

The 27th Annual Meeting of the Canadian College of Neuropsychopharmacology

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The 27th Annual Meeting of the Canadian College of Neuropsychopharmacology (CCNP) was held in Kingston, Ont., May 29 to June 1, 2004. This report summarizes the 3 plenary lectures, 3 award lectures and 8 symposia.

Plenary lectures

The first plenary lecture, entitled "Dopamine: a neurochemical link between motivation and memory," was given by Dr. Anthony G. Phillips (University of British Columbia, Vancouver). The presentation described a series of studies investigating how the medial prefrontal cortex (mPFC), basolateral (BLA) and central amygdala (CeN), hippocampus and nucleus accumbens (NAcc) function together to regulate memory-guided motivated behaviour. These studies suggest that the CeN regulates tonic mesocorticolimbic dopamine (DA) activity, thereby influencing the incentive value of affectively relevant stimuli (both rewarding and aversive events). In comparison, glutamatergic inputs from the mPFC, BLA and ventral subiculum of the hippocampus (vSub) modulate phasic changes in

DA release, affecting the voluntary selection and coordination of goal-directed behaviour. Each of the glutamatergic inputs might affect phasic DA release and voluntary appetitive behaviour under different conditions. For example, projections linking the vSub with the mPFC and NAcc appear to be involved in foraging memory for incentive stimuli; in comparison, links from the BLA to the NAcc and mPFC might modulate context-related changes in DA release and instrumental behaviour, as well as responses to appetitive events that are better or worse than expected. Because limbic DA transmission is activated during both preparatory and consummatory behaviour, it may be more closely related to incentive motivation than hedonic assessment. Ongoing studies are attempting to delineate further the distinct contribution of different components of this neurocircuit.

The second plenary lecture, "Mechanisms of action of atypical antipsychotic drugs," given by Dr. Herbert Y. Meltzer (Vanderbilt University, Nashville) introduced a number of hypotheses regarding the mechanism of action of atypical antipsychotic drugs, including the fast-off hypothesis, the dopamine D₂ receptor

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Medical subject headings: acetylcholine; antipsychotic agents; anxiety disorders; autistic disorder; benzodiazepines; choline; chorioamnionitis; depression; dopamine; electroconvulsive therapy; fetal alcohol syndrome; gamma-aminobutyric acid; glutamate; lithium carbonate; memory; menopause; models, animal; motivation; nicotine; phototherapy; premenstrual syndrome; psychotropic drugs; schizophrenia; serotonin; serotonin uptake inhibitors; sleep deprivation; substance-related disorders; transcranial magnetic stimulation.

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antagonism hypothesis, the anti-muscarinic hypothesis, and the hypothesis that atypical antipsychotic agents selectively inactivate the mesocortical/mesolimbic dopamine (DA) system while sparing the nigrostriatal DA system.

Meltzer suggested that the serotonergic effects of atypical antipsychotic drugs likely contribute to their clinical efficacy, because there is a considerable degree of interaction between the serotonin (5-HT) and DA neurotransmitter systems. At clinically relevant doses, atypical antipsychotics exhibit greater 5-HT_{2A} receptor occupancy in the cortex than D₂ occupancy in the striatum. Recent microdialysis studies suggest that these 5-HT_{2A} antagonist properties lead to preferential DA release in the cortex as compared to the limbic system. Behaviourally, haloperidol combined with a 5-HT_{2A} antagonist substituted for clozapine (an atypical antipsychotic agent) in drug discrimination studies, and 5-HT_{2C} antagonists blocked the catalepsy-inducing effects of typical antipsychotic drugs. Clinically, M100907 (a selective 5-HT_{2A} antagonist) has been reported to be almost as effective as haloperidol at treating positive symptoms and total psychopathology in schizophrenia. Finally, the 5-HT_{2A} inverse agonist, SP 43469B, is reported to decrease total psychopathology and negative symptoms, while having mild effects on positive symptoms. In comparison, Meltzer argued, the fast-off hypothesis is not an adequate explanation for these effects, because most atypical antipsychotics are not fast off. He noted that the drugs with the least extra-pyramidal side effects dissociate from the D₂ receptor more slowly than haloperidol and other typical antipsychotic agents.

A possible role for muscarinic receptor activation in the action of atypical antipsychotics was also discussed. Atypical, but not typical, antipsychotics increase acetylcholine (ACh) release in the cortex and hippocampus. Moreover, patients with schizophrenia exhibit a reduction in the number of M1 receptors in Brodmann's areas 9 and 46 of the frontal cortex as well as in the hippocampus. M1 and M4 receptor agonists improve cognition, inhibit conditioned avoidance and block amphetamine-induced locomotion without causing catalepsy in animal models. Further, the major metabolite of clozapine (an atypical antipsychotic) *N*-desmethylclozapine (NDMC) is an M1 agonist and increases cortical DA. Finally, in clinical trials xanomeline, a muscarinic receptor agonist, improved short- and long-term memory and both positive and negative

symptoms of schizophrenia. Together, Meltzer proposed, the studies suggest that 5-HT, DA and ACh each contribute to the clinical efficacy of atypical antipsychotics.

The third plenary lecture was given by Dr. David J. Nutt (University of Bristol, Bristol) about the neurobiology of various anxiety disorders: panic disorder, generalized anxiety disorder, post-traumatic stress disorder and obsessive-compulsive disorder ("Why worry? The brain mechanisms of anxiety"). Among the many theories that have been advanced to explain anxiety disorders, Dr. Nutt proposed that neurotransmitter imbalances in the γ -aminobutyric acid (GABA)/benzodiazepine and/or serotonin (5-HT) systems may be of primary importance. Positron emission tomographic (PET) data suggest that there are reductions in [¹¹C]flumazenil binding to benzodiazepine receptors in the cortex and the hippocampus of patients with panic disorder. Benzodiazepine receptor abnormalities in anxiety disorders may be driven by genetic variations in the GABA receptor subunits, previous use of the drug, stress or altered 5-HT inputs. The 5-HT system is implicated in anxiety disorders from various lines of evidence. For example, selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants and the 5-HT_{1A} agonist buspirone are effective anxiolytic drugs, whereas 5-HT_{1A} gene knockout mice are anxious. PET studies suggest that 5-HT_{1A} receptor densities are reduced in both the cell body and terminal regions (amygdala and orbitofrontal cortex) of drug-free individuals with panic disorder. Moreover, diminishing 5-HT transmission with the tryptophan depletion method can reinstate symptoms in patients with panic and social anxiety disorders. In conclusion, he stated that modern antidepressants are the best first-line treatment for anxiety disorder. Although benzodiazepines also work, their side-effect liability indicates that they are better viewed as a second-line treatment option.

Award lectures

CCNP Heinz Lehmann Award lecture

Dr. Guy Chouinard (Université de Montréal, Montréal) presented the Heinz Lehmann Award lecture entitled "State of confusion: measurement and classification regarding drug-induced movement disorder (DIMD) and Canadian off-label psychotropic drug discoveries." The talk illustrated a career of careful

clinical observation and the insightful recognition of off-label uses for existing treatments. As a first illustrative example, he suggested that the growing use of psychotherapeutic drugs with potential to cause movement disorders in patients calls for a better understanding of the origin, diagnosis and management of DIMD. He proposed a new classification scheme of different movement and posture disorders that distinguishes DIMD from pathophysiological movement disorders. Data on the incidence of and risk factors for movement disorders from large-scale epidemiologic studies of patients with schizophrenia taking typical antipsychotic drugs as well as from clinical trials of typical and atypical antipsychotics were presented. A long-acting injectable formulation of risperidone was shown to reduce parkinsonism and tardive dyskinesia in patients with schizophrenia. He also showed data suggesting that the age of the patient, schizoaffective symptoms and negative scores on the positive and negative syndrome scale (PANSS) are significant risk factors for the development of DIMD. Finally, Dr. Chouinard reviewed data on off-label indications for benzodiazepines (clonazepam, alprazolam) and gabapentin in anxiety and panic disorders. In double-blind placebo-controlled trials, he observed significant benefit of alprazolam in generalized anxiety and panic disorders. Similarly, clonazepam was found to be an effective anti-panic and anti-manic agent. Based on his research, Dr. Chouinard made the first proposal to use gabapentin as a treatment for insomnia and anxiety.

CCNP Innovation in Neuropsychopharmacology Award lecture

Drs. Philip Seeman and Shitij Kapur (University of Toronto, Toronto), joint winners of the award, gave a talk entitled "From receptors to response: thoughts on the mechanism of action of antipsychotics." Dr. Seeman provided an overview of the dopamine hypothesis of schizophrenia and summarized several decades of work in his laboratory suggesting that overactivity of the dopamine D₂ receptors is a key neurochemical abnormality in the brains of patients with schizophrenia. He also noted that differences in the effectiveness and side-effect profiles of typical and atypical antipsychotic drugs relate to the kinetic binding parameters of the drugs toward D₂ receptors. Atypical drugs bind "loosely" to D₂ receptors and come off the receptor more quickly than typical ones. Dr. Kapur elaborated

on the concept that blockade of D₂ receptors is necessary and sufficient for antipsychotic response. He presented PET imaging data showing that an optimal level of striatal D₂ receptor occupancy (~65%) by antipsychotic drugs is necessary for a favourable clinical response in the patients. Higher occupancy, often attained with typical antipsychotics, leads to extrapyramidal side effects (EPS). At the doses usually given, most atypical antipsychotic drugs occupy D₂ receptor to a level of about 65%, which may explain why they produce fewer EPS. Dr. Kapur explained that quetiapine, an outlier atypical drug that generally occupies 20% of D₂ receptors, works faster and has transient early high occupancy of the D₂ receptors. He also presented animal data supporting the idea that D₂ receptor affinity is a primary determinant of atypicality. Dr. Kapur also argued that, contrary to general belief, there is no significant delay in the onset of antipsychotic action. His meta-analysis of clinical trials with typical and atypical antipsychotics showed that both drugs improved symptoms within the first week. Finally, he presented a psychologic framework that tries to explain how the neurochemical action (D₂ blockade) of antipsychotic drugs leads to reduction in psychosis. Because dopamine is involved in reward and motivational salience to stimuli, the proposal is that psychosis is a result of an aberration in these processes due to a disordered dopamine system. By blocking D₂ receptors, antipsychotic drugs might exert clinical efficacy by diminishing the motivational salience of hallucinations and delusional thoughts.

CCNP Young Investigator Award lecture

The CCNP Young Investigator Award was given this year to Dr. Louis-Éric Trudeau (Université de Montréal, Montréal). His presentation was entitled "Dopamine neurotransmission: moving beyond the textbook description." Its main purpose was to show how recent studies indicate that dopaminergic neurotransmission is substantially more complex than previously thought. The recently discovered features have implications for the treatment of psychiatric disorders, because the dopaminergic system is the primary target of several psychotherapeutic agents. Of particular interest to Dr. Trudeau is recent evidence that dopamine cells release glutamate as a co-transmitter. Cultured mesencephalic dopaminergic neurons have been shown to establish glutamatergic synapses, and their

electrical activation can induce a fast postsynaptic current that is blocked by a glutamate receptor antagonist. Direct in-vivo evidence that glutamate is released from dopamine cells has been more difficult to obtain. Dr. Trudeau has approached this problem by examining the presence of vesicular glutamate transporters in postnatal rat mesencephalic neurons in primary culture. Vesicular glutamate transporters (VGLUT) are transmembrane proteins that uptake the neurotransmitter from the cytoplasm into the releasing vesicles. If dopaminergic neurons express VGLUT immunoreactivity, it is very possible that they have the ability to release glutamate. Dr. Trudeau's work revealed immunoreactivity for VGLUT in dopamine neurons. These neurons are immunoreactive for VGLUT2, but not VGLUT3 or VGLUT1. He has also found that not all terminals of dopamine neurons express VGLUT2, suggesting that the co-release occurs only at some synaptic sites. In a triple-labelling experiment, Dr. Trudeau showed co-expression of synaptic vesicle protein 2 (SV2) and VGLUT2 in dopaminergic cells. Again, he observed that most terminals express SV2, but only some show both SV2 and VGLUT2. These findings suggest that there are 2 types of dopaminergic synapse, one specialized in dopamine release and another specialized in dopamine and glutamate co-release. Expression of VGLUT2 in single dopamine neurons has been confirmed with single-cell reverse-transcriptase polymerase chain reaction (RT-PCR) experiments. Dr. Trudeau is now trying to address the important question of whether VGLUT2 expression in dopamine neurons can be regulated by pharmacologic manipulations.

Symposia

Female-specific psychopharmacology (Chair, Dr. Meir Steiner)

Dr. Meir Steiner (McMaster University, Hamilton) opened the session with a talk entitled "PMS/PMDD — diagnosis and treatment: Any short cuts?" His main point was that the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) diagnostic criteria for premenstrual syndrome (PMS)/premenstrual dysphoric disorder (PMDD) are very strict, perhaps overly so (only 3%–8% of the relevant population are diagnosed with the disorder), and as a consequence many women with the disorder do not have their

condition diagnosed. For this condition, selective serotonin reuptake inhibitors (SSRIs) taken continuously or during the luteal phase only are effective and should be considered first-line therapy. To facilitate the identification of affected women, a new tool has been developed in Dr. Steiner's clinic, the "premenstrual symptoms screening tool (PSST)." The PSST translates categorical DSM-IV criteria into a rating scale with degrees of severity. With this tool, 5% of women aged 18 years or more were identified as having PMDD and 20% as having severe PMS. Among younger women (aged 12–17 years), 10% met threshold criteria for PMDD and 28% for severe PMS. The results, he pointed out, are in line with reported prevalence rates from several recent large prospective studies. Moreover, they emphasize the concern that many women who need to be treated are not being identified or helped. Because the PSST can be used effectively during the follicular phase of the cycle, it is less time consuming and more practical than obtaining 2 cycles of prospective charting.

Dr. Gideon Koren (University of Toronto, Toronto) spoke about "The safety of psychotropic medications during pregnancy and post-partum: the 'Motherisk' perspective," that is, about ways to treat the mother while protecting the unborn child. He mentioned that one reason women do not obtain treatment during pregnancy is anxiety about possible drug-induced birth defects, an anxiety triggered in great part by the thalidomide incidents. However, Dr. Koren's central point was that most psychoactive drugs are safe for the unborn child and that what is unsafe is *not* to treat the mother. The Motherisk Program was developed in 1985 to convey the message that women have a right to rational drug therapy in pregnancy and that much of the fear of damage inflicted on children by drugs during fetal life or soon after birth can be prevented through public education, counselling and research. For example, 87% of depressed women think they are at risk and, in spite of counselling, 15% of depressed patients terminate treatment. In comparison, despite similar low risks, only 4% and 1%, respectively, terminate treatment when they take gastric drugs and antibiotics. About 20% of women develop mood disorders during pregnancy. Again, there is a reluctance to initiate or continue treatment, even though lack of treatment actually increases perinatal risk and can result in cognitive and neurobehavioural insult to the unborn child. Stopping medication (cold turkey syndrome) in pregnant women can increase the risk of

suicide attempts, alcohol abuse and neonatal SSRI discontinuation syndrome, each of which is more harmful than the medication. Lithium treatment is sometimes discontinued during pregnancy because of fears of Ebstein syndrome, but this occurs in only 1 of 5000 women. Antipsychotics taken during pregnancy also have a low risk of teratogenicity; one report suggests the development of 1 case of malformation out of 151 pregnant women treated with neuroleptics. In 1978, 40% of pregnant women in Canada and the United States took the drug bendectin (doxylamine succinate, dicyclomine and pyridoxine) to treat the nausea and vomiting that affects 80% of women. When the drug was removed from the market in 1983, nausea and vomiting in pregnancy (NVP) increased 3-fold and there was a 40% increase in NVP-related admissions to hospital.

Dr. Lori Ross (University of Toronto, Toronto) spoke about the "Management of substance dependence during pregnancy." Her first point was that there is little research to guide treatment of substance dependence during pregnancy, even though it has crucial implications for the unborn child. The incidence of pregnant women testing positive for drugs of abuse is substantial (7.8%–14.8%), and the frequency for alcohol abuse is increasing. Nicotine is the most common drug used during pregnancy. Its adverse effects include spontaneous abortions, low birth weight and high incidence of substance abuse in the children. Few clinical studies have tested the effects of nicotine replacement during pregnancy. But so far it appears that nicotine replacement is safer than smoking and is associated with higher birth weight, although it is not clearly effective in decreasing smoking. She noted that nicotine clearance is markedly elevated in late pregnancy. She also mentioned results from an unpublished study showing that the antidepressant bupropion reduces smoking significantly in pregnant women without having teratogenic effects. The teratogenic effects of alcohol are well known. However, pharmacotherapy is limited. Disulfiram, for instance, has teratogenic effects and there are not sufficient studies of the use of naltrexone. Opiates have fewer teratogenic effects than alcohol, but multiple lifestyle risk issues. Methadone replacement therapy has been shown to provide stable blood opioid levels, reduce maternal withdrawal symptoms and decrease lifestyle risks. Importantly, methadone replacement appears to result in a birth outcome similar to that of the general population. However, careful attention should be paid to the fact that opiate withdrawal can lead to

pre-term labour, and cessation of treatment can result in neonatal abstinence syndrome. Buprenorphine is an alternative to methadone: it appears to reduce the risk of neonatal abstinence syndrome. Dr. Ross mentioned that although drug use during pregnancy is an important public health problem, few women seek or get professional help. It was suggested that pregnant women with substance abuse problems are afraid of losing custody of their children and, in most instances, are poor, unstable and lack a support network. Together, these observations indicate the need for studies aimed at seeking treatment alternatives.

Dr. Claudio Soares, (Harvard Medical School, Boston) in his talk entitled "To HRT or not to HRT? A menopausal dilemma," discussed the benefits and risks of hormone replacement therapy (HRT) during menopause and its implications for depression. He began by directing attention to the fact that unipolar major depressive disorder (MDD) is the number 2 cause of disease burden in women in the United States (the first is cardiovascular disease). Menopause is associated with an increased risk of depression. However, the available data are difficult to interpret, have been collected in different settings, are inconsistent in the definition of menopause and exhibit confusion between biologic versus psychosocial factors. Menopause is usually defined as 12 months without menses but, as noted by Soares, menopause is a developing process. The *transition* to menopause can begin as early as the early 40s (manifested as small changes in menstrual cycle), and it appears that this is the period of highest increased risk of depression. He spoke about the Harvard Study of Moods and Cycles, which is now in year 7. This is a prospective study of the changes in endocrine variables and psychopathology. Roughly 1000 women enrolled, one-third with a history of depression. Preliminary results show that early age of menarche (at 9–11 years) is associated with a 2-fold increase in depression. Heavy menstrual flow and cycle irregularity during first years after menses are also associated with increased risk of later depression. Women with a history of MDD had faster onset of perimenopause. Women without a history of depression are 3 times more likely to develop depression once they enter perimenopause than premenopausal women. Is there a "perimenopausal" depressive syndrome? In terms of treatment, Dr. Soares mentioned evidence showing that HRT alone, or in combination with antidepressants, is effective in the treatment of depression in

perimenopausal and menopausal women. Estrogen replacement can improve depressive as well as menopausal symptoms. Antidepressants might also reduce menopausal symptoms. There is in fact some preliminary evidence suggesting that HRT treatment increases clinical efficacy of SSRIs. Unfortunately, the results of the Women's Health Initiative (WHI) reported in *JAMA* (2002) suggested that HRT increases risk of cardiovascular disease and invasive breast cancer and has no effects on cognition. Dr. Soares, as well as many others, have found several flaws with the design of the study and strongly suggest interpreting this result with caution. In conclusion, there is increased risk of depression in women in periods of intense changes in hormone levels. During these periods, women may benefit from HRT. In fact, HRT for 3 years during perimenopause may be enough to prevent depression and may not lead to other diseases. Unfortunately, the WHI study led to lack of interest on the part of companies to conduct these studies.

Understanding relapse to drug-seeking behaviour (Chair: Dr. Francesco Leri)

The session's first talk was given by Dr. Jane Stewart (Concordia University, Montréal) and was entitled "The role of CRF and noradrenaline in stress-induced relapse to drug seeking." Relapse into drug-seeking and drug-taking behaviour can occur after extended periods of abstinence. Common precipitants of relapse include re-exposure to the drug and psychologic stressors. Recent studies from Dr. Stewart's laboratory indicate that the mechanisms mediating these effects are largely distinct. For example, although dopamine (DA) receptor antagonists potently diminish drug-induced relapse, they have little effect on stress-induced relapse. In comparison, stress-induced, but not drug-induced, relapse is prevented by injections of corticotropin-releasing factor (CRF) antagonists into the bed nucleus of the stria terminalis (BNST). Recent studies suggest that this mechanism is engaged by stressor-induced activation of noradrenaline (NA) projections from lateral tegmental nuclei (LTG) to the amygdala and ventral portions of the BNST. Low doses of the alpha-2 agonist clonidine prevent stress-induced relapse, as do lesions of the ventral NA bundle and intra-amygdaloid or intra-BNST infusions of beta-1 and beta-2 antagonists. Highlighting the neuroanatomical specificity of this effect, lesions of NA neurons in

the locus coeruleus are ineffective. Together, these studies suggest that stress-induced activation of LTG NA projections to the amygdala and BNST induce CRF release and behavioural arousal, increasing the probability that drug-related stimuli will be identified, attended to and approached.

The session's second presentation was by Dr. Rajita Sinha (Yale University, New Haven). In a talk entitled "Stress neurobiology: correlates of drug craving and relapse," she described clinical research studies that investigate the relation between stress, craving and relapse in humans. As noted by Dr. Sinha, substance-dependent patients often report high levels of distress and difficulty coping with challenging life events. Some treatment strategies have aimed to improve coping skills, but the patients report difficulty applying the skills to their life, and stress-induced episodes of relapse continue to occur frequently. Dr. Sinha's research has investigated the neurobiological substrates of this stress-vulnerable phenotype and has begun to assess how these perturbations might mediate the association between stressors, craving and reinstatement. For example, when substance-dependent patients participate in stress imagery experiments (stressful life events that have been rated as 8/10 in aversiveness are recalled for 5 minutes), subjects report increased drug craving and anxiety, and they exhibit increases in heart rate, cortisol release and peripheral catecholamine activity (plasma epinephrine [E] and norepinephrine [NE] levels increase). Inpatient treatments can have some clinical benefits, but 65% relapse within 90 days. Relapse is predicted by a larger craving response to the stressor but smaller E, NE and cortisol responses. In a functional MRI study, the stress imagery paradigm activated the anterior cingulate and hippocampus in healthy subjects but not in cocaine-dependent patients; among the patients, the lower the cingulate activation, the higher the stress-induced craving. Consistent with the recent animal literature discussed by Dr. Stewart, an alpha-2 agonist, lofexidine, decreased stress-induced craving in the laboratory and improved abstinence rates during a small 4-week, double-blind clinical trial in naltrexone-maintained opiate addicts. Together, the results suggest that decreased frontal lobe function might increase vulnerability to stress-induced craving and relapse.

Dr. Anthony G. Phillips (University of British Columbia, Vancouver) gave a talk entitled "Hippocampal modulation of dopamine efflux in the ventral striatum:

a tool for studying the neural substrates of relapse." Recent studies from Dr. Phillips' laboratory suggest that electrical stimulation of the ventral subiculum of the hippocampus (vSub) can potently reinstate drug self-administration in abstinent animals, possibly providing a mechanism for relapse that is induced by drug-associated contextual stimuli. To explore this mechanism further, Dr. Phillips' group has been conducting a series of technically complex studies in which electrical stimulation of the vSub is combined with microdialysis in the striatum and both intravenous and intra-cranial drug injections. In brief, the vSub sends glutamatergic projections to the nucleus accumbens (NAcc), and high-frequency (> 5 Hz) electrical stimulation of the vSub elicits long-lasting increases in NAcc dopamine (DA) release. Intra-NAcc injections of DA D₁ and ionotropic glutamatergic antagonists prevent the effects of vSub stimulation on reinstatement. Because subthreshold doses of the antagonists are behaviourally effective when they are microinjected together, the DAergic and glutamatergic mechanisms appear to function together synergistically. Interestingly, the NAcc also receives glutamatergic input from the basolateral amygdala (BLA) and medial prefrontal cortex (mPFC), and recent evidence suggests that these inputs also affect aspects of drug-taking behaviour. Together, these studies suggest that mesolimbic DA release modulates the behavioural effects of input from the vSub, BLA and mPFC, integrating the information from each source and translating it into memory-guided, context-dependent, goal-directed appetitive behaviour.

Dr. Francesco Leri (University of Guelph, Guelph) gave a talk entitled "From lapse to relapse: animal studies." One of the most potent stimuli for inducing relapse to drug-taking behaviour is re-exposure to the drug itself. Dr. Leri's studies suggest that this period of elevated vulnerability can persist beyond the acute effects of the drug, lasting instead for up to 96 hours. To investigate these behaviours, rats were trained in 4 phases: (1) acquisition of drug-taking behaviour, (2) extinction, (3) re-exposure to the drug, and (4) drug seeking 24 hours or more after the drug exposure. In conditioned place preference (CPP) studies, re-exposure to heroin was found to increase drug-seeking behaviour for as long as 3–4 days. Similarly, experimenter-administered and self-administered heroin increased later self-administration behaviour. Heroin given in the home cage was also able to reinstate later self-

administration, though not CPP. Together, these observations provide a laboratory model in which to study neurobiological mechanisms related to long-lasting effects of drug re-exposure on susceptibility to relapse. Preventing these long-lasting effects might point the direction toward novel treatments that could prevent a brief "slip" from becoming a prolonged relapse.

Neurodevelopmental aspects of neurological/psychiatric illnesses (Chair, Dr. Khem Jhamandas)

Dr. Jeanette Holden (Queen's University, Kingston) gave a talk entitled "Autism spectrum disorders: novel approaches for identifying culprit genes" and described a number of approaches and strategies for identifying culprit genes in autism. Autism spectrum disorders (ASD) are neurodevelopmental disorders that are characterized by deficits in reciprocal social interactions, communication and stereotyped behaviour. Their cause is unknown, but genetic factors strongly influence their development, as shown by high family risk and concordance between identical twins. Dr. Holden's group is recruiting and assessing a large number of families with 1 or more individuals with ASD and obtaining buccal swab samples for DNA analysis. As ASD is likely to be due to actions of multiple genes with each contributing to a specific behavioural or clinical symptom, the strategy of the Genetics Group of the Autism Spectrum Disorders — Canadian–American Research Consortium is to subgroup the patients based on behavioural, clinical and physical features as well as family history and characteristics. They have an online registry for recruiting (www.autismresearch.ca), and so far 1259 families representing 5000 individuals have enrolled. Genetic studies of samples from these individuals are ongoing.

Drs. James Brien and James Reynolds (Queen's University, Kingston) spoke on "Fetal alcohol syndrome: brain injury mechanisms and innovative therapeutic approaches." Their research group is focusing on whether abnormalities in glutamate–N-methyl-D-aspartate (NMDA)–nitric oxide synthase and GABA_A receptor pathways and/or increased cellular oxidative stress contribute to neuronal and cognitive abnormalities in guinea pigs exposed to alcohol during gestation, an animal model of fetal alcohol syndrome (FAS). Their data show that the offspring of guinea pigs administered 4 g/kg ethanol during pregnancy have a broad range of neurobiological and behavioural

disturbances. These include decreased brain weight, a 20%–30% loss of pyramidal cells in the CA1 region of the hippocampus, deficits in long-term potentiation, decreases in NMDA receptor binding and nitric oxide synthase (NOS) activity, decreases in the GABA synthesizing enzyme, glutamic acid decarboxylase, and increased GABA_A receptors in the cerebral cortex. These neurobiological perturbations are associated with disturbances in spontaneous locomotion and water-maze learning. It was proposed that ethanol-induced suppression of NMDA transmission and overactivity of GABA_A receptors may be responsible for neural and behavioural abnormalities in FAS.

Dr. Graeme Smith (Queen's University, Kingston) gave a talk entitled "Chorioamnionitis and fetal brain injury." As discussed by the speaker, chorioamnionitis (ChA) resulting from in-utero infection of the chorion and amnion is a significant risk factor for perinatal brain injury, particularly cerebral palsy. Dr. Smith's hypothesis is that ChA-associated increases in proinflammatory cytokines may be responsible for the spectrum of brain injury ranging from minor developmental abnormality to cerebral palsy. In a guinea-pig model with intracervical *E. coli* infection at embryonic day 60, he observed an increase in tumour necrosis factor- α (TNF α) and interleukin (IL) 1 β and IL6 in the amniotic fluid and maternal blood. Further, caspase III and NeuroTACS staining were increased in the periventricular brain regions of the fetuses suggesting apoptotic cell death. Behaviourally, animals born to infected mothers show reduced activity in the open field. Ongoing studies in Dr. Smith's laboratory are looking at the detailed time course of neural and behavioural changes and the sources of fetal cytokines that trigger brain injury. He is also proposing to use magnetic resonance imaging in the guinea pigs as well as humans to assess brain developmental changes following ChA.

In a talk entitled "Neurotransmitter and behavioural deficits following neonatal blockade or overactivation of NMDA receptors," Dr. Khem Jhamandas (Queen's University, Kingston) discussed the neurodevelopmental hypothesis of schizophrenia and attempts by his research group to test this hypothesis in animal models. He presented data on neuronal and behavioural changes in 2 putative neurodevelopmental animal models of schizophrenia: neonatal (postnatal day 3 [PD3]) MK-801 (0.3 mg/kg) treated rats and neonatal (PD7) ventral hippocampus (VH) lesioned rats. He showed that MK-801, an *N*-methyl-D-aspartate (NMDA)

glutamate receptor antagonist, produced apoptotic cell death in the brains of rat pups as revealed by increased TUNEL staining and caspase activity in the cortex and the striatum. Interestingly, as reported in the brains of patients with schizophrenia, a loss of NADPH-diaphorase-positive neurons was also observed in the cingulate and lateral medial prefrontal cortices of these animals. Behaviourally, these animals show increased amphetamine-induced locomotor activity and apomorphine-induced stereotypy at PD35, but not at PD56. Neonatal VH lesioned rats also show reductions in cortical NADPH-d-positive neurons; however, hyper-responsiveness to amphetamine in the lesioned animals is seen post puberty at PD56 but not at PD35. Dr. Jhamandas discussed the relative merits of the 2 models in studying the neurodevelopmental origins of schizophrenia.

Stress, aversion, reward and mesolimbic DA: new twists on old ideas (Chair, Dr. Sandra Boye)

Laurie Sellings (McGill University, Montréal) opened the session with a talk entitled "Functional compartmentalization of nucleus accumbens in psychostimulant reward and arousal." As the speaker noted, the nucleus accumbens (NAcc) can be divided into core and shell subcompartments. Dopamine (DA) transmission in both regions has been implicated in reinforcing effects of abused drugs. Recent studies, though, suggest that the core has a larger role than the shell in the motor activating effects of nicotine and amphetamine. Sellings' studies have investigated this hypothesis further. In brief, rats were given selective 6-hydroxydopamine (6-OHDA) lesions of the shell or core. Individual differences in DA transporter (DAT) densities were then used as an index of remaining DA innervation. Within the NAcc core, DAT densities correlated with the motor activation induced by amphetamine, cocaine and methylphenidate, but not with their ability to induce a conditioned place preference (CPP). DAT densities in the NAcc shell showed the converse pattern; that is, DAT levels in the shell predicted CPP, but not motor activation, as induced by amphetamine and intravenous cocaine but not with morphine, cocaine given intraperitoneally, or methylphenidate. The results suggest that the locomotor-activating properties of stimulant drugs might share the NAcc core as a substrate, but that the NAcc shell might mediate the appetitive effects of only some. The observations are consistent with a

view that multiple areas can affect drug reinforcement. For a particular drug the relevant regions might depend on its unique pharmacologic and pharmacokinetic properties.

Dr. Derek van der Kooy (University of Toronto, Toronto) presented a talk entitled "The neurobiological substrates for the motivational properties of nicotine." As the speaker noted, nicotine-induced conditioned place aversions (CPA) are elicited more easily than place preferences (CPP). To test whether these aversions are related to peripheral effects, nicotine was microinjected directly into the ventral tegmental area (VTA), the cell-body region of mesocorticolimbic dopamine (DA) cells and a site known to contain nicotinic receptors. Both CPA and CPP could be elicited, the former by low doses of nicotine, the latter by higher doses. Co-administration of DA receptor antagonists converted CPA into CPP, suggesting that DA was mediating the motivation to avoid nicotine's effects. In comparison, appetitive effects of intra-VTA nicotine could be prevented by alpha-7 nicotine receptor antagonists and lesions of the tegmental pedunculopontine nucleus (TPP). Together, the results suggest that activation of the VTA induces 2 effects, a reinforcing effect that is largely mediated by descending projections to the TPP, a midbrain site that sends cholinergic neurons to the VTA, and an aversive effect that is mediated by ascending limbic DA projections. One implication is that psychiatric patients who are being treated with neuroleptics might be particularly susceptible to rewarding effects of nicotine, perhaps accounting in part for the high rates of smoking among patients with schizophrenia.

Dr. Marco Leyton (McGill University, Montréal) gave a lecture entitled "Cocaine and alcohol self-administration in humans: the effect of dopamine depletion." As noted by each of the speakers in this session, the exact role of dopamine (DA) neurotransmission in drug reinforcement remains unclear. The recent development of new tools to measure and manipulate DAergic effects in humans may be helpful. Functional neuroimaging studies suggest that across pharmacologic classes drugs of abuse increase extracellular DA levels with preferential effects occurring in the limbic striatum. Individual differences in this effect correlate with 2 indices of elevated DA reactivity, high novelty-seeking scores and elevated cardiac responses to alcohol. Preventing drug-induced increases in DA release, using the acute phenylalanine/tyrosine depletion

method (APTD), diminishes drug craving and self-administration breakpoint ratios. These effects of APTD are not prevented by L-dopa, possibly related to its ability to decrease DA cell firing. Overall, the results suggest that limbic DA transmission is closely related to the incentive value of abused substances and that individuals with indices of high DA reactivity are particularly susceptible to these effects.

Isabelle Boileau (McGill University, Montréal) described a series of PET/[¹¹C]raclopride studies in a talk entitled "The effect of natural rewards and abused drugs on the dopamine system: similarities and differences." As noted, decreases in [¹¹C]raclopride binding can provide a measure of increased extracellular dopamine (DA) levels within the human striatum. Using this method, a series of studies have compared the effects of natural and drug rewards as well as aversive, psychologic challenges. These studies suggest that food and monetary reward elicit DA release in the dorsal, but not ventral, striatum. In comparison, drug rewards, such as *d*-amphetamine (0.3 mg/kg, by mouth) and alcohol (1.0 mL/kg, by mouth) increase DA release in the ventral, but not dorsal, striatum. Because a psychologic stressor also decreased [¹¹C]raclopride binding in the ventral striatum, it was suggested that limbic DA release might be more closely related to attention or arousal than pleasure. Individual differences in drug-induced DA release were also noted. In response to acute drug administration (amphetamine or alcohol), increased DA release was predicted by the personality trait of novelty seeking. Repeat amphetamine administration led to progressive increases in the ability of the drug to elicit DA release, and individual differences in this potentiated response were also predicted by novelty seeking. Together, these studies suggest that (1) DA sensitization can occur in humans, (2) individual differences in the acute DA response to drugs and susceptibility to sensitization are related to pre-existing personality traits, and (3) DA release in the ventral striatum might be more closely related to attentional processes than mood elevation.

Somatic treatments for depression (Chair, Dr. Roumen Milev)

Dr. G. Abraham (Queen's University, Kingston) opened the session with a talk entitled "Role of repetitive transcranial magnetic stimulation (rTMS) in the treatment of depression." Although depression is one

of the best-treated chronic psychiatric illnesses, a large proportion (30%–45%) of individuals do not respond to traditional pharmacotherapies. Transcranial magnetic stimulation (TMS) is a noninvasive technique used to stimulate the human brain by generating a magnetic field that penetrates the skull and induces action potentials in the underlying cerebral cortex. Like other treatments for depression (medications and electroconvulsive therapy [ECT]), TMS alters regional cerebral blood flow, decreases the hypercortisolism associated with overactivation of the hypothalamic–pituitary–adrenal axis, increases thyroid-stimulating hormone (TSH) release thereby regulating the hypothalamic–pituitary–thyroid axis, and normalizes the latency to rapid eye movement sleep. TMS has antidepressant efficacy and a relapse rate that is about equal to that of ECT. It is well tolerated, without the negative effects on cognition, endocrine function or neurophysiology (i.e., electroencephalogram) seen following ECT. Together, the accumulating findings suggest that TMS could be an efficacious treatment for patients who fail to respond to antidepressant medications. However, questions remain. Additional research is needed to determine (1) the treatment parameters (including intensity, duration, number of pulses) that provide a maximal antidepressant effect, (2) the robustness of its antidepressant effect and (3) which patients are likely to respond to TMS treatment.

Dr. Nicholas J. Delva (Queen's University, Kingston) gave the second talk of the session entitled "Electroconvulsive therapy: interaction between electrical dose, electrode placement and benzodiazepines." Delva and colleagues previously found that 59% of patients showed a clinically significant improvement in depression following the use of right unilateral (RUL) electrode placements during electroconvulsive therapy (ECT). This response rate was substantially higher than those reported by others. Delva speculated that the discrepancies in past research may be due to variable ECT parameters and the use of benzodiazepines. To test these hypotheses, Delva and colleagues assessed 12 clinical trials of brief pulse ECT. In RUL ECT, there was a positive linear association between electrical dose and mean improvement after 6 ECT treatments 1 week after treatment. Electrical doses greater than 200–300 mC did not enhance improvement. As hypothesized, the degree of improvement was increased in the study that did not employ benzodiazepines. The efficacy of bifrontal (BF) ECT was also influenced by the

use of benzodiazepines: in patients treated with benzodiazepines the electrical dose had to be increased above seizure threshold (ST) in order to see "good" improvement on the Hamilton Depression Rating Scale. In contrast, the efficacy of bitemporal ECT was not influenced by benzodiazepines. Delva suggested that the use of benzodiazepines during RUL ECT should be minimized, and further studies of the optimal electrical dose for RUL ECT without benzodiazepines should be investigated. BF ECT at or near ST may provide the best treatment outcome.

Dr. Michela David (Queen's University, Kingston) presented the third talk of the session, entitled "Light therapy and sleep deprivation as somatic treatments for depression." Since the 1980s, light therapy has been used to treat major depressive disorder (MDD) with seasonal patterns (i.e., seasonal affective disorder), which is characterized by depressed mood, hypersomnolence (up to 20 h of sleep per day) and carbohydrate craving. The recommended mode of administration of light therapy involves the use of a fluorescent light box that emits full-spectrum bright light. There is a reciprocal relation between the intensity of light used and the duration of daily exposure (e.g., with 10 000 lux light the recommended exposure time is 30 min/d, whereas with 2500 lux light the recommended daily exposure time is 2 h/d). The antidepressant effects of light exposure are apparent in 60%–90% of patients as early as 2 weeks after initiation of treatment, and side effects are mild. Light therapy is also being used to treat non-seasonal depression. Some studies report that light therapy is effective for 12%–35% of patients when used as monotherapy and can have synergistic therapeutic effects when combined with antidepressant medications or sleep deprivation.

In the second half of her talk, David discussed sleep deprivation as a treatment for depression. Sleep deprivation has a rapid (within 23–29 h of wakefulness) and dramatic antidepressant effect in 60% of depressed patients, particularly those with severe or psychotic depression or patients with marked diurnal variation in mood. However, its use as treatment has been limited because the beneficial effects are usually temporary, dissipating after even brief sleep. There is evidence, though, that the clinical benefits of sleep deprivation can be extended by concurrent administration of lithium carbonate, T₄ agonists (e.g., levothyroxine), 5-HT_{1A} antagonists (e.g., pindolol) and light therapy. Although the relapse rate is high, David pointed out

that it is still a useful therapeutic tool to allow for diagnostic assessment, cognitive assessment, treating of depression in bipolar patients, treating of acute suicidality and as well as providing a window into the well state.

Dr. Roumen Milev (Queen's University, Kingston) gave the final talk of the session entitled "Vagus nerve stimulation and other new methods for treatment resistant depression." Milev began the session by noting that 25%–35% of patients with major depressive disorder exhibit only minimal clinical improvement irrespective of their treatment. There appear to be different degrees of treatment-resistant depression (TRD), and hence a staging of TRD has been proposed, the final stage being a failure to respond to bilateral ECT. For these individuals, novel treatments may be necessary and 3 were described: vagal nerve stimulation (VNS), deep brain stimulation (DBS) and magnetic seizure therapy (MST). VNS involves the implantation of a pacemaker-type device that connects to the vagus nerve. The device emits electrical impulses with a 30-second on-time followed by a 5-minute off-time. As a therapeutic agent, VNS is most effective in patients with milder TRD. DBS involves bilateral implantation of electrodes (connected to pacemaker-like devices) into various subcortical sites. Treatment has been approved for Parkinson's disease and movement disorders, and there have been encouraging results in refractory obsessive-compulsive disorder. Research assessing its efficacy as a treatment for TRD is currently under way. MST uses magnetic stimulation like that used in TMS to induce a seizure. Similar to ECT, MST is performed while the patient is under general anesthetic, and the treatments occur once a day, 3 times per week. Preliminary data from a randomized double-blind study suggest that MST is a promising new treatment for TRD and, compared with ECT, side effects are less severe. In sum, promising new therapies for TRD are being developed, but more research is needed to determine their relative efficacy.

Serotonin function (Chair, Dr. Andrew Greenshaw)

Dr. Paul Albert (University of Ottawa, Ottawa) began the symposium by talking about "The C(-1019)G 5-HT_{1A} functional polymorphism: association with depression, suicide and antidepressant response." Reduced serotonin neurotransmission is implicated in the pathogenesis of depressive illnesses and suicide. Activation of 5-HT_{1A} autoreceptors inhibits serotonin

neurotransmission. Selective serotonin reuptake inhibitors (SSRIs) are known to desensitize 5-HT_{1A} autoreceptors in the dorsal raphe, enhancing serotonin transmission. Conversely, studies of postmortem brain tissue suggest that depressed suicide victims, compared with healthy controls, display elevated 5-HT_{1A} receptor density in dorsal raphe, but not in postsynaptic sites. The C(-1019)G polymorphism of the 5-HT_{1A} receptor gene is prevalent in the healthy population and is located in a region of the 5-HT_{1A} gene that is associated with significant repressor activity. Dr. Albert hypothesized that variation in the sequence of this repressor region could lead to impaired repression of 5-HT_{1A} receptor expression and might be correlated with depression or suicidal behaviour or both. Indeed, he has shown how the regulation of the repressor region of the 5-HT_{1A} receptor gene is altered in depression and suicide. In blood samples of depressed patients, he found that the only alteration detected within the repressor region of the 5-HT_{1A} receptor gene was the C(-1019)G polymorphism. Specifically, there was a 2-fold increase in the frequency of the homozygous G/G allele in severely depressed patients versus controls. Patients who had attempted suicide also showed higher frequency of the C(-1019)G polymorphism than controls, that is, increased frequency of the homozygous G(-1019) allele. Both antinuclear deformed epidermal autoregulatory factor (DEAF)-1-related protein (NUDR) and hairy/enhancer-of-split-5 (Hes5) function are transcriptional repressors and Dr. Albert has shown strong expression of these transcription factors in serotonin neurons in the raphe. He showed that a C(-1019)G polymorphism inhibits the binding and function of these transcriptional repressors, leading to overexpression of raphe 5-HT_{1A} autoreceptors. The C(-1019)G change dramatically impaired transcriptional repression of the 5-HT_{1A} receptor gene by NUDR and Hes5. These results are consistent with postulated roles of the 5-HT_{1A} receptor and dysregulation of the serotonin system in depression and suicide and represent the first evidence associating specific transcription factors (NUDR and Hes5) with major depression and completed suicide. Toward the end of his talk, he mentioned a study showing that patients with the C(-1019)G polymorphism show a reduced response to antidepressant treatment. These studies suggest that the C(-1019)G polymorphism is a marker for antidepressant response and indirectly implicate repression of the 5-HT_{1A} gene in adaptive responses to antidepressant treatment.

Dr. Paul Fletcher (University of Toronto, Toronto) talked about the role of “5-HT in the regulation of motivation and reward.” Most studies investigating the neurobiology of motivation and reward have focused on dopamine. Dr. Fletcher’s talk presented evidence that serotonin, via activation of 5-HT_{2c} receptors, modulates the activity of the mesolimbic dopaminergic system and regulates motivated behaviour. For example, 5-HT_{2c} agonists and antagonists inhibit and stimulate, respectively, dopamine cell firing and release in the nucleus accumbens. In locomotor activity experiments, the 5-HT_{2c} agonist Ro60-0175 blocked cocaine-induced locomotion, whereas the 5-HT_{2c} antagonist, SB242084, enhanced it. Neither compound affected locomotor activity when given alone. Similar effects were observed with methylphenidate-, MDMA-, nicotine- and morphine-induced locomotion. Drug self-administration studies revealed an inverse relation between activation of 5-HT_{2c} receptors and cocaine self-administration, using both fixed and progressive ratio schedules. Finally, the 5-HT_{2c} agonist and antagonist diminished and augmented, respectively, the ability of cocaine to reinstate self-administration behaviour. These studies show a bidirectional modulation of the behavioural effects of cocaine and other drugs of abuse by 5-HT_{2c} receptors. Results from a study of the effects of 5-HT_{2c} receptor agonists and antagonists on food reward suggested that these drugs modulate the effects of drugs of abuse, but not of natural rewards. These findings raise the possibility that 5-HT_{2c} ligands may be useful therapeutic agents for treating drug abuse and that altered function of these receptors may be a contributory factor in the development of drug abuse and impulse control disorders.

Dr. Pierre Blier (University of Ottawa, Ottawa) talked about “Serotonin and norepinephrine drug interactions and antidepressant drug actions.” His main point was that serotonin and norepinephrine neurons have reciprocal interactions making it likely that antidepressant drugs affect both systems. This proposed interaction between serotonin and norepinephrine might contribute to antidepressant efficacy. For example, serotonin neurons project to the locus coeruleus (LC), which expresses 5-HT_{2A} receptors that inhibit norepinephrine cell firing. Serotonin lesions increase norepinephrine firing in the LC, whereas 14- to 21-day treatment regimens with a selective serotonin reuptake inhibitor (SSRI) decrease norepinephrine cell firing, which is possibly related to the anxiolytic effects of the SSRIs. In comparison, long-term treatment with

antidepressant drugs that inhibit norepinephrine uptake, and hence norepinephrine transmission, augments postsynaptic 5-HT_{1A} receptor activation. Long-term treatment with the atypical antidepressant bupropion increases burst firing of both serotonin and norepinephrine cells, presumably through increased norepinephrine release in the dorsal raphe. Similarly, treatment with mirtazapine was also found to increase the firing rate of both norepinephrine and serotonin neurons. Because both serotonin and norepinephrine depletion lead to the recurrence of depressive symptoms, the combination of drugs with complementary mechanisms might have a better outcome. Recent work supports this proposition. Combined treatment with the SSRI paroxetine and the atypical antidepressant mirtazapine led to a significantly better outcome than treatment with either antidepressant alone.

Dr. Gary Remington (University of Toronto, Toronto) closed the session with his talk “Does serotonin have a role to play in antipsychotic atypicality?” Three subtypes of antipsychotic have been proposed, conventional (dopamine D₂ receptor antagonists), second generation (D₂ antagonists with serotonin 5-HT₂ receptor antagonist properties) and third generation (partial dopamine agonists). The D₂ antagonists are effective antipsychotics but elicit marked extrapyramidal symptoms. Clozapine, which does not induce extrapyramidal symptoms, has higher affinity for serotonin 5-HT₂ receptors than for dopamine D₂ receptors. However, as Dr. Remington noted, the importance of the 5-HT₂ > D₂ affinity of atypical drugs may have been overstated. For instance, high doses of risperidone (partial dopamine agonist) or olanzapine (serotonin 5-HT₂ antagonist) have been shown to produce extra-pyramidal symptoms. In comparison, clozapine and quetiapine do not increase risk for extrapyramidal symptoms even at high doses. Moreover, at low doses, the effects of the typical antipsychotic haloperidol are more similar to those of the atypical drugs. Finally, drugs that are selective 5-HT₂ receptor antagonists do not seem to have antipsychotic efficacy. Taken together, these studies suggest that what makes neuroleptic drugs atypical is not their actions on serotonin receptors, but instead their lower affinity for D₂ receptors.

Cholinergic mechanisms in brain function (Chair, Dr. Mary Olmstead)

Dr. Sandra M. Boye (Université de Montréal, Montréal)

opened the symposium with a talk entitled "First-stage cells and the lateral pontine tegmental nucleus." Using electrophysiologic techniques, Boye noted that cholinergic neurons in the lateral pontine tegmental nucleus (LPTg) have characteristics of first-stage cells (cells that directly link the ventral tegmental area [VTA] with the posterior mesencephalon [PM]); for example, they activate both the VTA and the PM, their activity follows high-frequency stimulation, they have a refractory period in the range of 0.4–1.2 ms, and there is a direct link from the LPTg to the VTA and PM. However, as Boye pointed out, if these neurons are truly first-stage neurons, then destruction of the LPTg should attenuate the rewarding effects of self-stimulation. To test this hypothesis, bilateral stimulation electrodes were implanted in the VTA, and rats were given unilateral electrolytic lesions of the PM centred in the LPTg. Contrary to Boye's hypothesis, there was no effect on reward threshold if the stimulation electrode was ipsilateral to the lesion, whereas reward thresholds decreased if the stimulation electrode was in the contralateral VTA. Boye suggested that one possible reason for the unexpected findings is that electrolytic lesions cause a large insult and the contralateral site may "overcompensate" for this insult. Looking further into the role of the LPTg in reward, Boye found that TTX infused into the LPTg attenuated the rewarding effects of lateral hypothalamic and PM stimulation. In summary, although LPTg neurons have the characteristics of first-stage cells, the conflicting behavioural data necessitate future research to determine whether they truly have this role.

Dr. John Yeomans (University of Toronto, Toronto) gave the second talk of the symposium, entitled "Cholinergic genes involved in reward, arousal and psychiatry." The main thesis of Dr. Yeomans' talk was that cholinergic neurons of the pedunculopontine tegmental nucleus (PPTg)/laterodorsal tegmental nucleus (LDT) function to activate exploration and reward and to facilitate movement via innervation of the ventral tegmental area (VTA)/substantia nigra (SN) dopamine (DA) neurons, while inhibiting the startle reflex by way of the ventral pontine reticular formation. Moreover, lateral hypothalamic (LH) stimulation increases acetylcholine (ACh) release in the VTA during eating and drinking in deprived animals, and drugs that modulate ACh activity modulate these behaviours. Stimulation of ACh neurons in the LDT results in a 3-stage increase in DA in the nucleus accumbens, and

pharmacologic manipulations suggest that in the final stage the prolonged increase in DA is mediated by muscarinic M5 receptors. Using M5 knockout mice, Yeomans and colleagues supported this hypothesis. In the knockout mice, stages 1 and 2 were normal, whereas stage 3 was absent; that is, there was no prolonged increase in DA following LDT stimulation. Because of the effect of LDT stimulation on DA release, Yeomans and colleagues manipulated the expression of the M5 receptor and assessed reward. First, when M5 expression was decreased in the VTA using antisense oligonucleotides, reward thresholds were increased (by about 43%). Conversely, when M5 expression was increased in the VTA by means of electroporation, a decrease (by about 20%–30%) in reward threshold was observed. In addition, M5 knockout mice do not show an opiate-conditioned place preference, but they exhibit reduced amphetamine-induced locomotion and decreased latent inhibition, but normal prepulse inhibition. In relation to arousal, carbachol injected into the intergeniculate leaflet (IGL) nucleus of the thalamus results in a 2-hour shift in circadian rhythms. A similar phase shift is observed following exposure to either rewarding or aversive stimuli suggesting that arousal, perhaps by means of a change in ACh, shifts circadian rhythms. Finally, Yeomans and colleagues found that rewarding signals can reduce startle in the prepulse inhibition test and that this effect is mediated by the PPTg/LDT ACh neurons. In conclusion, Yeomans suggests the role of the mesopontine ACh neurons is to coordinate a variety of approach/risk-taking strategies while inhibiting defensive strategies.

Dr. Carlyle Smith (Trent University, Peterborough) gave the third talk of the symposium entitled "Sleep states: memory and acetylcholine." After reminding the audience that rats spend about 10%–15% of their sleep time in rapid eye movement (REM) sleep and this percentage increases when animals are trained on a task, Smith discussed numerous findings suggesting that REM sleep deprivation and/or modulating acetylcholine (ACh) activity during REM sleep affects performance on learning and memory tasks. In one study, anisomycin dihydrochloride (a protein synthesis inhibitor) injected at the onset of the REM sleep window (RSW, the time during which REM deprivation impairs task performance) caused later memory impairments. Further, AChE and ACh levels were decreased in rats treated with anisomycin. In the same task, scopolamine (0.4 mg/kg) impaired memory when injected at the

onset of the RSW. Animals trained on the Morris water maze showed increased levels of ACh 1–4 hours after testing, a time corresponding to the RSW, but ACh levels were not changed at times outside the RSW. Further, when tested 7 days after training in the Morris water maze, non-REM-deprived rats exhibited a greater increase in ACh than did REM-deprived or cage-control rats. In the conditioned cued preference, both 9–12-hour REM-deprived rats and rats treated with scopolamine injections 9–12 hours after training spent less time in the food paired arm than did control rats. Both systemic and bilateral intrastratial injections of scopolamine during the RSW (1–4 h after training) impaired performance in the working/reference memory version of the 8-arm radial maze. In summary, REM deprivation at specific times following training impairs task acquisition and, for the most part, the RSW coincides with a time during which ACh blockade impairs learning and memory.

Dr. V. De Luca (University of Toronto, Toronto) gave the final talk of the session entitled “Neuronal alpha7 nicotinic and M5 muscarinic cholinergic receptors in the pathogenesis of schizophrenia.” De Luca began his talk by explaining that the different subtypes of schizophrenia (paranoid, disorganized and catatonic) have not been associated with specific genetic susceptibilities. However, in some studies, hereditary catatonic schizophrenia has been associated with chromosome 15q13–q15, the same chromosome on which the acetylcholine (ACh) muscarinic M5 receptor is located. In animal models, the M5 receptor is known to modulate dopamine (DA) release and in M5 knockout mice DA release is decreased in the nucleus accumbens. For this reason, the M5 polymorphisms were typed in 82 Canadian families in which at least 1 member of the family met criteria for schizophrenia. Using the transmission disequilibrium test, the M5 gene was not found to confer susceptibility to schizophrenia. The gene for the alpha7 nicotinic ACh receptor is located near the gene for the M5 receptor, and the disequilibrium test also showed that this gene was not associated with an increased risk of schizophrenia. However, using the Family-Based Association Test to perform a haplotype analysis on both genes, De Luca and colleagues found that the combination of the cholinergic genes was biased in individuals with schizophrenia as compared with individuals without schizophrenia. Hence, both genes in combination may confer susceptibility to schizophrenia.

Smoking among individuals with schizophrenia is more common than in the general population. In addition, the number of alpha7 nicotinic receptors can be normalized by high doses of nicotine, indicating that smoking among individuals with schizophrenia may be an attempt to self-medicate. Thus, De Luca and colleagues analyzed the frequency of the 113 allele of the alpha7 nicotinic receptor gene and found it to be higher in smoking and nonsmoking individuals with schizophrenia. Finally, reverse-transcriptase polymerase chain reaction (RT-PCR) was used to analyze alpha7 mRNA and alpha7-like mRNA in postmortem brain tissue of individuals with no psychiatric disorder and in those with schizophrenia and bipolar disorders; the number of alpha7 and alpha7-like expression was negatively correlated in the control group, but was weakly associated in the schizophrenia group. In summary, the interaction between M5 genes and the alpha7 nicotinic receptor gene may be associated with schizophrenia.

CCNP: the next generation (Chair, Dr. Janet Menard)

The symposium, “CCNP: the next generation symposium,” consisted of 5 short talks from research trainees who had submitted the best abstracts. The first talk was given by Faïza Benaliouad (Université de Montréal, Montréal) who gave a talk entitled “Attenuation of brain stimulation reward by typical and atypical antipsychotics: Is there a role for 5-HT_{2A} receptors?” Rats were trained to bar press for electrical stimulation of the lateral hypothalamus. As expected, both the typical and the atypical neuroleptics, haloperidol and clozapine, respectively, dose-dependently increased self-stimulation thresholds. In comparison, the selective 5-HT_{2A} antagonist, MDL-100907, had no effect, either when administered alone or when co-administered with haloperidol. Together, the results suggest that the ability of atypical neuroleptics to alter the motivational effects of electrical stimulation are unrelated to their affinity for 5-HT_{2A} receptors. To the extent that the mechanisms mediating the motivational and antipsychotic effects overlap, the study also suggests that activity at DA receptors is sufficient to account for their clinical efficacy.

Francois Laplante (Douglas Hospital Research Centre, Verdun) gave a talk entitled “Alterations in the behavioural response to oxotremorine in post-pubertal rats with neonatal ventral hippocampal lesions.” Neonatal

ventral hippocampal lesions induce a range of behavioural and dopaminergic alterations that, it has been proposed, may model aspects of schizophrenia: hyperactive responses to stress and amphetamine and impaired working memory, prepulse inhibition, and social interactions. Because many of these behavioural disturbances are improved by neuroleptics, hyperdopaminergic activity is an implicated mechanism. Laplante's studies contribute evidence that acetylcholine (ACh) may also play a role. Rats with lesions of the ventral hippocampus exhibited increased ACh release in response to dopamine (DA) D1 agonists and stressors. Compared with sham lesioned rats, the lesioned animals exhibited increased muscarinic type 1 (M1) receptors in the frontal cortex and nucleus accumbens plus increased M2 receptors in the NAcc. Each of these receptor changes develops at puberty, the time at which psychotic symptoms commonly emerge in schizophrenia. Also at puberty, the lesioned rats exhibited a wide range of altered responses to the muscarinic agonist, oxotremorine, including greater analgesic, salivary and tremor responses as well as lower body temperature. Together, the experiments suggest that neonatal lesions of the ventral hippocampus increase ACh activity, and this may account for some of the resulting behavioural disturbances.

James Wasserman (Queen's University, Kingston) gave a lecture entitled "Non-declarative memory in schizophrenic patients grouped according to their medications: risperidone produces effects more like typical antipsychotics than clozapine or olanzapine." In his study, nondeclarative (implicit) memory was evaluated in patients with schizophrenia using a probabilistic classification task (PCL) and a gambling task (GAT). Previous work suggests that poor performance on the PCL task can indicate striatal dysfunction, whereas GAT performance can reflect function in the ventromedial prefrontal cortex (VMPFC). Compared with medication-free healthy controls, patients who were treated with typical antipsychotic drugs (phenothiazines, flupenthixol, haloperidol and loxapine) showed deficits on the PCL task only. In comparison, those treated with the atypical antipsychotic medications, clozapine or olanzapine, exhibited deficits primarily on the VMPFC-sensitive GAT. However, patients treated with risperidone performed on the GAT more like the typical than the atypical antipsychotic treated group. The results might reflect the differential ability of typical versus atypical antipsychotic medications to affect

positive ("striatal") versus negative ("PFC") symptoms. Risperidone, though, has a profile similar to that of the typical antipsychotic drugs.

Mélissa Perreault (McMaster University, Hamilton) gave a talk entitled "Stimulation of kappa opioid receptors potentiates locomotor sensitization induced by the dopamine agonist quinpirole." As noted by the speaker, repeated administration of the direct dopamine (DA) D₂/D₃ agonist quinpirole leads to progressive increases in locomotor activation and perseveration. It has been proposed that this behavioural sensitization may model aspects of obsessive-compulsive disorder (OCD). In the presented study, co-administration of the kappa opioid agonist U69593 potentiated the locomotor and rearing responses to quinpirole. It was proposed that the kappa agonist accomplishes this by having effects on excitatory amino acids or by decreasing presynaptic DA release; for example, lower synaptic DA levels would allow quinpirole-induced stimulation of DA D₂/D₃ receptors to take place without concomitant stimulation of DA D₁ receptors. One implication is that opioid systems might be perturbed in patients with OCD.

Fanny Botreau (Paris-Sud University, Orsay, France) gave a talk entitled "The effects of retrieval cues on memory depend critically on CRF receptor activation, as demonstrated by behavioural deficits and reduced stress hormone levels induced by CP154,526 and by naloxone." The research presented investigated whether the ability of retrieval cues to facilitate performance in avoidance tasks was related to activation of the hypothalamic-pituitary-adrenal (HPA) axis. Administration of the corticotropin-releasing factor type 1 receptor (CRF1) antagonist CP154,526 decreased the ability of retrieval cues to facilitate performance and induce the release of ACTH and corticosterone. Because decreasing cue-induced HPA axis activation with the opioid antagonist naloxone also prevented the behavioural facilitation, the results bolster the suggestion that activation of the HPA axis facilitates avoidance performance. It was proposed that both CRF and opioids engage cells in the central nucleus of the amygdala that project to the hypothalamus, locus coeruleus, ventral tegmental area and raphe nucleus. Retrieval cues might enter the same pathway via projections from the cortex to the thalamus to the lateral nucleus of the amygdala and then to the basolateral and central nuclei.

Competing interests: None declared.