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The Canadian College of Neuropsychopharmacology held its 42nd Annual Meeting in the vibrant city of Montreal. This meeting brought forward diverse leaders, from early to veteran career scientists, women and underrepresented minorities, to discuss their research uncovering the neuropsychopharmacological bases of mental illnesses. Research utilizing traditional, translational (neuroimaging), and artificial intelligence–based tools in basic and clinical fields yielded many novel findings. This report summarizes a public talk, a presidential special lecture, 3 award lectures and 7 symposia presented at the conference.

Public talk

How artificial intelligence can contribute to the prevention of substance use disorders

Dr. Patricia Conrod, Université de Montréal, Montreal

In this public talk, Dr. Patricia Conrod discussed the use of artificial intelligence to identify preventative interventions for substance use disorders. To this end, machine learning was applied to a large dataset of high school students to identify factors that can predict substance use disorders. This analysis revealed a number of factors, including personality traits, neuroimaging features and cognitive measures, that were correlated with each other and were predictive of substance use disorder. The model was further cross-validated to ensure strength of the findings. For example, the Substance Use Risk Profile Scale (SURPS) identified personality traits that can predict substance use patterns, such as hopelessness, anxiety, impulsivity and sensation-seeking, with 90% accuracy. Low cognitive function could predict cannabis use, which can further impair cognitive function. These predictive measures in turn were used to design personality-targeted preventative interventions. These interventions are currently being applied in different schools. Dr. Conrod presented an evidence-based method of design for mental health interventions using the sophisticated analytical power of artificial intelligence.

Presidential lecture

Deciphering the neurobiology of cannabis as "drug" and "medication"

Dr. Yasmin L. Hurd, Icahn School of Medicine, Mount Sinai University, New York

Dr. Yasmin Hurd examined the neurobiological basis of cannabis use for recreational and medical purposes using human and animal models. She discussed that the CB_1 receptor of the endocannabinoid system is widely expressed across the brain, including in axonal tracts and growth cones, suggesting that endocannabinoid signalling plays an important role in the wiring of the brain. She showed that fetal exposure to cannabis is associated with a reduction in SCG10 expression, involved in cytoskeletal organization, a decrease in dopamine D_2 receptor mRNA in the amygdala and the nucleus accumbens (NAcc), and a decrease in proenkephalin in the striatum of the midgestational fetal brain. No changes in dopamine D1R mRNA or prodynorphin levels were observed. Animal studies of prenatal tetrahydrocannabinol (THC) exposure further replicated these changes, showing a maintained reduction in D2R expression throughout adulthood, changes in proenkephalin and impaired long-term depression induction in the striatum. These animals behaviourally showed an increased sensitivity to heroin self-administration, increased drug intake under mild stress exposure, a greater motivation for sucrose reward based on a progressive ratio task, and increased immobility in a forced swim test. In addition, epigenetic changes were observed.

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The histone methyltransferase, MLL1, was enriched; knockdown of MLL1 in the NAcc was able to reverse the heightened motivational behaviour for rewards. Similarly, adolescent exposure to THC was associated with changes in the prefrontal cortical circuitry, including premature pruning of dendritic spines, reduced complexity of dendritic branching, changes in the expression of genes involved in cytoskeletal organization, and epigenetic modifications. These animals behaviourally showed a reduction in social interaction and increased self-administration of food rewards. In addition to THC, cannabis can contain cannabidiol (CBD), which is being investigated for medical purposes. Dr. Hurd showed that CBD administration in rats was able to reduce cue-induced reinstatement of heroin-seeking behaviour and normalized heroin-induced alterations in glutamate AMPA receptors, and that these effects were long-lasting. These benefits also translate to humans, who show a sustained reduction in cravings for opioids in addicts. The take-home message of Dr. Hurd's talk was that cannabis consumption has widespread effects on brain circuit development and function.

Award lectures

Heinz Lehmann Award: Exploring the genetic basis of neurodevelopmental disorders
Dr. Guy Rouleau, McGill University, Montreal

Neurodevelopmental disorders, including schizophrenia and autism-spectrum disorder (ASD), have an estimated heritability of 80% and 90%, respectively. A large proportion of this heritability remains unexplained. Dr. Guy Rouleau investigates the contribution of de novo mutations to the pathogenesis of these neurodevelopmental disorders. In this regard, a combination of clinical and basic science approaches was applied. De novo mutations were characterized in patient populations, and animal models were generated to validate the roles of these mutations in pathogenesis. A higher frequency of de novo mutations was characterized in patients with schizophrenia and ASD compared with healthy controls. The proportion of nonsense to missense mutations was much higher than expected by chance. Mouse models of these mutations, including KIF17 (schizophrenia) and IL1RAPL1 (ASD), implicate altered dendritic trafficking and differentiation, respectively. These results suggest that de novo mutations may contribute to neurodevelopmental disorder pathogenesis.

Young Investigator Award: Interaction between current stress and genome-wide methylation in conferring risk for suicidal ideation
Dr. Vincenzo de Luca, Centre for Addiction and Mental Health, Toronto

Dr. Vincenzo de Luca's work highlighted the importance of employing disorder-specific approaches in clinical settings to decrease suicidal ideation (SI). More specifically, his research focused on suicidal ideation in patients with schizophrenia. In recent work, he found that childhood trauma experience along with recent stress increased the risk of SI in patients with schizophrenia, with early-life trauma having a greater effect. Therefore, it is clinically important to consider childhood history along with recent stress when treating patients with schizophrenia. Through patient follow-ups, it was also found that physical issues from the past 3 months and interpersonal issues from the past 12 months were associated with severe and new SI. In another line of research, Dr. de Luca's lab also examined DNA methylation as a predictor of SI, as it is known that methylation is altered in suicidal behaviour. He utilized the Illumina 450 array to measure methylation in white blood cells, with the aim of identifying a peripheral biomarker for SI. Interestingly, genome-wide analysis of methylation levels found increased methylation level on chromosome 2 at the CpG site cg06121808 to be associated with present SI. Future work from Dr. de Luca's group will aim to identify single-nucleotide polymorphisms (SNPs) associated with increased SI in patients with schizophrenia and will include the study of suicide attempters. His research exemplifies the potential of studying molecular biomarkers of SI related to stress in a manner that is disorder-specific.

Innovations in Neuropsychopharmacology Award: Does the netrin-1 pathway guide resilience and susceptibility in adolescence?
Dr. Cecilia Flores, McGill University, Montreal

Dr. Cecilia Flores presented her work on the study of adolescent brain development and how experiences can impact such processes. Her lab is particularly interested in the study of long distance dopaminergic (DA) axon growth from the nucleus accumbens (NAcc) to the prefrontal cortex (PFC). Using a dual viral technique, Dr. Flores' team demonstrated that mouse DA axons continue to grow in adolescence and target both the medial PFC and orbitofrontal cortex. More specifically, their lab's work highlighted the importance of netrin-1, a molecule that acts as a guidance cue to attract axons expressing the DCC receptor and repel those expressing the UNC-5 receptor. Thus, the function of netrin-1 depends on the expression of the DCC versus UNC-5 receptors. Following the deletion of 1 copy of DCC in adolescence, the Flores lab demonstrated that DCC determines when and where DA axons target, as many axons failed to remain in the NAcc and ectopically grew to the PFC. The development of the dopaminergic pathway to the PFC is critical as it has the potential to affect various PFC-dependent behaviours, such as cognitive flexibility, behavioural inhibition and sensitivity to the rewarding effects of stimulant drugs of abuse. In the second portion of her lecture, Dr. Flores described how recreational-like amphetamine use in adolescent animals impacts developmental processes. Recreational-like amphetamine administration in mice in adolescence, but not adulthood, was found to downregulate DCC and netrin-1 expression in the NAcc, decrease netrin-1 in the PFC, and increase ectopic DA axons in adulthood. In terms of behavioural consequences, the animals presented with impaired behavioural inhibition as adults, which was measured by a go/no-go task. Interestingly, the DCC receptor is necessary

in order to observe the behavioural effects, and no effect on behavioural inhibition was seen when amphetamine was administered in adulthood. Moreover, the effect of amphetamine dysregulation of DCC is sexually dimorphic as early adolescence is a sensitive period for males, but mid-adolescence is critical in females. Therapeutic-like levels of amphetamine, on the other hand, do not dysregulate the expression of DCC or netrin-1 and do not result in the re-routing of DA axons to the PFC. The Flores lab also studied the effect of social stress and found decreased DCC expression and altered PFC DA connectivity as a result. Finally, via in silico and in vitro analysis, the Flores lab identified miR218 as a promising molecular link controlling DCC expression. miR218 is increased by recreational-like amphetamine and stress exposure in adolescence and mediates the amphetamine-induced DCC downregulation. Furthermore, peripheral levels of miR218, as measured in blood in adolescents, predicts susceptibility to stress in adulthood. Resilience or susceptibility to social stressors may be influenced by adolescent experiences through the miR218/netrin-1/DCC-mediated disruption of dopaminergic networks during development.

Symposium 1

Gender and addiction. A balancing act: females prioritize avoiding aversive stimuli when making value-based decisions
Dr. Erin Calipari, Vanderbilt University, Nashville

To open the symposia, Dr. Erin Calipari discussed her work developing new behavioural tasks to identify sex differences in how neural circuits integrate experiences with positive and negative stimuli to guide future behaviour. More specifically, her lab aims to address how sex differences in valence encoding mechanisms make females especially vulnerable to addiction. In a form of operant conditioning, rats were simultaneously presented with a cue indicating a reward and another to avoid shock. This was done to determine whether animals value avoiding a negative stimulus or attaining a positive stimulus and how a decision is made using such conflicting environmental information. It was found that females acquire positive reinforcement tasks quicker and negative reinforcement slower. Moreover, females value avoiding negative consequences over obtaining a reward, while males allocate their efforts equally to both avoiding punishment and obtaining reward. Therefore, females have different behavioural strategies, which call for new models that incorporate these complexities. In the second part of her talk, Dr. Calipari addressed how basal differences in reward systems can interact with drugs of abuse to drive vulnerability in females. Her lab found that when in the estrus phase of the menstrual cycle, conditioned females are more motivated to self-administer cocaine. Through single-unit electrophysiology, slice voltammetry and fiber photometry, her lab found the ventral tegmental area (VTA) to be more excitable in estrus females. Interestingly, cocaine acts as a more potent inhibitor of the dopamine transporter in estrus, thus preventing dopamine clearance at the synapse. Finally, her group employed a chemogenetic approach, using an excitatory DREADD (designer receptor exclusively activated by designer drugs) to stimulate VTA dopaminergic projections to the nucleus accumbens. It was found that increasing firing rate in males and diestrus females was sufficient to increase cocaine potency. This is critical as it results in long-lasting plasticity, causing drug seeking. Dr. Calipari's research highlighted the importance of understanding the complexities related to sex differences and how biological interactions with drugs can shape behavioural strategies, contributing to the vulnerability to addiction.

Cigarette use in the developing adolescent brain
Dr. Adriana Galvan, University of California, Los Angeles

Dr. Adriana Galvan's work is focused on brain development in adolescence and how the characterization of apparent vulnerabilities provides opportunities that can be leveraged to redirect behaviour. First, her group explored whether adolescents show differences in mesolimbic circuitry when presented with reward. It was found that in response to reward, adolescents show increased ventral striatal activation. Additionally, adolescents have greater mesolimbic dopamine release and receptor binding that results in greater reward-seeking behaviour. Her lab then looked to characterize the potential advantages of the observed increased mesolimbic excitability in adolescents. In collaboration with Dr. Daphna Shoshamy (Columbia University), it was found that adolescents learn more from positive feedback than adults and this is related to greater activation of learning systems in the striatum and hippocampus. Thus, the neural excitability present in adolescents is not unique to the processing of rewards, but is also related to ameliorated learning. Expanding the implications of these results, she wanted to determine whether exploiting adolescent sensitivity to emotionally reactive stimuli could serve as a means of cigarette smoking prevention. It was found that when presented with videos of individuals smoking, adolescent smokers showed greater activation of the ventral striatum than adult smokers. Additionally, the extent of this activation was correlated with the urge to smoke only in adolescent smokers. Therefore, this suggests that the activation of the mesolimbic system is associated with cigarette craving from observing others smoking. Next, they aimed to determine whether warning labels on cigarette packaging evoke differing neural responses between adolescents and adults. Adolescents demonstrated a significantly greater reduction in craving, such that those who had the greatest reduction in craving showed a parallel increase in communication between the amygdala and dorsolateral prefrontal cortex. Dr. Galvan's research is in support of the efficacy of health warning labels and demonstrates that they are particularly effective in adolescents. In future, her lab aims to analyze the longitudinal effects of nicotine on the developing adolescent brain, determine the mechanisms explaining changes in cigarette use over time, and elucidate how circadian systems may interact with these processes.

Gender differences in the effects of substance misuse on structural and functional brain measures in adults and adolescents
Dr. Patricia Conrod, Université de Montréal, Montreal

Dr. Patricia Conrod closed the symposium describing her progress in the development of low-cost, effective interventions for preventing adolescent drug use and her recent work venturing into the effects of sex differences. With the cooperation of 31 high schools in the greater Montreal area, she was able to track the 5-year outcomes of substance use, particularly alcohol and cannabis, on adolescent cognitive development. Interestingly, it was found that if adolescents used cannabis in the year prior, they showed a lag in the expected development of spatial working memory and inhibitory control. In other words, cannabis users in their final year of high school performed at a level equivalent to non-users in the seventh grade. In terms of sex differences, it is known that adolescent girls are less likely to be smokers, drinkers and substance users; however, it appears as though, thus far, some sex differences may be apparent in terms of working memory, but they remain small. Dr. Conrod also introduced the novel use of ENIGMA, a dataset led by Dr. Paul Thompson (University of Southern California), wherein neuroimaging data can be shared to allow for the comparison of results obtained across studies and labs. Her group is now collaborating with the growing consortium and is leading the ENIGMA addiction project. Some future aims include the charting of sex differences in brain aging throughout life in healthy individuals in the largest ever normative study of the brain and the identification of sex differences in the trajectory of brain abnormalities in psychiatric conditions. In addition, she developed metrics to quantify brain impairments related to substance use disorders and demonstrated that they are comparable to those seen in psychiatric conditions. Moreover, she aims to develop a standardized method of quantifying and comparing brain-related correlations of mental and substance use disorders for cross-disorder comparisons and meta-analyses. She is also pursuing the development of mega-analyses to capture the general regions most compromised across addiction behaviours for alcohol, cannabis, nicotine, cocaine and amphetamines. Dr. Conrod's work highlights the importance of employing a neuropsychological approach to addictive behaviours and the need to consider drug users as similar to psychiatric patients in terms of cognitive changes and therapeutic needs.

Symposium 2

Brain adaptations to diet: how fats and sweets mess with our head. Your brain on junk food
Dr. Susanne E. La Fleur, University of Amsterdam, the Netherlands

Dr. Suzanne La Fleur elucidated the role of the hypothalamic–striatal circuitry in junk food consumption. To examine this question, her lab first established a junk food diet for rodents that best models human consumption. They identified that volitional (free-choice; FC) consumption of a varied diet of nutritional chow, water, lard (high fat; HF), and sucrose solution (high sugar; HS) results in hyperphagia, obesity and insulin resistance — hallmarks of junk food consumption in humans. In contrast, FC-HF, FC-HS and the equivalent of the HFHS diet in pellet form did not result in sustained overeating behaviour. Moreover, despite free access to a HFHS diet, these rats were highly motivated for a food reward in a progressive-ratio lever press for food reward task. To understand the relationship between junk food consumption and motivation for food rewards, the La Fleur lab examined the hypothalamic–striatal circuitry, which is involved in satiation and motivational behaviours. In the arcuate nucleus of the hypothalamus, an increase in the expression of neuropeptide Y (NPY) mRNA was observed in FC-HFHS animals. This peptide promotes food intake. Hypothalamic neurons expressing this peptide project to the nucleus accumbens (NAcc) of the striatum. NPY administration in the NAcc increased fat, but not sugar or chow intake; reduced neuronal firing activity; and reduced preproenkephalin mRNA. These effects were mediated by NPY receptors Y1, which are coexpressed in enkephalin neurons of the NAcc. Together, these results suggest that a junk food diet promotes overconsumption through altered hypothalamic NPY neuronal–striatal enkephalin neuronal activity.

How the orbitofrontal cortex adapts to an obesogenic diet
Dr. Stephanie L. Borgland, University of Calgary, Calgary

The orbitofrontal cortex (OFC) functions in decision-making; it integrates external sensory information and internal motivational states to select an action. Dr. Stephanie Borgland hypothesizes that an obesogenic diet may promote poor diet choices through altered function in this cortical area. To examine this hypothesis, the Borgland lab performed electrophysiological experiments in the OFC of rats on an unrestricted cafeteria diet. Pyramidal cells of the OFC of these rats show a reduction in the frequency of inhibitory inputs. This reduction is reversed when the CB1 receptor of the endocannabinoid system is blocked. In addition, endocannabinoid mediated inhibitory long-term depression (LTD) is impaired. These results suggest heightened endocannabinoid activity in the OFC reduces inhibitory inputs to pyramidal cells. This heightened endocannabinoid activity is associated with increased endocannabinoid synthesis through increased metabotropic glutamate receptor 1 (mGluR1) activity. Increased mGluR1 activity in turn is attributed to increased availability of extrasynaptic glutamate. Astrocyte recordings following glutamate uncaging showed a reduction in current passing through glutamate-transporter 1 (GLT1), but no changes in GLT1 receptor expression were observed. These results suggest a deficit in astrocytic glutamate reuptake, leading to increased extrasynaptic glutamate availability. Administration of *N*-acetylcysteine restores GLT1, mGluR1 and endocannabinoid function. An obesogenic diet disrupts astroglial-neuronal interactions, resulting in an enhanced endocannabinoid tone that alters the excitatory–inhibitory balance of the OFC circuit.

Dietary manipulations alter impulsivity and risky decision making in rats
Dr. Catharine Winstanley, University of British Columbia, Vancouver

Dr. Catharine Winstanley examines the relationship between impulsivity, decision-making and unhealthy diets in rodents. To measure impulsivity, rats were trained to nose poke in the aperture that was illuminated for a sucrose reward in a 5-choice serial reaction time task (5CSRTT). A premature nose poke indicates impulsive action. Rats of the same weight on a high-fat, but not high-sugar diet showed increased action impulsivity and reduced dopamine receptor D_2 (D2R) expression in the striatum. Leptin knockout (KO) rats, an animal model of obesity, additionally showed increased action impulsivity without changes in D2R expression, but only when challenged with amphetamine. To measure choice impulsivity, rats were trained in a gambling task where each aperture was associated with differing risk/gain probabilities for a sucrose reward. Low-risk, low-reward decisions were most optimal in maximizing reward in this task. Cues, including bright lights and sounds, were paired with reward delivery (cued rat gambling task). Interestingly, rats that performed optimally prior to consumption of an unhealthy diet showed no change in choice impulsivity or risky decision-making in this task. In contrast, rats that performed suboptimally were more likely to engage in risky decision-making following consumption of a high-fat diet. Inhibiting the OFC during acquisition of this task results in better decision-making. Therefore, there is a dynamic interplay between diet choice, impulsivity and risky decision-making.

Dietary and neural components of obesity-induced motivational deficits
Dr. Stephanie Fulton, Université de Montréal, Montreal

Obesity and type 2 diabetes, both attributed to an unhealthy lifestyle, are associated with depression and anxiety. Dr. Stephanie Fulton investigates the relationship between unhealthy diets and depressive conditions using rodent models. Specifically, she discussed the effects of different types of fats: olive oil (monounsaturated fat) and palm oil (saturated fat). She showed that whereas olive or palm oil consumption was associated with increased weight gain compared to control animals, palm oil consumption was further associated with increased insulin, glucose intolerance and hyperglycemia. Palm oil consumption was also associated with increased indicators of inflammation, including higher blood plasma levels of C-reactive protein, corticosterone and tumour necrosis-factor α (TNF-α) and increased gliosis, interferon-γ (IFN-γ), and nuclear factor-κ-B (NF-κB) transcriptional activity in the NAcc. Palm oil consumption also resulted in increased compulsive sucrose-seeking behaviour. Knocking down NF-κB in the nucleus accumbens (NAcc) offset the inflammatory response and compulsive behaviour induced by the palm oil diet. These rodents further showed a blunted preference for amphetamine in the conditioned place preference assay, suggesting a dampening of the mesolimbic sensitivity. Further examination of the mesolimbic system demonstrated reduced dopamine D1R-PKA signalling in the NAcc. Interestingly, D1R in medium spiny neurons (MSN) of the NAcc is thought to confer resistance to chronic social defeat–induced depression. In line with this, DREADD (designer receptor exclusively activated by designer drugs) mediated activation of D1R expressing MSN of the NAcc rescued sucrose anhedonia and despair in the forced swim task, depressive-like behaviours induced by the palm oil diet. A diet high in saturated fats may therefore contribute to the onset of depressive behaviours through heightened inflammation and reduced D1R activity in the NAcc.

Symposium 3

Unveiling pro-neuroplasticity mechanisms of cannabinoids, but not in front of the kids! Role of the endocannabinoid system in adolescent brain remodelling
Dr. Tiziana Rubino, University of Insubria, Varese

Adolescent use of cannabis increases the risk of mental illnesses such as schizophrenia. Dr. Tiziana Rubino investigated the effects of adolescent cannabis use on the maturation of brain circuits. Adult rats that were administered tetrahydrocannabinol (THC) during adolescence (postnatal day [P] 35–45), but not during adulthood (P75), show signs of psychosis, depression and cognitive deficits. These female rats showed an altered development of the endocannabinoid system, including reduced CB_1 receptor density and anandamide levels. Electrophysiological data further showed impaired endocannabinoid-mediated induction of long-term depression (LTD) in layer V of the prefrontal cortex (PFC). The altered maturation of the endocannabinoid system was associated with altered PFC development. Pyramidal cells in layer 2/3 showed reduced spine density in basilar dendrites, increased expression of the GluN2B subunit of NMDA receptors, and increased expression of the GluA1 subunit of AMPA receptors. This change in AMPA receptor composition was functionally associated with increased calcium permeability. These rats additionally showed changes in myelin-associated proteins, including MOG and MBP. Administration of a CB_1 receptor antagonist, AM251, during adolescence could rescue the THC-induced changes in glutamatergic activity in the PFC and myelin-associated proteins. Adolescent THC exposure can therefore induce changes in brain circuit maturation through altered endocannabinoid system activity.

Long-term cognitive effect of developmental cannabis exposure
Dr. Ryan J. McLaughlin, Washington State University, Pullman

There is a growing trend of cannabis use in pregnant females. Limited longitudinal data exist on the effects of maternal cannabis use on offspring development. In addition, current animal models of cannabis use fail to capture the volitional and inhalational aspects of human cannabis consumption. To address this latter issue, Dr. Ryan McLaughlin trained rats to nose poke for cannabis vapour, which increased plasma tetrahydrocannabinol (THC) levels. These rats were motivated

to receive cannabis, as assessed by a progressive ratio task for THC, and the behaviour underwent extinction and reinstatement, indicating a conditioned drug-seeking behaviour. To determine the maternal effects of cannabis use on offspring development, female rats were exposed to cannabis vapour between the timepoints of mating and the day before birth of their offspring. These offspring show reduced behavioural flexibility, as assessed by a set-shifting test. In this assay, rats are trained to lever press for a sucrose reward with shifting rules. For example, rats may be initially trained to lever-press for sucrose based on cued light, then based on position of the lever, and then based on the reversal of the previous rule. Rats prenatally exposed to cannabis require a greater time to reach criterion during the acquisition of the set-shifting task, produce greater regressive errors (unable to maintain the correct strategy), and produce greater never-reinforced errors (strategies that were never reinforced). Adolescent self-administration of THC was also associated with greater number of regressive errors. Prenatal and adolescent exposures to THC can thus impair behavioural flexibility.

Bridging preclinical and clinical data in elucidating the age-dependent impact of cannabis use on mood disorders
Dr. Gabriella Gobbi, McGill University, Montreal

Dr. Gabriella Gobbi examines the relationship between adolescent cannabis use and mood disorders, including depression and suicidal behaviours. A meta-analysis of adolescent cannabis consumption shows an increased odds ratio (OR) of 1.37 for depression and 1.50 for suicidal ideation. These adolescents showed no signs of premorbid depression. To better elucidate how cannabis use can mediate depressive behaviours, rats were administered tetrahydrocannabinol (THC) during adolescence. These rats show a reduced preference for sucrose solutions, a reduced latency to immobility in the forced swim test, but no changes in the elevated plus maze assay. These results indicate the onset of depressive behaviours, but no changes in anxiety, in adolescent THC-exposed rats. Further, in vivo recordings of the dorsal raphe demonstrated a reduction in the firing frequency and an irregularity of the firing patterns of serotonergic neurons, which co-express CB_1 receptors. Adolescent THC exposure can therefore increase the risk for mood disorders through endocannabinoid mediated alterations in dorsal raphe serotonergic activity.

Symposium 4

Translational neuroimaging in neurodevelopmental disorders: from animal models to clinical populations and back again. Reward and sensorimotor brain systems in autism-spectrum conditions
Dr. Signe L Bray, University of Calgary, Calgary

Dr. Signe Bray explores whether individuals with autism-spectrum disorder (ASD) attribute lower reward values to social stimuli due to reduced interests. To ascertain this hypothesis, Dr. Bray applies the social motivation framework. This framework comprises an examination of (1) imaging features of reward brain regions, (2) ratings of stimuli, (3) effort put in for stimuli, and (4) eye-tracking of stimuli. In a reinforcement learning task, males with ASD learned to associate a stimulus (computer pictogram) with personalized high-interest pictures and another stimulus (a different pictogram) with personalized low-interest pictures. Both ASD and control individuals learned these associations equally, acquired the same strategy for selecting the same pictogram that yielded the high interest picture, showed similar eye-tracking patterns, and showed similar MRI patterns in the ventromedial prefrontal cortex and the posterior cingulate cortex. Electroencephalography recordings obtained during a passive viewing task also showed similar activity patterns. Reward processing for high- and low-interest stimuli therefore does not appear to be altered in individuals with ASD.

Subcortical changes in the development of psychosis: a longitudinal study of youth at familial risk for schizophrenia
Dr. Synthia Guimond, University of Ottawa, Ottawa

Dr. Synthia Guimond performed a 4-year longitudinal imaging study in individuals at high risk for psychosis to determine neural imaging signatures that can predict later onset of psychosis. Individuals with a familial risk for psychosis were selected in this study. A meta-analysis of brain volumes in patients with schizophrenia reveals a reduced volume of the hippocampus and amygdala. Imaging of these regions show significant shape abnormalities (negative inward displacement) of the right dorsomedial amygdala and a trending but nonsignificant reduction in volume of the subiculum in familial high-risk individuals that convert to psychosis. Baseline performance in an emotion-recognition task was impaired in the high-risk individuals who convert to psychosis, and verbal learning was impaired in high-risk individuals independent of whether they convert to psychosis. Performance in both of these tasks was positively correlated to the volume of the subiculum. These results indicate that abnormalities in the shape of the dorsomedial amygdala and poor emotion recognition in familial high-risk individuals can be used to predict which individuals convert to psychosis. This information can be used in the targeting of preventative measures.

Translational brain imaging in neurodevelopmental disorders using large-scale clinical data and mouse models
Dr. Mallar Chakravarty, McGill University, Montreal

Dr. Mallar Chakravarty emphasizes a translational approach to neuroimaging using both clinical and animal populations to further elucidate brain mechanisms underlying mental illnesses. Autistic patients show increased cortical volume and mean thickness, with some differences between males and females. Females, for example, showed increased cortical thickness in frontal and occipital areas. In addition, cortical thickness was correlated with IQ levels, but not at very high IQ levels. A developmental mouse model of autism was further used to elaborate on imaging

findings. Pregnant female mice were administered the immunostimulant poly (I:C), and structural MRI was performed on the offspring at weaning, adolescence, and early and late adulthood. This longitudinal animal imaging substantiated the human imaging data, demonstrating altered developmental patterns in different brain regions. For example, the development of the striatum in these mice progresses from undershooting to overshooting compared to controls. His research highlighted the strengths of combining clinical and animal neuroimaging data in elucidating brain mechanisms underlying mental illnesses.

Maternal immune activation and brain development: relevance to psychiatric disorders

Dr. Anthony C. Vernon, King's College London, London

Dr. Anthony Vernon examines the biological underpinnings of altered neural circuitry in rodent models of autism. He discussed that offspring of maternally poly (I:C) administered rodents show deficits in social interaction, prepulse inhibition and working memory. Longitudinal proton magnetic resonance spectroscopy showed deficits in glutathione over time, but no changes in *N*-acetyl-aspartate or glutamate. Longitudinal structural MRI showed deficits in cortical and subcortical volumes that normalized by late adulthood. These developmental changes in volume are associated with a reduction in parvalbumin expression, reelin expression, synaptopathy, increased C1q and C3a expression of the complement system, delayed microglial maturation, changes in microglial activation, but not changes in the number of neurons. These biomolecular changes suggest altered synaptic pruning may mediate volumetric changes in cortical and subcortical regions of autism animal models. mcDESPOT imaging of myelin tissue showed a reduction in myelin wraps around axons in the prefrontal cortex (PFC). Molecular analysis further revealed a decrease in myelin oligodendrocyte glycoprotein (MOG) expression in the PFC and nucleus accumbens (NAcc). Molecules associated with inflammation were also examined. The translocator protein (TSPO) was decreased in the PFC but not the hippocampus. No changes in IBA11, CD68, or GFAP expression were observed; however, an increase in cytokines in the PFC was measured. These results suggest that heightened inflammatory action and synaptic pruning may underlie deficits in myelination, and cortical and subcortical volumes in autistic rodent models.

Symposium 5

The multilingual brain: interactions between several neurotransmitters during development, reward, and decision-making. Investigation of the developmental downregulation and pathological upregulation of Vglut2 expression in DA neurons

Dr. Willemieke Kouwenhoven, Université de Montréal, Montreal

Dr. Willemieke Kouwenhoven studies dopamine neurons expressing Vglut2, a vesicular glutamate transporter, rendering these neurons capable of packaging and releasing both dopamine and glutamate. It is already known that such Vglut2 dopaminergic neurons are important for neuronal survival when exposed to toxins. Dr. Kouwenhoven's lab aims to define the role of Vglut2 and explain why knockout mice show enhanced vulnerability to the dopaminergic toxins 6-OHDA and MPTP. In overexpressing Vglut2 in cultured dopaminergic neurons, her group found that it promoted axon growth. In collaboration with the lab of Dr. Rajeshwar Awatramani (Northwestern University), it was found that Vglut2 expression occurs as early as embryonic day 11.5 (E11.5) and decreases by E14.5. Dr. Kouwenhoven described a developmental model used to explain the role of Vglut2 and how it contributes to the innervation of the striatum. This model was tested by comparing the reinnervation of the striatum postlesion in wildtype versus Vglut2 knockout mice. Through the injection of fluorescent retrobeads, it was found that dopaminerginc neurons spontaneously reinnervate the striatum at 7 weeks, but not in the knockout model. Therefore, following a 6-OHDA lesion, striatal reinnervation is perturbed in animals lacking Vglut2. The perturbed reinnervation results in the absence of positive feedback by trophic factors, causing larger lesions. This confers an increased vulnerability, making an animal less likely to survive postlesion due to decreased trophic factors

Afferent regulation and prefrontal maturation during adolescence

Dr. Kuei Tseng, University of Illinois at Chicago, Chicago

Dr. Kuei Tseng presented recent unpublished work uncovering the normal developmental trajectory of the prefrontal cortex (PFC) and characterizing the risk factors that can perturb such development systems in adolescence. It is known that fast spiking interneurons show increased spiking in the PFC during adolescence. To further explore the role of such interneurons, his team used a shRNA system to knockout approximately 30% of fast spiking parvalbumin-positive (PV) interneurons in the PFC. The amount of PV inhibition within the PFC was thus proven to be critical as this limited decrease in PV resulted in a significant decrease in GABAergic transmission. Looking upstream at what may drive fast spiking interneurons in development, Dr. Tseng's group expressed an inhibitory DREADD (designer receptor exclusively activated by designer drugs) in the ventral hippocampus (vHPC) to elicit transient inhibition during adolescence on postnatal days 35–40. When recorded in adulthood on postnatal days 65–75, a lack of upregulation in γ-aminobutyric acid transmission was observed in the PFC. Thus, vHPC activity is critical in the adolescent developmental window and has coordinated activity with PV interneurons. In order to address potential behavioural implications, a trace fear conditioning and extinction task demonstrated that both vHPC activity and PFC PV interneuron activity in adolescence are necessary for the expression of normal extinction behaviour. As a consequence, if either glutamatergic vHPC or PV interneuron activity in the PFC is disrupted in adolescence, then maturation is altered.

Regulation of reward and habits by cholinergic interneurons from the striatum

Dr. Salah El Mestikawy, McGill University, Montreal, and Pierre & Marie Curie University, Paris

The regulation of striatal neurons by cholinergic inputs and its implication in habit formation was discussed by Dr. Salah El Mestikawy. His focus is on the role of the caudate in goal-directed behaviours and the putamen in habit or automatic behaviours. He proposed that the nucleus accumbens (NAcc) encode reward, leading to goal-directed behaviours from the caudate; then this becomes habit and an automatized behaviour by the putamen. Dr. El Mestikawy highlighted the importance of understanding this striatal mechanism, as it can lead to detrimental habit-forming behaviours, such as bulimia and anorexia nervosa. It is known that the striatum is locally modulated by acetylcholine (ACh) interneurons, and his group previously demonstrated that they release both ACh and glutamate. To study the impact of the neurotransmitter cotransmission on the striatum in habits, his group conditionally knocked out either vGluT3 or vAChT to respectively silence glutamate or ACh transmission in ACh interneurons. Following operant reward conditioning, it was found that when ACh was silenced in the striatum, these animals showed more habit behaviour and were more compulsive. Using the sucrose binge-eating model of bulimia and the activity-based anorexia model, it was found that ACh knockout mice demonstrated both bulimia- and anorexia-like behavioural phenotypes. A Cre-mediated partial deletion of vAChT, further demonstrated that a 30%–50% partial decrease in ACh interneurons was sufficient to elicit pathological eating behaviours. This consequentially leads to decreased dopaminergic transmission, specifically in the caudate and putamen. Finally, with the commercial drug Aricept (donepezil), an acetylcholinesterase inhibitor, it was shown that pathological eating behaviours were rectified in the ACh knockout animals. As a result, donepezil is predicted to be effective in restrictive anorexic patients who are prone to developing excessive habits.

Dorsal raphe combinatorial serotonin-glutamate neurons drive reward by establishing excitatory synapses on VTA mesoaccumbens dopamine neurons

Dr. Marisela Morales, National Institute on Drug Abuse, National Institute of Health, Rockville

To conclude the symposium, Dr. Marisela Morales described her work studying the composition of the ventral tegmental area (VTA) and its inputs from the dorsal raphe (DR). Utilizing Fluoro-Gold as a retrograde tracer and vesicular glutamate transporter 3 (vGluT3) and tryptophan hydroxylase as markers of glutamate- and serotonin (5HT)-releasing neurons respectively, her group was able to demonstrate that the majority of DR neurons projecting to the VTA were exclusively glutamatergic and preferentially synapsed on dopaminergic neurons. More specifically, retrograde tracing in a Cre transgenic mouse line, as well as optogenetic activation of the DR, demonstrated that such DR glutamatergic neurons targeted dopaminergic neurons, which innervated the nucleus accumbens (NAcc). In terms of behaviour, stimulation of channelrhodopsin in DR glutamatergic neurons projecting to the VTA resulted in a preference for a chamber paired with the activation of this pathway. Therefore, her group defined a rewarding pathway from the DR, which releases glutamate onto the VTA, causing the release of dopamine in the NAcc. Given the traditional role of 5HT as being aversive, her lab then went on to study the ~30% of DR neurons projecting to the VTA that released both glutamate and 5HT. Interestingly, these neurons also lead to dopamine release in the NAcc and produced a place preference when optogenetically activated. Dr. Morales suggested that the glutamatergic DR neurons carry a rewarding signal, while those also releasing 5HT lead to the formation of memory for the reward. In future, her lab aims to test this hypothesis and further uncover how the various neuron subtypes in the DR–VTA–NAcc pathway are regulated and interact with each other.

Symposium 6

Hippocampal mechanisms underlying depression vulnerability and treatment. Sex-specific neural signatures of stress-induced behavioral adaptation

Jessie Muir, McGill University, Montreal

Jessie Muir, a doctoral student in the lab of Dr. Rosemary Bagot, aims to predict future susceptibility to a chronic stressor prior to stress exposure by identifying neural correlates of susceptibility in animals that will undergo a chronic variable stress paradigm. Their group is interested in ventral hippocampal (vHPC) projections to the nucleus accumbens (NAcc), which were previously shown by Dr. Bagot to be hyperactive in animals susceptible to chronic stress. Ms. Muir aims to identify how stress modifies the vHPC–NAcc pathway and various behaviours (e.g., passive coping, anxiety- and depression-like behaviours) in both male and female mice. Preliminary results utilizing fiber photometry showed that chronic variable stress increases vHPC–NAcc peak firing amplitude and frequency in both sexes, which correlates with increased anxiety and passive coping behaviour. In addition, increased vHPC–NAcc activity prior to stress was predictive of the expression of greater anxiety-like behaviours following chronic stress. Thus, following chronic stress, the vHPC–NAcc pathway contributes to anxiety vulnerability in both sexes. However, this pathway contributes to social interaction behaviour differently, as prestress increased activity was positively correlated with social interaction, but a negative correlation was observed poststress. Further teasing apart from the relationship between the vHPC–NAcc pathway and susceptibility as it pertains to gender will aid in the understanding of the neural mechanisms of the vulnerability to developing depression.

Hippocampal negative memory engrams enhance stress susceptibility
Dr. Tak Pan Wong, McGill University, Montreal

Dr. Tak Pan Wong is interested in exploring whether the memory for a negative stimulus is enhanced in animals that are susceptible to expressing depression-like behaviours. Depressed patients are known to demonstrate a negative memory bias, or have an easier time forming and recalling memories of negative events. Additionally, the hippocampus, a brain region critical to the formation of episodic memory, is known to be hyperactive in depressed individuals. Dr. Wong's lab utilized TetTag animals, a transgenic mouse line that enables the quantification of neurons that were activated and later reactivated by exposure to chronic social defeat stress (CSDS). Hippocampal CA1 neurons active at both time points can be termed engram cells, or the neurons encoding for the memory of the stressor. It was found that susceptible animals possessed a significantly greater density of such stress-related engram cells in the dorsal CA1. Moreover, the engram cell density positively correlated with the level of social avoidance. Engram cell density in the dorsal CA1 was also greater for a negative compared to a neutral memory in susceptible, but not resilient, animals. It was also demonstrated that depression-related behaviour could be promoted or dampened through optogenetic activation or inhibition, respectively, of engram cells. In support of these findings, further in vivo calcium imaging experiments demonstrated a progressive increase in the frequency of calcium spikes, as exposure to CSDS progressed in susceptible animals. Additionally, susceptible animals showed a significantly greater density of engram cells, or those neurons that were reactivated across days of CSDS. Future work from the Wong lab looks to utilize in vivo calcium imaging techniques to identify neuronal ensembles associated with specific depression-related behaviours.

Molecular and neural circuit mechanisms underlying antidepressant treatment resistance.
Dr. Benjamin Samuels, Rutgers University, Piscataway, NJ

Dr. Benjamin Samuels' recent work is aimed at characterizing the biology of antidepressant resistance. His lab utilizes chronic corticosterone administration in drinking water to mimic the effects of chronic stress. It was previously found that following this stressor with a 4-weeks of fluoxetine treatment continued to leave one-third of the chronically stressed mice as nonresponders (novelty-suppressed feeding test, forced swim test, open field test). Prior work from Dr. Samuels demonstrated that antidepressant-resistant animals had a significant decrease in the signalling of the growth factor activin in the dentate gyrus region of the hippocampus. His lab found that all fluoxetine nonresponders and nonresponders to second-line medications were converted to responders following bilateral infusion of activin in the dentate gyrus. Conversely, all responders were converted to nonresponders through the bilateral infusion of inhibin, an antagonist to the activin receptor, into the dentate gyrus. In future, the Samuels lab aims to conduct analogous experiments in females utilizing a social instability and chronic nondiscriminatory social defeat model as chronic corticosterone administration is an ineffective stressor in females.

Searching for exercise mimetic to improve stress resilience using animal models
Dr. Sonata Suk-Yu Yau, Hong Kong Polytechnic University, Hong Kong

Characterizing the biological impact that exercise has upon brain health is critical, particularly in terms of the resulting improvement noted in neurodegenerative disorders and major depression. Dr. Sonata Suk-Yu Yau's previous work demonstrated that voluntary wheel running in mice increased neurogenesis, brain-derived neurotrophic factor (BDNF), dendritic spine length and density. She also found that both increased neurogenesis and BDNF are required for exercise to confer an antidepressant effect. Adiponectin, a peripheral hormone secreted by adipocytes, is known to mimic the metabolic effects of exercise, has antidepressant effects, and promotes neurogenesis. Dr. Yau's lab has tested the adiponectin receptor agonist AdipoRon and found it to promote neurogenesis at low doses. Moreover, when administered to a diabetic mouse model, it was found to improve spatial memory deficits, promote cell proliferation, neuronal differentiation, dendritic remodeling and to restore soma size and synaptic plasticity. Dr. Yau's future work will try to uncover the mechanism of AdipoRon and address whether it can serve as a potential treatment for depression.

Symposium 7: next generation symposium

Six young scientists-in-training selected by a CCNP committee presented their research discoveries.

The evolution of the hippocampus subfields volume across lifespan in healthy aging
Aurelie Bussy, McGill University, Montreal

The hippocampus plays a central role in memory processing, and is implicated in the pathophysiology of Alzheimer disease. Aurelie Bussy examined the developmental changes in hippocampal volume across an individual's lifespan. Healthy male and female participants aged 18–80 years underwent magnetic resonance imaging. Analysis of the obtained images revealed a decline in total hippocampal volume following the age of 60, with differential volumetric changes of hippocampal subfields with age. Whereas the CA1 volume was positively correlated with age, the CA4-DG volumes were negatively correlated with age. These findings provide insights into the normal aging process of the hippocampus.

Effects of maternal smoking during pregnancy on brain development in children with ADHD: maternal recall does not tell the whole story
Nellie H. Fotopoulos, McGill University, Montreal

Maternal smoking during pregnancy increases the risk for attention-deficit/hyperactivity disorder (ADHD) in offspring. Nellie wanted to examine how maternal smoking may influence the development of the brain in offspring with ADHD. Children with an epigenetic marker for maternal exposure to smoking showed reduced surface area in the orbitofrontal cortex, an area implicated in impulsivity, in addition to temporal areas. This reduction in cortical surface area was proportional to performance in an attention based cognitive task. On the other hand, no significant findings were obtained when children were categorized based on maternal recall of smoking during pregnancy. These findings point out that epigenetic markers may be a better tool in evaluating the presence of environmental exposures, and that maternal smoking during pregnancy is associated with changes in cortical surface areas.

Fatty acid amide hydrolase levels in amygdala linked with functional connectivity in fear-related circuitry: a combined positron emission tomography and magnetic resonance imaging study
Duncan G.J. Green, University of Toronto, Toronto

Fatty acid amide hydrolase (FAAH) is an enzyme involved in the catabolism of the endogenous endocannabinoid, anandamide. Knockout of this enzyme in mouse models, thereby enhancing anandamide signalling, is associated with reduced anxiety and pain perception. Duncan Green investigated how FAAH levels in the amygdala of healthy individuals influenced the functional connectivity between the amygdala and ventromedial prefrontal cortex (vmPFC), a pathway involved in fear regulation. Using positron emission tomography (PET) scans and MRI, Mr. Green found that lower FAAH levels in the amygdala were associated with increased functional coupling between the amygdala and vmPFC. Changes in endocannabinoid signalling may therefore influence the functional circuit processing of fear.

Dopamine neurons and transients in the ventral tegmental area reduce prediction error about aversive outcomes
Virginia Opara, Concordia University, Montreal

In learning, the blocking effect occurs when the association between a cue and an outcome is not learned because another cue reliably predicts the outcome already. To examine how dopamine signalling influences this blocking effect, Ms. Opara used optogenetics to bidirectionally manipulate dopamine levels in rodents. Optogenetic stimulation of ventral tegmental neurons, which increased dopamine levels, is associated with blocking of novel cue association, and inhibition of ventral tegmental neurons, which decreases dopamine levels, is associated with unblocking and therefore learning of the novel cue association. These effects were mimicked by optogenetic manipulation of the activity of ventral tegmental neurons projecting specifically to the nucleus accumbens (NAcc). These results indicate dopaminergic signalling within the NAcc mediates prediction-based associative learning.

Aβ(1-38) is a negative regulator of Aβ(1-42)-mediated neurotoxicity
Maa O. Quartey, University of Saskatchewan, Saskatoon

The β-amyloid peptide of 42 amino acids (Aβ(1-42)) has been implicated in the pathophysiology of Alzheimer disease. Ms. Quartey examined the interaction and effects of Aβ peptides of varying lengths. Interestingly, a shorter sequence peptide, Aβ(1-38), negates the pathophysiological effects of Aβ(1-42) by rescuing its effects on light scattering, and on the electrophysiological properties of cultured neurons, including the ability to induce long-term potentiation. Shorter sequence Aβpeptides therefore modulate the effects of the pathogenic Aβ(1-42) peptide.

Do human laboratory models of smoking lapse behaviour generalize to non-treatment seeking smokers?
Toni C. Spinella, Dalhousie University, Halifax

Toni Spinella demonstrates that pharmacological interventions are insufficient in reducing nicotine addiction. A group of female smokers uninterested in quitting smoking underwent 4 different pharmacological interventions and the delay before their next smoke was examined. These interventions included nicotine inhalers, placebo inhalers, nicotine-containing tobacco, and nonnicotine-containing tobacco. None of these interventions influenced the delay until the next smoke, suggesting that additional factors, such as motivation, may be important in treatment effectiveness.

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