The 26th Annual Meeting of the Canadian College of Neuropsychopharmacology

Montréal, Quebec, Canada, June 1–4, 2003

Marco Leyton, PhD; Ridha Joober, MD; Simon N. Young, PhD

Department of Psychiatry, McGill University, Montréal, Que.

The 26th Annual Meeting of the Canadian College of Neuropsychopharmacology (CCNP) was held in Montréal, Que., June 1–4, 2003. This report summarizes 3 plenary lectures, 2 award lectures and 9 symposia.

Plenary lectures

The first plenary lecture, titled "Developmental trajectories of anatomic abnormalities in attention-deficit/hyperactivity disorder (ADHD)," was presented by Dr. F.X. Castellanos (New York University Child Study Centre). After discussing the defining symptoms of ADHD and problems related to the quantitative definition of these symptoms, he presented a summary of genetic epidemiologic studies suggesting that genetic factors, together with environmental factors, such as brain injuries and maternal smoking during pregnancy, play an important role in causing ADHD.

The main research question that was addressed in this talk was how these causative factors affect the developing brain of children diagnosed with ADHD. A second question, with important clinical implications, was to determine whether or not treatment with psychostimulant medications affects the brain morphology and developmental trajectories. As an initial proof that the brain of children with ADHD may present structural abnormalities, 3 cases of children with complex behavioural syndromes resembling ADHD were presented. The first 2 children had midgestation right basal ganglia lesions provoked by needle penetration during amniocentesis. The third case was a pair of monozygotic twins discordant for ADHD with the affected subject presenting a circumscribed infract in the head of the right caudate. Although these cases with gross brain abnormalities represent rather exceptional patients with ADHD, they suggest that subtle brain abnormalities, possibly in the basal ganglia, may sustain ADHD in most cases. Dr. Castellanos and his colleagues at the Montreal Neurological Institute use sophisticated brain imaging techniques to identify these abnormalities and track their developmental trajectories.

To achieve these purposes, regional brain volumes at initial scan and their changes over time in medicated and previously unmedicated male and female patients with ADHD and healthy controls were compared. One hundred and thirty-five children and adolescents with ADHD (age at initial scan 9.4 years for girls and 10.5 years for boys) and 139 age- and sex-matched controls

Correspondence to: Dr. Marco Leyton, Department of Psychiatry, McGill University, 1033 Pine Ave. W, Montréal QC H3A 1A1; fax 514 398-4866; marco.leyton@mcgill.ca

Medical subject headings: aggression; alcoholism; Alzheimer disease; anorexia nervosa; antipsychotic drugs; attention deficit disorder with hyperactivity; autistic disorder; behavior, addictive; brain mapping; bulimia; central nervous system; depression; drug therapy; eating disorders; estradiol; gene expression; mood disorders; motivation; panic disorder; Parkinson disease; receptors, dopamine; Rett syndrome; reward; schizophrenia; steroids; suicide.

J Psychiatry Neurosci 2003;28(6)

were scanned using the Montreal Neurological Institute automated pipeline approach. On initial scan, patients with ADHD had significantly smaller brain volumes in all regions, even after adjustment for significant covariates. This global difference was reflected in smaller total cerebral volumes (–3.2%) and in significantly smaller cerebellar volumes (–3.5%). The brain developmental curves in children with ADHD paralleled those of healthy children in all the explored regions of the brain with the exception of the caudate volume, which continued to decrease in control children up to around the age of 18–19 years but reached a plateau before this age in children with ADHD. An interesting and surprising observation of this study, which is one of the first prospective imaging studies of brain development, is that brain size reaches a plateau at around the age of 11 years and tends to decrease in size thereafter in all the groups, including the healthy controls.

The second question addressed in this presentation was the effect of treatment with psychostimulants on brain morphology and development. The study sample included a substantial proportion of children who had not received medication before their first brain imaging session (30%). It was, therefore, possible to compare this group of previously unmedicated children with those who were previously treated with psychostimulants and with controls. Previously unmedicated children demonstrated significantly smaller total cerebral volumes (–5.8%) and cerebellar volumes (–6.2%). Unmedicated children with ADHD also exhibited smaller total white matter volumes compared with controls (–10.7%) and with medicated children with ADHD (–8.9%).

Dr. Castellanos concluded this part of his talk by suggesting that genetic and/or early environmental influences on brain development in ADHD may be fixed and nonprogressive. He also suggested that treatment with psychostimulants may have an effect on brain development (possibly accelerating normal physiologic maturation), although he emphasized that this conclusion needs further confirmation and analyses. He cautioned against using brain morphology data as a diagnostic tool for ADHD, because abnormalities observed in children with ADHD are neither specific nor sensitive.

In a second part of the presentation, it was suggested that using endophenotypes, traits that are quantifiable, dimensional and index disease liability, may be help in the quest for a better understanding of the genetic and environmental determinants of ADHD. As published in a recent review paper by Castellanos and Tannock (*Nat Rev Neurosci* 2002;3(8):617-28), the ideal endophenotype should be anchored in the current neuroscience knowledge about ADHD. Among the traits that may be considered relevant and promising for ADHD, delay aversion, deficits in temporal processing and deficits in working memory were briefly discussed.

In the second plenary lecture, Dr. H. Mayberg (University of Toronto) gave a talk entitled "Modulating dysfunctional limbic-cortical circuits in depression: towards development of brain-based algorithms for diagnosis and optimized treatment." Underlying this work was the perspective that there is no 1 neurotransmitter, brain centre or even neurocircuit that accounts for all facets of clinical depression. Instead, it was proposed that an interacting network of distinct limbic-cortical circuits mediate specific symptom profiles, vulnerability traits and treatment responsivity. In support of these propositions, Dr. Mayberg and colleagues have made the following observations. First, the most common disturbance identified in functional neuroimaging studies is frontal hypoactivity. This hypofunction might reflect a severe depressive state associated with impaired executive function, psychomotor retardation and an inability to initiate goal-directed behaviour. Frontal hyperactivity has also been reported, possibly reflecting, in some patients, a compensatory response associated with psychomotor agitation and ruminating thoughts. Treatment response to both selective serotonin reuptake inhibitors (SSRIs) and placebo are associated with increased activity in frontal cortex and posterior cingulate and decreases in the subgenual cingulate. Unlike placebo, though, SSRI treatment response is associated with additional changes in the caudate, hippocampus and brain stem, changes that might contribute to making the medication response more robust. SSRI treatment responsivity is predicted by elevated activity in the rostral anterior cingulate (BA24a). There is evidence that this might be a trait. Increased activity in BA24a predicts treatment response and does not change following treatment. Finally, patients who respond to cognitive–behaviour therapy exhibit changes in the same regions as SSRI and placebo responders, but the direction of effects is strikingly different: decreases in the prefrontal cortex and hippocampus coupled with increases in the rostral cingulate. When the full dataset was analyzed together,

the findings raised an intriguing speculation: 3 depression subgroups, each with its own personality structure and symptom profile, and each related to the same limbic-cortical circuits yet in different ways: (i) physician-referred medication- and placebo-responders with symptoms suggestive of atypical/reactive depression, (ii) self-referred medication-responders with endogenous/melancholic depression and (iii) self-referred psychotherapy-responders.

The third plenary lecture was by Dr. C.P. O'Brien (University of Pennsylvania, Philadelphia) and was entitled "Translating basic research findings into improved medications for addiction." Dr. O'Brien began by noting that a large animal literature has identified in substantial detail many of the neurobiologic mechanisms likely related to substance abuse. Few of these findings, though, have been well explored in clinical research or treatment development. For example, some of the overlap between effects of different drugs might reflect the overlap between addiction and learning. Following thousands of pairings between the drug and events, robust associations are formed. Extinction training can diminish subjective and physiologic responses to videos depicting cocaine use and, in these patients, relapse is delayed though not prevented. A better understanding of the underlying neurobiology could lead to more effective medication *cum* psychologic treatments. For example, both drugs and drug-associated stimuli might induce the release of glutamate, endogenous opioids and dopamine, the last perhaps through enkephalin-mediated inhibition of gamma aminobutyric acid (GABA). Administration of the GABA-B agonist, baclofen, prevents cocaine-video-induced craving and limbic-cortical activation. Very preliminary clinical studies suggest that baclofen has promising treatment efficacy. Naltrexone has also shown encouraging clinical results. The long-lasting opioid receptor antagonist decreases alcohol self-administration in rodents and nonhuman primates. Clinical studies also identify treatment efficacy, and recent evidence suggests that this might be specific to individuals characterized by a family history of alcoholism, high craving, a large endorphin response to alcohol and a mu opioid receptor polymorphism associated with higher receptor function (the Asp40 variant). Finally, recent studies suggest that combination therapy with naltrexone plus acamprosate (decreases glutamate release and receptor excitability) is more effective than either therapy alone. Overall, these studies exemplify a career characterized by rigorous and innovative clinical research that has taken advantage of the basic science literature and pointed toward previously unsuspected mechanisms.

Award lectures

CCNP Heinz Lehmann Award lecture

This year the CCNP Heinz Lehmann Award went to Dr. T. Di Paolo (Laval University, Quebec), whose talk was titled "Hormonal modulation and protection of brain neurotransmission: potential therapeutic application for schizophrenia and Parkinson's disease." She covered a wide range of research that started in the late 1970s with the demonstration that treating rats with chronic estradiol increases the density of dopamine D_2 receptors in the striatum. Hormones can have a variety of effects on many different transmitters that are mediated by both genomic and nongenomic mechanisms. For example, estradiol can alter dopamine release and metabolism as well as pre- and postsynaptic dopamine receptors and the dopamine transporter. It can also modulate membrane properties, with potential implications for a variety of effects on neurotransmission. Some of the effects on dopaminergic function may account for the different expression of schizophrenia in men and women; it tends to occur later in women with a second peak of onset around menopause. In rats, estradiol increases 5-HT_{2A} receptors and the serotonin transporter, which is of interest because atypical antipsychotics seem to be blockers of this receptor and because several studies have found a low density of 5-HT_{2A} receptors in the frontal cortex of patients with schizophrenia. Selective estrogen receptor modulators (SERMs), such a tamoxifen and raloxifene, seem to have an estrogenic effect on the density of 5-HT_{2A} receptors. Whereas much work has focused on the role of biogenic amines in the pathogenesis of schizophrenia, glutamate has also been implicated. In rats, ovarian steroid withdrawal decreases glutamate N-methyl-D-aspartate (NMDA) receptors in the hippocampus, an effect reversed by estradiol treatment. Progesterone has no effect on its own but reverses the effect of estradiol. Both estradiol and SERMs seem to act specifically on the NR_1 and NR_{2B} subunits of the NMDA receptor. Estradiol treatment has no effect on alpha-amino-3-hydroxy-5-methylisoxazolepropionate (AMPA) receptors in the hippocampus but decreases receptor density in the frontal cortex, striatum and nucleus accumbens.

Overall, ovarian steroids have complex effects on neurotransmitters, and much more work is needed to fully elucidate the clinical implications of these hormonal/neurotransmitter interactions.

In addition to their effects on neurotransmitters, ovarian hormones may have neuroprotective effects. The incidence of Parkinson's disease (PD) is higher in men than women, and there is some evidence for a protective effect of estrogen in early PD. In mice, estrogen protects against the toxic effect of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) on dopaminergic neurons. Neuroprotective hormones include 17β-estradiol, progesterone and dehydroepiandrosterone (DHEA), but not androgens. In mice, raloxifene has a neuroprotective effect, but this effect was less in the monkey because less raloxifene crosses the blood–brain barrier in the monkey. In a monkey model of PD, DHEA may reduce the dose of dopa needed. A full understanding of the effects of ovarian steroids on the brain may have implications for prevention as well as the treatment of various neurologic and psychiatric disorders.

CCNP Young Investigator Award lecture

The CCNP Young Investigator award was given this year to Dr. G. Turecki (McGill University, Montréal). Dr. Turecki's presentation, "Clinical and genetic studies of suicide," reviewed his work on suicide, one of the leading causes of death in the general population (tenth cause), especially in young people aged between 15 and 34 years (first cause). These figures are highest in the North-West Territories, the Yukon and Quebec.

The difficult question that Dr. Turecki is trying to answer is why do people kill themselves? He uses a multifaceted approach combining epidemiology and molecular biology to provide some answers.

Psychologic autopsy, whereby information is collected using semistructured interviews, formulation of clinical vignettes and best-estimate DSM-IV diagnosis, was applied to a sample of 197 persons who committed suicide. Major depression followed by drug and alcohol dependence were the leading psychiatric conditions associated with suicide. The quasi-majority of subjects who committed suicide met criteria for a DSM-IV axis I diagnosis, with no specificity of any one of the diagnoses to predict suicide.

In order to better understand why some people with psychiatric disorders kill themselves, whereas others with the same psychiatric diagnosis do not, Dr. Turecki compares patients with major depression who committed suicide to patients with the same diagnosis who do not have suicidal behaviour. Data collected on 110 patients indicate that borderline and antisocial personality disorders are highly represented in patients who committed suicide. Suicide was also associated with higher impulsivity as measured by the Barratt Impulsiveness scale-11 and a higher history of aggression as measured by the Brown–Goodwin scale. On the Temperament and Character Inventory, patients with major depression who committed suicide showed a trend toward higher scores on novelty seeking and lower scores for self-directedness. Alcohol and substance use disorders were significantly more frequent in patients with major depression who committed suicide compared with patients with major depression without suicidal behaviour. Dr. Turecki concluded this part of his talk by indicating that high levels of impulsive and impulsive-aggressive behaviours combined with behavioural disinhibition facilitated by substance use disorders may mediate suicide in major depression.

The second part of Dr. Turecki's presentation focused on the genetic factors implicated in suicide. Comparing the rate of psychopathology in 317 first- and second-degree relatives of 173 subjects who committed suicide and 144 controls (best acquainted), it was found that relatives of the former subjects are at a higher risk of alcohol use, major depression, history of aggressive behaviour, past admission to hospital, death and suicidal behaviour. Relatives of subjects who committed suicide were also differentiated from relatives of controls on several items of the Siegel's Multidimensional Anger Inventory, which lead Dr. Turecki to conclude that familial aggregation of suicidal behaviour may be mediated by impulsive-aggressive behaviours.

The third and last part of this presentation discussed some biologic determinants of suicide. One of the interesting connections that Dr. Turecki is exploring is the link between low cholesterol levels and suicide. This link has been suggested by several observations, in particular the association between prescription of cholesterol-lowering drugs and an increased rate of suicide/violent deaths. In addition, the Smith-Lemli-Opitz syndrome (SLOS), which is caused by a mutation in 7-dehydrocholesterol reductase, an enzyme implicated in the final stages of the biosynthesis of cholesterol, presents often with a phenotype associated with aggressive and self-injurious behaviours. As

SLOS is an autosomal recessive metabolic disorder, carriers of one single mutation may present with increased risk for suicidal or related behaviours. Dr. Turecki compared 49 carriers of 1 mutation in this gene to 54 group-matched controls. Preliminary data from this study is supportive of the hypothesis relating the 7-dehydrocholesterol reductase mutation and increased risk for suicidal and related behaviours. Another monogenic disorder that has been associated with an increased risk of suicidal behaviour is Wolfram syndrome. This rare autosomal recessive syndrome is associated with diabetes mellitus, diabetes insipidus, optic atrophy and deafness. Behavioural traits associated with this syndrome include violent behaviours, depression and attempts at suicide. To further study the implication of this gene in suicidal behaviour, Dr. Turecki investigated 3 polymorphisms located in one of the exons of the Wolfram syndrome gene, WFS1. One of these polymorphisms (H611R) showed significant association with suicidal behaviour, impulsivity and novelty seeking.

Finally, Dr. Turecki presented some new and exciting data on mRNA expression in the brains of 10 subjects who committed suicide compared with that of 10 patients with major depression but without a history of suicide attempts and with 10 healthy controls who died of causes unrelated to suicide. The results of these studies are described in the review of Dr. Turecki's talk in the symposium "Update on the neurobiology of suicide and related behaviours."

Symposia

Eating disorders: neurobiological and genetic factors

Dr. K.L. Klump (Michigan State University, East Lansing) opened the session with a talk entitled "Twin studies of eating disorders: genetic, environmental and developmental influences." She pointed out that although cultural factors play a role in eating disorders, the relatively low rates of anorexia nervosa (AN) (0.5%) and bulimia nervosa (BN) (1%–3%) in the North American population suggests that factors besides culture play an important role. Studies of 11- and 17-year-old twins have revealed genetic influences and also important developmental factors. Eleven-year-old twins exhibited less genetic and greater shared environmental influence on eating attitudes and behaviours than 17-year-old twins. The relation between body mass index (BMI) and eating attitudes was mediated primarily by common shared environmental influences in 11-year-old twins and common genetic influences in 17-year-old twins. Nonetheless, the majority of genetic influences on eating attitudes and behaviours in older twins were due to genetic effects that are independent of those operating to determine BMI. These results raise the possibility that during puberty there is activation of genes that are etiologic for eating disorders.

Dr. H. Steiger (McGill University, Montréal) talked about "Serotonin function in bulimia nervosa: neurobiological and genetic findings." There are 2 types of BN: one associated with dysregulation and impulsivity, and the other with excessive dietary restraint and compulsivity. The former group shows reduced platelet paroxetine binding, reduced prolactin response to m-chlorophenylpiperazine (mCPP) and to buspirone, suggesting low serotonin tone. Measures of paroxetine-binding density (Bmax) and affinity (Kd) contributed significantly to a classification of bulimic women into groups with "low density/high affinity" or "high density/low affinity" binding. The serotonin-based classification did not predict eating-symptom severity. However, the high-density pattern was associated with increased perfectionism and compulsivity, reduced risk of childhood sexual abuse and (to some extent) reduced probability of borderline personality disorder. Finally, a polymorphism in the promoter region of the serotonin transporter gene (designated short or long) was studied in relation to symptoms in BN patients. Carriers of the short allele showed significantly more affective instability, interpersonal insecurity and behavioural impulsivity; higher probability of comorbid borderline personality disorder; and a lower density of platelet paroxetine-binding sites. Overall, the findings indicate a convergence of serotonergic, trait and developmental tendencies in BN.

Dr. W.H. Kaye (University of Pittsburgh) spoke about "The role of 5-HT_{1A} and 5-HT_{2A} receptor activity in symptoms of anorexia nervosa." Positron emission tomography (PET) with WAY 100635 was used to measure the binding potential of 5-HT_{1A} receptors and with altanserin for 5-HT_{2A} receptors. In AN, there was increased 5-HT_{1A} and decreased 5-HT_{2A} receptor activity. These changes persisted after recovery, although the changes were less pronounced. There was an inverse relation between postsynaptic 5-HT_{1A} and 5-HT_{2A} receptor activity in AN. Animal studies indicate that the 2 serotonin receptors are involved in modulating locus

coeruleus activity. Moreover, these 5-HT receptors may be colocalized and have inverse relations on layer V pyramidal neurons. This raises the possibility that the receptor changes in AN result in increased noradrenergic firing and reduced pyramidal neuronal activity. This might account for the increased sensitivity to stress, anxiety or obsessional thought patterns in patients with AN.

Dr. A.S. Kaplan (University of Toronto) reviewed "New findings in the genetics of anorexia nervosa." In spite of considerable evidence for a heritable component in AN, a genome-wide linkage analysis of patients with eating disorders showed only modest evidence for linkage. However, analyses that control for heterogeneity in the sample would be more likely to yield positive results. A second linkage analysis included only families with at least 2 affected relative pairs with AN restricting subtype. This sample showed greater evidence for linkage, notably on chromosome arm 1p. In a second analysis, a multipoint affected sibling pair (ASP) linkage analysis was done on psychologic attributes thought to typify individuals with eating disorders. Two variables, drive for thinness and obsessionality revealed a cluster of ASPs that were extreme and concordant, with close to genome-wide linkage significance also on chromosome 1. This region of the chromosome contains both serotonin- and opioid-related candidate genes.

Neuropsychopharmacology of motivation and reward: implications for psychiatric disorders

Dr. R.A. Wise's (NIH/NIDA/IRP, Bethesda, Md.) talk was entitled "Brain circuitry of drug reward." He began by noting that although most work focuses on the role of nucleus accumbens (NAcc) dopamine (DA) transmission, the electrical brain stimulation studies of Olds and Milner had implicated a much more extensive network. In the early 1980s, Wise, with Bozarth, reported that rats would self-administer morphine into the ventral tegmental area (VTA), the cell-body region for the ascending mesocorticolimbic DA pathway. Later studies indicated that this reflected the stimulation of mu and delta opioid receptors. The mu receptors appeared to play a particularly important role: intra-VTA injections of mu, compared with delta agonists stimulated DA release in the NAcc at much lower doses and were self-administered at 100-fold lower concentrations. Recent studies have identified additional components of the reward circuit. For example, the cholinergic agonist carbachol and the endogenous mu opioid agonist endomorphin-1 are both self-administered at low doses into the posterior VTA. Endomorphin-containing neurons project to the VTA from the hypothalamus. The effect of carbachol might reflect cholinergic projections from the laterodorsal (LDTg) and pedunculopontine tegmental nuclei (PPTg) to the VTA. Cocaine is self-administered into the prefrontal cortex (PFC) and NAcc shell, but rats will also work for particularly low cocaine doses delivered to the olfactory tubercle (OT). Finally, intravenous cocaine self-administration is associated with increased glutamate release in the PFC and acetylcholine (ACh), GABA and glutamate in the VTA. Together, the results suggest that the mechanisms mediating drug reward are not restricted to the VTA-NAcc DA projection but, instead, reflect a broader multitransmitter network that includes the PPTg, LDTg, hypothalamus, VTA, NAcc, PFC and OT.

Dr. P.P. Rompré's (Université de Montréal) talk was entitled "Neurotensin and behavioural sensitization to drugs of abuse." As summarized by Dr. Rompré, repeated intermittent exposure to abused drugs produces a progressive increase in behavioural responses. This augmented response — behavioural sensitization — might increase susceptibility to drug addiction. A now-compelling literature indicates that the development of behavioural sensitization requires the stimulation of DA D_1 receptors in the VTA and increased extracellular glutamate levels in both the VTA and the medial prefrontal cortex (mPFC). Work by Dr. Rompré suggests that the neuropeptide neurotensin also makes a critical contribution. Investigations of neurotensin's effects are complex, though, because it appears to have at least 2 distinct actions: (i) inhibition of DA receptors and (ii) DA-independent effects on muscle relaxation, blood pressure and body temperature. Consistent with DA-antagonist-like effects, microinjections of neurotensin into the VTA and NAcc both increase DA cell firing, with the former enhancing and the latter inhibiting DA-mediated behaviours. In comparison, systemic or intracerebroventricular injections can produce complex combinations of the DA-mediated plus DA-independent effects. This noted, Dr. Rompré has reported that repeated administration of neurotensin receptor agonists can induce cross-sensitization with amphetamine, whereas neurotensin antagonists can prevent amphetamine sensitization. The latter observation suggests that

endogenous neurotensin function is required for the development of sensitization. Very recent work suggests that mPFC glutamatergic mechanisms might also be relevant. For example, the ability of neurotensin to induce sensitization is prevented by lesions of the mPFC.

Dr. M. Leyton (McGill University, Montréal) presented a talk entitled "Alcohol, nicotine, amphetamine and cocaine: PET [^{11}C]raclopride and dopamine depletion studies in humans." As the speaker noted, although a large animal literature suggests that drug-induced increases in dopamine (DA) transmission play a critical role in drug self-administration, there is little evidence for this in humans. Dr. Leyton's studies have used PET to investigate the ability of abused substances to increase synaptic DA levels, and DA depletion to assess the behavioural and subjective effects of diminishing the ability of drugs to increase DA transmission. The PET studies suggest that, in humans, both amphetamine and alcohol — abused substances from 2 different pharmacologic classes — preferentially increase DA release in the ventral striatum. Individual differences in amphetamine-induced DA release correlate with drug-induced drug wanting and the personality trait of novelty seeking. DA depletion, as achieved with acute phenylalanine/tyrosine depletion (APTD), decreases drug wanting in cocaine users, withdrawal-related craving in nicotine-dependent smokers, and alcohol self-administration in social drinkers. In comparison, APTD did not alter self-administration behaviour in substance-dependent smokers. The results suggest that, in humans, as in other animals, interest in drug reward is closely tied to DA transmission. The relation to self-administration, though, might vary across populations: in the substance-dependent, non-DAergic mechanisms might come to play a larger role.

Dr. H. Breiter (Massachusetts General Hospital/Harvard University, Boston) gave a talk entitled "fMRI studies of human reward circuitry response to drug and non-drug stimuli." He began with an ambitious overview of models of information processing, communication and motivation, and their potential application to our understanding of the mechanisms mediating approach toward, and interactions with, rewards. Guided by these models, a series of fMRI studies have investigated the effects of social, monetary and drug rewards. In a study of social stimuli, subjects looked at faces that had been rated as being esthetically average or beautiful. Viewing the beautiful faces activated the NAcc, VTA, sublenticular extended amygdala (SLEA) and orbitofrontal cortex (OFC). The pattern of activation corresponded to subjects' choice to view the faces rather than ratings of esthetic beauty, suggesting that the identified limbic cortical–subcortical circuit might correspond to "wanting" more than "liking." A second study, conducted with Dr. P. Shizgal, employed an innovative task. Subjects were presented with 1 of 3 circles. Spinning the "bad" circle could lead to the loss of $0, $1.50 or $2.50. An "intermediate" circle produced a win of $2.50 or a loss of $1.50 or $0. The "good" circle led to wins of $0, $2.50 or $10.00. Presentation of the "good" circle activated the SLEA and OFC; namely, these regions appeared to signal expectation that reward was likely. Money won from spinning the "good" circle correlated with activity in the SLEA, NAcc and VTA. These same regions were identified during drug-challenge studies. Together, the results suggest that the limbic cortical–subcortical regions described here estimate expected probabilities of reward and punishment, affecting motivation to interact with appetitive stimuli.

On the causes of autism, Rett syndrome and other neurodevelopmental disorders

The first presentation in the symposium was made by Dr. E. Fombonne (McGill University, Montréal), who reviewed the fast-evolving field of the epidemiology of autism. A review of 35 surveys (from 1966 to 2003) covering 14 countries and populations with a median size of 66 000 published in English-language journals concluded that the prevalence of autism is 10/10 000. The ratio between pervasive developmental disorders and autism was reported to be between 1.0 and 2.1 in several studies. Childhood disintegrative disorder was reported only very rarely (< 0.7/10 000). The ratio of autism to Asperger's syndrome is estimated to be between 1.5 and 16.0. Taken together, these estimates indicate that the prevalence of pervasive developmental disorders is about 27.5 per 10 000 individuals, with the most recent studies generally reporting higher prevalence (67.5 in the study at the Child Development Centre, Derbyshire Children's Hospital, Derby, UK). The most frequently associated medical condition reported in the different surveys is epilepsy (17%). No clear association with social class, immigrant status or geographic variations was clearly demonstrated.

The question of an increased incidence of autism in recent years is currently highly debated in the litera-

ture. Dr. Fombonne pointed out that the case definition has changed over time, with the newer case definitions generally resulting in a higher prevalence of autism. Also, it appears clear that the reported prevalence of autism depends heavily on the methods of case identification. Intense screening and assessment lead generally to higher prevalence rates. Interestingly, Dr. Fombonne presented the California Client Development Evaluation Report data showing the number of people with autism over the years (from 1960 to 1990), which shows a clear increase in the absolute number of cases starting in 1978. Interestingly, when this curve is compared to the one of diagnosed cases of mental retardation, it appears clearly that the increase in the autism cases goes with a concomitant decrease in mental retardation cases, which may suggest these opposite changes may be due to changes in case recognition and labelling rather than a real change in the prevalence of autism. This conclusion is supported by prospective studies of the prevalence of autism. Indeed, Chakrabarti and Fombonne (in preparation) found no change in the prevalence of autism, Asperger's, PDDNOS (pervasive developmental disorder not otherwise specified) in 2 surveys (1992–1995 and 1996–1998) conducted in Stafford.

Another question that was heatedly debated in the recent literature is the possible association between the measles vaccine (MMR) and autism (the so-called Wakefield hypothesis). Dr. Fombonne reviewed a number of epidemiologically well-conducted studies that do not support this hypothesis.

Dr. M. Tudor, from the Whitehead Institute for Biomedical Research, Cambridge, Mass., presented an example of what could be considered the first qualitative jump in our understanding of the pathogenesis of one pervasive developmental disorder: Rett syndrome. This disorder was completely mysterious until the discovery of its causative gene (methyl-CpG-binding protein 2, or *MECP2*), coding for a methyl-CpG-binding protein, in 1999. Mutations in *MECP2* were reported in more than 80% of cases of classic Rett syndrome. MECP2 protein binds methylated CG DNA sequences and represses transcription by recruiting a histone deacetylase complex to methylated DNA. In order to understand the function of the *MECP2* gene, Dr. Tudor constructed a conditionally inactive allele and generated transgenic mice harbouring this allele. The hemizygous mutant mice developed a phenotype (seizure/tremor, breathing irregularities, cognitive impairment) at the age of 4 weeks and died prematurely at the age of 8–10 weeks. The animals presented with smaller brains with smaller neural somata and nuclei. Because *MECP2* is believed to act as a global transcriptional repressor, the transcription profile of the brain of transgenic mice was studied. Several samples from different brain regions were analyzed using Affymetrix oligonucleotide microarrays. Surprisingly, no genes were found to be differentially expressed between control and mutant mice when stringent criteria were used to define changes in expression. In a secondary analysis, it was postulated that changes in the expression of single genes may not be biologically meaningful, whereas it may be interesting to identify clusters of genes that are regulated in a coordinated way. Using supervised learning programs to classify mutant versus wild-type tissue, it was possible to identify a cluster of genes that were either downregulated (Rho GDP dissociation inhibitor gamma, serum/glucocorticoid regulated kinase, calcium channel beta 3, alpha synuclein and Fabp-7) or upregulated (parvalbumin). Remarkably, the changes in the expression of these genes were not very striking, as the ratio between the wild-type and the mutant mice ranged between 0.57 and 1.1. It was concluded that the *MECP2* mutant does not show global changes in transcription but, rather, subtle and robust low-fold changes that may be used as markers of the phenotype.

Dr. H. Fatemi (University of Minnesota Medical School, Minneapolis) presented his work on the dysregulation of the Reelin signalling system in autism. After an overall review of the cerebral and cerebellar macroscopic and microscopic anomalies observed in autism, Dr. Fatemi described several studies conducted in his laboratory indicating that the levels of Reelin and glutamic acid decarboxylase (GAD) 65 and 67 proteins are altered in autism. Reelin is implicated in a highly complicated signalling pathway that leads to the polyadenylation of spine-resident mRNA and the initiation of translation, which is necessary of synaptic plasticity. Investigation of postmortem tissues revealed that Reelin (in its different isoforms) is underexpressed in various regions of the brains of patients with autism. Interestingly, the level of different isoforms of Reelin were also decreased in the circulating blood of autistic subjects. In the second part of his presentation, Dr. Fatemi reported the results of studies investigating GAD 65 kDa and 67 kDa. These 2 enzymatic isoforms are involved in the synthesis and metabolic regulation

of GABA and show differential profiles with regard to their neural localization and functionality. Preliminary data suggest that patients with autism show decreased expression of both GAD 67 kDa and GAD 65 kDa in the parietal cortex and cerebellum. Dr. Fatemi ended his presentation by discussing these results in the context of the recent literature.

The final speaker in this symposium was Dr. L. Zwaigenbaum (McMaster University, Hamilton) who focused on recent progress in the genetics of autism. First, Dr. Zwaigenbaum reviewed genetic epidemiologic studies, the results of which strongly implicate genetic factors in autism. Then he reviewed published genome scans that allowed the identification of several chromosomal regions (2q, 13q, and 7q) likely to harbour genes that increase the risk of autism.

As an interesting strategy for the refinement of the phenotype linked to the different loci identified in linkage studies, it was noted that speech problems and delay in the "age at first phrases" may index cases with mutations on chromosome arms 2q and 7q.

In the last part of his presentation, Dr. Zwaigenbaum presented data indicating that the level of functioning as measured by IQ (using the Leiter scale) and the Vineland Adaptive Behavior scale on the one hand and behavioural symptoms of autism on the other hand may represent 2 independent dimensional phenotypes, with only the former showing familiality. Finally, Dr. Zwaigenbaum alluded to a prospective study of high-risk subjects (infants with an older affected sibling) that was initiated in their centre. It is expected that such a study will shed light on the familiality of the early phenotype such as age at onset of symptoms, age at onset of phrased speech, and the presence or not of regression.

Neurosteroids, CNS function and mood disorders

Dr. S.S. Smith (State University of New York Downstate Medical Centre, Brooklyn) discussed her work on "Neurosteroid-mediated changes in $GABA_A$ receptor subunit expression: effects on anxiety and hippocampal physiology." Chronic exposure to the neurosteroid 3α-OH-5α/β-pregnan-20-one increases anxiety in the rat and at the same time increases expression of the $GABA_A$ receptor α4 subunit. Synaptic current exhibited a faster decay and altered pharmacology, with 50% of the current insensitive to the benzodiazepine lorazepam, but potentiated by the benzodiazepine partial inverse agonist Ro15-4513. In addition to these neuronal changes, there is an increase in expression of α4βδ receptors. Following chronic steroid exposure, Ro15-4513 was anxiolytic in the elevated plus maze, but lorazepam was ineffective. These data indicate that $GABA_A$ subunit composition and function is altered by neurosteroid exposure. The results may be relevant to premenstrual dysphoric disorder (PMDD) and reflect the known insensitivity to benzodiazepines in PMDD.

Dr. A. Guidotti (University of Illinois, Chicago) presented data on the "Putative role of allopregnanolone and 5α-DHP in psychiatric disorders." Allopregnanolone and 5α-dehydroprogesterone (5α-DHP) are the 2 most important neuroactive steroids synthesized in the brain in a region-specific manner. In patients with severe depression, there is a decrease in the cerebrospinal fluid (CSF) allopregnanolone, which is normalized by drug treatment (fluoxetine). SSRIs seem to normalize CSF allopregnanolone by a direct stimulation of 3α-hydroxysteriod-oxidoreductase, the enzyme that reduces 5α-DHP to allopregnanolone. This was studied further in an animal model, using socially isolated mice that exhibit increased anxiety, aggression and decreased response to GABA-mimetic drugs. These animals exhibit a marked decrease in both allopregnanolone and 5α-DHP, which is normalized by fluoxetine. This is not related to the blockade of serotonin reuptake; ability to block reuptake is the same for S and R isomers of fluoxetine, but they differ in their effects on the neurosteroids. These data raise the possibility that a deficient production of allopregnanolone or 5α-DHP in specific brain areas may lead to mood disorders, such as the anxiety and dysphoria associated with unipolar depression and PMDD. Drugs that act on enzymes involved in neurosteroid metabolism may be useful psychopharmacologic agents.

Dr. J.M. Le Melledo (University of Alberta, Edmonton) discussed "Neuroactive steroids and human anxiety." Although extensive work is being done on the role of progesterone-derived neuroactive steroids in anxiety in animals, there is much less clinical work. One approach in humans is to use challenge studies. Three days of treatment with methoxyprogesterone decreased panic induced by pentagastrin. Another approach is to measure plasma levels of the neurosteroids in patients. This approach reveals important differences between different anxiety disorders. For example, levels of allopregnanolone were unchanged in patients with generalized anxiety disorder (GAD), social

anxiety disorder (SAD) and panic disorder. However, while pregnenolone sulphate was normal in patients with GAD and SAD, it was low in panic disorder. DHEA and DHEA sulfate were both normal in patients with GAD, SAD and panic disorder, but were elevated in post-traumatic stress disorder. It remains to be seen which of these changes are etiologic and which occur in response to the disorder.

New insights into the mechanism of antipsychotic drug action: the dopamine D_2 receptor and beyond

Dr. Philip Seeman (University of Toronto) discussed the role of the high-affinity state of the dopamine D_2 receptor in the mechanism of action of atypical neuroleptics. He initially mentioned that this functional state of the D_2 receptor was not widely studied in the nervous tissue, because ligand competition studies reveal that D_2 receptors are mostly in the low-affinity state. However, in the presence of low concentration of NaCl dopamine/ligand competition, dopamine recognizes 40% of D_2 receptors in the high-affinity state. Dr. Seeman presented data indicating that the phenomenon of amphetamine sensitization is the result of D_2 receptor conversion toward the high-affinity state, because he found the density of D_2High to be 360% higher in the striata of amphetamine-sensitized rats compared with controls. No difference between the sensitized rats and controls was observed in the total density of D_2 receptors. He also showed that anesthetics, both in vivo and in vitro, inhibit the D_2High (as well as myriad other receptors' high-affinity states). Also, subanesthetic concentrations of the anesthetics, including ketamine, were found to stimulate the incorporation of guanosine triphosphate into the cloned dopamine D_2 receptors. Dr. Seeman postulated that the classic stage 2 excitement phase, which occurs with subanesthetic concentrations of general anesthetics and ketamine, may be associated with this general stimulation of a variety of G-protein-linked receptors.

The third point discussed in this presentation is the cross talk between the D_1 and D_2 receptors, with D_1 blockade revealing the D_2 high state. Finally, it was argued that the specificity of atypical neuroleptics (compared with conventional ones) may stem from their loose binding to the dopamine D_2High receptors, because their dissociation constant is higher than the dissociation constant of dopamine to D_2High.

In the second presentation, by Dr. P Strange (University of Reading, UK), it was argued that inverse agonism of the antipsychotic drugs at the D_2 dopamine receptors may be, at least in part, responsible for their antipsychotic action. Inverse agonism refers to the fact that certain drugs are able to reduce the activity of receptor systems that are active in the absence of agonists. Dr. Strange presented experimental data using [^{35}S]GTPγS binding, potentiation of adenylyl cyclase activity and studies of the inhibition of prolactin secretion to prove that antipsychotic drugs, both typical and atypical, possess inverse agonist activity. This inverse agonistic effect was observed both acutely (as measured by immediate early gene transcription) and chronically (as measured by the upregulation of D_2 receptors in cerebral cortex). At the end of his presentation, Dr. Strange discussed the implications of these results for the mechanisms of action of antipsychotics and the development of new drugs for psychotic disorders.

Dr. P Albert (University of Ottawa) presented his work on the functional differences between the D2Long (D2L) and D2Short (D2S) isoforms. Specifically, it was shown that the D2S is more sensitive to uncoupling by acute (2-min) protein kinase C (PKC) activation than D2L. Ser228/229 was the key site for D2S PKC-induced phosphorylation and uncoupling. Differential effects on the thyrotropin-releasing-hormone-induced p42/44 mitogen-activated protein kinase (MAPK) was also observed, with D2S having inhibitory (via G alpha i3 and o) and D2L-enhancing effects. It was hypothesized that, because of its presynaptic location, its enhanced desensitization and negative regulation by MAPK, D2S could mediate the hyperdopaminergic status observed in schizophrenia.

In the last presentation of this symposium, Dr. D. Lévesque (Laval University, Quebec) discussed the possibility that some of the effects of neuroleptics may be mediated through their action on nuclear receptors. Dr. Lévesque, used nerve growth factor inducible gene B (*NGFI-B*) gene-deficient mice to investigate the effects of antipsychotic drugs that may be mediated by nuclear receptors. *NGFI-B* is a member of the nuclear receptor family highly expressed in dopamine neurons and differentially regulated by haloperidol and clozapine. It was found that mice deficient in *NGFI-B* were resistant to the cataleptic effects of haloperidol and showed a significant increment in the expression of neurotensin and enkephalin mRNA. In contrast, these animals were sensitive to the dyskinetic effects (vacuous chewing) of haloperidol compared with wild-type

mice. All these effects were reversed by retinoid ligands. Dr. Lévesque concluded that these data establish a direct link between the biologic and behavioural effects of haloperidol and *NGFI-B*.

Update on the neurobiology of suicide and related behaviours

Dr. R.J. Nelson's (Ohio State University, Columbus) talk was entitled "Using gene-knockout mice to understand aggression." As Dr. Nelson noted, the neurocircuitry mediating aggression might be similar to that related to suicidal behaviours. As a research tool, gene knockout mice have a number of advantages, particularly the specificity of the effects and the potential to identify the molecular bases of diseases. Disadvantages include the risk of gross developmental effects, high lethality, compensatory effects and the fact that knockout mice offspring are usually raised by knockout mouse mothers. Dr. Nelson's talk focused on a recently developed nitric oxide synthase (NOS) knockout mouse. NOS is necessary to synthesize NO from arginine. Male, but not female, NOS knockout mice exhibit extremely high levels of aggressive behaviour. In the males, the aggressive phenotype is expressed only if the mice are raised in isolation and only in the presence of androgens; that is, both social housing and gonadectomy prevent the effect. Serotonin (5-HT) innervation is normal, but postmortem tissue indices of 5-HT turnover are decreased in various regions, including cortex, hypothalamus, midbrain and cerebellum. Behaviour can be normalized by the administration of 5-$HT_{1A/1B}$ antagonists and the immediate 5-HT precursor, 5-hydroxytryptophan. The effect does not seem to reflect developmental or secondary compensatory responses to the genetic manipulation, because the same aggressive behaviours can be elicited by administering a NOS inhibitor. Nor does the effect seem to reflect nonspecific behavioural decrements; the NOS knockouts perform well in other tasks and better than wild-type mice in olfactory tasks. Together, these studies point toward a novel mechanism relevant for the effective regulation of aggressive behaviour.

Dr. G. Turecki (Douglas Hospital, McGill University, Montréal) gave a talk entitled "Gene changes in suicide: brain gene expression in suicide with and without major depression." Dr. Turecki presented recent work using microarray measures to assess gene expression in postmortem cortical tissue of patients, either with or without major depression, who died from suicide. The method enables one to assess the expression of many genes at the same time; it also, though, leads to complex statistical analyses of enormous datasets. Dr. Turecki's group is developing novel analytic methods for handling the data. Preliminary results are encouraging. Compared with cardiac arrest controls, both patient groups exhibited differences in gene expression throughout many regions of the frontal cortex, with more differences seen in suicide victims with major depression than without. The identified genes include some that affect previously suggested mechanisms related to suicide (e.g., genes that affect serotonin function, at least indirectly), mechanisms that had not been previously considered (e.g., genes that affect NMDA and nerve growth factors) and mechanisms that are completely novel. The results highlight the ability of these studies to refine our understanding of previously suspected mechanisms and identify completely new ones.

Dr. J.J. Mann (Columbia University, New York) spoke about "Abnormalities in brainstem related to suicide or mood disorders." As noted by the speaker, a series of postmortem studies in the 1960s and 1970s suggested that death by suicide was associated with low levels of 5-HT and 5-hydroxyindoleacetic acid (5-HIAA) levels in the brain stem. However, few of these differences were statistically significant, and it was unclear whether the association reflected suicidality or depression. An ongoing series of studies by Dr. Mann aims to address the issue more definitively. His studies suggest that there is little evidence of there being fewer or smaller 5-HT neurons in the brain stem, but there may be lower densities of 5-HT transporter mRNA and, possibly, increased expression of the type 2 gene encoding for the rate-limiting enzyme in 5-HT synthesis, tryptophan hydroxylase (TPH-2). The increased TPH-2 expression might indicate that TPH does not function normally in individuals vulnerable to suicide. Dr. Mann and his colleagues have also assessed brainstem noradrenergic function. These studies suggest that there are fewer locus coeruleus (LC) norepinephrine (NE) neurons in individuals who have died from suicide, decreased LC tyrosine hydroxylase (TH) staining in depressed patients with bipolar disorder and, possibly, increased LC TH staining in patients with bipolar disorder who died during a manic phase. Overall, the results suggest that the noradrenergic changes could be state-related (particularly in patients with

bipolar disorder), whereas the serotonergic disturbances might identify a vulnerability trait.

Dr. M. Leyton (McGill University, Montréal) gave a talk entitled "Brain regional α-[^{11}C]methyl-L-tryptophan (α[^{11}C]MTrp) trapping in suicide attempters." Dr. Leyton and colleagues recently reported that α[^{11}C]MTrp trapping, an index of serotonin (5-HT) synthesis, was decreased in the ventral and medial aspects of the prefrontal cortex of impulsive patients with Cluster B personality disorders. A post hoc analysis suggested that these levels were especially low in individuals who had made suicide attempts. The new study assessed this possibility in a prospective design. Patients were recruited and PET scanned within 2 weeks of a serious suicide attempt. Compared with matched healthy controls, the suicide attempters exhibited significantly lower normalized α[^{11}C]MTrp trapping in the medial prefrontal (PFC) and orbitofrontal cortices (OFC). The lower the α[^{11}C]MTrp trapping in the PFC and OFC, the higher the suicide intent. Follow-up studies suggested that the group differences might reflect stable traits. α[^{11}C]MTrp trapping did not change in the healthy controls and in the suicide attempters tended to decrease further in the lateral OFC. The decreases were not secondary to depressed mood; in a parallel study, depressed patients, compared with controls, exhibited decreased α[^{11}C]MTrp trapping in the rostral anterior cingulate but not the OFC; in comparison, suicide attempters exhibited low α[^{11}C]MTrp trapping in the OFC but not in the cingulate. Together, the results suggest that low α[^{11}C]MTrp trapping in ventral and medial aspects of the PFC might reflect diagnostic independent traits that increase risk for suicidal behaviour.

Emerging experimental therapies for Alzheimer's disease

Dr. S. Darvesh (Dalhousie University, Halifax) spoke about "Butyrylcholinesterase as a potential target for the treatment of Alzheimer's disease." As discussed by Dr. Darvesh, butyrylcholinesterase is an enzyme that hydrolyses acetylcholine (ACh), leading to decreased Ach. The distribution of butyrylcholinesterase is particularly dense in areas related to cognitive function. In Alzheimer's patients, butyrylcholinesterase levels are elevated and covary with neuritic plaques, neurofibrillary tangles and β-amyloid protein. In white patients with late-onset Alzheimer's, the disease might be associated with the K variant of the gene that encodes for butyrylcholinesterase. In animal studies, butyrylcholinesterase inhibitors reduce β-amyloid levels. Very preliminary clinical studies suggest that butyrylcholinesterase inhibitors might improve cognitive function in Alzheimer's patients. Together, these observations suggest that butyrylcholinesterase is a regulator of ACh transmission, is expressed in areas important for cognition and could be an important target for treating Alzheimer's disease.

Dr. J. Poirier (Douglas Hospital Research Centre, McGill University, Montréal) gave a talk entitled "APO E, cholesterol lowering agents and HMG CoA reductase in sporadic Alzheimer's disease." He began by summarizing the literature on the genetics of Alzheimer's. Although only 15% is considered familial, the apolipoprotein E4 allele (APO-E4) appears to account for 50%–60% of all cases. APO-E4, a cholesterol transporter, also affects a wide range of physiologic functions, including cholesterol homeostasis, lipid redistribution, neuronal repair, β-amyloid scavenging and maintaining the synaptodendritic cytoskeleton. During neuronal damage, astrocytes are activated, engulfing and metabolizing dead tissue and releasing cholesterol that promotes synaptic reconnections and sprouting. A cholesterol-lowering drug, probucol, increases APO-E levels in the hippocampus of aged rats. In patients with Alzheimer's disease, probucol increased CSF APO-E levels and reduced cognitive deterioration. Cholesterol-lowering drugs, it was suggested, might reduce amyloid production, slowing clinical progression in patients with Alzheimer's disease, and possibly even reduce the risk for developing the disease.

Dr. F. Gervais (Neurochem. Inc, Dorval, Quebec) gave a talk entitled "Targeting soluble Aβ for the development of disease-modifying therapeutics in AD." β-amyloid (Aβ) is a cleavage product of the amyloid precursor protein (APP). In Alzheimer's disease, Aβ production exceeds clearance. A hallmark of the disease is the production of amyloid fibrils from Aβ that form the proteinaceous core structure of senile plaques. As summarized by Dr. Gervais, studies are underway with a compound that might inhibit Aβ formation, NC-758. Preclinical studies indicate that NC-758 crosses the blood–brain barrier. Various routes of administration have similar pharmacokinetics, each exhibiting linear associations between plasma and brain levels. With repeated administration, concentrations in the brain plateau after 3 days. Plasma half-life is about 14 hours,

whereas clearance from the brain takes 48–72 hours. In rats and dogs, NC-758 is safe, well tolerated and non-mutagenic, and clinically significant effects on major organs have not been observed. It does not bind to plasma proteins, has a low volume of distribution and is not metabolized by liver enzymes, nor does it alter them. In mice treated for 8 weeks, NC-758 decreases Aβ and Aβ42 levels in plasma and Aβ levels, inflammation and microglia in the brain. Phase 1 studies suggest that the drug is safe and well-tolerated without significant changes to vital signs or laboratory tests. A Phase 2 study in patients with mild-to-moderate Alzheimer's disease has been started and will be completed soon.

Dr. P.S. Aisen (Georgetown University Medical Center, Washington DC) gave a talk entitled "Can Alzheimer's disease be successfully treated with anti-inflammatory drugs?" As summarized by the speaker, it has been proposed that an inflammatory response to β-amyloid toxicity, including microglial activation and cytokine release, might be part of the causal pathway leading to Alzheimer's disease. This hypothesis has been bolstered by a series of anecdotal reports that anti-inflammatory drugs reduce risk for Alzheimer's disease. Based on these observations, prospective, multicentre clinical trials have been initiated. The first study assessed the possible beneficial effects of prednisone, a widely used corticoid anti-inflammatory. One hundred and thirty-eight subjects were enrolled in 22 sites. No beneficial effects were found. A second study assessed the effects of more focused anti-inflammatory suppression, 2 inhibitors of COX-2, naproxen (COX-1 and COX-2 inhibitor) and rofecoxib (selective COX-2 inhibitor). Three hundred and fifty-one subjects with mild-to-moderate Alzheimer's disease were treated for 12 months. Neither treatment affected cognitive decline or other clinical measures. Despite these disappointing results, there remains the possibility that anti-inflammatory drugs diminish or delay risk of onset even if they do not benefit the currently ill. Trials are underway.

Attention deficit hyperactivity disorder: selected genes for selected behaviours

The first presentation in this symposium was made by Dr. R. Tannock (University of Toronto). This presentation complemented very nicely the plenary lecture given by Dr. Castellanos, as Dr. Tannock expanded on the notion of endophenotypes in ADHD. As indicated in the title of her presentation, "Significance of inattention, gender and working memory for genetic investigations of attention-deficit/hyperactivity disorder," Dr. Tannock is focusing on inattention symptoms as a phenotype that may be more specific for genetic studies. She initially showed that inattention has some predictive validity, because children who present with attention problems in their preschool years have more difficulty achieving the same academic levels as their peers without attention problems. Also, some data indicate that inattention, but not hyperactivity or impulsivity, clusters with neurocognitive impairment observed in ADHD. Moreover, it is well known that the most protracted symptom of ADHD is inattention, because it tends to persist until adolescence and adult age, whereas hyperactivity and impulsivity tend to decrease with age. After this introduction, Dr. Tannock discussed the notion that attention and working memory are related. Indeed, it has been proven that an overload of working memory is a source of distractibility. On the basis of these observations, Dr. Tannock proposed the hypothesis that the subgroup of patients with severe inattention, poor working memory and positive response of cognitive deficits to methylphenidate may represent a separate phenotype. Data supporting the validity of this hypothesis were then presented. A group of children with severe inattention (n = 16) was compared with a group of children with mild inattention (n = 9). Both groups consisted of children with ADHD. Both groups were impaired on tasks assessing spatial span and working memory, but the severely inattentive group showed greater impairment. Interestingly, only the severely inattentive group experienced an improvement in spatial span and manipulation (spatial working memory) under methylphenidate, with a good dose–effect curve. Additional findings from this study suggest that relatives of patients with severe inattention are more likely to have a history of ADHD, have a lower level of maternal education and are more often from single-parent families.

Dr. S.L. Andersen (Harvard Medical School, Boston) presented a provocative and stimulating work. As ADHD symptoms are mainly treated with psychostimulant drugs, which are used as drugs of abuse, the question of whether these drugs, used for therapeutic purposes in children with ADHD, may play a role of "gateway" to substance use disorders was lingering. Supporting this view, some studies have reported that,

in adult animals, chronic exposure to psychostimulants results in long-lasting enhancement of the rewarding effects of these drugs. In a series of studies using the place conditioning paradigm, Dr. Anderson showed that exposure to methylphenidate in juvenile rats increases the aversive effects of moderate doses of cocaine and reduced the rewarding effects of high doses when the animals are tested at adulthood. These behavioural effects were associated with an increased level of the CREB (cyclic AMP response element-binding) protein in nucleus accumbens, a change that was found to be associated with increased aversion to cocaine. Interestingly, these effects were observed only in males. Dr. Anderson concluded her presentation by making a parallel between her findings and clinical data indicating that children with ADHD who are treated with methylphenidate are 85% less prone to abuse drugs when they grow up compared with those who have not been treated.

The presentation entitled "Oculomotor assessment of frontal-striatal function in subtypes of ADHD," by Dr. G. O'Driscoll (McGill University, Montréal), explored eye movements in ADHD under the assumption that attention and eye movement share many of the same neural structures and that oculomotor circuits are parallel to circuits subserving motor control. Two questions were addressed: (1) do the different subtypes of ADHD have the same oculomotor performance and (2) do subtypes respond to methylphenidate in the same way? The study population that was presented consisted of 10 healthy controls, and 12 and 11 children with inattentive and combined types of ADHD, respectively. These children (all boys) were evaluated on 3 saccade tasks: reflexive, direction predictable and completely predictable saccades. ADHD children were tested after a washout period of at least 24 hours. They were then randomly allocated to receive either placebo or 0.5 mg/kg methylphenidate in a double-blind crossover design. The only statistically significant difference was a reduction of the percent of predictive saccades on the completely predictable task in children with combined-type ADHD compared with children with inattentive type and controls. Methylphenidate improved performances on the predictable task in both types of ADHD. These results were interpreted as an indication of response preparation impairment in children with combined-type ADHD, who may have greater frontal involvement in the determination of their disorder compared with boys with the inattentive subtype.

The last presentation in this symposium was made by Dr. M. Gill (Trinity College, Dublin), who presented genetic data on 270 children with ADHD and their parents. The genes that were found to be associated with ADHD were the dopamine transporter gene ($p = 0.0062$), the dopamine beta hydroxylase gene ($p = 0.002$), the dopamine receptor 5 gene (0.00005) and the synaptic associated protein 25 gene ($p = 0.01$). No association with the dopamine receptor 1, 2, 3, 4 genes and the catechol-O-methyl transferase and tyrosine hydroxylase genes were identified. It was emphasized that in spite of the small relative risk conferred by each of the associated genes (1.8–2.5), these associations may be important from a population health point of view because of the high frequency of the alleles associated with the disease (attributable fractions between 0.16 and 0.20). Dr. Gill discussed the functional significance of the different findings and pointed out that the associations of ADHD with the dopamine transporter and the synaptic associated protein 25 genes may suggest a hypodopaminergic state in ADHD, whereas the association with dopamine-b-hydroxylase suggests the opposite.

In the final part of his talk, Dr. Gill showed results from a collaborative study in which 1980 probands with ADHD and 2788 parents were genotyped with regard to polymorphisms in the dopamine receptor 5 gene. The size of this sample allowed a stratification of the sample according to ADHD subtypes. This approach showed a strong association of this gene with inattentive and combined subtypes of ADHD, but not with the hyperactive subtype. Other illustrations of the usefulness of stratifying patients according to several other clinical characteristics (comorbid disorders, family history) were presented in conjunction with the *DRD4* gene investigations.

CCNP the next generation: CCNP Travel Awardees' presentations

The symposium "CCNP the next generation" consisted of 6 short talks from research trainees who had submitted the best abstracts. The first talk, titled "Examining concurrent drug and alcohol use: implications for the neuropsychopharmacology of alcohol addiction," was given by S. Barrett (McGill University, Montréal). Self-reports by polydrug users indicated that hallucinogenic drugs attenuated the subjective effects of alcohol, cocaine-augmented alcohol craving, intake and eupho-

ria, and increased ethanol intake and euphoria were associated with methylphenidate coadministration. These results suggest that whereas 5-HT may be involved in the production of certain alcohol effects, increased dopamine is associated with heightened ethanol intake and reinforcement. The next talk, "Suppression of familiar food intake by wheel running in a model of activity anorexia," was given by A.M. Biondo (University of Alberta, Edmonton). She described an animal model of anorexia in which rats are given only 20 g of food for only 90 minutes per day. When given access to a running wheel, the animals showed a linear decrease in body weight and an exponential increase in running. Animals that were not given access to the wheel maintained their weight. Access to the wheel decreased consumption of a familiar food, although it did not affect consumption of a novel food, suggesting the development of an aversion to familiar foods. Next, M.G Legault (Queen's University, Kingston) spoke about "Impairment of cholinergic or dopaminergic neurotransmission in the striatum during the proposed paradoxical sleep window leads to deficits in learning the radial arm maze in rats." Injection of cholinergic and dopaminergic antagonist for up to 8 hours after training of rats on a radial maze, like rapid eye movement sleep deprivation, impairs performance. Scopolamine or flupenthixol infused into the dorsal striata (DS) of rats dose-dependently impaired learning, suggesting that an interplay between acetylcholine and dopamine in the DS during the proposed paradoxical sleep window plays a role in radial maze learning. M. Nishikawa (McGill University, Montréal) spoke on "Reduced human brain serotonin (5-HT) synthesis in depression using positron emission tomography (PET) and α-[^{11}C]methyl-L-tryptophan (α-MTrp)". Serotonin synthesis was measured in the brains of drug-free patients suffering from depression and healthy controls using α-MTrp as a tracer and PET. Statistical parametric analysis comparisons between patients and controls using proportional scaling revealed that depression was associated with low serotonin synthesis in the left anterior cingulate gyrus and a right prefrontal area. Hamilton Depression Rating Scale scores were negatively correlated with serotonin synthesis in the anterior cingulate gyrus and the dorsolateral prefrontal cortex. H. Xu (University of Saskatchewan, Saskatoon) gave a talk entitled "Chronic venlafaxine accelerates the recovery of hippocampal neurons from restraint stress-induced changes." Repeated restraint stress caused various changes in rat hippocampus including a decrease in cell proliferation and brain-derived neurotrophic factor (BDNF) and increased Cu/Zn-superoxide dismutase (SOD) protein and the number of Cu/Zn-SOD positive interneurons. Daily injections of venlafaxine increased the speed with which these changes reverted to normal, although the amount of Cu/Zn-SOD was still elevated after 3 weeks, even in venlafaxine-treated animals. Venlafaxine may help in the recovery of the hippocampus from stress. The final talk, entitled "Impact of selective GABA-ergic treatment on experimental induced panic," was given by P. Zwanger (Ottawa Institute of Mental Heath). A large body of evidence suggests decreased $GABA_A$ receptors and GABA concentrations in patients with panic disorder. Therefore, the anxiolytic effects of enhancing GABA function through inhibition of GABA transaminase with vigbatrin, or through inhibition of the GABA transporter 1 by tiagabine, were tested. In healthy volunteers both compounds reduced panic symptoms elicited by CCK-4. Moreover, preliminary investigations in patients with panic disorder revealed an improvement in panic and anxiety with both compounds.

Competing interests: None declared.