The Krembil

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Introducing *The Krembil*: the official newsletter of the Krembil Research Institute (formerly the Toronto Western Research Institute). *The Krembil* informs the Toronto Western Hospital community, external stakeholders and interested community members about the exciting news and innovative research happening at the Krembil Research Institute.

In this issue you can read about:

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News

Krembil Ready to Embrace Big Data

Big research questions at Krembil can be answered using “big data”—large datasets that include multiple data types, from patient outcomes and biomarkers to brain imaging data and even non-medical data that may be relevant to care decisions. Exploiting this torrent of data requires advanced computational methods to find relevant insights and connections.

One example of the big data challenge is in the lab of Krembil Senior Scientist Dr. Karen Davis, where large brain imaging datasets can be further analyzed to better understand how individuals respond to pain differently.

“While conventional brain imaging studies, which usually have less than 20 participants, may provide useful information about the overall effectiveness of a particular drug, these studies cannot tell us what the optimal treatment is for individual patients—for that we need to adopt a big data approach,” says Dr. Davis.

There are many challenges to overcome to leverage big data. These include balancing the need to make data easily accessible for research, while maintaining participant privacy and security. To exploit big data, institutes must also make an investment in software development and computing hardware—what Dr. David Jaffray, Executive VP of Technology and Innovation at UHN, calls the “big machine.”

However, with support from federal funding agencies and generous donors, UHN, as the largest research hospital in Canada—and the volume of patient data that it carries—can become a leader in big data research. Investing in big data will help researchers produce useful insights for understanding biology and clinical care across multiple diseases.

Modeling Brain Activity

The Krembil Research Institute recently recruited a computational neuroscientist—Dr. Jérémie Lefebvre—who will enhance its already-strong expertise in this area. Computational neuroscientists, also called theoretical neuroscientists, use mathematics and computer models to help explain how the cells and circuits of the brain work. In turn, these models can be used to predict how the brain processes information or how it will respond to a particular treatment intervention.

Brain oscillatory activity—coordinated electrical impulses within and across brain regions—occurs at very specific frequencies. This coordinated electrical firing can be impaired in disorders including major depression, autism and schizophrenia. Therefore, researchers have asked whether manipulating these brain rhythms, either by implanting an electrode into the brain or by electrically stimulating the brain surface via the scalp, could be of therapeutic value.

To address this question, Dr. Lefebvre developed a computational model, recently published in PLoS Biology (PMID: 27023427), to explain how abnormal brain activity might be rescued by electrical stimulation and how treatment response differed according to participants’ changing state of mind. Experimental results in humans were in line with Dr. Lefebvre’s model’s predictions, showing that stimulation response differed according to participants’ attention levels. The next step will be to use his model to personalize electrical stimulation treatment based on individuals’ oscillatory activity.

You can find out more about Dr. Lefebvre’s work by visiting his lab website. He is currently accepting postdoctoral research fellows and graduate students. Interested applicants should contact him directly.

Research

Dangers of Drinking

Fetal alcohol spectrum disorder (FASD) is the leading preventable cause of intellectual disability in the western world. It encompasses all of the conditions that can occur in a person whose mother drank alcohol during pregnancy, including stunted growth and seizures. Little is known about how alcohol exposure during this critical time in a baby's development leads to physical and behavioural problems after their birth.

Using advanced electrophysiological techniques, Krembil Senior Scientist Dr. Peter Carlen and his research team evaluated the effects of first trimester alcohol exposure on brain activity, specifically in the hippocampus. They targeted the hippocampus because it is the well-documented epicentre of seizure activity in the brain, it plays a critical role in learning and memory, and it is highly susceptible to the toxic effects of alcohol.

The study team found that moderate alcohol exposure during early pregnancy led to increased electrical activity in the hippocampus, similar to that observed in models of epilepsy and dementia. Thus, the inability to maintain excitatory/inhibitory balance may contribute to the increased risk for seizures and memory deficits in FASD patients.

"The first trimester is a time when women may consume alcohol before knowing that they are pregnant," comments Dr. Carlen. "Our findings suggest that women should refrain from drinking alcohol if there is a chance that they are pregnant."

This work was supported by the Canadian Institutes of Health Research, NeuroDevNet, and the Toronto General & Western Hospital Foundation. G Zoidl holds a Tier 1 Canada Research Chair in Molecular and Cellular Neuroscience.

Hippocampal hyperexcitability in fetal alcohol spectrum disorder: pathological sharp waves and excitatory/inhibitory synaptic imbalance. Krawczyk M, Ramani M, Dian J, Florez CM, Mylvaganam S, Brien J, Reynolds J, Kapur B, Zoidl G, Poulter MO, Carlen PL. Experimental Neurology. *2016 Mar 17. doi: 10.1016/j.expneurol.2016.03.013.* [Pubmed abstract]

Slow Pursuit

Lazy eye (amblyopia) is a condition in which the vision in one eye decreases due to inadequate use during childhood. It develops when the signals between the brain and the affected eye deteriorate, causing the brain to favour one eye. This can affect eye-hand coordination and limit a person's ability to perform certain tasks like driving or reading.

Although a lot is known about the visual problems that stem from a lazy eye, it still remains unclear which eye movements are altered in individuals with the disease. To address this gap, Krembil Senior Scientist Dr. Agnes Wong conducted a study in which participants with or without a lazy eye were asked to visually track a moving target as quickly and accurately as possible.

The study revealed that compared to individuals with normal vision, those with a specific type of lazy eye (anisometropic amblyopia) took longer to start following the target with their eyes; however, the speed with which they continued to visually follow the target was similar to that measured in participants with normal vision.

Explains Dr. Wong, "To the best of our knowledge this is first study to compare this type of eye movement in people with lazy eye. Our findings could help researchers design new rehabilitation therapies for adults with a lazy eye who continue to experience visual problems despite treatment."

This work was supported by the Canadian Institutes of Health Research, the Canada Foundation for Innovation, the John and Melinda Thompson Endowment Fund in Vision Neurosciences and the Department of Ophthalmology and Vision Sciences at The Hospital for Sick Children.

The initiation of smooth pursuit is delayed in anisometropic amblyopia. Raashid RA, Liu IZ, Blakeman A, Goltz HC, Wong AM. Investigative Opthalmology &Visual Science*. doi: 10.1167/iovs.16-19126. 2016 April 1.* [Pubmed abstract]

Helping Those in Need

Many people who suffer a mild traumatic brain injury, known as a concussion, quickly recover. But others develop postconcussion syndrome (PCS)—a condition with symptoms that can persist for weeks, months, years or indefinitely. Currently, it is difficult to know how many people suffer from PCS because consistent clinical standards—those used by physicians to diagnose the condition—are lacking.

In order to establish consistency in how this condition is diagnosed, Krembil Emeritus Scientist Dr. Charles Tator and his collaborators proposed a new definition of PCS. The new definition requires that patients experience any three or more symptoms for at least one month. The old definitions are stricter, requiring that the symptoms are experienced for at least three months.

When people were diagnosed using the new definition, the research team was able to identify previously unknown risk factors of PCS. These predictors included being female, experiencing amnesia and/or loss of consciousness at the time of injury, having extracranial injuries and being involved in legal proceedings around the injury. In contrast, when standard definitions were used, only the number of previous concussions was a risk factor of PCS.

“Our results suggest that the criteria we currently use to diagnose PCS in the clinic may only be capturing the most severe cases,” says Dr. Tator. “By revising these criteria, we have identified patient populations who do not receive the care that they need.”

This work was supported by the Canadian Concussion Centre at Toronto Western Hospital, which is funded by the Toronto General & Western Hospital Foundation.

Postconcussion syndrome: demographics and predictors in 221 patients. Tator CH, Davis HS, Dufort PA, Tartaglia MC, Davis KD, Ebraheem A, Hiploylee C. Journal of Neurosurgery*. 2016 Feb 26.* [Pubmed abstract]

Gambling on Parkinson Disease

The brain sends a reward sensation in response to certain behaviours. These behaviours include those that are inherently pleasurable (eg, helping others), culturally desirable (eg, gaining prestige, winning money) or necessary for survival of the species (eg, eating).

These sensations are created by the brain’s ‘reward system’—a network of brain cells (neurons) found in specific brain regions. Combined, these neurons act to either reinforce behaviours or deter behaviours.

Given the complexity of the brain and the difficulty of studying it in humans, many of the brain regions thought to be involved in the reward system are poorly defined.

To address this issue, Krembil Senior Scientist Dr. William Hutchison*,* in collaboration with Dr. Valerie Voon at Cambridge University UK, used an advanced approach to measure the activity of single neurons in a brain region known as the globus pallidus pars interna (GPi). This region was chosen because, to date, the GPi’s role in the brain’s reward system has only been suggested through preliminary data.

The approach involved inserting extremely small electrodes (microelectrodes) through the skull and into the GPi. The inconvenience of this procedure was minimized by carrying it out on patients who were already undergoing neurosurgery to treat motor diseases, including Parkinson disease and dystonia.

Once the microelectrodes were in place, patients were asked to complete a computer-based task in which they could gain or lose virtual money by responding to visual cues. The results showed that certain neurons in the GPi became active when patients lost virtual money.

Dr. Hutchison comments, “While the GPi is a known target for Parkinson disease, we are the first to show that individual neurons in this brain region respond to reward stimuli. This is particularly exciting because certain antiparkinson drugs have been shown to cause impulsive behaviours such as excessive gambling. Future studies will reveal whether GPi neurons are involved in these side effects.”

This work was supported by the Canadian Institutes of Health Research, the Wellcome Trust and the Toronto General & Western Hospital Foundation. AM Lozano is a Tier 1 Canada Research Chair in Neuroscience. University of Toronto MD PhD candidate Nicholas Howell carried out the work and is first author of the study.

Preliminary evidence for human globus pallidus pars interna neurons signaling reward and sensory stimuli. Howell NA, Prescott IA, Lozano AM, Hodaie M, Voon V, Hutchison WD. Neuroscience*. doi: 10.1016/j.neuroscience.2016.04.020. 2016 Apr 22.* [Pubmed abstract]

Researcher’s Toolbox: New Insight

Age-related macular degeneration is an eye condition in which cells in the central part of the retina deteriorate, leading to vision loss. The disease damages a particular type of cell, known as a cone cell, which controls our ability to see detail and color.

Researchers have been exploring new ways to repair the damage caused by macular degeneration by transplanting healthy cone cells into the retina. A major barrier to progress with this approach has been the lack of a suitable method for tracking the integration and survival of the transplanted cells.

Krembil Senior Scientist Dr. Valerie Wallace and her team have overcome this challenge by using a cell tracking strategy in which a fluorescent tracer is linked to a protein called CCDC136 that is found in cone cells. The fluorescent protein serves as a “reporter” that can be detected by microscopy.

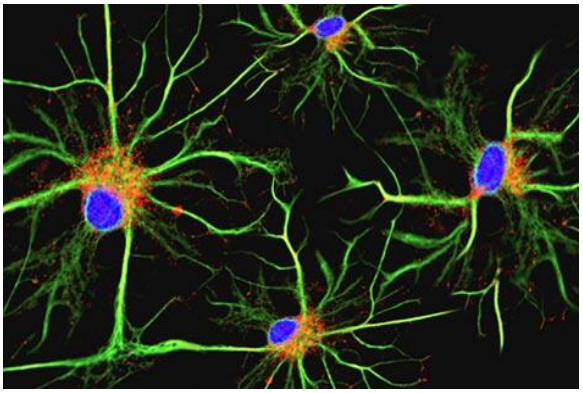
The team showed that this reporter protein does not change the behaviour of cone cells in healthy retinas. Moreover, cone cells expressing the protein can be accurately tracked within the eye after they are transplanted into an experimental model of age-related macular degeneration.

Comments Dr. Wallace, “This model will finally give us an opportunity to study cone development and survival in more detail. This should accelerate our ability to develop new strategies for restoring eye function.”

This work was supported by The W. Garfield Weston Foundation/Brain Canada Foundation, The Foundation Fighting Blindness and The Krembil Foundation. V Wallace is the Donald K. Johnson Chair in Vision Research.

Establishment of a cone photoreceptor transplantation platform based on a novel cone-GFP reporter mouse line. Smiley S, Nickerson PE, Comanita L, Daftarian N, El-Sehemy A, Tsai EL, Matan-Lithwick S, Yan K, Thurig S, Touahri Y, Dixit R, Aavani T, De Repentingy Y,Baker A, Tsilfidis C, Biernaskie J, Sauvé Y, Schuurmans C, Kothary R, Mears AJ, Wallace VA. Science Reports*. 2016 Mar 11. doi:10.1038/srep22867.* [Pubmed abstract]

The Brain's Emergency Response



Microglial cells (microglia) are the brain and spine's first line of defense: they clear unwanted pathogens and debris—which can prevent new tissue growth and promote more damage--through a process called phagocytosis. This process, however, also may produce reactive oxygen species (ROS) that can damage surrounding cells.

The amount of ROS that is created depends on the microglial cells' 'activation state'. It is believed that when microglia are in an 'anti-inflammatory activation state', they support tissue repair; however, when they are in a 'pro-inflammatory activation state', ROS levels are high and unwanted tissue damage can occur. When the inflammatory balance shifts towards the pro-inflammatory state, microglia can cause chronic damage that can lead to neurological diseases such as Parkinson disease.

Despite the critical difference between pro- and anti-inflammatory behaviours, very little is known about how microglial cells change between activation states.

Krembil Senior Scientist Dr. Lyanne Schlichter and her team explored this balance in microglia activation state by exposing the cells to various factors—known as pro- or anti-inflammatory cytokines—in the presence or absence of debris from damaged neurons. By observing the cells under different regimens, they were able to identify how different conditions affect microglial cell properties, including whether they produced ROS or carried out phagocytosis.

"If we can determine how to influence microglial activation states to promote beneficial effects of phagocytosis while suppressing damaging effects of ROS, then we can help develop therapeutic interventions to reduce neurodegeneration and to promote cellular recovery following brain damage," says Dr. Schlichter.

This work was supported by the Canadian Institutes of Health Research, the Heart and Stroke Foundation of Canada and the Toronto General & Western Hospital Foundation.

Complex molecular and functional outcomes of single versus sequential cytokine stimulation of rat microglia. Siddiqui TA, Lively S, Schlichter LC. Journal of Neuroinflammation*. doi: 10.1186/s12974-016-0531-9. 2016 Mar 24.* [Pubmed abstract]

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