its way and turns against us. The troops begin to target and kill our own valued cells. This condition, known as autoimmunity, may lead to several diseases based on the target of immune attack. In the case of MS, that target is the myelin sheath, which protects nerves and maintains proper signal and function.

Identifying the triggers for autoimmunity is no easy challenge, particularly for MS. Over the years, numerous options have been presented. Most research has focused on exposure to environmental factors such as prior infection or tobacco. Research has shown there are definite correlations yet no actual causal mechanism has been proven.

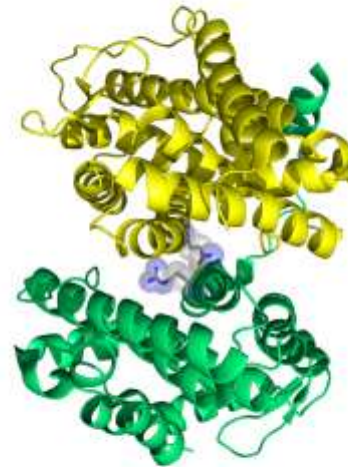
While environmental exposure does present a compelling

argument, a similar amount of work has been devoted to an internal suspect: our genetic code. Several genes have been examined for their potential role in disease onset. Results often show a single genetic change can increase the risk for disease.

There are currently over a dozen genes capable of contributing to disease. Some, such as the human leukocyte antigen and the immunological sensor protein CD45 are not surprising. Others, including the Vitamin D receptor, may not be as evident and yet still play a role.

Now there is another gene to put on the list. It's officially called nuclear receptor subfamily 1, group H, member 3, but it is better known as NR1H3. The addition comes as a result of recent work from a group at the University of British Columbia, headed by Drs. Weihong Song and Carles Vilariño-Güell. Their discovery, now published in the journal, *Neuron*, reveals the increasing complexity of MS and suggests a need to more widely explore the genetic code.

The group wanted to gain perspective on an inherited form of the disease, known as familial multiple sclerosis. They acquired samples from nine individuals from one family spanning three generations. Five had already been diagnosed with MS while the others acted as controls. Once the samples were acquired, the DNA was sequenced for any signs of genetic change. This wasn't an easy task as the team



Nr1H3 protein with a mutation

discovered over 47,000 different variants of genes. However, closer examination of these changes allowed the team to figure out which ones would actually have an impact on cell function. This thankfully reduced the number to 37.

The next stage of analysis involved determining if any of the 37 changes associated with disease in the individuals. In this case, 33 did not. That left four possible options, but only one seemed to be more prevalent in those suffering from MS. This was NR1H3. The team found in the familial cases, there was a mutation in the protein, named p.Arg415Gln. The team felt this could be the key to numerous troubles.

The group performed assays in the lab to determine if the p.Arg415Gln mutation would cause a change in cellular function. Their study showed the mutation affected the way the protein could regulate the expression of other genes. This dysregulation affected many biological pathways, most notably cholesterol metabolism, which is important for proper development of the protective myelin sheath. The change prevented the formation of genes responsible for transport, breakdown and elimination of cholesterol. The mutation also affected the production of immunological proteins, which led to a reduction in the ability of the cell to prevent inflammation. On a larger scale, this effect would lead to worsening of symptoms as the disease progressed.

This study reveals how a single genetic change can have potentially drastic effects on the entire body. For the authors, the identification of this mutation provides an opportunity for treatment. By figuring out how to reverse or deal with the effects of mutation, the team may be able to alleviate symptoms. While this milestone may be years away, this study shows how genetic analysis in families may help to better understand diseases like MS and determine ways to improve the quality of life for those who suffer.

## About Dr. Carles Vilariño-Güell, Ph.D.

Assistant Professor,  
University of British  
Columbia



Canada Research  
Chair in Molecular Characterization of  
Neurological Diseases

Dr. Carles Vilarino-Guell's research aims to better understand the molecular components implicated in multiple sclerosis.

Vilarino-Guell's research to identify the genes and mutations involved in the development of disease has led to better diagnostic tools and models to study the cellular processes causing disease. It also helps in the development of new therapies that target the treatment of multiple sclerosis, and its prevention in future generations.

More on the MS genetics lab website:  
<http://msgeneticslab.med.ubc.ca/>

# Can we rewire the nervous system?

Imagine repairing injured spinal cords or brains. Many may relegate this idea to the realms of science fiction yet researchers around the world continue to strive for this goal. They have developed and tested ways to rebuild the damage nervous system and bring back proper function. Some have even shown success in the lab.

One such method was published in the *Journal of Neuroscience* when a group of scientists led by Dr. Peter Grütter found a way to improve neural repair using what would best be described as microsurgery. Using a combination of microtools – and indeed nanotools – these researchers have found they can mechanically control the regeneration process and improve the likelihood of proper neural function after injury.

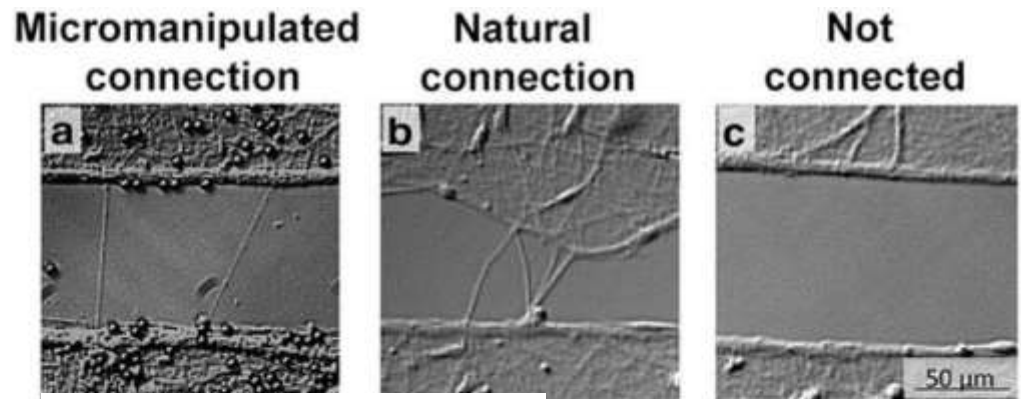
The process wasn't easy as it required some of the most sophisticated techniques available with names such as micromanipulation, microfabrication, and atomic force microscopy, which can visualize areas as small as 10 billionth of a metre. The team also had to rely on research stemming back almost thirty years in order to make it work. All in all, the process represented decades of trial and error to reach this pivotal stage.

They first needed a supply of actual neurons, the building blocks of the nervous system, for their experiments. For this, the team took neurons from rat brains and grew them in the lab. But unlike the petri dishes commonly seen, these neurons were grown in small compartments known as microfluidic chambers. The small volume would allow for

individual observation and manipulation of the neurons. After two to three weeks, the neurons were ready for the next step.

Using an atomic force microscope, the team attempted to add beads to the neurons. These beads were coated with a chemical known as poly-D-lysine. The team had found several years earlier this molecule could help neurons attach to one another and develop the most important part of function, the synapse. If the team were correct, adding the bead would help to promote generation of neural signals.

But the bead also served another purpose. After attaching the particle to a number of neurons, the team could stretch the neurons to elongate them forming structures called neurites. This was a tricky step as too much tension risked harming the cells themselves. In addition, the tensile strength of the neuron bundle had to be taken into consideration in terms of the distance pulled. Yet the group figured out the mechanics and found they could extend a neuron close to a millimetre in length. While this may seem quite small, in terms of nervous



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system repair, it represents a significant distance.

The next stage required the merging of two bundles of neurons to see if synapses would form and connections would be made. Incredibly, within 30 minutes, a connection was established meaning they could not only culture the elongated neurons but also help them form proper neural links with a target neuron. An examination of the biology of the connections showed they were just as good as those formed naturally.

While the process worked, there was still one important requirement of this new linkage. It had to be able to send an electrochemical signal. After all, without the ability to transmit, the connection would be worthless. When the tests were performed, there was no need for concern. The neurites could fire a signal and it would be picked up and transmitted by other neurons. The effect was almost the same as two neurons connected through natural growth.

The immediate results of the experiment reveal neurons can be manipulated to elongate and also form connections with other neurons. That in itself is an incredible achievement. Yet, in terms of spinal cord and brain repair, this represents a possible novel direction for regenerative therapy. The method may be able to help deal with the formation of neural scar tissue, which is known to halt proper signalling. In addition, the length of the neurite could help to cover more distance making the potential for larger scale repair more effective. However, these options are still years away as technology needs to be able to expand from the microfluidic chamber to larger biological entities.

There is, however, a more immediate application of this research in the form of bio-inorganic networks. Using this method, a brain-machine interface may be possible to better track the activity of cerebral cells. This could provide stronger information on the workings of the brain. But even more impressive is the possibility of bringing another science fiction staple to reality in the form of a standalone artificial nervous system. Though not possible for human analyses, the team believes it could replicate a neurological model organism such as *Caenorhabditis elegans*, which only has 300 neurons. Should this be achieved, the development of larger synthetic neural networks may be eyed.

## About Dr. Peter Grütter, Ph.D.



Professor  
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Dr. Peter Grutter's research aims to push the limits of instrumentations using the latest discoveries of physics to understand phenomena of all fields of science, including biology. The development of Atomic Force Microscopy in combination with fluorescent molecules allows his group to study biological events at the molecular level, bringing a new perspective to this research.

Learn more about Peter Grutter's research on his website:

<http://www.physics.mcgill.ca/~peter/research.html>



# About us

## About the Canadian Association for Neuroscience

The Canadian Association for Neuroscience - Association Canadienne des Neurosciences (CAN-ACN) is a not-for-profit organization dedicated to the promotion of neuroscience research and of the interest of Canadian Neuroscientists.

We are an association of approximately 1000 independent researchers, professors and trainees actively involved in neuroscience research.

CAN-ACN organizes the Canadian Neuroscience Meeting yearly since 2007. Our next meeting will be held in Montreal, May 28-31 2017.

We maintain an active website, at <http://can-acn.org>, which we use to showcase neuroscience research, to provide important information for our members about meetings, scientific and social events, funding opportunities, and employment offers, and to promote neuroscience advocacy initiatives.

Visit our website for more information:

<http://can-acn.org>

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Jason Tetro is a visiting scientist at the University of Guelph. He has authored and co-authored numerous scientific articles, chapters, and technical reports and is the co-editor of The Human Microbiome Handbook. He has written two bestselling books for Doubleday Canada, The Germ Code, and The Germ Files. He is weekly blog contributor to the Huffington Post Canada and can be regularly heard on CBC Radio One and SiriusXM radio. He lives in Toronto.

He has worked with the Canadian Association for Neuroscience since May 2016.

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Produced by the Canadian Association For Neuroscience

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