# The 31st Annual Meeting of the Canadian College of Neuropsychopharmacology

## Toronto, Ontario, June 6–9, 2008

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The 31st Annual Meeting of the Canadian College of Neuropsychopharmacology (CCNP) was held in Toronto, Ontario, June 6–9, 2008. This report summarizes the 3 CCNP award lectures, plenary lecture and 7 symposia.

### CCNP Heinz Lehmann Award lecture

Dr. William Honer (University of British Columbia, Vancouver) was the recipient of this year's Heinz Lehmann award, and his talk was entitled "Combining antipsychotic drugs to treat schizophrenia." As Dr. Honer noted, in recent years it has become common practice to administer combinations of neuroleptic medications in patients who have not responded to a monotherapy. The strategy is based on a number of observations. For example, the clinical efficacy of antipsychotic drugs might reflect actions on multiple transmitter systems. Indeed, among different neuroleptics, there is striking variability in the degree of dopamine (DA) $D_2$ receptor blockade associated with the reduction in psychotic symptoms and amphetamine-induced behavioural activation. Second, there is variability in the maximal $D_2$ occupancy possible for different compounds; e.g., clozapine can achieve about 80% occupancy, whereas risperidone can achieve 90%. Finally, there is anecdotal evidence that combination therapies are effective in treatment-resistant patients. As a test of this hypothesis, Dr. Honer and colleagues conducted a double-blind clinical trial in patients meeting criteria for either schizophrenia or schizoaffective disorder. Among patients who were exhibiting an inadequate response to clozapine monotherapy, the addition of risperidone improved symptoms in some patients, but the benefit was not greater than that achieved by the addition of placebo. Individual differences in the treatment responses were not predicted by duration of illness, previous treatment with risperidone or other examined variables. The combination treatment did not aggravate motor side effects or weight gain, but it did increase fasting blood glucose levels and mildly diminished working memory performance. Despite these findings, recent reviews raise the possibility that combination strategies might be beneficial; however, scrutiny of these meta-analyses reveals that the positive effects are driven by studies with multiple limitations. Dr. Honer proposed that the empirical data suggest switching antipsychotic medication is a better strategy than adding 2 together. Clozapine, it was proposed, should be tried sooner than is currently the norm; although clozapine carries some risks (e.g., agranulocytosis in 1%–2% of patients), so do combination therapies. For the treatment of poorly responding psychosis, switching appears to be the better choice.

### CCNP Innovations in Neuropsychopharmacology Award lecture

The winner of this year's Innovations award was Dr. Glenda MacQueen (McMaster University, Hamilton). The title of her lecture was "Regional brain volumes as a predictor of remission in patients with major depression." Dr. MacQueen noted that hippocampal size is related to depression but that this is nonspecific, since the hippocampus is also implicated in psychosis and posttraumatic stress disorder. She then summarized recent meta-analysis findings that most studies report hippocampal volumes that are 5%–6% smaller in patients with depression than in controls. Hippocampal size may also be correlated with the number of depressive episodes. However, other studies have shown that volume loss occurs primarily during the initial course of the illness. She then discussed the overlap in symptomatology between major

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depression and anxiety including fear, apprehension, panic, pain, gastrointestinal disturbances, worry, agitation, difficulty concentrating and sleep disturbances. It was proposed that the high rate of co-occurrence of these 2 disorders could mean that depression is a common result of anxiety. If this is the case, it raises the possibility that depression and anxiety share a common biological substrate. Although some studies have shown no differences in hippocampal volume in patients with anxiety disorders, MacQueen and colleagues[1] recently reported that anxiety is associated with small hippocampal volumes in treatment-naïve patients with symptoms of anxiety and depression. Dr. MacQueen then summarized the evidence that a longer duration of illness results in larger decreases in hippocampal volume and that patients in the lowest quartile for hippocampal volume were less likely to achieve remission. In comparison, women with larger hippocampi are more likely to respond to treatment. Overall, she concluded, several clinical factors predict hippocampal volume. There may be an interaction between clinical factors such as anxiety and the course of depressive illness. Baseline regional brain volumes may predict clinical outcome and some medications may be associated with short and long-term changes in regional brain volumes.

## CCNP Young Investigator Award lecture

When applied to psychiatry, cognitive neuropsychology has focused on cognitive tasks related to specific behaviours and symptoms rather than diagnoses. This year's Young Investigator Award winner, Dr. Todd Woodward (University of British Columbia, Vancouver), addressed these issues in a talk entitled "Cognitive underpinnings of delusions in schizophrenia." In his work, Dr. Woodward uses both cognitive neuropsychology and neuroimaging to identify dysfunctional cognitive operations and neural networks in relation to psychosis. Three aberrant processes were identified that appear to affect delusions: i) a bias against disconfirming evidence, ii) premature terminations of information-gathering and iii) a greater acceptance of implausible interpretations. In addition, a cognitive dysfunction of impaired ability to distinguish internally from externally generated information was considered in relation to producing hallucinations.

A number of innovative designs in cognitive testing were presented. For example, during testing, participants were asked to interpret scenarios with the response options of luring answers, an absurd answer and a true answer. In the process of testing, additional disconfirming information was added to the scenario to prompt the participant toward the true answer and away from the lures. People with delusions had a tendency to miss the disconfirming evidence. The strategy of disconfirming evidence was also introduced in a functional magnetic resonance imaging paradigm in which a picture may be interpreted in 2 different ways, with information in the pictures weighted at different proportions, prompting the participant to recommend a particular interpretation. As the proportions are changed, the healthy participant shifts his/her interpretation, whereas a person with delusions adjusts less to the disconfirming evidence and activates different neural structures.

Dr. Woodward also presented interesting evidence that psychotic patients prematurely terminate information-gathering. In an innovative design, a scenario was presented for which an event has an increasing probability of occurring. People with delusions anticipate the event prematurely, discounting evidence against the outcome.

The third type of disturbed cognitive process investigated by Dr. Woodward was related to the distinction between internal and external origins of sensory information. Participants performed a task in which they were asked to identify whether the source of a stimulus (e.g., a word spoken and heard) was internal or external. Interestingly, people with hallucinations demonstrated a bias toward interpreting the source as being internal. The left parietal cortex, which may be activated during tasks of working memory, and an area near this region were activated during this task among hallucinating participants but not in nonhallucinating participants.

Finally, these tests and the characterized processes formed the underpinnings for metacognitive training, a program designed to increase awareness in people with psychosis of the biases that may be generating their delusions. Encouragingly, preliminary evidence supports the use of these techniques.

## Servier distinguished lecture

The Servier distinguished lecture was given by Dr. Russell Foster (University of Oxford, Oxford, England) and was entitled "Photoreception, phototransduction and biological rhythms." He provided an overview on circadian rhythms and their regulation by light. In mammals, light information reaches the suprachiasmatic nucleus, the master circadian pacemaker, through a monosynaptic pathway originating in the retina, called the retinohypothalamic tract. Although this pathway was well described in the 1970s, the mechanisms by which light entrains the suprachiasmatic nucleus remained obscure. In the early 1990s, it was unexpectedly found that mice with hereditary retinal disorders that eliminated most of their rod and cone photoreceptors were still able to adjust (entrain) their circadian rhythms to the environmental light/dark cycle and do so with normal sensitivities. These observations suggested the existence of another class of photoreceptor in the eye. However, the experiment did not exclude the possibility that rods and/or cones could be involved in photoentrainment, since it was possible that a small number of photoreceptors remained in the animals and that this might be all that was required. To directly address this question, Foster's group conducted a series of studies using engineered mice with genetically and functionally ablated rods and cones (rd/rd cl mice). They first examined circadian entrainment to light in blind mice that lacked rod but not cone receptors. Remarkably, these mutant animals, which were blind, were shown to be capable of normal photoentrainment of behavioural and neuroendocrine rhythms. Similar findings were obtained in rodless and coneless mice, indicating the existence of a non-rod, non-cone ocular photoreceptor. Subsequent studies conducted on isolated retinas of rd/rd/ cl mice in combination with calcium imaging techniques revealed that the murine retina contains a plexus

of photosensitive ganglion cells that are electrically coupled through gap junctions. In addition, these studies showed that photosensitive ganglion cells mediate other irradiance detection tasks, such as light-induced pupil constriction, because under relatively high environmental irradiances, rd/rd cl mice show a full pupillary light response.

Dr. Foster then showed that rd/rd cl mice have also been valuable in characterizing the photopigment of photosensitive ganglion cells. Action spectrum studies (i.e., assessing the relative effectiveness of different wavelengths of light at generating a particular response) conducted in these mice revealed a previously uncharacterized, opsin/vitamin A–based photopigment with peak sensitivity at 479 nm (blue). This photopigment was tentatively named $OP^{479}$ (opsin photopigment $\lambda_{max}$ 479 nm). Follow-up studies showed that the opsin gene, melanopsin (officially designated *Opn4*), is expressed by a subpopulation of retinal ganglion cells and that the anatomy and distribution of these melanopsin-positive retinal ganglion cells are remarkably similar to the retinal ganglion cells that form the retinohypothalamic tract. The definite link between melanopsin and the capacity of photosensitive ganglion cells to respond to light came from melanopsin ablation studies. *Opn4* knockout mice were shown to have a significantly attenuated phase shifting response to light, to fail to show pupil constriction and to exhibit diminished light-induced expression of the immediate early gene *fos* in the suprachiasmatic nucleus. In addition, crossing *Opn4* knockout mice with mice lacking functional rods and cones results in the complete loss of light responses. Professor Foster's group is now trying to determine the phototransduction cascade of melanopsin in vivo. They have developed a microarray-based approach to identify elements of this cascade based on a technique they termed "trancriptional recalibration." The first screening showed 8 genes that colocalize with melanopsin photosensitive ganglion cells. The impact of genetic ablation of one of these genes, protein kinase C zeta (*Prkcz*), on light entrainment was then determined in Foster's laboratory. It was found that *Prkcz* knockout mice exhibit attenuated phase-shifting responses to light and attenuated pupillary responses at high irradiances, as well as impaired light-induced gene expression in the suprachiasmatic nucleus. Remarkably, this phenotype is indistinguishable from the one observed in *Opn4* knockout mice. Dr. Foster ended his talk by presenting his exciting and most recent findings on rd/rd cl and Ops4 knockout mice, showing that melanopsin photosensitive ganglion cells also predominantly regulate photic regulation of sleep. An important implication was that the photosensitive ganglion cells/melanopsin signalling system can serve as a new pharmacological target for the selective manipulation of sleep and arousal states.

## Symposia

*Presidential symposium. Neurodevelopment and behaviour*
*Co-chairs: Dr. Meir Steiner (McMaster University, Hamilton) and Dr. Harold Robertson (Dalhousie University, Halifax)*

*Speakers: Dr. Michael Meaney (McGill University, Montréal), Dr. Stephen Matthews (University of Toronto, Toronto), Dr. Stephen Suomi (National Institute of Child Health and Human Development, Bethesda, Md.)*

The session's opening speaker was Dr. Michael Meaney (McGill University, Montréal), and his talk was entitled "Maternal care, gene expression and epigenetic programming of the HPA stress response." As Dr. Meaney noted, early life variability in social support and other social interactions likely alters the ability to adapt to changing resources and affects vulnerability to adverse events. A carefully investigated and compelling illustration of this principle in rats is that maternal care alters behavioural and endocrine responses to environmental stressors. The mechanisms for these "maternal effects" involve differential expression of genes through epigenetic mechanisms and the subsequent expression of proteins. For example, low levels of maternal care, such as lower maternal licking and grooming, increases secretion of glucocorticoids later in life. This elevated excessive glucocorticoid secretion does not appear to be beneficial; for example, it can suppress growth and it is present during episodes of major depression. In comparison, in high maternal care rodents, greater expression of glucocorticoid receptors leads to enhanced feedback at the level of the pituitary and hypothalamus leading to reduced glucocorticoid secretion later in life and the more rapid termination of stress-induced increases. Since similar differences in glucocorticoid secretion (later in life) can be demonstrated after cross-fostering conditions, the effect is not solely due to pre-existing inherited traits. Instead, accumulating evidence indicates that the effects of maternal licking and grooming are related to changes in gene expression. For example, increased licking and grooming is associated with demethylation of the 5_ CpG dinucleotide within a nerve growth factor–inducible protein A (NGFI-A) transcription factor response element within the exon $1_7$ glucocorticoid receptor promoter. This difference in the methylation levels of the CpG site is present after the first week of life, can be reversed with cross-fostering and lasts into adulthood. A mechanism of thyroid hormone–dependent serotonin (5-HT) agonism upon $5\text{-HT}_7$ receptors influencing cyclic adenosine monophosphate (cAMP) and cAMP-dependent protein kinase A was implicated in altering levels of NGFI-A within the exon$1_7$ glucocorticoid receptor promoter. Pharmacological manipulations that block maternal effects upon cytosine methylation at the glucocorticoid receptor promoter also reverse maternal effects at the level of glucocorticoid receptor expression and stress responsivity. Tests of whether these same processes affect behaviour in humans are just in their early stages; however, it has been reported that less glucocorticoid receptor expression is present in the hippocampus of suicide victims with histories of abuse. These extremely important studies demonstrate persisting effects of early maternal care upon glucocorticoid regulation and implicate specific epigenetic mechanisms.

The session's second speaker was Dr. Stephen Matthews (University of Toronto, Toronto), and his talk was entitled

"Fetal experience programs endocrine function across generations." As Dr. Matthews noted, a striking 7% of pregnant women in Europe and North America are treated with synthetic glucocorticoids to promote lung maturation in fetuses at risk of preterm delivery. This treatment might actually mimic an effect of maternal adversity, greater endogenous glucocorticoid secretion. This could have adverse effects on the fetal brain. Animal models suggest that, in the developing brain, glucocorticoids influence neurogenesis, apoptosis, synapse formation and dendrite extension. Prenatal glucorticoid exposure in rhesus macaques is associated with reduced pyramidal neuron density in CA regions of the hippocampus, reduced granular neuron density in the dentate gyrus and reduced hippocampal volume. Fetal glucocorticoid receptors may be particularly vulnerable to glucocorticoids because they cannot desensitize. To investigate these issues further, Dr. Matthews has been studying the effects of glucocorticoids on fetal brain development in guinea pigs, since they have a long gestational period and are neuroanatomically mature at birth. In this paradigm, the consequences of exposure to synthetic glucocorticoid exposure are sex-specific and include decreased levels of fetal plasma cortisol in males but increased cortisol levels in females as well as increased levels of mineralocorticoid and glucocorticoid receptor mRNA in CA1/2 regions of the hippocampus and mineralocorticoid mRNA in the dentate gyrus. Fetal exposure to dexamethasone was also associated with an early increase in hippocampal NGFI-A expression. Longer-term effects of prenatal synthetic glucocorticoid exposure include a blunted hypothalamic–pituitary–adrenal axis response to maternal separation in young males and downregulation of mRNA expression of the NR1 subunit of the *N*-methyl-D-aspartate receptor in females postnatally. Sex-specific behavioural effects were noted also, such as greater activity by females in open-field testing and hyperactivity in the Morris water maze. The effects of maternal adversity can also cross generations. For example, maternal stress on day 60 led to greater stress-induced rises in plasma cortisol in males and to lower stress-induced cortisol responses plus decreased activity in open-field testing during the estrous phase of the menstrual cycle in females. Collectively, these data indicate that it might be premature to assume that there are no long-term consequences of prenatal synthetic glucocorticoid exposure in humans. They also highlight the possibility that a lower stress pregnancy may be a healthier environment for long-term fetal outcome.

The concluding talk of the symposium was given by Dr. Stephen Suomi (National Institute of Child Health and Human Development, Bethesda, Md.) and was entitled "Risk resilience and gene × environment interactions in primates." As Dr. Suomi noted, rhesus monkeys have a number of social and behavioural characteristics that make them a well-suited model for maternal and genotype effects in humans. During the first month of life, they stay in close contact with their mothers, whereas the second month involves more exploration and return to the mothers as a safe base. As time away from the mother progressively increases, there is also more social play, which is considered to be the equivalent of practice for adulthood. Substantial variability in behavioural–temperamental traits can become evident. For example, about 20% of monkeys in naturalistic settings exhibit unusually fearful and anxious behaviours accompanied by greater hypothalamic–pituitary–adrenal axis activation. Another 5%–10% of monkeys exhibit overly impulsive and aggressive behaviours, and the most aggressive males have the lowest cerebrospinal fluid concentrations of 5-hydroxyindolacetic acid (5-HIAA). Monkeys that are removed from their naturalistic environment and reared with their peers instead of their mothers are particularly likely to develop impulsive and aggressive behaviours plus low cerebrospinal fluid 5-HIAA concentrations. Investigations of genotype × environment interactions find that peer-reared monkeys develop aggressive behaviours and low cerebrospinal fluid 5-HIAA levels if the "s" allele of the serotonin transporter functional promoter polymorphism (5-HTTLPR) is present; they are protected from these effects if they are "ll" homozygous. The aggressive behaviours are also associated with greater vulnerability for excessive alcohol intake. A similar interaction is present between polymorphisms related to monoamine oxidase expression and peer rearing with respect to likelihood for aggression. Together, these data have important implications for understanding and overcoming problematic behaviours associated with early adverse life events in humans.

*Symposium 2 (AstraZeneca sponsored session). Novel approaches from new investigators: toward understanding the neurobiology of mental illness*
*Chair, Dr. Glenda MacQueen (McMaster University, Hamilton)*

Dr. Catherine Winstanley (University of British Colombia, Vancouver) opened the session with a talk entitled "Vulnerability to impulsivity: interactions between the noradrenergic system and CREB." Although most research on the neurobiology of impulsive behaviours has focused on 5-HT and DA, the norepinephrine system is implicated also. Stress, for example, is known to exacerbate impulsive symptoms in certain psychiatric disorders, an effect thought to be mediated in part by norepinephrine. To investigate this link further, Dr. Winstanley's examined the effects of yohimbine, an α-2 receptor antagonist, on cAMP response element-binding protein (CREB) activity and behaviour in rats. CREB activity is norepinephrine-responsive and has been implicated in the pharmacological treatment of bipolar disorder. Consistent with these observations, Dr. Winstanley found that acute exposure to yohimbine increases impulsive behaviour in rats. This effect is associated with selective increases in CREB phosphorylation in the orbitofrontal cortex, but not the medial prefrontal cortex or nucleus accumbens. Selective increases in CREB expression in the orbitofrontal cortex, through viral-mediated gene transfer, significantly enhanced the number of premature responses rats make on a 5-choice serial reaction time task, an index of impulsive behaviour. CREB activity in the orbitofrontal cortex appears to mediate norepinephrine-induced impulsivity, since overexpression of dominant negative mutant CREB in this region attenuates yohimbine-

induced impulsive responding. Together, Dr. Winstanley's studies strongly suggest that stress exacerbates impulsive behaviour via norepinephrine-mediated increases in orbitofrontal cortex CREB.

Dr. John Armstrong (University of Guelph, Guelph) gave a talk entitled "Development of dendritic spines, synapses and spontaneous synaptic activity in the medial prefrontal cortex: the role of adenomatous polyposis coli." Alterations in dendritic spine density and morphology in medial prefrontal cortex neurons appear to affect several developmental psychiatric disorders, including schizophrenia. Dr. Armstrong's studies track the developmental course of synapse formation in layer V and layer III medial prefrontal cortex pyramidal cells using Golgi-Cox staining. He then examines whether the spine developmental events correlate with changes in synaptic function, via whole cell voltage clamp recordings of spontaneous miniature excitatory postsynaptic currents of medial prefrontal cortex pyramidal neurons. His results to date show that changes in spine density and length precede changes in synaptic strength and number. The spines mature (shorten) during the second week after birth, while spine density peaks around postnatal day 16 before decreasing considerably afterward. Spine maturation coincides with enhanced synaptic activity. Synaptic strength and the number of miniature excitatory postsynaptic currents increase throughout the first 3 weeks of postnatal development. Changes in spine density depend on dendritic regions (apical versus basilar), but no differences were observed between layer V and layer III medial prefrontal cortex pyramidal cells. To complement his work on the development of synapse formation, Dr. Armstrong also studies the role of adenomatous polyposis coli in medial prefrontal cortex synapse formation. Adenomatous polyposis coli is a transynaptic signalling molecule expressed in dendritic spines of medial prefrontal cortex pyramidal cells during early postnatal development. Adenomatous polyposis coli seems to be implicated in developmental disorders because single nucleotide polymorphisms in the adenomatous polyposis coli gene have been associated with autism and schizophrenia. Dr. Armstrong has begun to address a role for adenomatous polyposis coli in synapse formation by examining changes in synapse formation and function in the medial prefrontal cortex of adenomatous polyposis coli mutant mice. Although adenomatous polyposis coli heterozygous mice exhibit normal spine density, they have significantly more immature spines than wild-type controls at 3 weeks of birth. In addition, 3-week-old adenomatous polyposis coli heterozygous mice have more miniature excitatory postsynaptic currents than wild-type controls, indicating changes in synaptic strength and number. Based on these findings, Dr. Armstrong suggested that adenomatous polyposis coli plays a critical role in synapse formation by promoting spine maturation and, in turn, regulating synaptic function. Learning more about the mechanisms involved in medial prefrontal cortex synaptic organization will likely contribute to the understanding of neurodevelopmental psychiatric disorders.

Dr. Jane Foster (McMaster University, Hamilton) delivered a talk entitled "Gut microflora influences CNS development of stress-reactivity and learning." First she discussed how throughout life there is an ongoing interaction between the gastrointestinal system and the central nervous system, and how this interaction seems to affect behaviour. She then presented recent findings from studies with germ-free mice that suggest that intestinal microflora mediate the bidirectional communication between the gut and the brain. Germ-free mice are used as an animal model to study the consequences of having no commensal intestinal microflora. Dr. Foster uses these mice to examine whether alterations in intestinal microflora can influence brain development and, as a consequence, modify adult behaviours. Previous findings showed that germ-free mice exhibit exaggerated activation of the hypothalamic–pituitary–adrenal axis in response to stress in adulthood. Thus, Dr. Foster is focusing her studies on the influence of gut microflora on stress-related behaviours in adulthood. Her preliminary data suggest that under stress conditions, adult germ-free mice show increased anxiety, compared with control groups. This finding is consistent with a hyper-responsive hypothalamic–pituitary–adrenal axis. Interestingly, the enhanced stress-induced anxiety observed in germ-free mice is reversed by microflora restoration. At baseline, however, adult germ-free mice exhibit reduced risk-avoidance behaviour, but this is not reversed after microflora restoration. Finally, preliminary evidence suggests that intestinal microflora modify learning in adults: under stress conditions, germ-free mice showed impaired performance in tasks that required cued and contextual learning. Dr. Foster speculated that because microflora gut colonization takes place during early postnatal life, it may overlap with certain brain developmental events, including those implicated in the stress response.

*Symposium 3. Dopamine and clinical depression*
*Chair: Dr. Marco Leyton (McGill University, Montréal)*

Dr. Marco Leyton opened the symposium with a talk entitled "Dopamine and the regulation of mood and motivational states: a brief review." Over the past 50 years, DA has become one of the most studied neurotransmitters in behavioural neurobiology. Concurrent with Arvid Carlsson's identification of DA as an independent transmitter in the brain was also the first evidence that it facilitated the initiation of movement in rabbits and mice. Clinical researchers were quick to appreciate the implications of this work, and patients with neurologic diseases characterized by an inability to initiate movement were found to have evidence of decreased DA levels and to respond well to administration of the immediate DA precursor, dihydroxy-phenylalanine (L-DOPA). Since 40%–50% of patients with Parkinson disease also develop episodes of clinical depression, this raised the possibility that DA might also contribute to symptoms of primary depression. Subsequent studies indicated that extended high-dose L-DOPA administration regimens could reinstate hypomanic symptoms in bipolar patients, whereas extended reductions in DA transmission could elicit symptoms of depression. In and of themselves, these clinical observations did not indicate which psychological processes accounted for the

effects. However, studies in laboratory animals have consistently found that limbic DA transmission regulates interest in rewards and the stimuli associated with them. Moreover, in humans also, a wide range of motivationally relevant stimuli elicit striatal DA release, whereas experimentally lowering DA leads to a sense of apathy and diminished interest in rewards but not a consistent change in the ability to experience pleasure. Dr. Leyton proposed that, overall, DA is likely to be involved in selective symptoms of depression, particularly psychomotor retardation, reduced motivation and low positive affective tone, but probably not the impaired ability to experience pleasure.

Dr. Pierre Blier's (University of Ottawa Institute of Mental Health Research, Ottawa) presentation was entitled "Functional connectivity between dopamine, serotonin and norepinephrine neurons." His recent studies have focused on the reciprocal interaction that exists among these monoamine systems and the implications that understanding this interaction can have on antidepressant therapies. First, he showed that selective 5-HT lesions increased cell firing rates of ventral tegmental area DA neurons. This inhibitory effect of 5-HT appears to be mediated 5-$HT_{2C}$ receptors, and long-term treatment with the selective serotonin reuptake inhibitor citalopram results in 5-$HT_{2C}$–mediated reductions in DA activity. Second, DA neurons appear to have an excitatory effect on 5-HT neurons, and selective ventral tegmental area DA cell lesions decrease 5-HT cell burst firing. This effect, which may contribute to the high incidence of depression in patients with Parkinson disease, seems to be mediated by $D_2$ receptors localized directly on 5-HT neurons. Moreover, Dr. Blier showed data that suggest that certain antidepressant agents, such as pramipexole ($D_{2/3}$ receptor agonist) and nomifensine (NE/DA reuptake inhibitor), may exert their delayed therapeutic effects by increasing DA activity and, in turn, augmenting 5-HT function. Lastly, he reported evidence that increased firing of norepinephrine neurons in the locus coeruleus seems to result in enhanced activity of dorsal raphe 5-HT cells. In fact, this phenomenon is observed in rats treated with the antidepressant bupropion. In conclusion, Dr. Blier proposed that enhancement of the activity of all 3 monoamine systems should lead to a better antidepressant effect.

Dr. Jeffrey Meyer (University of Toronto, Toronto) gave a talk entitled "Elevated monoamine oxidase A binding during major depressive disorder: state or trait." Using [$^{11}$C]raclopride positron emission tomography in drug-free, nonsmoking participants experiencing a major depressive episode, Dr. Meyer found that striatal $D_2$ binding potentials were elevated in the patients compared with controls, consistent with decreased extracellular DA levels in this region. Indeed, $D_2$ binding potential was particularly elevated in the depressed subgroup with high levels of motor retardation and, among the patients, a significant correlation between striatal $D_2$ binding potential and motor speed was observed. Dr. Meyer emphasized that this subtype of depression would be expected to preferentially benefit from DA-enhancing medication and strongly suggested that this question be examined in clinical trials. In the second part of his talk, Dr. Meyer summarized recent studies aimed at assessing the role of monoamine oxidase A in monoamine loss in patients with major depression. Monoamine oxidase A is an enzyme that metabolizes 5-HT, norepinephrine and DA. In a positron emission tomography study conducted in nonmedicated patients with major depressive episodes and healthy controls, Dr. Meyer's group found that, compared with matched healthy controls, monoamine oxidase A binding was significantly elevated (34%) in depressed patients in several brain regions, including the prefrontal cortex and striatum. They also found that serotonin reuptake inhibitor agents did not seem to target the monoamine oxidase A system because the elevated levels of this enzyme observed in patients with major depression persisted after a 6-week treatment with serotonin reuptake inhibitors. However, as Dr. Meyer noted, the effects of longer therapies need to be assessed. Interestingly, monoamine oxidase A density in recovered asymptomatic patients was found to be somewhat lower than in patients experiencing major depressive episodes, but greater than in healthy controls. Dr. Meyer suggested that this might render depressive patients more vulnerable to monoamine loss. Dr. Meyer considers that because of the sizeable increase in monoamine oxidase A density observed in depressed patients and because of the lack of other compelling causal explanations for the monoamine loss, elevated monoamine oxidase A levels is likely to be the primary monoamine-lowering process in major depressive disorder. He then concluded by emphasizing the need to develop animal models of persistent monoamine loss and to consider targeting multiple monoamines to treat major depressive disorder.

Dr. Laurie Zawertailo (University of Toronto, Toronto) closed the session with a talk entitled "Functional neuroimaging studies of depression and tobacco dependence comorbidity." Although the comorbidity between major depression and tobacco dependence is highly prevalent, little is known about its underlying neurobiological mechanisms. Dr. Zawertailo presented evidence in support of the hypothesis that comorbidity between major depression and tobacco results, at least in part, from selective alterations in midbrain dopamine systems. In a positron emission tomography study, she measured striatal [$^{11}$C]raclorpride binding before and after amphetamine in groups of smokers with and without major depression and in nonsmokers with and without major depression. She found that smokers, in comparison with nonsmokers, showed significantly less raclopride displacement in response to the amphetamine challenge, an effect consistent with less dopamine release. Moreover, this reduced effect of amphetamine in smokers was primarily driven by those with comorbid major depression. In the second part of her talk, Dr. Zawertailo presented very recent results from an ongoing BOLD functional magnetic resonance imaging study on cue-induced craving in smokers with and without major depression. The study consisted of 2 scans: a first scan conducted after overnight abstinence (withdrawal condition) and a second scan conducted after the smoking of a cigarette (smoking condition). In both scans, smoking cues and neutral cues were presented in a block design. Her results showed that both groups experienced similar cue-induced craving in the "withdrawal" and in the

"smoking" conditions. However, in the withdrawal condition, the smoker group exhibited a greater BOLD response in the ventral striatum. In contrast, activity in the anterior cingulate cortex was greater in the comorbid group. Dr. Zawertailo speculated that this combination of group differences could indicate that depressed smokers have reduced mesolimbic dopamine activity, reduced sensitivity to the rewarding effects of drugs and their cues, yet increased cortically mediated attentional salience toward drug cues. Indeed, this latter proposal may account in part for why smokers with major depression have greater difficulty quitting.

*Symposium 4. Fear and anxiety disorders: from molecules to the clinic*
*Chair: Dr. Sheena Josselyn (University of Toronto, Toronto)*

The focus of Dr. Josselyn's (Hospital for Sick Children, University of Toronto, Toronto) talk, entitled "Targeting the Fear memory trace," was on the role of CREB in anxiety. As she noted, the lifetime prevalence of anxiety disorders in Canada is about 12%. One widely used animal model is auditory fear conditioning, and it has been proposed as a corollary for human anxiety. In this model, mice are first exposed to foot shocks that are paired with tones. When the animal is reexposed to the tone, mice typically exhibit behavioural immobility ("freezing"). The lateral nucleus of the amygdala is critical for the acquisition of auditory fear conditioning since amygdala lesions ablate this response. However, although 70% of amygdala neurons are activated during auditory fear conditioning, only 20%–30% are necessary. To identify the relevant neurons, Dr. Josselyn used a transgenic mouse model that allowed for the selective ablation of neurons infected with viral vectors containing a stop codon. The receptor was activated by splicing the stop codon out. CREB function could then be eliminated in a subset of amygdala neurons using herpes simplex virus vectors. She described a study where infusion of the CREB vector increased CREB function in a CREB-deficient transgenic mouse. This genetically deficient mouse became like a wild-type mouse in response to auditory fear conditioning training even though only 12%–15% of amygdala neurons were infected. Moreover, neurons with increased CREB levels were 10 times more likely to be activated by auditory fear conditioning. The opposite occurred when cells were infected with a vector that decreased CREB functions. Together, these results suggest that neurons with increased CREB function are preferentially incorporated into the amygdala and act to support fear memory. They also appear to be necessary for the storage of memories.

The next talk, by Dr. Paul Frankland (Hospital for Sick Children, Institute of Medical Science and Department of Physiology, University of Toronto), was entitled "Incorporation of adult-generated granule cells into memory networks of the dentate gyrus of the hippocampus," and it focused on the following research question: "At what maturational stage are adult-generated granule cells incorporated into memory networks of the dentate gyrus of the hippocampus?" Dr. Frankland first outlined some of the published studies where these cells were ablated using methylazoxymethanol acetate or irradiation. However, these methods produced impairment in only half of the studies. The inconsistency of these effects raises doubts about the efficacy and specificity of the ablation methods. As an alternative approach, Dr. Frankland used immunohistochemistry to visualize the proliferation of new neurons into the dentate gyrus. They used the Morris water maze task as their behavioural measure of spatial memory, because these memories are long-lasting and depend on the hippocampus regardless of the "age" of the memory and because if granule cells are treated with bromodeoxyuridine before training on the Morris water maze, progressively more bromodeoxyuridine cells express Fos over time. This raised the follow-up question, "What is the role of Fos in memory strength?" To answer this, they used contextual fear conditioning and saw no difference in Fos expression in bromodeoxyuridine cells between a memory that is 1 day old versus one that is 4 weeks old. Finally, in a third study, Dr. Frankland asked whether developmental and adult-generated granule cells are incorporated at the same or different rates. The results indicated that there was no difference in number of bromodeoxyuridine cells expressing Fos between 7-day-old pups and adults. Overall, these studies indicate that new neurons in the dentate gyrus contribute uniquely to memory processes.

The third speaker was Dr. Steven Maren (University of Michigan, Ann Arbor, Mich.) who presented a talk entitled "Building and burying fear memories in the brain." He asked the question, "How can we reduce fear memories, especially when they become pathological?" He provided a brief overview of animal studies on the role of the hippocampus in fear extinction and whether there is a temporal factor whereby extinguishing the memory soon after the conditioning may be more effective. He also summarized the role of the prefrontal cortex in fear suppression. He then showed data that indicated that lesions in the basolateral amygdala either before or after fear conditioning will ablate auditory fear conditioning compared with sham-operated animals. He then went on to describe the behavioural properties of extinction. He stated that fear will come back in 1 of 3 ways: spontaneously, with the delivery of foot shock (unconditional stimulus) (reinstatement) or outside of extinction context (renewal). Conditional stimulus exposure alone does not result in extinction. Fear extinction is context dependent, and there can be a renewal of fear following extinction. The hippocampus seems to play a role in fear renewal, as evidenced by a study that used reversible lesions with muscimol infusion into the hippocampus and found that it has an important role in determining in what context the conditional stimulus is safe and when it isn't. To summarize, there are layers of memory, and we need context as a retrieval cue. For example, there is conditional stimulus–evoked activity in many amygdala neurons, but hippocampus inactivation impairs "neuronal retrieval." Memory of safety increased firing in the prefrontal cortex during extinction, and the efficacy of extinction seems to depend on prefrontal cortex thickness. Therefore, extinction may control an inhibitory network that is under prefrontal cortex control.

Furthermore, plasticity in the amygdala is critical for extinction, since inactivation of the medial prefrontal cortex impairs the expression of extinction. There are also differences in fos expression in prelimbic (fear renewal) and infralimbic (fear extinction) cortices. To summarize, he proposed a theoretical model whereby hippocampus projection to infralimbic cortex suppresses amygdala output via inhibition of interneurons. Hippocampus activation also activates prelimbic areas. Finally, he showed evidence that early extinction is not effective: if rats undergo extinction paradigm 10 minutes after auditory fear conditioning versus 24 hours, at day 3 it is only the 24-hour animals that show extinction. Recent fear may impair the ability to have long-term extinction because extinction memory competes with fear memory, and both are under hippocampus and prefrontal cortex control.

The final speaker, Dr. Karim Nader (McGill University, Montréal) gave a lecture entitled "Treating PTSD by targeting reconsolidation." He began by noting that the inhibition of protein synthesis in the lateral amygdala, a region that encodes associations between conditioned and unconditioned stimuli, can block memory consolidation. After consolidation, though, memories can also re-enter a labile state during which they are highly modifiable before being "reconsolidated." Dr. Nader reported that reconsolidation blockade involves the reversal of cellular and molecular correlates of long-term memory and long-term potentiation. He then summarized Lewis' memory systems, which consist of active memory. Active memory lasts seconds to hours, is labile and does not require new RNA or protein synthesis. Inactive memory, which lasts days to weeks, is consolidated and does require new RNA and protein synthesis. Inactive memories can be reactivated; one implication is that this reactivation phase may be a point where we can alter a memory or one's reaction to it. One extreme clinical example of this phenomenon might be posttraumatic stress disorder, in which the trauma is a powerful unconditioned stimulus that leads to fear conditioning. The release of stress hormones increases the consolidation of fear memory. The β blocker propranolol blocks stress hormones; it does not block memory acquisition but does block the stress response to the memory. It therefore blocks the emotional aspects of memories by acting on β receptors in the amygdala. Studies have shown that propranolol administration within 1–2 hours of a trauma will decrease the strength of the conditioned emotional response. However, most trauma victims do not receive clinical attention right away. One possibility then is to use this treatment during controlled memory reactivation and reconsolidation. To test this possibility, Dr. Nader and colleagues conducted a randomized clinical trail conducted in patients with posttraumatic stress disorder who had suffered with the disorder for more than 10 years. Day 1 of the study consisted of trauma disclosure. Afterwards, the patients received either placebo or propranolol. Day 8 was the test day, consisting of a script-driven imagery procedure with physiologic measures thought to represent the conditioned fear response mediated by the amygdala. Propranolol significantly decreased the physiologic response to trauma memory, but there were no significant differences in subjective reports between placebo and propranolol groups. The implications of this research are that propranolol could possibly be used in treatment of other disorders, including addictions, chronic pain and obsessive–compulsive disorder, by targeting the reconsolidation of memories related to illness.

*Symposium 5 (Wyeth sponsored session). The complex depressed patient*
*Chair: Dr. Claudio Soares (McMaster University, Hamilton)*
*Pannelists: Dr. Pierre Blier (University of Ottawa, Ottawa), Dr. Arya Sharma (University of Alberta, Edmonton), Dr. Valerie Taylor (McMaster University, Hamilton)*

After an overview of challenges in the treatment of major depressive disorder, including nonresponse, poor compliance and difficulty recognizing the illness in nonpsychiatric settings, the symposium explored 2 different clinical cases. The first case identified specific issues related to onset of major depressive episodes in women, and the second focused on the problem of weight gain.

The patient in case 1 was a woman with a history of major depressive episodes beginning after the birth of her second child. Her symptoms included irritability, tiredness, impaired sexual desire, night sweats, sleep disruption and low mood at the time of perimenopause. Hormone replacement therapy had minimal impact. With further exploration, the panel and most of the audience diagnosed major depressive episode and major depressive disorder, recurrent.

Risk of major depressive episode onset is elevated during perimenopause. The mechanisms implicated include the reduction in estradiol, changes in life events that occur concurrently and symptoms of perimenopause, including hot flushes and sleep disturbance. Three clusters of symptoms were identified by the panel, including hot flushes, disturbed sleep and depression. The panel indicated that hormone replacement therapy can help all 3 clusters and that selective serotonin reuptake inhibitors and/or selective serotonin and norepinephrine reuptake inhibitors are helpful with sleep and depressed mood.

The impact of estrogen change on neurobiology implicated in mood disorders was discussed in a variety of contexts; for example, a positron emission tomography study of α-[$^{11}$C]methyl-L-tryptophan trapping found evidence of decreased 5-HT synthesis in women. The mean rate of 5-HT cell firing in dorsal raphe neurons is reduced in ovariectomized rodents. Selection of hormone replacement therapy before menopause is associated with greater hippocampal volumes in women later in menopause, and oophroectomy in young women has been associated with greater risk of cognitive impairment and dementia.

The optimal clinical approach for perimenopausal onset major depressive episode was reviewed. It was argued that risk of major depressive episode is elevated in perimenopause. A meta-analysis reported that Effexor (venlafaxine) was a better treatment for perimenopausal onset major depressive episode than other serotonin reuptake inhibitor

antidepressants. Dr. Blier discussed how 5-$HT_{2C}$ receptors create negative feedback for dopamine release and that 5-$HT_{2A}$ receptors create negative feedback for norepinephrine release, underscoring the need to develop novel treatment combinations that overcome these barriers.

The second case highlighted the problem of weight gain in a woman with bipolar disorder and a long history of recurrent major depressive episodes who also had a history of treatment with antipsychotic medications. A list of approaches to consider was discussed, which included adding medication to lose weight, switching medications and lifestyle modifications. A biopsychosocial model of obesity was presented considering lifestyle (diet, sleep deprivation, alcohol intake), psychosocial factors (stress, low income, binge eating, depression) and biological factors (genetics, medication, metabolism). Consequences were categorized into mental (mood, anxiety), mechanical (osteoarthritis, back pain, incontinence) and metabolic (diabetes, dyslipidemia, fatty liver, hypertension) conditions.

Recent advances in the understanding of obesity in relation to mood disorders were discussed. In the treatment of mood disorders, the use of atypical antipsychotics has been associated with obesity. The psychosocial index is a powerful predictor of recurrence of obesity, and factors such as a high ratio of fast food restaurants to grocery stores in community settings have been associated with obesity. The potential role of ghrelin, a peptide discovered fairly recently, to activate appetitive behaviour and reduce glucose tolerance was also mentioned.

Dr. Taylor reviewed a relation between body mass index (BMI) and interventions: lifestyle approaches were recommended for patients with a BMI between 25 and 30, pharmacotherapy was advised for those with a BMI between 30 and 40 and surgery for those with a BMI above 40. Examples of pharmacotherapy include xenical/orlistat, a lipase inhibitor that binds to fat. Another example was sibutramine, a serotonin and norepinephrine reuptake inhibitor, and a third example was the β 3 adrenergic agonists, which increase metabolism. Dr. Sharma pointed out that the overwhelming best evidence for reductions in mortality in people with obesity is with bariatric surgery.

Overall, a comprehensive clinical perspective on perimenopausal onset major depressive episode and the problem of obesity in relation to mood disorder was presented.

*Symposium 6. The Next Generation*
*Chair: Dr. Jane Foster (McMaster University, Hamilton)*

The first speaker in the CCNP Next Generation session was Julie Andrews (Douglas Hospital Mental Health Institute, McGill University, Montréal), and the title of her talk was "Sex-based differences in cortisol response to psychosocial stress." As Ms. Andrews noted, the widely used laboratory challenge, the Trier Social Stress Test, elicits multiple, subjective, physiologic and neurophysiological effects. Based on a previous suggestion that socially based stressors have more potent effects in women than men, Ms. Andrews administered the Trier Social Stress Test either with or without an audience observing the participants' performance. She found that, in men, salivary cortisol levels rose during the speaking task, irrespective of whether the panel was present to observe them. In comparison, cortisol levels rose in women only if the audience was in view. Similar findings were obtained when participants performed mathematics tests with or without an audience. Together, the results provide support for the hypothesis that hypothalamic–pituitary–adrenal axis responsiveness in men is driven by achievement-based tasks, whereas women respond more to social stressors.

The second speaker was Araba Chintoh (University of Toronto, Toronto), and the title of her talk was "Changes in insulin resistance and insulin secretion following antipsychotic administration." As Ms. Chintoh noted, many of the atypical antipsychotic medications can lead to rapid and sustained weight gain as well as a 3-fold increased risk for diabetes. To investigate potential mechanisms that could mediate these effects, Ms. Chintoh conducted experiments using an animal model of insulin sensitivity. Under euglycemic conditions, it was found that haloperidol and ziprasidone were without effect, whereas risperidone, olanzapine and clozapine induced insulin resistance, with the latter antipsychotic having the biggest effect. Under hyperglycemic conditions, only olanzapine and clozapine induced insulin resistance. These effects appear within minutes of drug administration, and appear to reflect increased glucose production coupled with decreased glucose utilization and insulin release. The model may be helpful for screening future potential neuroleptic patients.

The third speaker was Annie Duschesne (Douglas Hospital Mental Health Institute, McGill University, Montréal), and the title of her talk was "Gender differences in neural activation changes during psychosocial stress." As Ms. Duschesne noted, men and women are stressed by different events and exhibit different responses to the same stressor. To investigate these gender differences further, she conducted a functional magnetic resonance imaging study with the Montreal Imaging Stress Task. This test consists of mathematics challenges. Performance is then adjusted individually and automatically such that all participants are performing in the 45%–50% range; simultaneously, though, participants are told that this is below the population norm and that if they don't perform better, the scan will not be useable. Under these conditions, the Montreal Imaging Stress Task induced a cortisol response in men, but not women. Moreover, whereas men exhibited activations in the premotor cortex and insula along with deactivations in the orbitofrontal cortex, ventral anterior cingulate cortex and hippocampus, women exhibited increases in the dorsal anterior cingulate cortex plus deactivations in the orbitofrontal cortex and ventral anterior cingulate cortex but not in insula or hippocampus. Hippocampal deactivations were particularly absent in those women who exhibited no cortisol response. Together, these findings add to the evidence that men and women find different events stressful. By characterizing these differences and the relevant neural pathways, the studies could provide a better understanding of gender differences in susceptibility to stress-related disorders.

The fourth speaker was Carl Ernst (McGill University, Montréal), and the title of his talk was "Alternative splicing methylation state, and expression-profile of TrκB in frontal cortex of suicide completers." As Mr. Ernst noted, the tyrosine kinase, TrκB, is expressed in astrocytes and activated by brain-derived neurotrophic factor (BDNF). Disturbances to BDNF/TrκB signalling have been associated with mood disorders, including links to genetic polymorphisms and alterations in gene expression. In a preliminary study in human postmortem tissue, suicide victims compared with matched controls had decreased TrκBT1 mRNA and protein levels in the dorsolateral prefrontal cortex (BA9). In a follow-up study with a larger sample, the same reductions were seen across 9 frontal cortical regions and not in the cerebellum. Animal experiments suggested that these decreases were not due to differences in brain pH, postmortem interval, age or prior drug use (cocaine). As a follow-up study, he cloned the TrκB promotor but found that genetic variants also did not alter TrκB expression. Finally, he tested whether the group differences reflected the induction of DNA methylation. In these experiments, there was a significant negative correlation between methylation of the promotor of the CpG dinucleotide sites and TrκBT1 expression plus transcription. Together, these results suggest that, in at least a subpopulation of suicide completers, there are reductions in TrκB in the frontal cortex and that this difference is related to methylation of the promotor region.

The fifth speaker was Jerome Foo (University of Alberta, Edmonton), and the title of his talk was "Callosal changes in MDD associated with childhood emotional abuse and neglect." As Mr. Foo noted, the corpus callosum is the largest interhemisphere white matter tract in the brain, connecting homologous areas of cortex. It facilitates the integration of motor, sensory and cognitive function, and could be related to a wide range of neuropsychiatric disorders. Individual differences in corpus callosum size are related to various factors including the number of cells, density of cell packing and the degree of myelination. Dividing the corpus callosum anatomically has proven difficult, but using a model proposed by Witelson, 7 divisions are distinguished. Following this scheme, volumetric and diffusion tensor imaging analyses were performed on magnetic resonance imaging data from 38 patients with major depressive disorder and 34 matched controls. Overall corpus callosum volume did not distinguish the 2 groups. However, 2 anterior parts of the corpus callosum (the rostrum and genu) were larger in the patients than controls. The larger genual volume was specific to patients with a childhood history of severe emotional abuse and neglect, whereas the difference in the rostrum was apparent in both patient subgroups. Finally, among the patients, greater genu corpus callosum volume was correlated with lower integrity of genu white matter (fractional anisotropy) and with less grey matter in the ventromedial prefrontal cortex. Together, the results raise the possibility that early childhood abuse and neglect might reduce axonal pruning and myelenation of neurons projecting from the ventromedial prefrontal cortex. These perturbations might contribute to disturbances in the generation and regulation of emotional responses.

The concluding speaker was Florence Roullet (Brain Body Institute, St. Joseph's Healthcare and McMaster University, Hamilton), and the title of her talk was "Alterations in behaviour and gene expression in response to maternal challenge with anti-epileptic drug valproic acid." As the speaker noted, autism is a neurodevelopmental disorder that begins in the first 1–3 years of age, developing in boys 4 times as often as in girls. Autism's causes are not well understood but may reflect disturbances to synaptic maturation or connectivity as a consequence of predisposing genetic factors and prenatal exposure to environmental toxins such as valproic acid. The resulting fetal valproate syndrome is rare but characterized by developmental disabilities, spina bifida, and facial abnormalities and elevated risk for autism. A rodent model has been proposed and was explored in the present study. The offspring of pregnant mice given valproic acid exhibited reduced weight gain and a delayed age to first open their eyes, increased latency to reach home bedding, possibly reflecting perceptual or processing deficits, and altered social behaviours. These developmental and behavioural disturbances were associated with alterations in gene expression. Whereas striatal dopamine DRD2 mRNA expression is greater in females than males in healthy mice, this sex difference is not seen in VPA mice. Second, brain-derived neurotrophic factor (BDNF) expression in the somatosensory cortex was decreased in VPA versus control mice, reminiscent of lower serum BDNF levels in patients with autism. Finally, hippocampal and cortical neuroregulin (NL3) mRNA levels were also downregulated in VPA mice. Since autism has been associated with mutations to the genes that encode NL3 and NL4, both of which encode for postsynaptic cell adhesion molecules, the disturbances seen in VPA mice might reflect deficits in synaptic adhesion proteins.

*Symposium 7. Maternal adversity vulnerability and neurodevelopment (MAVAN): preliminary findings*
*Chair: Dr. Robert Levitan (University of Toronto, Toronto)*

Maternal adversity vulnerability and neurodevelopment (MAVAN) is an ambitious multi-disciplinary 5-year multisite project investigating, in humans and in animal models, factors that influence developmental physiology, neurobiology and behaviour. The session was opened by Dr. Leslie Atkinson (Ryerson University, Toronto), and he gave a talk entitled "The interaction of birth weight and maternal sensitivity influences attachment organization." As Dr. Atkinson reviewed, Bowlby's Attachment Theory proposes that the bond between infant and caregiver can be seen in evolutionary terms. The infant is predisposed to seek the caregiver, and the system that regulates the attachment behaviour is particularly active in response to stressful events. Problems can arise, though, when there are inappropriate activations of this system or when there is insufficient feedback to the infant whose system has been activated. Disorganized attachment can increase risk for a wide range of childhood difficulties and neuropsychiatric disorders. Parental behaviour alone, though, is a poor predictor of attachment; differential outcomes, it was proposed, reflect a combination of parenting behaviours and pre-existing vulnerabilities. To test

this hypothesis, prenatal health was indexed by birth weight, while maternal responses to infant emotional signals served as a measure of postnatal stress. Forty-one mother–infant dyads were followed for 18 months. Overall, 31 infants exhibited organized attachment responses, whereas 10 were disorganized. As hypothesized, these different attachment patterns were not predicted by either parenting or birth weight alone. However, there was a significant interaction effect, indicating that low birth weight infants who also had low responsive mothers exhibited disorganized attachment. Fostering the caretaking behaviours of parents of infants with low birth weights might have protective benefits.

The session's second presentation was entitled "Prenatal and early adversity: in relation to behavior, brain structure and genotype in Sprague-Dawley rats," by Drs. Alison Fleming and Marla Sokolowski (University of Toronto, Toronto). Complementing the above study in human infants, these MAVAN investigators used an animal model to examine the interaction between prenatal stress and early postnatal care. Pregnant Sprague-Dawley dams were exposed to daily restraint stress (4 h/d on gestation days 10–21), and the offspring were then raised without mothers from postnatal day 2 to 19. Half of the animals then received 8 daily bouts of stroking stimulation, half received only 2. The prenatally stressed, maternally separated rats that received limited daily stimulation exhibited a range of behavioural disturbances as well as decreased synaptophysin and BDNF gene expression in the medial prefrontal cortex and nucleus accumbens. These perturbations were not seen in prenatally stressed rats that were maternally raised nor were they as pronounced in animals that were maternally separated but received the greater levels of postnatal stimulation. Finally, preliminary studies suggest that polymorphisms of the genes that encode for the serotonin transporter and dopamine $D_2$ receptor might influence exploratory behaviour and effects of prenatal stress. Together, the findings suggest that a 3-way interaction between inherited vulnerability traits, prenatal stress and early postnatal care affects behaviour- and neuroplasticity-related proteins in the adult, accounting in substantial part for individual differences in susceptibility to stress-related disorders.

The session's third presentation was by Dr. Meir Steiner (McMaster University, Hamilton) and was entitled "Maternal depression, antidepressant use during pregnancy and infant autonomic and endocrine outcomes." As Dr. Steiner noted, perinatal mood and anxiety disorders can occur in 10%–20% of pregnancies, and they are associated with altered responses to novelty in infants and childhood behavioural and emotional problems. To investigate potential neurobiological mechanisms, they assessed infant parasympathetic nervous system activity and hypothalamic–pituitary–adrenal axis reactivity, as indexed by heart rate variability and salivary cortisol levels, respectively. Preliminary results from 85 infants suggest that, at 6 weeks of age, 24-hour heart rate variability is lowest in infants of untreated depressed mothers, intermediate in those of depressed mothers who received treatment and greatest in those of healthy mothers. At 3 months of age, the infants of mothers who had been depressed during pregnancy also exhibited evidence of altered sympatho–vagal balance, as compared with infants of healthy women and depressed women who received treatment. The 3 groups did not differ, though, in their cortisol or α-amylase responses to a fire alarm. This intriguing cohort will continue to be followed, and it is hoped that the findings will help our understanding of how maternal depression affects infants and children.

The session's concluding talk was by Dr. Robert Levitan (Centre for Addiction and Mental Health, University of Toronto, Toronto) and was entitled "Season of birth as a predictor of birth weight." As Dr. Levitant noted, obesity affects one-third of the adult population in the United States. The weight gain exhibits a seasonal pattern and is the highest in the fall and winter. These tendencies are particularly pronounced in those who meet criteria for seasonal affective disorder. In Dr. Levitan's first study, he found that, in women with seasonal affective disorder ($n$ = 182), birth season predicted the lifetime maximum body mass index score ($kg/m^2$). The highest body mass index scores were in women who had been conceived in the late summer and born in the spring, i.e., their prenatal period covered the period of greatest maternal weight gain. A second study measured the ponderal index ($kg/m^3$) at birth in 83 girls. Consistent with the above, ponderal index scores were highest for those infants who were born in the spring and lowest for those born in the summer. At 36 months of age, however, body mass index scores had reversed, i.e., they were now lowest in spring-born infants and highest in summer-born. This latter effect, Dr. Levitan proposed, might reflect an influence of compensatory weight gain in very low birth weight infants. Overall, the results indicate that, in infants born at 45 degrees latitude, season of birth strongly affects weight gain patterns with implications for growth trajectories and adult obesity.

## References

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