Advances in understanding and treating mental illness: proceedings of the 40th Canadian College of Neuropsychopharmacology Annual Meeting Symposia

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On June 7–9, 2017, the Canadian College of Neuropsychopharmacology (CCNP) held its 40th Annual Meeting in Kingston, Ontario. At the core of the scientific program were 6 symposia, where clinical and basic neuroscientists presented their ideas and most recent discoveries in the hope of significantly advancing our understanding and treatment of mental illness. This article reports the essential findings of these symposia and summarizes recent advances in translational neuropsychopharmacology shared by several research groups from Canada and visiting from the United Kingdom, The Netherlands and Sweden.

Symposium 1. Novel perspectives on the neurobiology of bipolar disorder across the lifespan

In the first symposium, novel perspectives on the neurobiology of bipolar disorder (BD) were discussed. Dr. Ana Andreazza (University of Toronto) opened with a talk on the role of NLRP3 inflammasome in BD. The NLRP3 pathway links mitochondrial dysfunction and inflammation, which are 2 key components in BD pathophysiology. Mitochondrial DNA mutations in the cell trigger NLRP3 inflammasome assembly, which activates Caspase 1, therefore increasing inflammation in the brain through inflammatory cytokines. Using this pathway, Dr. Andreazza and colleagues found an increase in NLRP3 inflammasome activation in the postmortem prefrontal cortices of individuals with BD compared with controls. On the other hand, they found a decrease in mitochondria Complex I and NDUF7 subunit in the same sample. This finding is consistent with mitochondrial dysfunction in BD, as Complex I is associated with normal adenosine triphosphate (ATP) production. In a recent collaborative study, Dr. Andreazza’s team compared the peripheral blood mononuclear cells of individuals with BD with those of healthy controls and detected an increase in lactate levels, a marker of mitochondrial dysfunction, in the patient group compared with controls. It is evident that there is an increase in inflammation in individuals with BD, resulting from mitochondrial dysfunction through the NLRP3 pathway and the disruption of Complex I. Future investigations should aim to provide evidence for mitochondrial dysfunction in other psychiatric illnesses, given the notable genetic overlapping between the major psychiatric illnesses.

The second speaker, Dr. Benicio Frey (McMaster University) stepped outside of the cell by looking at the intracortical myelin maturation (ICM) in bipolar I disorder. In humans, ICM follows an inverted U shape in growth trajectory, with an increase in myelination reaching its peak in the early 30s followed by a plateau that then begins to decline in the early 50s in all cortical layers. Interestingly, individuals with BD did not show the inverted U shape pattern in myelin maturation found in controls, specifically in the ACC, cuneus, orbital frontal cortex and the rostral MFG, which points to BD as a global brain disease. Furthermore, cognitive functions, such as executive function and verbal memory, are associated with ICM in the BD population only and not in healthy controls. This pattern was also seen in patients with major depressive disorder (MDD) and schizophrenia, with patients with MDD having the thinnest myelin in the superficial areas of the brain. Overall, there are clear differences in myelin maturation and thickness in individuals with BD compared with controls. To parse out within-group differences, Dr. Frey and his team are currently looking at the difference in ICM between patients with remitted and relapsed BD.
In the final talk by Dr. Benjamin Goldstein (University of Toronto), microvascular dysfunction in adolescents with BD was discussed. He showed that BD predisposes youth to accelerated atherosclerosis and early cardiovascular disease. Adolescents with BD have also been found to do significantly less strenuous exercises than matched healthy controls. To study the association between exercise and cardiovascular risks, Goldstein’s group looked at 4 MRI phenotypes of microvascular function: cerebral blood flow (arterial spin labelling [ASL]), small vessel pulsatility in white matter, cerebrovascular reactivity and cardiac-related brain pulsatility. They found that adolescents with BD showed elevated frontal ASL, which could be normalized following a single session of aerobic exercise. Adolescents with BD also demonstrated increased pulsatility in periventricular and deep white matter regions that was negatively correlate with global functioning. In summary, the MRI findings support the concept of microvascular dysfunction in adolescents with BD, which can be reversed following acute aerobic exercise. Future studies should capitalize on microvascular MRI phenotypes as a biomarker for the progression, treatment and risk prediction of BD. In conclusion, BD is a complex illness with a complex biology, with promising new directions that suggest a role of mitochondrial and microvascular dysfunctions and myelin maturation disturbances.

Symposium 2. Advances in brain stimulation for treating cognitive and psychiatric dysfunction

The second symposium included 4 talks on recent advances in brain stimulation techniques as treatment for cognitive and psychiatric dysfunction from both preclinical and clinical perspectives. Dr. Catherine Winstanley (University of British Columbia) discussed mitigating risky behaviours and addiction vulnerability with deep brain stimulation (DBS). Humans with addictions do poorly on the Iowa Gambling Task (IGT), making more suboptimal, risky decisions than controls. This performance on the IGT has been identified as a predictor of treatment outcomes. In this preclinical study, Dr. Winstanley’s group used a rat gambling task to assess the effect of DBS on risk-based decision-making. In this task, most rats mastered the optimal strategy to maximize reward output, which was to choose smaller, consistent rewards rather than larger, riskier rewards. However, some rats preferred risky choices in this task and made even riskier decisions after cocaine self-administration. Dr. Winstanley’s team found that DBS targeting the subthalamic nucleus could improve performance in the rat gambling task by reducing risky decisions — but only in rats that started out as preferring risk. Their work suggests that risk-prefering rats may be a model of a cognitive endophenotype for addiction vulnerability and that DBS may reduce the preference for risky behaviours that appears to be a key component of relapse in addicts.

The second speaker, Dr. Clement Hamani (University of Toronto), brought a clinical perspective to the symposium. Dr. Hamani talked about the utility of DBS for treating obsessive–compulsive disorder (OCD) and identified several well-designed studies that have provided evidence for its efficacy. Dr. Hamani advocates for more randomized clinical trials to follow up on these promising results in order to advance evidence-based medicine for the treatment of OCD.

The third speaker, Dr. Jonathan Downar (Toronto Western Hospital), discussed recent advances in translating research in noninvasive repetitive transcranial magnetic stimulation (rTMS) to clinical practice. Using a 0 burst protocol, Dr. Downar’s group has reduced the amount of time needed for an rTMS session from a standard 38 minutes to just 3 minutes and pioneered delivering multiple treatment sessions in a single day to achieve maximal therapeutic effect in minimal time. By introducing these brief stimulation protocols and shorter intervals, he hopes to improve access to treatment and increase the number of people who can be treated — without a loss of treatment efficacy. Because not all patients with a given psychopathology, such as depression, respond to rTMS, Dr. Downar is using MRI to generate connectivity signatures within patient groups to identify likely treatment responders. He has found 4 subtypes of depressive patients with distinct connectivity changes within their patient population. These subtypes of patients responded differently to rTMS, and targeting subtype-specific regions impacted by the disease could potentially improve the treatment response to rTMS.

Finally, Dr. Elise Gondard (Krembil Research Institute, Toronto Western Hospital) discussed the use of DBS on memory and neuronal plasticity in patients with Alzheimer disease. Deep brain stimulation has been shown to have a neurotrophic effect in patients with Alzheimer disease, with one-third of patients in a [recent] study showing growth in the hippocampus. In rats,DBS to the fornix increased neurotrophic factors and activity markers in the hippocampus, and DBS to the entorhinal cortex enhanced hippocampal neurogenesis and improved spatial memory. Using the 3xTg-AD mouse model of Alzheimer disease, Dr. Gondard found that chronic stimulation of the entorhinal cortex rescued the deficits in memory tasks, induced neurogenesis in the dentate gyrus and restored synaptic markers that are reduced in the mouse model. Furthermore, the plaques and t pathology seen in the 3xTg-AD mouse model were reduced following DBS. Together, these talks suggest that brain stimulation technology, such as DBS and rTMS, is increasingly useful to treat psychiatric and neurodegenerative disorders. This symposium makes a strong connection between preclinical and clinical studies, underscoring that as we increase our knowledge about why brain stimulation is effective and how it can be tailored to individual needs, we can design more effective evidence-based treatments for brain disorders.

Symposium 3. Gut–brain axis

Recent advances in determining the mechanisms for gut–brain axis communication and translation to clinical populations were presented by Canadian and international researchers in a symposium chaired by Dr. Sidney Kennedy (St-Michael’s Hospital). At the intersection of gene ×
environment interactions, the microbiota–gut–brain axis likely reflects the extent of heterogeneity in psychiatric populations and may be a source of biomarkers to predict treatment response in the future.

Dr. Jonathan Swann (Imperial College London) introduced metabolomics as a novel systematic approach to understanding how small perturbations in the microbiome can confer large effects on the brain. This functional approach builds on previous metagenomics studies that allowed researchers to measure the absorption and host interactions of microbial and environmental metabolites. Because of the roles microbes play in drug metabolism, detecting changes in host microbiota function may be able to predict drug response in some psychiatric populations in the future. This makes metabolomics an exciting prospect in biomarker research for psychiatric conditions, including neurodevelopmental and mood disorders. Although metabolomics provides researchers with functional read-outs of many gut–brain communication pathways combined, in-depth understanding of the component mechanisms of gut–brain axis communication is still needed in order to develop new strategies for manipulating microbes for better brain health.

Dr. Rochellys Diaz Heijtz (Karolinska Institutet, Sweden) presented her work focusing on gut–brain communication during early-life critical periods of neurodevelopment. Although bacterial products are among the 4 canonical pathways of gut–brain communication suggested by Collins and colleagues,14 pattern recognition receptors have only recently been suggested as a means for their recognition in the central nervous system.15 Nucleotide-binding oligomerization domain-like receptors (NOD-like receptors), Toll-like receptors and peptidoglycan recognition proteins are expressed in the brain during specific temporal windows of development with different, overlapping expression trajectories.15 These expression levels are affected by perturbations in the gut microbiota in a sex-dependent manner, demonstrated using germ-free (GF) and antibiotic-treated animals.

Dr. Jane Foster (McMaster University) also discussed the impact of manipulations of gut microbiota on brain and behaviour, adding that although animal models, including the GF mouse, have limited clinical significance, they point us in the right direction for mechanisms and manipulations that will likely translate to conventional rodents and even to different species. Building on studies that indicate behaviour,16–17 gene expression17 and microbiota18 disruptions in GF mice, her recent research also shows global brain structure changes. This association between microbes, brain structure, and behaviour has been proposed to explain strain and sex differences in behaviour and may suggest the need for further stratification in clinical studies aiming to identify groups in terms of their microbiome composition and function. The microbiome reflects interaction between host genetics and environment over the lifespan, and the bacterial metagenome is much more heterogeneous than the human genome.

Caroline Wallace (Queen's University) is aiming to translate recent advancement in understanding the biology of the gut–brain axis into the clinic with clinical trials of probiotic treatments for MDD. Although using probiotics for treatment of mood disorders is a hot topic in the news, there are very few studies to date investigating their efficacy in treating MDD. Probiotics reduce global inflammation, a common phenotype for depressed patients, and the consumption of probiotics reduces stress hormones, increases neurotrophic factors and modifies behaviour in rodents.20–22 A recent review by Wallace and Milev found a lack of standardization of probiotic dose in human studies, and most studies have been conducted only in healthy populations. The preliminary findings of Wallace and Milev suggest that patients with MDD report better sleep quality, among other mood outcomes, after probiotic treatment and suggest that standardized clinical trials manipulating microbes to treat brain disorders are an exciting future direction for the field. From these studies it is evident that our current understanding of gut–brain communication is just the tip of the iceberg, as there are more complex mechanisms of communication between gut and brain that have yet to be determined and translated to clinical research and treatment.

Symposium 4. What brain imaging can tell us about diagnosis, treatment and mechanisms

The fourth symposium focused on how brain imaging can further our understanding in 3 domains of diagnosis, treatment and mechanisms. The symposium was kicked off by Dr. Alexander Neumeister (University of Ottawa), who discussed the contributions of molecular imaging to the development of evidence-based treatment for posttraumatic stress disorder (PTSD). The need for developing novel interventions for PTSD necessitates gaining a deep understanding of its underlying mechanisms. In his studies, Dr. Neumeister used positron emission tomography (PET) and kinetic modelling to assess the volume distribution of [11C]OMAR and [11C]LY2795550. The measured volume of distribution was then linked to endophenotypes and individual symptoms of PTSD, with results showing that endocannabinoid and opioid systems underlay 2 symptoms (hyperarousal and dysphoria, respectively) of PTSD in trauma survivors with PTSD. These results are important not only because they deepen our understanding of the pathology of PTSD, but also because they provide an opportunity for developing evidence-based treatment interventions.

Dr. Natalia Jaworska (McGill University) then talked about neural profiles in depressed youth and their utility in treatment response prediction. It has already been established that treatment-resistant MDD in adults is correlated with volume reduction in the subgenual anterior cingulate cortex (sgACC) and hippocampus. The results of Dr. Jaworska’s research indicate that similar to adults, youth with MDD have a smaller hippocampus than healthy controls. Furthermore, according to her experiments there was an inverse correlation between sgACC volume and severity of depression, and individuals with MDD with comorbid anxiety had smaller sgACC volumes.24 In addition to structural differences, youths with MDD have altered hippocampal activity patterns during encoding and recall of verbal information. Dr. Jaworska’s team has also measured cortical
thickness, with the results indicating the existence of a thicker cortex in the left hemisphere in youths with MDD.\textsuperscript{25} Another domain of her research is emotion processing, and her results suggest that compared with healthy controls, patients with MDD have more false alarms and faster response times, indicative of emotion hyperactivity and reduced executive control.

The third speaker, Sara de la Salle (University of Ottawa), talked about electrophysiological effects of ketamine and its implications on antidepressant response. She used subanesthetic doses of ketamine in healthy volunteers and patients with MDD and measured resting-state electroencephalographic (EEG) activity and event-related potentials (ERP). In healthy controls, ketamine was shown to expand the frequency range and decrease the mismatch negativity (MMN) with MDD and measured resting-state electroencephalographic doses of ketamine in healthy volunteers and patients with MDD and measured resting-state electroencephalographic (EEG) activity and event-related potentials (ERP). In healthy controls, ketamine was shown to expand the frequency range and decrease the mismatch negativity (MMN) with MDD.

In summary, her findings may provide information regarding easy-to-use electrophysiological biomarkers of targeted engagement and functional effects.

The last speaker, Dr. Rebecca Robillard (Netherlands Institute for Neuroscience), talked about the potential for using chronobiology and sleep profiles to tailor treatment strategies for mood disorders. Disturbances in biological rhythms can have a role in the pathophysiology of mood disorders. The result of Dr. Robillard’s research has shown distinct profiles in 24-hour cycle of melatonin, core body temperature and abnormal heart rate changes across the sleep period. More severe depressive and manic symptoms are associated with later circadian preference, poorer circadian rhythmicity and lower sleep quality.\textsuperscript{27} The results of her research has shown that one-third of patients with treatment-resistant MDD referred to psychiatric sleep laboratories had unusual breathing patterns during sleep that correlated with persistent depressive symptoms. A body of research suggest that chronobiological and sleep interventions (phototherapy, melatonin supplementation and continuous positive airway pressure) in some patients might improve both mood and sleep. Early chronobiological and sleep assessment can thus inform treatment strategies for identifiable subgroups of patients with mood disorders.

In conclusion, different methods of brain imaging not only deepen our understanding of the underlying mechanisms involved in psychopathologies of psychiatric disorders, but also provide us with information that can be used for making more accurate diagnoses and for developing more efficacious treatment strategies or regimens.

**Symposium 5. Neurocircuitry of binge eating: alterations in reward processing**

Binge eating disorder (BED) is the most common eating disorder, with a lifetime prevalence of 1.4%.\textsuperscript{28} Binge-eating behaviour is characterized by eating large amounts of food in a short period of time and having a sense of loss of control during these periods. The behaviour is accompanied by guilt, and individuals will often eat in secrecy, embarrassed by the binge-eating behaviour and their perceived inability to control the urges to overeat.\textsuperscript{29} This CCNP symposium explored the different aspects of binge-eating behaviours: compulsive behaviours, sensitivity to food rewards, neurologic basis of reward processing and the genetic underpinnings of high reward sensitivity.

**Amanda Maracle (Queen’s University)** used a rat model to investigate the role of dopaminergic circuitry in compulsive behaviours. Compulsive behaviour is a key feature of eating disorders, including BED, and a phenotype that is commonly studied in animals. It was previously shown that compulsive behaviour can be induced in rats with periods of food deprivation followed by intermittent access to sucrose water (intermittent sucrose diet).\textsuperscript{30} Ms. Maracle has shown that a combination of aversion stimulus with intermittent sucrose diet led to the development of compulsive eating in rats. She then examined the brain circuitry that underlies this behaviour, with the results indicating that dopamine signalling plays a key role in food intake behaviour. Furthermore, adaptive behaviours involved in food consumption are coordinated by the bed nucleus of the stria terminalis (BNST).

To explore the link between dopamine signalling in BNST and compulsive behaviour, Ms. Maracle administered dopamine antagonist to oval BNST before testing the rats using the aversion paradigm. Compulsive behaviour was blocked in rats exposed to intermittent sucrose diet, suggesting that development of compulsive behaviour is mediated by dopamine signalling in oval BNST. Second, ghrelin is a stomach-secreted hormone that signals hunger and increases appetite and feeding behaviour.\textsuperscript{31} Ghrelin concentrations increase before the scheduled food intake, and the disruption in the ghrelin signalling can affect feeding behaviours.\textsuperscript{32}

**Dr. Alfonson Abizaid (Carleton University)** investigates the effect of ghrelin signalling in the ventral tegmental area (VTA) in relation to caloric intake in a preclinical model of BED. His team showed that rats receiving ghrelin injections between the scheduled meal times would choose higher-fat diets, signifying increased reward sensitivity to food caused by disrupted ghrelin signalling. Similarly, preference for a high-fat diet could also be induced through a chronic social defeat stress model in mice and was accompanied by increased expression of ghrelin receptors. Dr. Abizaid further showed that increased reward sensitivity in mice is mediated by signalling through ghrelin receptors in the ventral tegmental area (VTA). Taken together, this evidence suggests that signalling through ghrelin receptors in the VTA mediates sensitivity to food rewards and that factors affecting ghrelin signalling, such as stress, can have consequences on feeding behaviours. Moreover, anticipation of reward and inhibitory control are important factors in feeding behaviours, such as cravings and dieting.

**Dr. Iris Balodis (McMaster University)** investigates the neurologic basis of nonfood reward and anticipatory processing to better understand decision-making involved in feeding and cravings. Dr. Balodis found that during an anticipatory stage of the monetary reward/loss task, obese individuals seeking treatment for BED showed diminished bilateral ventral striatal activity compared with obese controls.\textsuperscript{33} Participants showed diminished frontal activity during an inhibitory control task, which was associated with impaired dietary restraint.\textsuperscript{33} These findings suggest that binge
eating is a distinct phenotype in obese individuals and that frontal striatal areas might be suitable therapeutic targets for such a condition.

Finally, Dr. Caroline Davis (York University) focuses on the etiology of reward sensitivity, which she believes is a key feature of many impulse-related behaviours, such as addiction and overeating. Reward sensitivity in humans is mediated by dopamine signalling. Therefore, Dr. Davis explored the genetic variants that affect dopamine availability in the ventral striatum, a key reward processing area. She created a multitissue genetic profile (MLGP), assigning a risk genotype in each variant (risk genotype in brackets): ANKK1 Taq1A (A1+), DAT1 VNTR (9-repeat), DRD2 141Ins/Del (DelC), DRD2 C957T (TT), DRD2 rs1236483 (C+), and COMT val/met (met/met). Considering the combined effect of selected genetic variants, she assessed the association between these risk genotype profiles and the ratings from self-reports completed by obese individuals with and without BED. Her study showed that obese individuals with BED reported higher rates of food intake, snacking and food cravings. They also had significantly higher MLGP genetic risk scores, suggesting a link between higher dopamine signalling in the ventral striatum and higher sensitivity to hedonic rewards, such as food.


Pharmaceutical therapies for mood disorders are currently limited, with approximately 30% of patients being treatment-resistant to the currently available medications. The last symposium focused on basic research investigating new and exciting targets to hopefully provide more treatment options or a better understanding of the current limitations of treatments available. Many mood disorders have a high rate of comorbidity; for example, depression and anxiety are common in patients with type 2 diabetes mellitus (T2DM).35 Dr. Hsiao-Huei Chen (University of Ottawa) is particularly interested in finding therapeutic targets that could be used for both mood disorders and metabolic disorders. LIM domain only 4 (LMO4) is small protein that inhibits a protein-tyrosine phosphatase 1B (PTP1B) enzyme that blocks leptin and insulin signalling.36,37 The group found that blocking PTP1B activity could also decrease anxiety-like behaviour.38 Specifically, chronic stress impairs LMO4 inhibition of PTP1B and inhibition of PTP1B, either by a small-molecule antagonist or by an shRNA knockdown within the amygdala relieving stress-induced anxiety.38 As such, the PTP1B antagonist could be an ideal target for both diabetes and anxiety disorders. Notably, not everyone develops mood disorder after chronic stress. The difference between susceptible versus resilient individuals is of great interest for neuroscientists studying mood disorders.

Dr. Cecilia Flores (McGill University) found an interesting biomarker associated with vulnerability to stress-induced social avoidance. Micro-mRNA miR-218 expression in the prefrontal cortex is a consistent trait of resilience in mice, and upregulation of miR-218 in this region protects against social avoidance.39 Using blood samples, this group also showed that miR-218 expression could also predict a vulnerability to stress-induced depression-like behaviours.39 Therefore, miR-218 could serve as a novel biomarker for assessing vulnerability to stress.

Another crucial piece of the puzzle is understanding why certain patients are treatment-resistant. Dr. Paul Albert (University of Ottawa) has shown that polymorphisms of the 5-HT1A autoreceptors are associated with depression, suicide and reduced response to antidepressants.40 Knockout mouse models that repress this promoter provide new models of treatment-resistant anxiety/depression and adaptive compensatory changes that correspond with clinical studies.41 From this, we could potentially screen patients to investigate whether they may likely be treatment-resistant.

Finally, Dr. Sheena Josselyn (University of Toronto) elucidated how certain memories are formed and stored in the lateral amygdala. Interestingly, she showed that a marker of neuronal excitability, cAMP response element binding protein (CREB), was crucial for memory formation as well as timing of events.42 Her research therefore provides a foundation based on which we can potentially study how certain disorders (e.g., PTSD) may change memory formation.

Recent scientific advances have certainly deepened our understanding of the limitations of current mood disorder treatment as well as the potentiality of some biomarkers as new therapeutic targets.

Conclusion

These 6 symposia provide us with some timely knowledge and information about preclinical and clinical research on various psychiatric disorders by different groups across Canada. As their findings are gradually published, more light will be shed on the etiology and pathophysiological genesis of these disorders. More importantly, such a conference involving multidisciplinary research affords researchers the chance to come together to solve common problems in mental health. Combining preclinical and clinical research, as we do annually at CCNP, provides great opportunity to discover novel therapeutic targets for treating and curing mental illness.

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