Centre for Addiction and Mental Health

Research Report

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Centre de toxicomanie et de santé mentale

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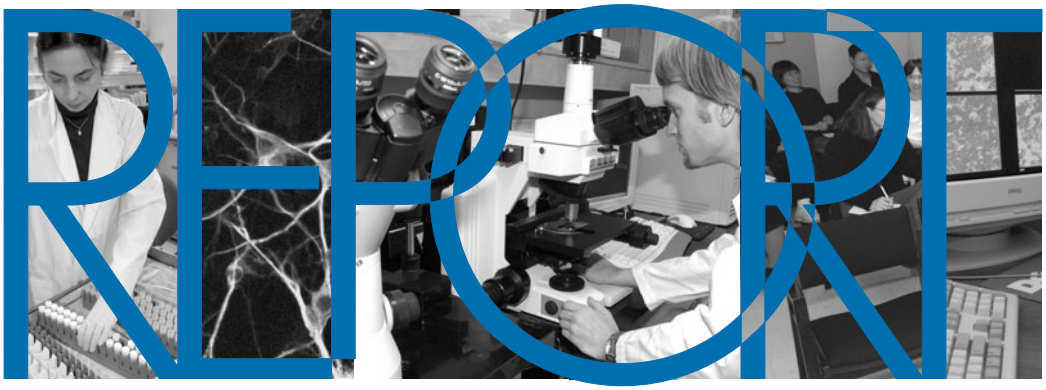

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Fax: 416 595-6881

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Ontario toll-free: 1 800 463-6273
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LETTERS

"...it is curiosity, initiative, originality, and the ruthless application of honesty that count in research—much more than feats of logic and memory alone." — Julian Huxley

The Centre for Addiction and Mental Health (CAMH) celebrated its fifth anniversary on March 8, 2003. The past five years have proven to be both challenging and exceptionally rewarding for the Research Program.

We can look back at the years since the merging of our four founding partners and recognize the opportunities that we realized, even in the context of uncertainty in the early days. During this time, our research staff and scientists continued to do what they do best: investigate, explore and discover.

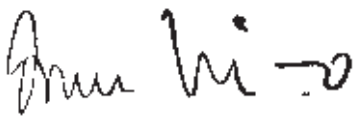
One of our goals following the merger was to create and implement a new departmental structure for the CAMH research program, to recognize biological, clinical and social levels of analysis, while also integrating mental health and addiction research. Although this was a challenging task, it was well worth the endeavour.

Over the past year, CAMH researchers have been awarded over $28 million in extramural funds—and over the past five years, more than $120 million—for research projects, studies, major equipment and other awards. As always, we are grateful to the hundreds of agencies, partnerships and philanthropic donations that have made this possible.

As we look forward to the coming years, we have set our sights on our goal of translating our research successes and findings into action for patients and clients. We will try to translate our discoveries from the bench to deliver new options and treatments at the bedside. We will also use our findings to inform our community work, health-care delivery and policy development. With these goals in mind, we hand the baton of this effort to our new incoming Vice-President of Research, Dr. Shitij Kapur.

Dr. Kapur is a psychiatrist and neuroscientist, a Canada Research Chair and a Professor of Psychiatry, recognized internationally for his work in understanding the mechanisms of antipsychotic action. His work extends from preclinical models in the laboratory to clinical research in the community. His research, which has made an important difference in the lives of people with schizophrenia, is a model for our translational efforts. His background, training, enthusiasm and energy will be ideal attributes as we take our research to the next level. Please join us in welcoming Dr. Kapur to this important leadership role.

It gives us great pleasure to acknowledge the excellent work of our researchers, and we are delighted to share with you this report that documents their achievements.



Franco J. Vaccarino, PhD
Executive Vice-President, Programs

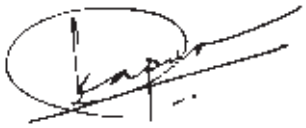
Paul E. Garfinkel, MD, FRCPC(C)
President and Chief Executive Officer

All times are interesting, but some times are more interesting than others—the field of mental health and addiction is in especially interesting times. The mapping of the human genome, the unprecedented power of neuroimaging technologies, the development of information technology that allows community-scale endeavours and the evidence-based approach to social and policy research promise great advances in the way we understand, prevent and care for substance use and mental health problems. It is thus an honour and a privilege to be chosen to lead our research efforts at such a time.

The Centre for Addiction and Mental Health (CAMH) has always been committed to research. This commitment edged a notch higher when, in our strategic plan, CAMH committed to "discovering, sharing and applying new knowledge" as one of our core goals. In meeting this goal, our researchers have kept up their efforts. Our scientists brought in close to $29 million in extramural funding for grants, contracts and awards. This accomplishment was spearheaded by two new Canada Research Chairs, awarded to Drs. Susan George and Anne Bassett. Dr. Art Petronis and I were the two recipients of the Ontario Mental Health Foundation's Special Initiative Grants, a province-wide competition addressing special opportunities in the new millennium. We enhanced our research infrastructure, by installing the world's highest resolution PET camera (HRRT) for clinical studies and by installing a new confocal scanning microscope with the help of the Ontario Innovation Trust and the Canada Foundation for Innovation. The Krembil Foundation and the CAMH Foundation provided a million-dollar award that led to the creation of the new Krembil Family Epigenetics Research Laboratory, under the direction of Dr. Art Petronis. These are just a few of the many notable accomplishments that are detailed in the pages that follow.

These successes did not happen by accident. They reflect the dedication of our scientists as well as the exemplary leadership provided by our outgoing Vice-President, Dr. Franco Vaccarino. Through a period when the four founding institutions merged to form CAMH, Dr. Vaccarino's leadership provided a steady helm as our research program organized itself, retained its scientific leaders, built capacity and secured our future. For all these contributions, thank you Franco!

This report documents the research highlights of the past year, the grants and awards received by CAMH scientists and the publications of our findings. It is a testimony to the achievements of our scientists and their dedication to discovering and applying new knowledge. The strength of their achievements and the depth of their commitment give me confidence that research at CAMH will continue to flourish—we will continue to make a difference in the lives of patients, clients, families and communities.



Dr. Shitij Kapur
Vice-President, Research

Sources of Extramural Research Funding

These organizations have generously supported CAMH's research initiative. Without their valuable funding, our advances in research would not have been possible. The Research Office gratefully acknowledges additional support from the Associates in Psychiatry.

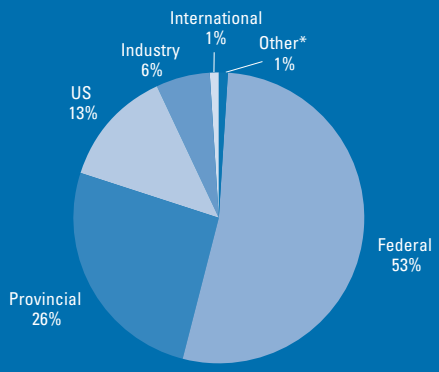
Alberta Heritage Foundation for Medical Research
Alcoholic Beverage Medical Research Foundation
Alzheimer's Association
Associated Medical Services Inc.
Bill Jefferies Schizophrenia Endowment Fund
Canada Foundation for Innovation
Canadian Mental Health Association
Canadian Psychiatric Research Foundation
Canadian Tobacco Control Research Initiative
(National Cancer Institute of Canada)
Change Foundation
Clera Inc.
Crohn's and Colitis Foundation of Canada
Cyberonics Inc.
Eli Lilly Canada Inc.
Friedreich's Ataxia Research Alliance
GlaxoSmithKline Inc.
Government of Canada
- Canadian Heritage & Multiculturalism
- Canadian Institutes of Health Research
- Canadian Institutes of Health Research, Institute of Neuroscience, Mental Health and Addiction
- Canadian Institutes of Health Research, Canada Research Chairs Program
- Canadian Population Health Initiative
- Citizenship and Immigration Canada
- Health Canada
- National Health Research and Development Fund Program
- Natural Sciences and Engineering Research Council
- Public Works and Government Services
- Social Science and Humanities Research Council

Government of Ontario
- Ministry of Community, Family and Children's Services
- Ministry of Community Mental Health Services
- Ministry of Correctional Services

Breakdown of Funding by Source

2002/2003

Federal	$15,211,032
Provincial	$7,415,844
US	$3,794,889
Industry	$1,818,892
International	$248,586
Other*	$312,071
Total	**$28,801,314**

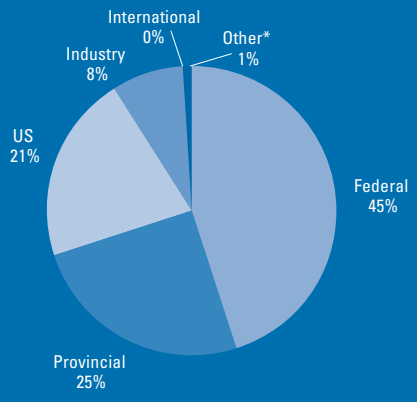


2001/2002

Federal	$12,288,174
Provincial	$6,995,445
US	$5,775,143
Industry	$2,262,987
International	$20,080
Other*	$362,283
Total	**$27,704,112**

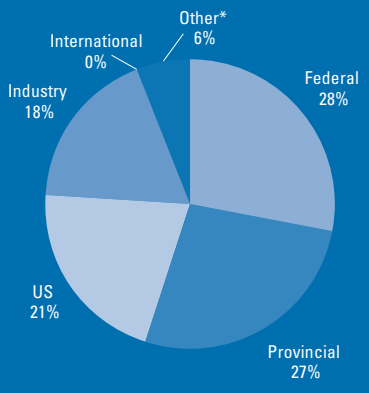
* "Other" includes all grants from Canadian universities and private (non-profit) foundations.

Ministry of Health and Long-Term Care
Ontario Research and Development Fund
Grey Bruce Huron Perth District Health Council
Hannah Institute for the History of Medicine
Heart and Stroke Foundation of Ontario
Hospital for Sick Children Foundation
International Development Research Centre
Merck Frosst Canada Inc.
Merck KGaA
Michael J. Fox Foundation
National Alliance for Research on Schizophrenia and Depression
National Cancer Institute of Canada
National Crime Prevention Centre
National Drug Council of the Cayman Islands
National Institutes of Health
National Institute on Alcohol Abuse and Alcoholism
National Institute on Drug Abuse
National Institute of Mental Health
Network of Centre of Excellence
North East Mental Health Implementation Task Force
Ontario HIV Treatment Network
Ontario Innovation Trust
Ontario Mental Health Foundation
Ontario Neurotrauma Foundation
Ontario Problem Gambling Research Council
Ontario Trillium Foundation
Pakistan Institute of Learning and Living
Region of Peel Public Health Department
Stanley Medical Research Foundation
The Bank of Sweden Tercentenary Foundation
University of Toronto
Worker's Compensation Board of British Columbia



2000/2001

Federal	$7,024,820
Provincial	$6,522,371
US	$5,056,829
Industry	$4,333,412
International	$72,643
Other*	$1,454,755
Total	**$24,464,830**



Neuroscience Research Department

DIRECTOR: Dr. James L. Kennedy

The Neuroscience Research Department seeks to understand how the brain functions in mental illness and addictions. To do this, we study all levels of the brain, from the molecules through the cells and neurons to the whole brain.

To study these levels, we focus on certain areas of research. In one area, we look at the chemicals that transfer messages from one brain cell to another, the neurotransmitters. These include dopamine, serotonin, noradrenalin and glutamate. We look at the genetic code, the "blueprints," that the body uses to manufacture different brain proteins and chemical messages. If we see a genetic variant in a group of people who have a particular addiction or mental illness, then we can study why that genetic variation might create a change in brain function, which would, in turn, result in or influence the addiction or mental illness.

Another important theme in our research is the action of medications and drugs of abuse. Understanding the details of this action could help us develop novel medications, with better efficacy and reduced side-effects.

Recently, we have made some very interesting developments in our research methods. As you will see in the following pages, we have expanded the range of animal models available to study drug response and behaviour. By administering drugs, using learning paradigms and discovering or creating genetic alterations in the animals, our researchers are revealing mechanisms of action that relate to psychiatric conditions.

For example, building on a fascinating discovery by Dr. Marla Sokolowski at the University of Toronto, investigators in the Neurogenetics Section looked at a gene that controlled fruit fly behaviour. One variant of the gene created a "rover" fly, which wandered around extensively. Another variant of the same gene determined a "sitter" fly, which did not roam around as much. This fruit fly gene, PKRG1, controls a biochemical process that has a direct parallel in humans. We tested for genetic variations in the human PKRG1 gene in people with attention-deficit/hyperactivity disorder. While our initial results have not shown an effect of this fruit fly gene in human hyperactive behaviour, it nevertheless is a fascinating model for future investigation.

We continue to use the nematode *C. elegans*, introduced into the department by Dr. Van Tol, in our studies. This tiny worm, less than a quarter of an inch long, has a very simple brain that consists of a small number of neurons. Despite its brain simplicity, the worm can still learn, for example, to turn right instead of left to find a food source. The simplicity of this tiny animal is a great help in investigating how brain cells function and how they alter behaviour, illuminating processes that are relevant to humans.

Another exciting development is the use of microarray technology. This technology allows us to investigate the activity of up to 10,000 or more genes or proteins at a time in the brain.

Neuroscience Research Department

An example of our use of microarray technology is the work done recently by Dr. Albert Wong and colleagues as a collaborative effort across the Molecular Neurobiology, Neurogenetics and Neuroimaging Sections. Dr. Wong treated a group of rats with the antipsychotic medication haloperidol. He then took portions of the brain tissue from the treated rats and compared these tissues with those from a group of untreated rats. From the comparison, he was able to create a mixture of all the message molecules from the rats' brain tissue affected by the haloperidol. He then poured the mixture over a series of microarrays—small glass wafers with thousands of genetic probes printed on them. This process allowed us to see which genes were increased and which were decreased in the rat brain following treatment with the medication. In one experiment, more than 10,000 components of the brain could be investigated; from this Dr. Wong found about a dozen genes that were significantly changed by the action of the medication.

One of these genes, called 14-3-3, was then tested in a large group of people who had been diagnosed with schizophrenia; we found that certain variants of this gene occurred more often in the group of people who had schizophrenia than in a control group of people who did not have schizophrenia. Our Neuroscience Department researchers are now trying to understand better what this 14-3-3 molecule does in the brain and how it might play a role in schizophrenia.

The use of microarray technology immediately creates an enormous amount of information. A study of 10 drugs, for example, may involve microarrays for 20,000 genes and 30,000 proteins each. Multiplication of all these numbers leads to millions of potential interactions, any one of which might be involved in a mental illness. In this context, computers and information processing are central.

This field of information management, also called *bioinformatics*, is becoming more and more critical to our activities in neuroscience research. Powerful computers and vast amounts of information from microarray methods and the human genome databases can be combined with equally vast amounts of clinical information, including lists of symptoms and

variable response to drugs, to create a massive database. Computers can then probe these enormous databases to try to find the metaphorical "needle in a haystack"—a key part of the puzzle of how the brain functions in a psychiatric disorder.

We are submitting some of our discoveries for patent protection. Patent protection encourages private companies to invest in research toward new treatments or diagnostic tests. We are fortunate to have Dr. Klara Vichnevetski providing support and guidance to our researchers in the processes of patenting selected findings. This increasing collection of patents at CAMH also represents a potential source of significant financial return for our hospital, our researchers and our laboratories.

The Neuroscience Research Department continues to work closely with the Clinical Research Department. Dr. Leslie Atkinson is leading a large team of scientists to investigate the response of young children to stress; this project may help us understand how humans develop both adaptive and maladaptive responses to stress. We are also studying childhood-onset depression, attention-deficit/hyperactivity disorder, aggressive behaviour and autism.

We are beginning to investigate ways to bring neuroscience research results to a wider population; to do this, we are collaborating on education programs and joint research with the Social, Prevention and Health Policy Research Department. For example, we may conduct large-sample surveys that ask questions such as, "If we developed a blood test that could tell you if you were at risk for an addiction, how valuable would this be?" or "If a test could predict your risk for depression, would you ask your doctor for it?"

Meaningful discoveries in the molecules and mechanism of the brain can be used to develop new treatments for mental disorders and addictions. In the Neuroscience Research Department, one of our great strengths is that we are able to interact with clinical researchers. We expect that our discoveries at the laboratory bench will have applications in which predictive tests and new treatments can be evaluated at the bedside and the clinic. These evaluations will then be brought back to neuroscientists to help us refine our experiments, offering progressive improvements to psychiatric care.

Biobehavioural Pharmacology

SECTION HEADS: Drs. A.D. Le & Denise Tomkins

THE RESEARCH GOALS OF THE BIOBEHAVIOURAL Pharmacology Section are: to understand the underlying behavioural and neurobiological mechanisms that initiate and maintain alcohol dependence; and to use this understanding to explore therapeutic agents for treating alcohol dependence. The majority of our research focuses on issues related to alcohol's reinforcing ability and relapse to alcohol drinking behaviour, with an emphasis on the role of stress in relapse. We continue to explore the role of specific central neurochemical systems in regulating these behavioural processes, in addition to examining the possible role of genetic factors involved in problem drinking and concurrent problems with other substances, such as nicotine.

Neurobiological Mechanisms of Stress-Induced Relapse to Substance Use

Our research has focused on the mechanisms underlying relapse to alcohol or other drug use caused by stress. Our working hypothesis has been that exposure to stress produces behavioural disinhibition (loss of control), which leads to relapse to substance use.

We have found that, in rats, the median raphe nucleus plays a critical role in stress-induced relapse to alcohol use. This brain area sends projections containing the neurotransmitter serotonin throughout the limbic system (a brain system that underlies emotion and learning).

While serotonin originating from the median raphe nucleus is important in stress-induced relapse, we found that another neurotransmitter, GABA, also has a critical role in relapse to alcohol. Injection of the drug muscimol, an agonist of $GABA_A$ receptors, into the median raphe caused reinstatement of alcohol-seeking. We also found that injecting bicucculine, a blocker of $GABA_A$ receptors, into the medial septum (a limbic brain structure involved in behavioural inhibition) also modestly reinstated alcohol-seeking. This is further evidence that the GABA system is involved in relapse. Changes in the activity of a direct or indirect GABA-containing projection between the median raphe and the medial septum may underlie these effects.

Our preliminary data show that direct injection of muscimol into the median raphe also activates *c-fos*, a marker of activated neurons, in various brain structures in a way that is similar to that induced by exposure to footshock stress. We believe that the observed effect on relapse to alcohol induced by injection of muscimol into the median raphe is due to its impairment of inhibitory control rather than through effects on incentive mechanisms, as the results of conditioned place preference testing did not indicate that injections of muscimol into the median raphe were rewarding.

Interaction between Alcohol and Nicotine

We have also furthered our research into the co-abuse of alcohol and tobacco. We have previously shown that repeated exposure to nicotine can enhance alcohol self-administration in rats.

Using our animal model of relapse, we have found that treatment with nicotine can also promote relapse to alcohol, by producing alcohol-seeking in animals whose alcohol self-administration has been extinguished. In animals that have previously experienced both alcohol and nicotine, injection of nicotine potently reinstated alcohol-seeking.

The results from these studies have strong implications for the treatment of concurrent alcohol and tobacco addiction.

5-HT Receptor Subtypes and Alcohol Reinforcement Processes

Studies in humans and animals suggest that the central neurotransmitter, 5-HT, is associated with problem alcohol use and dependence. We continue our work to assess how modulating activity at various 5-HT receptor subtypes affects alcohol self-administration behaviour. Through this work, we hope to better understand the neurobiological mechanisms underlying excessive alcohol consumption.

One receptor of particular interest is the $5\text{-}HT_{1B}$ receptor. Human studies suggest that a locus predisposing people to antisocial alcoholism is linked to the $5\text{-}HT_{1B}$ receptor gene.

Previously, we clearly demonstrated that $5\text{-}HT_{1B}$ receptors play an important role in regulating alcohol intake in our animal models. Over the past year, we have extended these findings by exploring the behavioural basis of this phenomenon, as well as the specific brain areas that regulate it. Our data suggest that $5\text{-}HT_{1B}$ receptors are important for regulating both the initial drive to obtain alcohol as well as its consumption, particularly in highly motivated animals. Furthermore, we have now confirmed that two brain areas, the amygdala and the ventral tegmental area, are important in mediating these effects. Interestingly, activation of $5\text{-}HT_{1B}$ receptors within the ventral tegmental area leads to decreased alcohol intake, while in the amygdala, the same manipulation leads to increased alcohol intake. This difference in action shows that the regulatory effect of $5\text{-}HT_{1B}$ receptors within the brain is site-specific.

The collection of data on the amygdala is particularly intriguing, as very few reported pharmacological manipulations have increased alcohol intake in animal models. Our findings may suggest that the amygdala exerts an important modifying influence on alcohol consumption under normal circumstances. Because this brain area has been linked with

mediating the conditioned effects of psychoactive drugs that may elicit craving in humans, it is interesting that 5-HT_{1B} receptors also modify motivation to obtain alcohol in our animal models.

The 5-HT_{2C} receptor is also of interest to us. We previously reported a role for 5-HT_{2C} receptors in tonically regulating alcohol intake.

Recently, we have been trying to find how other members of the 5-HT_2 receptor family may modify the motivation to consume alcohol, by comparing our previous findings with those elicited by 5-HT_{2A} and 5-$HT_{2B/2C}$ manipulations. Our data demonstrate that 5-$HT_{2A/2B}$ receptors do alter alcohol intake; however, this alteration only occurs when the receptor is activated, not inhibited, and is most likely due to non-specific effects. Taken together, these findings suggest that, in this family of receptors, only the 5-HT_{2C} receptor constantly modulates alcohol intake.

We are continuing this line of research in the hope of better understanding the neural circuitry that helps regulate drinking behaviour.

$GABA_A$ Receptor Subunits, Drinking Behaviour and Voluntary Intake

Compelling evidence suggests that central GABAergic systems play an important role in regulating alcohol's effects, particularly those effects mediated via the $GABA_A$ receptor.

We continue to investigate regional differences in the expression of the $GABA_A$ receptor subunits. These differences have been demonstrated in the brains of high-alcohol preferring rats, and humans with drinking problems; therefore, they may represent one of the neurobiological factors underlying problem alcohol use.

The data generated thus far demonstrate that regional differences in $GABA_A$ receptor expression and subunit conformation affect drinking behaviour. We have found that these differences also affect the binding profile of some pharmacological agents that interact with this receptor complex, including muscimol, flunitrazepam and diazepam, but not others, such as zolpidem. There appears to be a complex interaction between inherent alcohol preference, alcohol drinking history and the binding ligand employed.

Currently, we are analysing and interpreting the extensive database generated over the last year. Our data will provide important insights not only into the genetic and non-genetic $GABA_A$ receptor influences on alcohol preference and consumption, but also into potential interactions with, and/or influences over, other clinically used pharmacological agents that interact with this receptor complex, such as the benzodiazepines.

Sex Differences in Susceptibility to Alcohol-Induced Cognitive Deficits

To develop more effective treatment and prevention strategies for problem alcohol use in women, we must conduct basic research on the differences in alcohol's effects on brain function in men and women.

Clinical evidence suggests that women are more vulnerable to some of the negative effects of alcohol than men. While tests of psychomotor performance have consistently reported that men and women are equally impaired by alcohol ingestion, women appear to be more sensitive to the cognitive deficits induced by long-term alcohol exposure, particularly on tasks demanding divided attention or delayed recall.

Over the past year, we have continued to explore the long-term effects of alcohol exposure on cognitive function and behaviour, with specific emphasis on potential differences in susceptibility between males and females.

To support the clinical relevance of our experimental approach, we showed that, similar to humans, chronic alcohol exposure caused equal impairment of female and male rats

on measures of psychomotor performance. As predicted from the human literature, female rats showed greater impairments on measures of delayed recall compared to their male counterparts when chronically exposed and then withdrawn from alcohol. Alcohol-exposed female rats also demonstrated a blunted response for obtaining a sweetened food reward compared to males. One possible interpretation of this finding is that alcohol exposure has elicited a dysphoric state in the females but not the males. We are interested in this difference because, clinically, women are more likely to present with concurrent alcohol problems and depression than are men. Currently we are examining the brain mechanisms that may potentially explain these sex differences.

In our work, we hope to unravel some of the gender differences in susceptibility to alcohol-induced cognitive impairments and uncover the role of $GABA_A$ receptors in these impairments. Ultimately, this research could help identify risk factors, protective factors and treatments for alcoholism that are specific to women.

THE BIOPSYCHOLOGY SECTION STUDIES THE biological foundations of normal and abnormal behaviours relevant to psychiatry. Our work focuses on the role that brain neurotransmitter systems—particularly the serotonin and dopamine systems and the interactions between these systems—play in controlling behaviour. We mainly use pharmacological and/or lesioning procedures to manipulate specific aspects of neurotransmitter function and to observe the resulting changes in behaviour. Our work includes studies of the neurochemical mechanisms involved in addictive behaviour, cognitive behaviour relevant to schizophrenia and impulsive behaviour.

Serotonin Receptors and the Effects of Drugs of Abuse

Dopamine has been the neurotransmitter most closely linked to the behavioural and neurochemical effects of drugs of abuse. However, manipulating serotonin (5-HT) function also leads to changes in the behavioural effects of drugs of abuse.

In recent years, we have shown differing roles of two serotonin receptor subtypes, the $5\text{-}HT_{2A}$ and $5\text{-}HT_{2C}$ receptors, in modulating effects of cocaine. We have found that activating the $5\text{-}HT_{2C}$ receptor reduces the locomotor stimulant and reinforcing effects of cocaine. Blocking this receptor leads to the opposite profile of effects. In contrast, blocking the $5\text{-}HT_{2A}$ receptor reduces the stimulant effects of cocaine. In interpreting these results, we are trying to find whether the effects of $5\text{-}HT_{2C}$ receptor agonists and antagonists alter the effects of other types of reinforcers, or whether they are specific to drug reinforcers.

We now have shown that, while the $5\text{-}HT_{2C}$ agonist also reduces the reinforcing effects of food, the $5\text{-}HT_{2C}$ antagonist does not enhance the reinforcing effects of food. The former effect is consistent with the notion that elevations in serotonin result in a generalized reduction in motivated behaviour. However, the latter finding implies that reducing serotonin

We have found that treatment with nicotine can also promote relapse to alcohol.

transmission via the 5-HT$_{2C}$ receptor may have an effect that is restricted to cocaine.

Amphetamine Sensitization and Schizophrenia

Dr. Fletcher is part of a large, multidisciplinary project, led by Dr. Shitij Kapur (Schizophrenia Research Section), that received funding from the Ontario Mental Health Foundation to investigate amphetamine sensitization as a model for schizophrenia. Part of the rationale for this study is the observation that repeated psychostimulant use can induce psychosis in humans. In the Biopsychology Section, we will first examine whether amphetamine sensitization results in cognitive deficits that are also found in schizophrenia.

We have focused our attention on measuring changes in three behaviours; these behaviours are impaired in some people who have schizophrenia. The first is prepulse inhibition of the acoustic startle reflex, which reflects abnormal sensorimotor gating. The second is latent inhibition, which measures the ability to tune out, or ignore, irrelevant stimuli. The third can loosely be described as "cognitive flexibility," which is measured in humans by the Wisconsin Card Sorting Test.

Our results to date strongly indicate that amphetamine sensitization markedly disrupts these behaviours; this disruption is analogous to the disruptions that are observed in schizophrenia. Our results suggest that amphetamine sensitization appears to be a valid model for cognitive disturbances in schizophrenia.

In our future work, we will examine whether deficits caused by amphetamine sensitization can be reversed by antipsychotic drugs, and we will explore the neurobiological changes that may underlie these deficits.

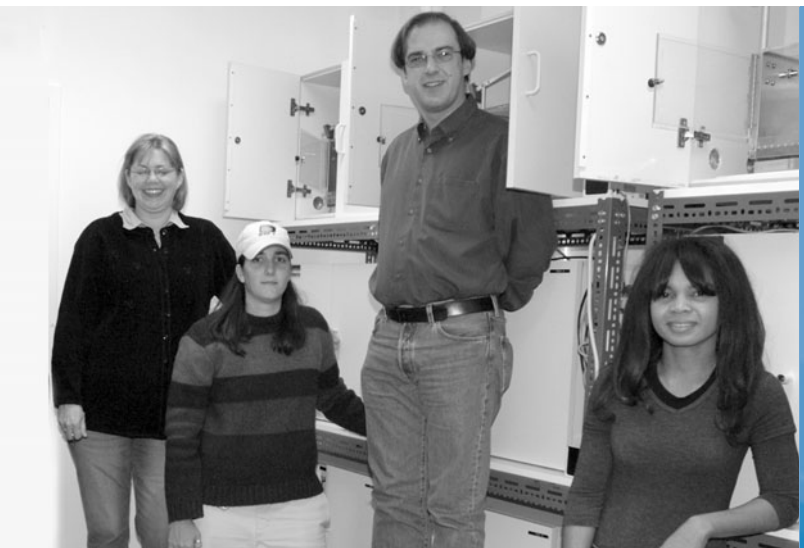
Serotonin and Impulsivity

Impulsive behaviour is associated with reduced serotonin function, both in humans and in animals. However, we know little about which areas of the brain are involved in mediating impulsive behaviour, or which serotonin receptors are involved. We continued to explore both questions in the past year.

We compared the effects of lesioning either the prefrontal cortex or the nucleus accumbens to deplete serotonin innervation of these areas in tasks where subjects receive food reinforcement if they show a degree of inhibitory control. Our results to date suggest that depleting serotonin in the nucleus accumbens, but not the prefrontal cortex, leads to reduced inhibitory control.

In a second project, in collaboration with Dr. Guy Higgins (Schering-Plough Research Institute, New Jersey), using subjects receiving reinforcement for inhibitory control, we have found that 5-HT$_{2A}$ receptor antagonists reduce impulsive behaviour, but 5-HT$_{2C}$ receptor antagonists enhance this behaviour. Overall, our findings suggest that the relationship between reduced 5-HT activity and impulsivity is complex and may depend on which brain areas and which receptor subtypes are affected.

Our observation that 5-HT$_{2A}$ and 5-HT$_{2C}$ receptors have opposing influences on impulsive behaviour is similar to our finding that these receptors exert opposing influences over the expression of cocaine-mediated effects. This work is beginning to reveal the diversity and complexity of 5-HT receptor function at the behavioural level.



Clinical Neuroscience

SECTION HEAD: Dr. Usoa Busto

THE CLINICAL NEUROSCIENCE SECTION CONDUCTS human experimental research to better understand the different factors that influence substance use and dependence as well as other forms of compulsive or addictive behaviour such as gambling. These factors can relate to the drug, the host and the environment.

HOST FACTORS CONTRIBUTING TO SUBSTANCE USE DISORDERS

Dr. Usoa Busto

WE CONTINUE OUR RESEARCH INTO HOST FACTORS contributing to substance use disorders, including multiple drug use, psychiatric comorbidity and genetics.

Depression and Dopaminergic Pathways

Ongoing studies in this area continue to examine the role of the brain reward system in major depressive disorder (with Drs. Claudio Naranjo, Helen Mayberg and Simon Graham). We have shown that the brain reward systems (mesocorticolimbic dopaminergic pathways) are altered in people who are severely depressed and that specific areas of the brain are involved in the response to a dopaminergic probe.

Nicotine and Depression

The role of nicotine in modulating symptoms of depression in depressed smokers and non-smokers is another area under active research (with Drs. Laura Cardenas, Martin Zack, Sylvain Houle, Shitij Kapur and Helen Mayberg). Data from ongoing positron emission tomography (PET) studies show that dopamine release in depressed smokers is significantly lower compared to depressed non-smokers. This difference suggests the possibility of a hypofunctional mesocorticolimbic dopaminergic system (Cardenas et al., 2002).

Dr. Peter Selby and colleagues have also received funding to train professionals to be more effective in treating nicotine dependence. We now have a protocol approved to examine the mechanisms of craving for nicotine in both current and abstinent smokers (with Drs. Selby and Laurie Zawertailo).

Brain Responses to Amphetamine and Hydromorphone

This year, we completed a neuroimaging study showing that changes occur in specific areas of the brain in the response to amphetamine (Tremblay et al., 2003, in preparation).

Other research in humans has shown that oral d-amphetamine administration is associated with a prolonged displacement of [11C] raclopride, which is sustained at six hours post-drug (Cardenas et al., in press), even though the subjective effects of the drug dissipate within three hours. This finding demonstrates longer-term effects of d-amphetamine on dopamine release than has been previously demonstrated.

We also completed a study using hydromorphone as a probe for the dopaminergic and opioid systems. Results suggest that hydromorphone acts differently from amphetamine on dopaminergic/opioid pathways—in people with depression, hydromorphone caused a reported decrease in negative symptoms (e.g., sedation) and little change in positive symptoms.

Hypnotic Medications in Older Adults

We continue to study the effects of hypnotic medications in older adults (with Drs. Beth Sproule and Nathan Herrmann), in the hope of learning more about age as a host factor for substance use problems.

In our comparison of prescription versus non-prescription sleeping medications, we have shown that valerian produced effects that were similar to placebo. We have concluded that valerian, when compared to a benzodiazepine and an antihistamine, is not an effective medication to help older adults with sleep problems (Glass et al., in press). We are currently

conducting a larger trial comparing the benzodiazepine with the antihistamine.

Prescription Drug Dependence

We have received approval for a novel adjunctive treatment for opioid dependence, using the NMDA antagonist dextromethorphan to alleviate withdrawal and tolerance. We also plan to further examine the mechanisms of craving in people who are opioid-dependent using functional magnetic resonance imaging (F-MRI) of brain activity (with Drs. Simon Graham and Laurie Zawertailo).

Abuse Liability of Drugs

The intrinsic pharmacological characteristics of drugs of abuse (such as potency, the ability to produce reinforcing effects and drug kinetics) are essential to drug-taking behaviour. One line of our research looks at the comparative abuse liability of available drugs and new compounds.

We have recently completed a study examining the comparative pharmacology, behavioural effects and abuse potential of heroin and hydromorphone in human subjects (with Drs. Bruna Brands and David Marsh), and we have funding for another crossover study of hydromorphone in people who are opioid-dependent (with Drs. Brands and Marsh). We also plan to expand our research to study aspects of alcohol dependence, such as gender differences in cognitive effects of alcohol (with Drs. Denise Tomkins, Constantine Poulos, Martin Zack and Laurie Zawertailo).

PHARMACOLOGICAL MODULATION OF ADDICTION-RELATED COGNITIVE NETWORKS AND RELATED PROCESSES

Drs. Martin Zack & Constantine X. Poulos

THE MAIN FOCUS OF OUR RESEARCH IS TO LEARN how addiction-related memory structures are activated, and how this activation underlies and interacts with the motivation or craving to engage in addictive behaviour, comorbidity factors (e.g., concurrent addiction and mental health problems), environmental factors (e.g., stress) and, in some cases, measures of addictive behaviour itself.

As we examine the key processes of activation and inhibition, we look at ways in which medications, alcohol, other drugs and addictive reinforcers like gambling alter semantic memory structures in healthy people and in people with addictive disorders. We are trying to determine if addiction-related disturbances contribute to deficits in self-regulation by activating or by inhibiting the cognitive processes that maintain regulation under normal circumstances. Activation of semantic memory networks is important for three reasons. 1) It occurs involuntarily and, in some cases, without conscious awareness. 2) It can bias decisions and overt behaviour toward addictive reinforcers and away from adaptive alternatives. 3) It can be measured simply and accurately, using response time tasks administered by computer. For these reasons, studying the activation of semantic memory networks is a useful way to define the motivation behind addictive behaviour.

We have developed a procedure, called The Lexical Salience Task, to assess the effect of a *pharmacological* prime rather than a verbal prime on substance use or other addictive behaviour. For example, if activation of brain catecholamines contributes to the motivation to gamble, this procedure can show us if the difference in reading speed to gambling words

In our comparison of prescription versus non-prescription sleeping medications, we have shown that valerian produced effects that were similar to placebo.

(e.g., wager) versus neutral words (e.g., window) is greater under a dose of the catecholamine agonist, amphetamine, than under placebo. Similarly, if activation of brain GABA transmission contributes to motivation to drink, the difference in reading speed to alcohol words (e.g., beer) versus neutral words (e.g., board) should be greater under a dose of the GABA agonist, diazepam, than under placebo. We have investigated these two areas in the research projects outlined below.

The Role of Dopamine in Gambling

In a previous study, we found that, in people who have gambling problems, amphetamine: primes gambling cognitions; inhibits neutral cognitions; increases urge to gamble; and decreases confidence to avoid gambling. Amphetamine had no such effects in controls.

Although dopamine is the primary neurochemical activated by amphetamine, amphetamine also activates other neurochemicals, including norepinephrine and serotonin.

In our current study, we hope to isolate the role of dopamine in motivation to gamble, gambling-related cognitions and actual betting behaviour in people who have gambling problems. We will assess the ability of the selective dopamine antagonist, haloperidol, to reduce desire to gamble and gambling-related semantic activation induced by a brief gambling episode in problem gamblers and in age- and gender-matched controls. We will also investigate the effects of dopamine blockade on patterns of betting behaviour during the gambling episode.

We predict that, relative to placebo, haloperidol will reduce post-gambling desire to gamble as well as activation of gambling cognitions on The Lexical Salience Task. If dopamine also influences patterns of gambling behaviour, haloperidol should dampen the overall escalation in bet size and reactivity to wins and losses that characterize problem gambling behaviour.

This project is funded by a grant from The Ontario Problem Gambling Research Centre.

Priming Effects of Benzodiazepines on Alcohol-Related Cognitions and Drinking Behaviour

This project examines the priming effects of two benzodiazepines on automatic alcohol-related cognitions and drinking behaviour in people who have drinking problems. We will compare the effects of diazepam, a drug with high abuse liability, with those of clonazepam, a drug with low abuse liability. We will also examine how drug dose, severity of alcohol problems and the degree of co-existing anxiety affect cognitive and behavioural responses to these drug probes. Our findings will lay the foundation for future research with other pharmacological probes to better characterize the specific neurochemical substrates of motivation to drink in people who have drinking problems and varying degrees of anxiety.

Preliminary data indicate that low-dose diazepam (5 mg) primes alcohol-related cognitions on The Lexical Salience Task. The degree of lexical priming also predicts the volume of beer consumed in a taste-test drinking procedure (cf. Marlatt et al., 1973). In addition, the degree of priming correlates with the severity of alcohol use, as measured by drinks per week. Drinks per week did not mediate the correlation between lexical priming and taste-test drinking.

Consistent with a previous study (Zack et al., 1999), high-dose diazepam (15 mg) significantly reduced the ability of negative-affect words (e.g., tense) to prime alcohol-related cognitions (e.g., beer) in a conventional lexical decision semantic priming task in drinkers with no history of benzodiazepine use. Notably, diazepam had no effect on neutral, categorical priming (e.g., cat-dog), and negative-affect alcohol priming was clearly evident under placebo.

Together, these diazepam data indicate a homeostatic priming and satiety process, moderated by dose, in people who have drinking problems. The findings corroborate the utility of drug priming of addiction-related memory networks as a means of assessing medications that may reduce problem drinking. This procedure may be especially useful for investigating individual differences in the neurochemical basis of alcohol priming to predict which medication(s) will be beneficial to a particular profile of drinking problem.

Effects of Alcohol on Stress-Induced Cognitive Activation in Young Drinkers

This project is being carried out in collaboration with Dr. Colin M. MacLeod of the Department of Psychology at the University of Toronto.

We are building on previous grant-funded research to evaluate the effects of alcohol on automatic alcohol- and anxiety-related cognitions, induced by a stressor, in university undergraduates with high or low anxiety sensitivity. People who have high anxiety sensitivity are more likely to use alcohol to cope with negative mood states; they have higher rates of drinking problems than do people who have low anxiety sensitivity. The current study will determine the possible mediating role of semantic network dampening in the negative reinforcing effects of alcohol in high-anxiety-sensitive drinkers.

Initial data indicate that, relative to placebo, a moderate dose of alcohol (BAC = .06%) primes alcohol-related cognitions in low-anxiety-sensitive but not in high-anxiety-sensitive drinkers. Relative to a soft drink, placebo alcohol

(de-alcoholized beer) reduces activation of anxiety-related and alcohol-related cognitions in both low- and high-anxiety-sensitive subjects.

If these preliminary results persist when the sample is complete, they will provide a basis for examining interventions to modify alcohol-induced and expectancy-related memory activation in young people at risk for alcohol problems (cf. Breslin, Zack & McMain, 2002).

This project is funded by a grant from The Alcoholic Beverage Medical Research Foundation.

Deficient Inhibitory Control and MDMA

This study is being carried out in collaboration with Dr. Paul Fletcher of the Biopsychology Section. Dr. Stephen Kish (Human Neurochemical Pathology Laboratory) and Dr. Constantine X. Poulos (Clinical Neuroscience Department) are consultants.

Chronic use of 3, 4-methylenedioxymethamphetamine (MDMA, ecstasy) has been linked with lasting damage to brain serotonin (5-HT) neurons in rodents and non-human primates. People who use MDMA consistently display deficits in memory, which correlate with deficits in 5-HT function. Although some research has found impulsivity in chronic MDMA users, these previous findings are of limited value, as study participants used a variety of other psychoactive drugs as well as MDMA.

In this study, we are trying to assess fully the cognitive inhibitory processes involved in impulsivity in MDMA users and to determine the impact on impulsivity of prior MDMA versus other drug use.

We have assessed three groups of subjects: (1) people who use MDMA plus low levels of other substances (the normative pattern of MDMA use), (2) people who use marijuana-only and (3) drug-free controls. We are also testing a fourth group (4) people who use MDMA plus marijuana-only (a minority of MDMA users).

All subjects were drug- and alcohol-free at the time of testing. They had been abstinent from all drugs for at least five days, as verified by urinalysis. Assessment of hair samples will verify drug use in the six months preceding testing.

The data in hand suggest that, across a range of tasks, people in the marijuana-only group show as much or more impulsivity as do the people who use MDMA plus other drugs. Both of these groups tended to be more impulsive than controls, although the differences were not consistent. In contrast to these group mean results, correlational analyses indicated a consistent positive correlation between lifetime use of MDMA (tablets) and impairment on the various tasks, whereas level of marijuana use was unrelated to impairment on any task.

These results suggest that, in chronic MDMA users, prior use of marijuana may contribute to some observed deficits in impulse control, but also that heavier MDMA use is associated with poorer impulse control. Because levels of MDMA and marijuana use were not inter-correlated, these substances may exert separate adverse effects on impulse control. However, marijuana is retained in the body long after ingestion, so the results may be affected by residual or hangover effects of recent use (i.e., one week pre-testing). We plan to assess prior users of MDMA and marijuana-only users with at least six months abstinence to clarify the lasting effects of these drugs on impulse control.

This project is funded by the CAMH Grants in Psychiatry program.

We predict that, relative to placebo, haloperidol will reduce post-gambling desire to gamble as well as activation of gambling cognitions.

Human Neurochemical Pathology Laboratory

SECTION HEAD: Dr. Stephen Kish

THE MANDATE OF THE HUMAN NEUROCHEMICAL Pathology Laboratory is to understand the causes of neuropsychiatric disorders by examining the human brain.

We continue to focus on studies of brain monoamine neurotransmitter systems in people who use amphetamine derivatives (including ecstasy) and in people with Parkinson's disease.

Ecstasy

Ecstasy is a widely used amphetamine derivative taken for its mild stimulant property and for its ability to increase the desire for friendliness.

We initiated a neuroimaging investigation, using positron emission tomography (PET) to determine if ecstasy causes brain damage in young users of the drug. All subjects were tested by forensic hair analysis to confirm that the person actually used the drug (rather than another drug or combination of drugs sold as ecstasy).

We found the following:

1. Many people in the Toronto area who assume that they are using only ecstasy are unknowingly using more dangerous drugs (including other amphetamine derivatives), which "contaminate" the "ecstasy" tablets. The general public needs to be educated more about the lack of consistency in the quality of "ecstasy" that is being sold.
2. Our forensic drug hair analyses suggest that most, but not all, ecstasy users respond, to the best of their knowledge, truthfully to questions about past drug use.
3. Although rare, a very small number of people in the Toronto area can be identified as using ecstasy in the absence of other drugs that cause brain damage.
4. We have conducted brain scans of a small number of these "pure-ecstasy users" and have preliminary data about ecstasy's ability to damage brain serotonin neurons. A large replication study is now in progress.

Parkinson's Disease

Parkinson's disease (PD) is a movement disorder commonly associated with clinically significant depression.

Recent studies now confirm the clinical impression that the depression in PD affects the quality of life of the patient more than the motor disability.

Based on the longstanding hypothesis that a brain serotonin deficiency might be responsible for the depression in PD, we conducted a PET investigation to measure the number of serotonin neurons in people with PD who are depressed.

Contrary to the hypothesis, our preliminary data suggest that people with PD who are depressed, who are early in the course of their disorder, do not show a reduced number of brain serotonin neurons. A replication study is in progress.

Laboratory of Cellular and Molecular Pathophysiology

SECTION HEAD: Dr. Jerry Warsh

RESEARCH IN THE LABORATORY OF CELLULAR AND Molecular Pathophysiology Section investigates the cellular and molecular processes that lead to the development of the major psychoses, principally bipolar affective disorder. We also explore the molecular pharmacology of current mood stabilizer and antidepressant medications to understand their mode of action, in hopes of finding more specific cellular targets for drug action against which new drugs can be developed. The research team includes Dr. Jerry Warsh, clinician scientist, Dr. Peter Li, senior basic scientist, and their graduate student and postdoctoral trainees.

Our team is internationally recognized for groundbreaking, innovative research on intracellular signalling abnormalities; these abnormalities are now recognized to play a critical role in the predisposition for, and development of, bipolar I disorder.

The closer we come to understanding the specific chain of cellular disturbances that lead to bipolar disorder, the more effectively we can work to develop new strategies to treat and prevent it. To reach our goals, we have set up new equipment and are developing techniques to measure cellular changes in patients. This measurement infrastructure will help us translate our research findings into clinical tests, which may make it easier to diagnose subtypes of bipolar disorder and guide the choice of mood-stabilizer medications in treatment. Our research also sets the stage for the development of new drugs to treat this disorder and prevent relapses.

The important directions of the research in the section have been recognized in recent research grants from the Canadian Institutes for Health Research, the Ontario Mental Health Foundation and the National Alliance for Research in Schizophrenia and Depression.

cAMP Signalling System and Bipolar Disorder

During the past year, we elaborated more in-depth details of the nature and extent of abnormalities in the cyclic adenosine monophosphate (cAMP) signalling system in brain of people with bipolar disorder. These abnormalities appear to funnel through a key receiving protein, cAMP-dependent protein kinase. This protein "translates" dissonant signals into cellular signalling cascades. The resilience of cells in brain tissue can be affected if the cAMP signalling system is disrupted.

We have found key evidence that cAMP signalling is increased in bipolar disorder in specific brain regions involved in mood regulation. Also, the target protein (cAMP-dependent protein kinase) changes its composition, levels and response in a way that may be maladaptive.

The patterns of changes in cAMP-dependent protein kinase suggest that the processes that regulate its composition and positioning have been changed in a way that affects its breakdown in brain neurons. This is a second, key piece of evidence we have found, suggesting that altered proteomic mechanisms are likely involved in the development of bipolar I disorder.

Calcium Signalling in Bipolar Disorder

We continue our in-depth analysis of parts of the intracellular calcium signalling system, which is also disturbed in bipolar disorder. Calcium signalling also plays critical roles in maintaining the resilience of cells: disruption of calcium signalling can lead to cell death. The abnormalities found in the cAMP signalling cascade in bipolar disorder take on even greater importance in light of their relationship with calcium signalling: there are several bridging points at which cAMP signalling modifies what the calcium signalling systems are doing.

Molecular Pharmacology of Mood Stabilizers

Investigations on the molecular pharmacology of mood stabilizers have led us to identify several novel genes that are regulated by long-term lithium treatment. One of the genes codes for a key enzyme in the metabolism of a type of sugar, inositol; inositol is converted to chemical messengers, the high-energy inositol polyphosphates. The other gene encodes a membrane-spanning protein that may act as a "signal complex," co-ordinating the localized formation of signalling lipids and the positioning of the target signalling protein, protein kinase C, at the inner side of nerve cell membrane.

These observations have uncovered previously unknown targets of lithium. Because these targets are affected in the same range as the blood levels achieved during lithium treatment, they are likely related to lithium's therapeutic actions.

Molecular Neuroscience

SECTION HEAD: Dr. Hubert H.M. Van Tol

THE GOAL OF THE MOLECULAR NEUROSCIENCE Section is to understand the mechanisms by which neural communication takes place. We seek to understand the molecular components involved in communication between neurons, how these components may contribute to mental illness and how they serve as therapeutic targets.

The section has four principal investigators directing their own research groups. Dr. Hubert Van Tol is a University of Toronto Professor in the Departments of Psychiatry, Pharmacology and Institute of Medical Science, and Canadian Research Chair in Neurobiology (tier 1). Drs. Fang Liu and Albert Wong are University of Toronto Assistant Professors in the Department of Psychiatry, and Dr. Xian-Min Yu is an Assistant Professor at the University of Toronto Faculty of Dentistry.

Our investigators use molecular, genetic, biochemical and electrophysiological approaches to study the molecules involved in neuronal signalling. Our scientists mainly use in vitro approaches and model systems, including transgenic mice and the nematode *C. elegans*, for their research. We collaborate with other scientists—usually from the Neurogenetics Section at CAMH—to extend our findings to human disease.

We associate with many neuroscientists in Toronto (http://www.uoftphysiology.com/neurosciencenet/governance.html) and outside Toronto; we are also members of the CIHR group The Synapse (http://www.utoronto.ca/synapse/).

MOLECULAR NEUROBIOLOGY I

Dr. Hubert H.M. Van Tol

THIS GROUP FOCUSES ON THE DOPAMINE SIGNALLING system in the central nervous system. The dopamine signalling system is often considered the origin of, and/or one of the main targets for therapeutic intervention for, the symptoms of several psychiatric and neurological disorders, including schizophrenia, bipolar disorder, Huntington's disease, Parkinson's disease, Tourette's syndrome, addictions and attention-deficit/hyperactivity disorder. We hope to understand the individual components involved in the dopamine signalling system, so we can evaluate how the system contributes to development of disease, improve therapeutic interventions and minimize treatment side-effects.

In our current research, we are trying to unravel the intracellular signalling pathways that mediate the effects of dopamine.

Intracellular signalling cascades are initiated through the interaction of dopamine with a specific receptor on the plasma. In humans, five different dopamine receptors have been identified. These receptors mediate different physiological and biochemical effects, but are all members of the so-called G protein-coupled receptor (GPCR) family.

New research by our group has revealed that these GPCRs, particularly the dopamine receptor subtypes that are targets for antipsychotic medication, can activate growth factor receptors, such as the platelet-derived growth factor receptor beta. Growth factor receptors are critical for the development, survival, differentiation and synaptic plasticity of neurons.

This was a novel observation; however, we did not know its relevance in vivo. In collaboration with Dr. John F. MacDonald (Department of Physiology, University of Toronto), we found that transactivation is also critical for the mechanism by which dopamine receptors can reduce N-methyl-D-aspartate (NMDA) receptor activation in hippocampal and cortical neurons. We continue our studies to understand the mechanism by which dopamine receptors modulate NMDA receptor activity. The NMDA receptor is an ion channel that is activated by the major neurotransmitter glutamate, and it is known to be critically involved in synaptic plasticity, learning and memory and has been strongly implicated in psychosis. Our work identified a novel signalling

cascade by which antipsychotic medication may modulate NMDA receptor signalling.

G protein-activated inwardly rectifying K+ channels (GIRK; a.k.a. Kir3) are known effectors of dopamine receptors. These channels regulate the excitability of the cell and play an important role in the feedback regulation of dopamine release. We still do not know the precise nature of the channel-receptor relationship. We used molecular and biochemical approaches to show that the dopamine receptor and GIRK channel form a stable complex early during their synthesis. The observation that the receptor-channel complex is stable may help us understand how temporal control of synthesis of the individual components regulates GPCR-activation of different signalling pathways. We continue to investigate the molecular determinants of this interaction.

MOLECULAR NEUROBIOLOGY II
Dr. Fang Liu

OUR LAB CONTINUES TO FOCUS ON THE MOLECULAR mechanisms by which G-protein coupled dopamine D1 receptors exert functional cross-talk with NMDA receptors. Previously, we found that dopamine D1 receptors modulate NMDA glutamate receptor-mediated functions through a direct interaction of these two proteins. One interaction is involved in the inhibition of NMDA receptor-gated currents, and the other is implicated in the attenuation of NMDA receptor-mediated excitotoxicity.

The D1 receptor subtype is not a target for classic antipsychotic medication, but has been shown to play a role in working memory. This subtype is often thought to contribute to the "negative" symptoms of schizophrenia, which are not readily treated with classic antipsychotic medication.

The NMDA receptor is one of the ligand-gated ion channels that is activated by the major excitatory neurotransmitter glutamate. Functionally, this ion channel is implicated in synaptic plasticity, learning and memory, but it also plays an important role in excitotoxicity and stroke. Psychotropic drugs like phencyclidine (PCP), that mimic schizophrenic symptoms, are known blockers of NMDA receptors. Furthermore, genetic disruption of the gene encoding this channel in mice results in animals that exhibit behaviour changes related to schizophrenia.

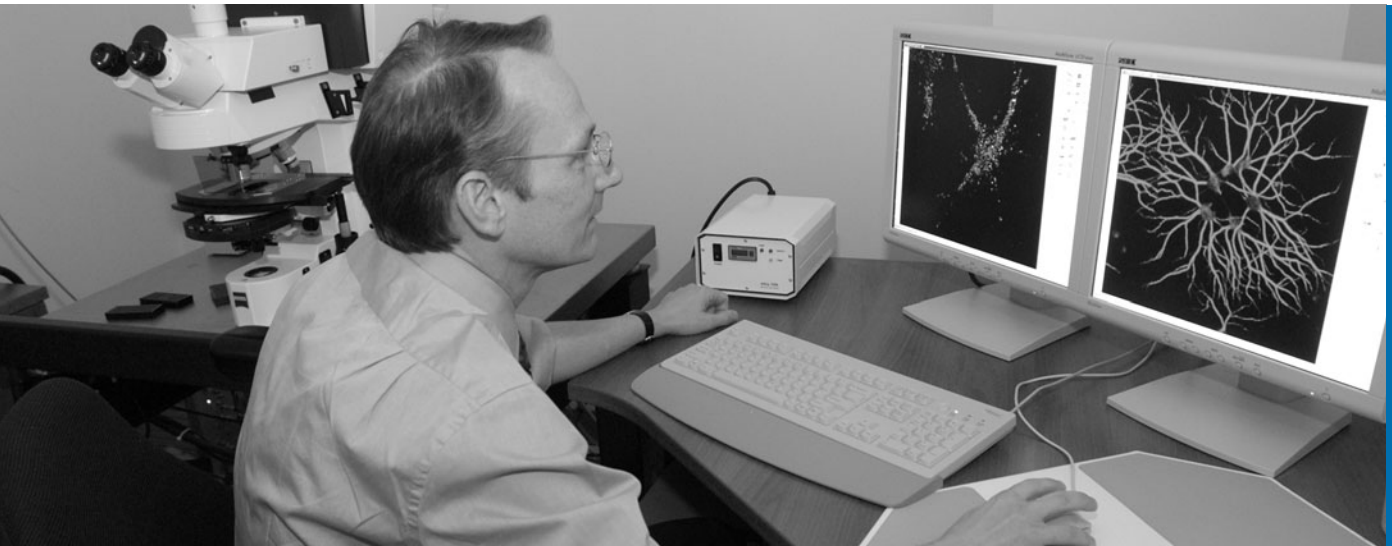
Our ongoing study appears to be the first to provide the possible functional implications of inhibition of the NMDA-mediated cell death without jeopardizing NMDA-mediated excitatory neurotransmission, which is essential for maintaining the normal function of the central nervous system. Thus, the selective modulation of multiple NMDA receptor-mediated functions by direct interactions with D1 receptors may form a new avenue to identify specific targets for drug development to modulate NMDA receptor-governed synaptic plasticity, neuronal development and disease states.

MOLECULAR PHYSIOLOGY
Dr. Xian-Min Yu

OUR RESEARCH FOCUSES ON THE REGULATION AND biophysics of the NMDA receptor, one of the ligand-gated ion channels activated by the major excitatory neurotransmitter glutamate. As indicated above, this ion channel is implicated in synaptic plasticity, learning and memory, excitotoxicity and stroke, and schizophrenia.

Complementary to our investigations on the organization and function of the NMDA receptor signalling complex, we continue to collaborate with Dr. Fang Liu in studies of NMDA channels and their interaction with D1 dopamine receptors (see Dr. Fang Liu).

We continue to study how kinase, kinase activator(s) and kinase substrate(s) may exist in the same complex and



how this structure affects the initiation and maintenance of the constitutive regulation of NMDA receptors by Src family PTKs.

Our earlier research shows that NMDA channel activity is sensitive to intracellular sodium ion concentrations and that this sodium sensitivity of the channel was regulated by Src kinases.

We continue to study how, during NMDA receptor activation, Na+ influx may enhance Ca2+ influx and remove Ca2+ influx induced-inhibition of NMDA receptors by remote NMDA.

MOLECULAR PSYCHIATRY

Dr. Albert H.C. Wong

SCHIZOPHRENIA IS A COMPLEX GENETIC DISORDER best reflected by a multiplicative multilocus model. Its complexity is a huge challenge for genetic studies, a challenge best met by using candidate gene analysis in family-based association studies. Candidate genes for these studies are mainly selected on the basis of their role in development or the functioning of the dopamine system or on the basis of being a target for drugs inducing psychosis. Current molecular technologies, particularly micro-array technologies, allow for the rapid screen of the expression of many genes.

Our research aims to discover factors that contribute to the development of schizophrenia. Our main approach is to use rodent models for schizophrenia and post-mortem brain tissue of schizophrenia patients to identify genes that are altered in their expression and are consequently considered candidate genes underlying the disorder. Once identified, these candidate genes are further analyzed in human genetic studies. Genes with an altered expression in schizophrenia may be labelled as candidate disease genes.

This approach led to the discovery of 14-3-3eta and syntaxin1a. Both these genes demonstrated a genetic association with schizophrenia. These genes affect the release of brain chemicals and are also involved in brain development. Now, our studies are looking into how these genes lead to schizophrenia.

Molecular Pharmacology

SECTION HEADS: Drs. Susan R. George and Brian F. O'Dowd

IN THE MOLECULAR PHARMACOLOGY SECTION, WE continued our research on the biology of neurotransmitter receptors for the G protein-coupled receptors (GPCRs) for dopamine, opioids and apelin. In this work, we focus on the ability of the receptors to interact directly with each other to alter pharmacology and signal transduction. We have also continued investigating D1, D3 and D5 receptor-gene-deleted mice to analyze the role of the individual receptors in discrete behaviours.

Our search for novel human genes continues; in this past year we identified novel orphan receptors and a mutated receptor in the human population. These genes, potential candidate genes in neuropsychiatric disease, will now be included in the search for and development of diagnostic tests or novel drugs.

We have also developed a novel cell-based assay, which has several components. This assay can, for example, perform rapid screening for compounds targeting GPCRs, including the many orphan GPCRs we have identified. The assay can also screen for receptors or proteins that interact with each other.

During the past year, we have submitted 19 papers for publication; 11 of these papers have now been published.

Receptor Biology

Our laboratory previously discovered that receptors for neurotransmitters, such as dopamine, function not as individual molecules, but as highly ordered complexes on the cell surface. This discovery has been shown to be true for many members of the family of GPCRs and is probably universal. We also discovered that individual receptors formed complicated higher-order structures with other receptors, greatly enlarging the complexity of novel functional therapeutic targets in the brain.

We continue to investigate receptor-receptor interactions, and the sites of interaction between two receptors has been precisely identified to involve specific transmembrane regions. Previously, we studied dopamine and opioid receptors, finding that they form homodimeric and heterodimeric (i.e., mixtures of receptors) complexes. We have shown the existence of these receptor complexes in cultured living neurons and human and rat brain by immunocytochemistry and state-of-the-art confocal microscopy. Using confocal microscopy, we are studying further the colocalization of the receptors, not only within single neurons, but also within cellular microdomains of the neurons. Our work has revealed that hetero-oligomerization of receptors may generate novel pharmacological and functional properties and that hetero-oligomerization is a specific process, with rules governing which receptors participate in the hetero-oligomeric complex.

Novel GPCR Assay

We have developed a novel method incorporating a strategy suitable for the identification of chemicals interacting with or modifying the activity of both known and orphan GPCRs, transporters and other plasma membrane receptors. The method will also allow us to evaluate the ability of GPCRs and transporters to selectively oligomerize with other GPCRs, transporters or other proteins to generate novel heteromeric drug targets. We will use this assay method to screen for novel compounds and to identify the dimerization partners of various receptor proteins.

Novel Receptor Genes

We continue to discover novel GPCR genes and to identify novel orphan receptors.

As orphan receptors we cloned are being identified, such as GPR 7 and 8, it is apparent that these are completely novel ligand-receptor systems. Identifying the receptor and its endogenous ligand will now allow us to elucidate its physiological effects and functions.

One of the first receptors we identified was the apelin receptor, which is highly expressed in brain. We have recently completed studies showing localization of the apelin receptor in human brain regions, with a unique nuclear localization within the neuron, highly novel for GPCRs. This suggests unique functions for this receptor, as the vast majority of other GPCRs are located on the cell surface; this receptor will be the focus of detailed study in future.

We are searching through genomic databases and DNA of people with neuropsychiatric diseases for mutations and polymorphisms in the receptor genes that may predispose humans to disease. Recently we discovered a mutated GPCR that was present in a highly significant percentage of the population, including those with and without a neuropsychiatric disease. The prevalence of this mutation is the highest among documented receptor mutations; we plan to study the functional significance of this mutation and its role in mental disorders.

More excitingly, as we uncover the functions of additional orphan receptors, we will be able to elucidate distinct novel CNS functions, the role of the receptors in CNS disorders may become apparent, and the receptors may be targets for the development of new therapeutics.

Role of Receptors in Behaviour

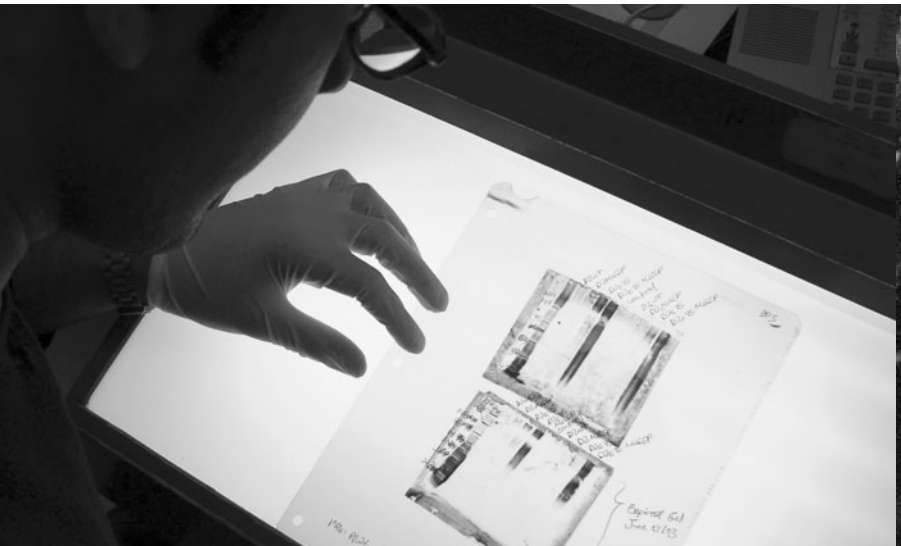
Our analysis of the effects of receptor gene deletions on specific brain functions has helped us understand the role of the receptors in important higher level functioning, with specific corollaries to several human CNS disorders. To explore the functional role of specific dopamine receptors, we studied various receptor gene knockout models for the functional consequence of deletions of the D1, D3, D5 and D1+D3 receptor genes.

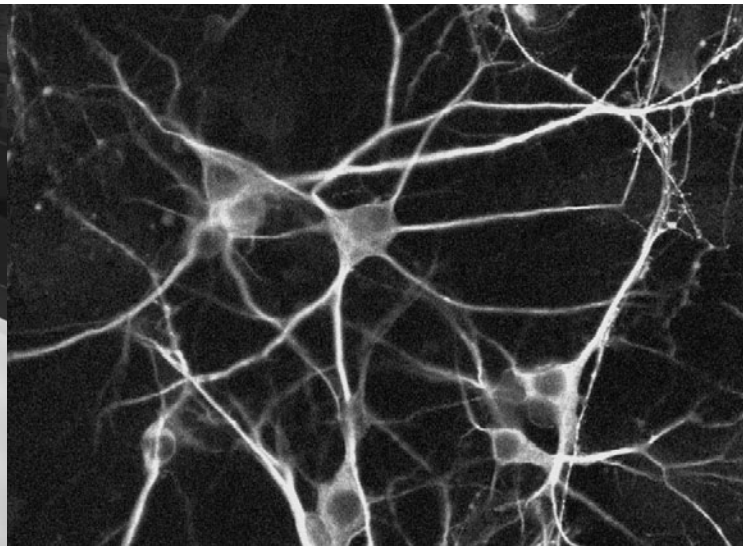
The localization of the D1 dopamine receptor in the hippocampus prompted us to analyse learning and memory processes in the D1-deleted mice.

Our results showed that their fear conditioning responses were intact, although the extinction of the fear memory was abnormally prolonged compared to their wild-type littermates. This finding suggested a role for the D1 receptor in promoting the extinction of fearful memories, with implications for human disorders such as abnormal fear/anxiety states and post-traumatic stress disorder. These mice also show a markedly reduced motivation to work for rewarding stimuli.

To our knowledge, this was the first demonstration of a single gene disruption that has resulted in specific attenuation of drug-seeking and pleasure-seeking behaviour and enhancement of fear memory.

Because the D3 dopamine receptor is colocalized with the D1 receptor in the nucleus accumbens, we studied D1 receptor mediated functions in D3-/- mice, and generated double-gene-deleted animals, deficient in both D1 and D3 receptors. We continue to study the interaction of these receptors to regulate exploratory behaviour and gene expression in specific brain regions.





Neuroimaging

SECTION HEAD: Dr. José N. Nobrega

RESEARCH IN THE NEUROIMAGING SECTION IS AIMED at mapping changes in specific brain areas, neuroanatomical pathways and chemical mechanisms in neuropsychiatric disorders, primarily through the use of appropriate animal models. In 2002, we focused on three broad areas.

MODELS OF DEPRESSION AND STRESS REACTIONS

Learned Helplessness Model of Depression

We continue to test genes identified by cDNA microarray analyses in brains of animals showing propensity to develop depressive-type symptoms in response to stress, using the *learned helplessness model of depression*. This behavioural model also allows us to identify subjects that are resistant to stress-induced reactions.

Our current data indicate that different sets of genes may be associated with propensity versus resistance to stress-induced behavioural deficits. While a number of candidate genes have proved to be false positives in this model, our PhD student, Beatrice Setnik, using in situ hybridization, has identified the first clear changes in gene expression in the frontal cortex of susceptible animals.

Because human females are more prone to depressive episodes than males, we have extended the behavioural model to include gender comparisons. Our initial behavioural evaluations of female animals at different points in the estrous cycle did not reveal significant differences.

We have, however, uncovered a significant overall difference between males and females in effects of stress on plasma levels of homocysteine (Hcy), an amino acid that has been associated with symptoms of depression, stress effects and cardiovascular risk. We found that, while males have higher basal Hcy levels than females, females appear to be more vulnerable than males to stress-induced elevations in Hcy.

Chronic Mild Stress Model of Depression

Using the *chronic mild stress model of depression*, we began to examine possible changes in the GABA-benzodiazepine receptor complex, seeking to isolate anxiety-related components of this model. This work is being conducted in collaboration with Dr. Nylson Silveira-Filho's group at the Federal University of São Paulo, Brazil. An extensive autoradiographic mapping analysis, using [3H]Ro-154513 to label diazepam-insensitive benzodiazepines binding sites, suggested that behavioural changes in this model are not likely to be mediated by alterations in this binding site.

Sleep Deprivation and Depression

We continue to study sleep deprivation, seeking to identify mechanisms involved in its beneficial (antidepressant) effects as well as in its potentially harmful effects. In collaboration with Dr. Sergio Tufik's group at the Federal University of São Paulo, we found that sleep deprivation was followed by localized changes in the expression of b1 thyroid hormone receptors in brain, suggesting a potential involvement of these receptors in antidepressant effects.

We also conducted the first detailed examination of the serotonin transporter in the brain after sleep deprivation, using [11C] DASB. In this collaboration with Dr. Alan Wilson from the PET Centre at CAMH, we developed and validated experimental protocols for the use of short-lived PET tracers in in vitro autoradiographic analyses.

This overall approach is now being extended to other areas, such as the preclinical imaging of potential PET probes for markers of pathology in Alzheimer's disease. This extension is part of a larger effort led by Dr. Paul Verhoeff of the Baycrest Geriatric Centre.

In 2002, we published evidence that sleep deprivation, unlike stressful procedures in general, has unexpected beneficial effects on blood levels of homocysteine. High blood levels of

homocysteine (Hcy) are a risk factor for cardiovascular disease. Stress increases Hcy levels, but sleep deprivation decreases Hcy levels in blood.

On the other hand, we confirmed that sleep deprivation negatively affects the acquisition of a simple avoidance learning task, an effect that was blocked by muscarinic agonists. A detailed autoradiographic analysis indicated that this behavioural effect was not mediated by changes in the muscarinic M1 receptor binding in the brain.

We also completed an extensive examination of two receptors for orexin (hypocretin), a neuropeptide that has been identified a key element in narcolepsy. In situ hybridization analyses revealed that both orexin1 and orexin2 receptors are significantly altered after sleep deprivation. Changes in the expression of the two receptor subtypes were different in kind from each other and were noticed in different parts of the brain. These receptor expression changes were not seen immediately after deprivation, but were seen after the animals were allowed to recover lost sleep for one day.

BRAIN DOPAMINE AND MOVEMENT DISORDERS

Paroxysmal Dystonia

We continue to collaborate with investigators from Germany to build a comprehensive map of brain alterations in *the dt^{sz} mutant hamster model of paroxysmal dystonia*. This year we have identified significant changes in the hamsters' expression of the mRNA encoding two important neuropeptides in the basal ganglia circuits controlling movement, namely enkephalin and dynorphin.

Tardive Dyskinetic Syndromes

Our study continues of the *VCM model of tardive dyskinetic syndromes* induced by long-term antipsychotic treatment. Work published by Peter Turrone, a PhD candidate, in collaboration with Drs. Gary Remington and Shitij Kapur from the Schizophrenia Section, shows that, after long-term haloperidol treatment, variables such as dose and of continual drug availability affect the likelihood that dyskinetic symptoms will emerge. Long-term treatment by single daily injections produces fewer motor side-effects than are seen when the same daily doses are given by continuous release (e.g., via osmotic minipumps).

We believe these effects may relate to sustained versus discrete occupation of D2 receptors by antipsychotic medications, and we are currently testing this hypothesis on other antipsychotic drugs.

BRAIN MECHANISMS OF COMPULSIVE DRUG-TAKING

Behavioural Sensitization to Alcohol

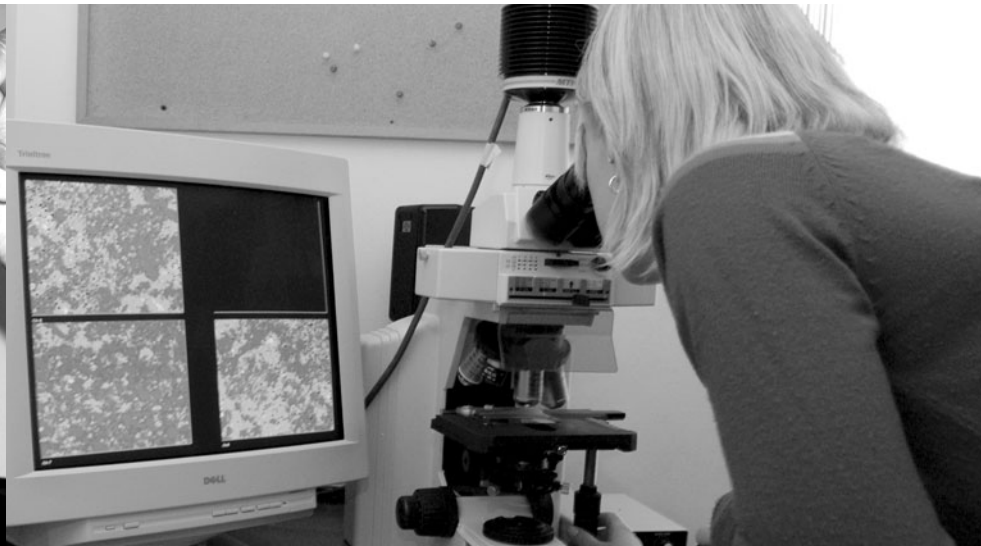
We continue to study the brain mechanisms underlying differential susceptibility to behavioural sensitization to alcohol.

This year, we found that alcohol-sensitized mice have higher [^{3}H] flunitrazepam binding levels in the ventral tegmental area—an important region of the mesocorticolimbic pathway—than do non-sensitized animals. These binding differences may have functional correlates, because our sensitized mice also showed an enhanced locomotor response to a benzodiazepine challenge.

In a separate study, we examined the relationship between ethanol sensitization and learning variables. The results show that the development of ethanol sensitization seems to be positively associated to contextual learning. This confirms that the expression of sensitization depends heavily on contextual cues.

GABA Receptor Changes and Alcohol

In collaboration with Drs. Denise Tomkins (Biobehavioural Pharmacology) and Rachel Tyndale (Pharmacogenetics), we began analyses of GABA receptor changes in brains of two types of rats: one that shows innate high preference for alcohol and one that shows innate low preference for alcohol.



Pharmacogenetics

SECTION HEAD: Dr. Rachel F. Tyndale

PEOPLE HAVE GENETIC DIFFERENCES IN THE AMOUNT and type of drug-metabolizing enzymes they produce. Genetic variation can cause people to metabolize drugs slowly or quickly, resulting in wide ranges in levels of drugs and drug metabolites (products of drug metabolism) among different people. Such variations can result in therapeutic failure and unanticipated toxicity.

Researchers in the Pharmacogenetics Section are interested in genetic variations in enzymes and the effect these variations can have on the metabolism of drugs of abuse. Specifically, we are investigating how genetic variations in drug metabolism affect the pharmacology of specific drugs, the risk for specific drug dependencies and the amount of a drug used by people who are dependent on it (pharmacogenetics). We investigate this using studies involving abuse liability, and epidemiological, genetic, biochemical and therapeutic intervention studies.

At the same time, we are examining how exposure to drugs of abuse may alter or regulate the levels of metabolizing enzymes. These studies use humans and animal models combined with behavioural, biochemical, immunological and molecular biological techniques. We hope that our studies will help us to develop novel approaches to identify and treat people who have a high risk for substance dependence.

Our data illustrate how genetic variation in drug metabolism, such as the inactivation of nicotine or alcohol, can alter the risk for becoming dependent on nicotine or alcohol. We can now initiate studies where we manipulate the activity of an enzyme (e.g., with inducers or inhibitors) to imitate the protection from drug dependence found in the genetic studies.

This year, we also published a number of reviews on pharmacogenetics and drug dependence, as well as a review on the potential roles of CYP enzymes within the brain.

Variation in Nicotine Metabolism

Much of our recent work has focused on how genetic variation in the inactivation of nicotine affects aspects of smoking.

Nicotine is the psychoactive substance (drug) responsible for tobacco dependence; smokers adjust their cigarette consumption to maintain nicotine levels in the brain. In humans, 80 per cent of nicotine is metabolized to the inactive metabolite cotinine.

In our earlier work, we identified and characterized the liver enzyme responsible for this metabolism as the genetically variable CYP2A6. Genetic variation in this enzyme results in slower nicotine removal, prolonged higher brain levels of nicotine and, consequently, decreased smoking. People with defective CYP2A6 were protected from becoming tobacco-dependent and may be at lower risk for cancer due to both decreased smoke exposure and decreased activation of tobacco smoke procarcinogens.

We are studying the role of genetic variation in adults who have already become, or have not become, smokers. In addition, through collaborations in Montreal and California, we are investigating how variable metabolism of nicotine alters the development of nicotine dependence and smoking behaviour. In one study, we have been following adolescents as they learn to smoke; in another, we are studying college students and their smoking behaviours.

Recently, we have been identifying novel defective alleles in this gene. In 2002, we published the characterization of three new gene variants that also alter nicotine metabolism. Many more uncharacterized variants are likely to exist and remain to be investigated. We investigate these novel alleles in a number of ethnic populations as the frequency of a specific form of the enzyme can be very different among different groups.

We can mimic the effect of defective CYP2A6 by administering inhibitors of the enzyme. We have shown that use of an inhibitor can decrease the amount smoked and also decrease the amount of procarcinogen activation.

We have just completed a study of CYP2A6 in collaboration with a group in Kansas City, demonstrating that people who are slower nicotine metabolizers are able to quit smoking more effectively than those with more rapid metabolism. This increases our evidence that inhibiting the enzyme, thereby decreasing nicotine metabolism, may be useful for helping people quit smoking.

Variations in Alcohol Metabolism

In addition to the CYP2A6 gene, we continue to study the genetics of other CYP enzymes, including CYP2E1. CYP2E1 is able to metabolize alcohol and is thought to play a role in metabolizing different compounds in the brain.

We have found that people with a specific genetic form of this enzyme, when exposed to ethanol or other inducers, make much more of this enzyme. Our genetic studies have also shown that these people are more likely to become dependent on alcohol and also on nicotine. Again, like CYP2A6, the frequency of genetic variants for CYP2E1 varies substantially among ethnic groups.

Variations in MDMA Metabolism

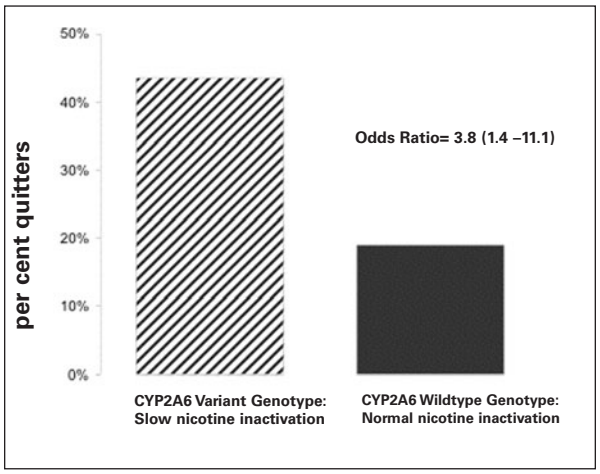
This year, we also discovered that a number of "designer drugs" and clinically used drugs are potent inhibitors of specific drug-metabolizing enzymes. A commonly used recreational drug, MDMA (ecstasy), is metabolized very differently among people with different genetically variable enzymes.

Enzyme Variations in the Brain

In addition to our genetic studies, we have studied the presence and regulation of drug-metabolizing enzymes in the liver and brain. In the brain, we have used animal studies and human autopsy tissues to show that both nicotine and alcohol can profoundly alter the levels of these enzymes and that the effects of these drugs are very different in different parts of the body.

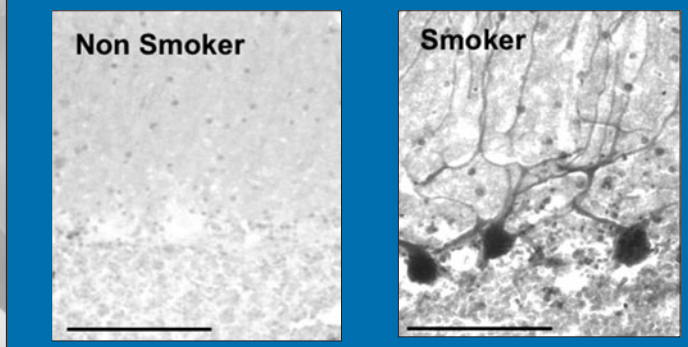
We have characterized the distribution in rat and human brain of three important enzymes, CYP2B6, CYP2E1 and CYP2D6. We found that the enzymes can be increased or decreased in rat brain by exposure to nicotine or alcohol and that the enzymes are higher or lower in brains from humans who were smokers or alcohol-dependent.

Besides alcohol and nicotine, these enzymes can activate or inactivate many drugs that act in the brain (e.g., antidepressants, neurotoxins); having more or less enzyme in the brain may alter the amount of active drug or neurotoxin in this organ. People who smoke or are alcohol-dependent may, therefore, have altered responses to drugs that act in the brain and may be more or less susceptible to neurotoxins. These enzymes may play a role in some of the psychiatric diseases where certain pathways in the brain are damaged (e.g., alcoholism, Parkinson's disease, Alzheimer's disease).



▲ People with genetically slow nicotine inactivation are almost four times more likely to successfully quit smoking than are people with normal rates of nicotine inactivation.

▼ CYP2B6, which metabolizes many drugs of abuse, clinically used drugs and neurotoxins, is found at higher levels in cerebellar Purkinje cells in smokers compared to non-smokers. Bar: 100mm.



Psychiatric Neurogenetics

SECTION HEAD: Dr. James L. Kennedy

Schizophrenia

The neurodevelopmental hypothesis of schizophrenia suggests that structural abnormalities of the brain, acquired during the development of the central nervous system, are responsible for the susceptibility to develop schizophrenia later in life. These structural abnormalities lead to the dysfunctional connectivity ("wiring") of several areas of the brain affected in schizophrenia.

The brain-derived neurotrophic factor (BDNF) is a protein molecule that plays an important role in the development and survival of dopaminergic and serotonergic neurons. Animal models of schizophrenia show altered expression of the BDNF gene: mice that were deprived of BDNF exhibit abnormalities of dopaminergic and serotonergic systems. Antipsychotic and antidepressant medications appear to affect the activity of the BDNF gene. All these pieces of evidence have led us to study BDNF as a genetic risk factor in schizophrenia.

Our first analysis of a study on families, consisting of a schizophrenia patient and both parents, collected from Italy and the Toronto area, shows an association between a DNA variant in the BDNF gene and schizophrenia. We then extended this study to additional variations of the BDNF gene and to a larger collection of these triad families, and also to families that consist of subjects with a mood disorder and their parents.

We are excited that our new analyses on new samples of patients and families continue to show association between two BDNF gene variations (and their combination, i.e. haplotype) and both schizophrenia and bipolar disorder. These findings suggested that BDNF could be a common genetic risk factor both for schizophrenia and for mood disorders.

The investigation of BDNF in schizophrenia has led to a publication in *Molecular Psychiatry* (Muglia et al., 2002) and our strong results for BDNF in bipolar disorder were published in *The American Journal of Human Genetics* (Neves-Pereira et al., 2002).

We are now investigating subtypes of schizophrenia and bipolar disorder to understand whether the BDNF gene is a risk factor for specific clinical symptoms common to these disorders.

Suicide

In the past year, we submitted funding proposals for genetic studies of suicide ideas and attempts in people who participated as research subjects in our schizophrenia and mood disorder investigations. We will investigate to see if genetic variants can predict risk for suicide in these disorders.

Dr. Vincenzo De Luca received a three-year award from the American Foundation for Suicide Prevention for his genetic investigations of suicidal behaviour in schizophrenia and bipolar disorder. Dr. John Strauss also received a similar award from the same foundation to examine genetics of suicide ideas and attempts in child-onset depression.

Also, our staff (Dr. Xingqun Ni and colleagues) are working on a proposal to study suicidal behaviour in the context of borderline personality disorder.

Pharmacogenetics and Pharmacogenomics

Strong evidence suggests that genetic variation plays an important role in inter-individual differences in medication response and toxicity. The rapidly evolving disciplines of pharmacogenetics and pharmacogenomics seek to uncover this genetic variation in order to predict treatment outcomes. The goal of these disciplines is to be able to tailor the therapy to the individual, by using the person's genetic make-up to select the drugs with the greatest likelihood of benefit and the least likelihood of harm.

In our laboratory, we investigated the dopamine D1 receptor gene's ability to predict response to clozapine treatment. So far, we have found that the D1 gene predicts improvement in memory and attention during clozapine treatment (Masellis et al., 2002, New York Pharmacogenetics Meeting presentation).

In addition, we studied candidate genes to try to determine the cause of clozapine-induced weight gain (Basile, Masellis, Potkin, & Kennedy, *Human Molecular Genetics,* 2002; Basile et al., *Lancet*, 2002). Using large, combined datasets, we have further examined antipsychotic-induced tardive dyskinesia and its association with the dopamine D3 receptor, first reported by our group in 1996.

We have also found that the pharmacogenetic principles developed in schizophrenia can be used to study many other psychiatric and addiction disorders (Masellis et al., 2002).

Obsessive-Compulsive Disorder

In collaboration with Drs. Peggy Richter and Emanuela Mundo, over the last year we made an important step forward in understanding the genetic basis of obsessive-compulsive disorder (OCD). Our group detected and, most importantly, replicated the finding that a serotonin system gene encoding the 5HT1D beta receptor (a.k.a. 5HT1B) can be a predisposing factor to OCD (Mundo et al., 2002).

The clue to this gene came from the unusual finding by Zohar et al. that the migraine drug sumatriptan, which binds to 5HT1B, increases OCD symptoms in the short term. Our

genetic finding, also reported in the lay press (*National Post*, Sept. 4, 2002), could have important implications for the molecular diagnostics and design of new therapeutic strategies in OCD.

Another interesting investigation, the first ever of OCD risk genes in children, is being led by Dr. Paul Arnold, who has reported a significant role for the NMDA receptor gene in OCD. He is now examining this gene in a sample of children from Wayne State University who have OCD and have undergone functional MRI studies testing glutamate activity in the living brain.

Attention-Deficit/Hyperactivity Disorder

In collaboration with Dr. Cathy Barr's lab at the Toronto Western Hospital, we investigated the role of catecholamine system genes in children with attention-deficit/hyperactivity disorder (ADHD) (Wigg et al., *American Journal of Psychiatry,* 2002; Barr et al., 2002). Our adult ADHD studies in collaboration with Dr. Umesh Jain (Muglia et al., 2002) continue to show a role for the dopamine D4, but not D3, receptor genes.

Problem Gambling

In collaboration with Drs. Umesh Jain, Nigel Turner, Michael Bagby and others, we obtained a grant from the Ontario Problem Gambling Research Centre to investigate genetic risk factors for gambling behaviour in people who have symptoms of ADHD. Early results suggest that dopamine system genes may be involved in predicting risk for gambling behaviour, but more work is needed to establish these findings.

Seasonal Affective Disorder

Dr. Robert Levitan is leading the effort to study the role of serotonin system genes in people who eat larger amounts of food in the autumn, become depressed and slowed-down in the winter, then return to normal mood and activity in the spring and summer.

Dr. Levitan showed that the serotonin 2A receptor gene was associated with a history of childhood attention-deficit/hyperactivity disorder in adult women who have seasonal affective disorder (Levitan et al., 2002). The next steps in this project include examining the interaction between the serotonin 2A and the dopamine D4 receptor genes.

Childhood Onset Depression

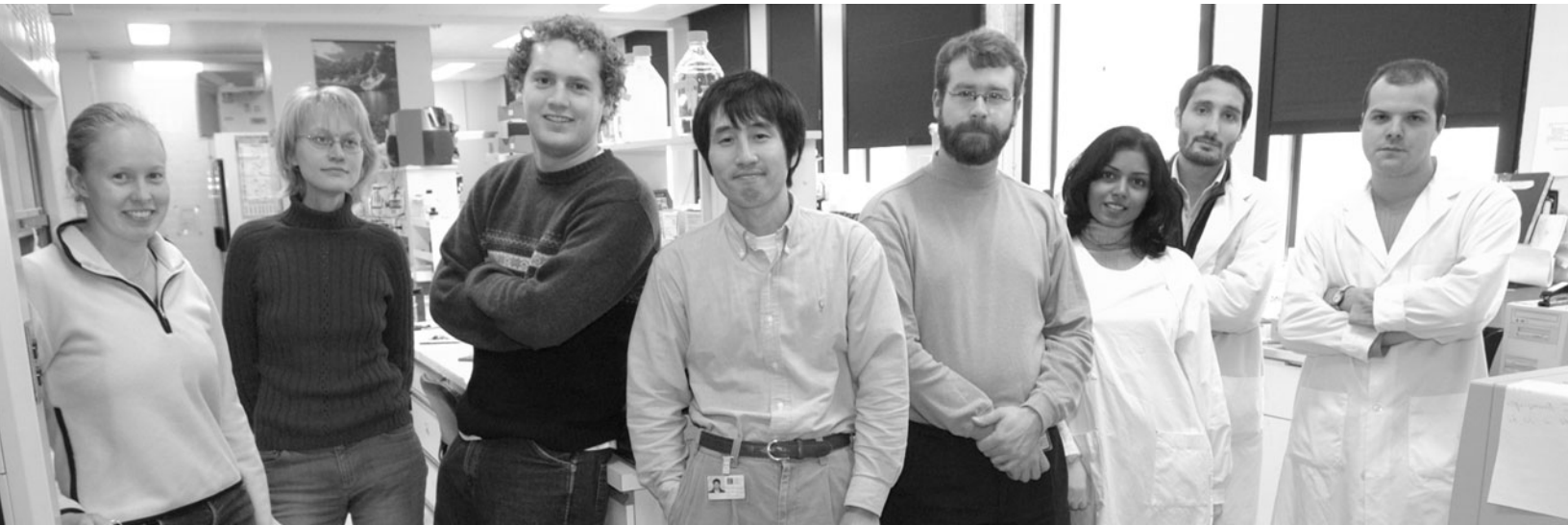
Dr. John Strauss, in collaboration with investigators at the University of Pittsburgh, reported a strong effect of a variant of the BDNF gene in predicting severe mood disorder in children. This finding has led us to study the role of this gene in suicidal behaviour and the tendency of depressed children to develop bipolar disorder in adulthood.

Bipolar Disorder

We have dedicated significant effort over the last year to genetic studies of bipolar disorder, which, together with schizophrenia, represents the group of major psychoses.

We investigated 300 small families (consisting of the person with bipolar disorder and his or her parents), first examining the dopamine D1 receptor gene. We found that a particular combination of genetic variants of D1 create increased risk for bipolar disorder (Ni et al., 2002). Dr. Ni also showed that a suspect gene, for the serotonin 2A receptor, was not involved in bipolar disorder.

In these 300 small families, we also examined how specific variants of the dopamine D4 receptor gene in the parents were transmitted to the affected child. Interestingly, we found that having the D4 gene transmitted from the mother increased risk for bipolar disorder, as opposed to having the same genetic variant coming from the father (Muglia et al., 2002). This finding suggests that regulation of this gene is complicated and likely to be subjected to genomic



imprinting, which links the traditional DNA sequence-based studies to epigenetic developments.

Epigenetics

The epigenetic theory of major psychosis puts the emphasis on looking at possible dysregulation of gene activity, rather than changes in DNA sequence. Psychiatric epigenetics is a relatively new field in psychiatric research. The great advantage of the epigenetic theory is that epigenetic mechanisms, unlike the traditional genetic ones, can explain unclear issues in major psychosis, such as age of disease onset, fluctuating course (remissions and relapses), common major differences in identical twins. To our knowledge, we represent the only group in the world fully dedicated to this development.

Dr. Art Petronis, head of the Epigenetics Laboratory, received a prestigious OMHF Special Project award to study epigenetic mechanisms in schizophrenia and bipolar disorder.

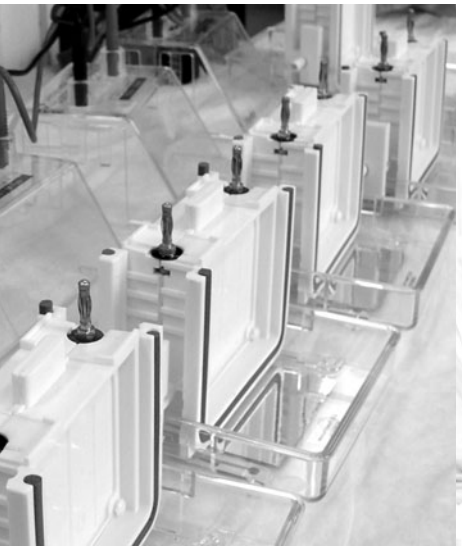
Over the last year, the Epigenetics group performed a series of laboratory experiments looking for molecular differences in identical twins, and compared epigenetic regulation of non-coding regions of the genomes of people who have schizophrenia or bipolar disorder with controls. Two manuscripts that describe the differences in DNA methylation patterns between ill and healthy control individuals are currently submitted to peer-reviewed journals.

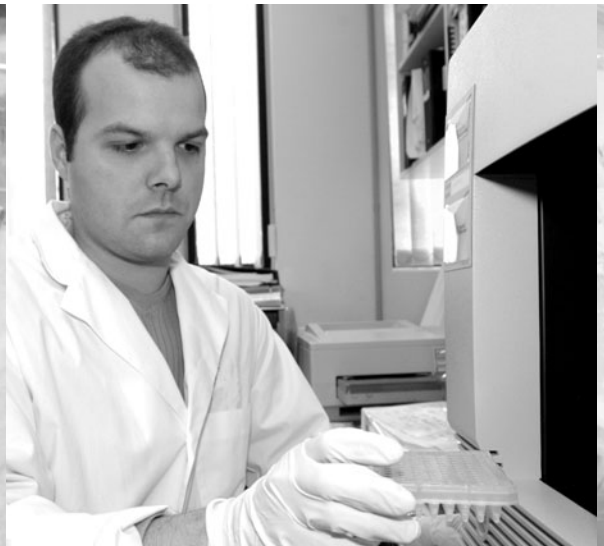
Developmental Neuropsychiatry and Autism

Dr. John Vincent, head of the Laboratory for Molecular Studies in Developmental Neuropsychiatry, has reported the cloning and characterization of a gene, called RAY1, that spans an area of breakage on the long arm of chromosome 7 in a person who has autism (Vincent et al., 2000). This gene has recently, and controversially, been reported to be a tumour-suppressor gene, although several reports have been unable to support this finding.

Dr. Vincent has continued to further characterize this gene and its surrounding DNA and has established the surprising situation that there are at least five other genes within RAY1 (Vincent et al., 2002). Mutations in RAY1 were identified in two families that have several members affected with autism. This work was recently published in a leading journal in the field, *Genomics*.

Dr. Vincent's work has also established the location of breakage regions within the suspected autism region on chromosome 7 for several other people who have autism. In one of these cases, the breakpoint maps to the same point identified in an unrelated person with autism. Both translocations are likely to disrupt a new gene that we have identified. This gene thus represents a very strong candidate for autism, and further characterization is under way.





Smoking and Nicotine Dependence

SECTION HEAD: Dr. Paul Fletcher (acting)

THE MAIN FOCUS OF OUR RESEARCH IN THE SMOKING and Nicotine Dependence Research Section is to better understand the neurochemical basis or mechanisms underlying nicotine dependence.

A limiting factor in finding therapies to prevent smoking is that underlying mechanisms involved in nicotine addiction, such as the positive reinforcing effects of nicotine, still remain unclear. Our research gives us valuable information about the brain mechanisms involved in nicotine addiction; this work should help us identify drug targets and thus help the search for more effective therapeutic agents for smoking cessation.

Previous studies in our laboratory have shown that nicotine is the primary rewarding compound in tobacco smoke. The study of nicotine dependence, like that of other drug dependence, profits from animal models, which allow us to examine the biochemical and behavioural consequences of acute and chronic drug treatment at a depth not possible with human studies.

Under the leadership of Dr. Shafiq Rahman (Research Scientist, CAMH), we continue to explore the mechanisms that mediate the positive reinforcing effects of nicotine in the brain. We use both conventional (qualitative) and quantitative (no-net-flux) in vivo microdialysis techniques in behaving animals to measure dopamine (brain chemical for reward) release in rat brain reward circuits. We have used both microdialysis methods in the nucleus accumbens (NAc) or ventral tegmental area (VTA) after acute and subchronic (pretreatment or pre-exposure regimen) and chronic nicotine treatment.

Nicotine Receptors in the Nucleus Accumbens

Nicotine is thought to exert its rewarding effects by activating dopamine neurotransmission in the mesocorticolimbic dopamine system, which is an integral part of the brain reward system. We have shown that acute and repeated nicotine exposure stimulates the release of dopamine in the NAc, a feature shared by other drugs of abuse, such as amphetamine and cocaine. Nicotine exerts these effects by attaching to and activating specific sites called receptor proteins and, more specifically, a type of receptor called neuronal nicotinic acetylcholine receptor.

Neuronal nicotinic acetylcholine receptors have several subtypes. We have determined that stimulatory effects of nicotine in the brain reward system are mediated by the high- and low-affinity nicotinic acetylcholine receptors. We have also found that low-affinity nicotinic receptors have a special role in modulating brain dopamine function in the NAc after repeated exposure to nicotine.

Nicotine and Release-Controlling Dopamine Autoreceptors

We are also investigating the role of dopamine autoreceptors in the NAc and VTA that control the release of dopamine.

In the NAc, we have found that dopamine autoreceptor subsensitivity may not contribute directly to the sensitization of dopamine releasibility. Additional studies on the role of dopamine autoreceptors in the VTA suggest that dopamine autoreceptor subsensitivity in this area is essential in nicotine-induced sensitization of dopamine release. The regulation of release-controlling dopamine autoreceptors is associated with sensitization and/or adaptive changes that are important for the development of nicotine addiction.

Chronic Nicotine Self-Administration

We have also started to use no-net-flux (quantitative) microdialysis to examine changes in dopamine transmission in the NAc after chronic nicotine self-administration. Recent advances in microdialysis methods show that quantitative methods are useful not only in determining the true extracellular concentration of dopamine but also in testing for

Transgenic Facility

SECTION HEAD: Dr. Hubert H.M. Van Tol

potential changes in dopamine transmission. Moreover, changes in tissue dopamine transmitter content are not necessarily paralleled by corresponding changes at the synaptic level of the reward centre.

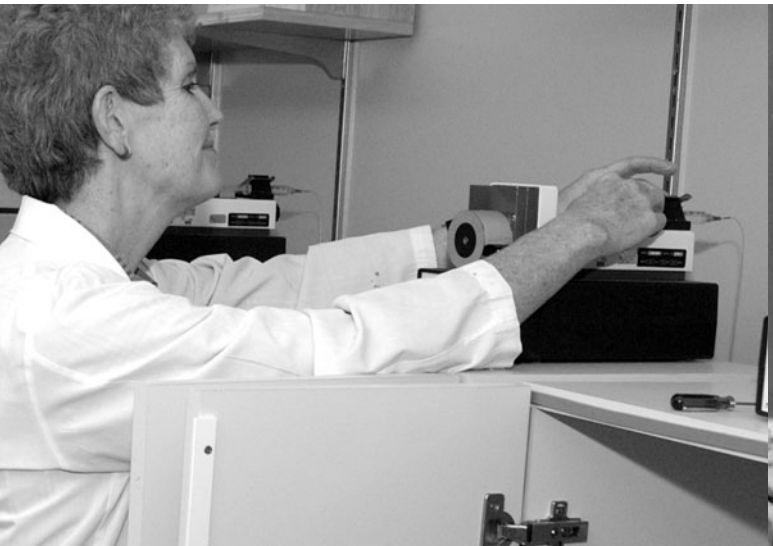
We hope to determine whether chronic voluntary nicotine self-administration alters or influences the functional integrity of the dopamine system in the NAc (i.e., dopamine release, uptake, synthesis and metabolism). We are measuring extracellular dopamine levels and in vivo extraction fraction.

Typically, extracellular dopamine levels represent dopamine release in the NAc, and dopamine extraction fractions reflect the uptake process or clearance of a known dopamine concentration. For example, a known dopamine concentration is given through microdialysis probe into the NAc, which is measured after a time interval (dopamine in–dopamine out is equal to extraction fraction).

Our results indicate that chronic nicotine self-administration significantly reduces basal dopamine levels, which is likely due to chronic intermittent exposure to the pharmacological effects of nicotine. More importantly, chronic nicotine self-administration creates a neuroadaptive change in the brain that alters the dopamine transporter and increases uptake in the NAc.

ADVANCES IN MOLECULAR AND GENETIC RESEARCH have increased our need to analyse the function of genes in physiological contexts. New technologies can easily modify genetic material in the germ line of mice or introduce new genetic material in selected tissues or organs through viral-mediated gene transfer. These technologies allow us to study the function of genes in whole animals, extending the molecular and genetic revolution to the realm of behavioural research.

The Transgenic Facility breeds and maintains transgenic mice strains for CAMH researchers. The facility can also help scientists create their own transgenic mice strains or employ viral-mediated gene transfer experiments. This year, the facility continued to lend its services to researchers in the Molecular Neuroscience, Biopsychology and Neuroimaging sections.



Vivian M. Rakoff Positron Emission Tomography Centre

DIRECTOR: Dr. Sylvain Houle

Research at the Vivian M. Rakoff Positron Emission Tomography (PET) Centre continues to concentrate on PET methodology (radiochemistry and PET instrumentation), schizophrenia, mood neurochemistry, basic neurosciences and addiction. In addition to our own research, we maintain active collaboration with other scientists within CAMH and with researchers at the University of Toronto and its teaching hospitals.

PET Radioligands Development

The radiochemistry group, led by Dr. Alan Wilson, continues its innovative work in radioligand development. In collaboration with Dr. Paul Verhoeff, from the Clinical Research Unit at Baycrest Centre for Geriatric Care, we have initiated human studies of potential PET imaging agents for amyloid plaques. Amyloid plaques are a characteristic feature of Alzheimer's disease. This work may lead to an objective way to assess potential therapies for Alzheimer's disease.

Our new radioligand for the serotonin transporter, [C-11]-DASB, continues to generate great interest. The serotonin transporter is the target of the selective serotonin reuptake inhibitors, medication widely used to treat depression. We can now measure accurately the effects of these antidepressants on the serotonin transporters. Several leading PET research groups around the world are now using [C-11]-DASB for their own research.

PET Instrumentation

Our new high-resolution, high-sensitivity 3D research brain PET tomograph is now installed. This scanner is currently the most sophisticated in existence for brain research and will strengthen our international leadership in psychiatric PET research. Funding for the new scanner was secured by a grant from the Canada Foundation for Innovation and the Ontario Innovation Trust fund. Peter Bloomfield, an internationally renowned PET physicist, continues to work on maximizing the potential of the new scanner.

Investigation of the Mechanism of Action of Antipsychotics

The PET Schizophrenia research program, under the leadership of Dr. Shitij Kapur, continues to explore how medications work. This work proceeds from the bench-to-bedside with studies in animal models and patients.

Using PET-like techniques in animal models, we have found that the doses of antipsychotics used in animal models do not represent usual clinical conditions. Some doses used are much higher than necessary. Using PET, Dr. Kapur and our team have proposed new clinically relevant doses, thereby providing a new standard for the field.

At a clinical level, the unique effects of clozapine remain a mystery. Dr. Johannes Tauscher and colleagues have shown that clozapine binds not only to dopamine D2 receptors, but also to dopamine D1 receptors. This opens up a new line of research examining the role of dopamine D1 receptors in helping patients with refractory schizophrenia.

Dr. David Mamo is examining the effects of different forms of administration of already available drugs. He is studying depot forms of olanzapine and risperidone and a long-acting form of seroquel. Dr. Mamo and colleagues have helped identify the "optimal" clinical doses of seroquel. These data are now being used to design clinical trials.

Finally, in related work, Dr. Jimmy Jensen is trying to combine fMRI, a brain imaging technique, with PET. While PET provides neurochemical sensitivity, fMRI has exceptional temporal resolution. Dr. Jensen and colleagues are developing conditioning paradigms that can be simultaneously used in PET and fMRI.

The Neurochemistry of Depression

Headed by Dr. Jeffrey Meyer, this program aims to investigate the neurochemical basis of symptoms for mood disorders and the neurochemical effects of antidepressant medications.

We continue to focus on the relationship between changes in serotonin and dopamine receptors and the specific cognitive and neuropsychological abnormalities that are observed during depressive episodes.

We continue to investigate serotonin and dopamine transporter regulation. We find that the regulation of these transporters has an important role as a vulnerability factor

for low monoamines and accompanying symptoms. Our treatment studies focus on the mechanism of selective serotonin reuptake inhibitors (SSRIs).

Using [C-11]-DASB, we measured the percentage of serotonin reuptake sites occupied during treatment with five different SSRIs at different doses. The results of our work will improve SSRI dosing and future antidepressant development.

Basic Neurosciences

Dr. Nathalie Ginovart has developed an extensive animal PET program aimed at complementing human PET studies. This program is based on multidisciplinary research using a variety of approaches. The central theme of this work is to use PET in research to investigate the serotonin and dopamine neurochemical systems that are of utmost importance for mental illnesses and addiction. For example, one of our projects explores the effect on the brain of different dosing regimens of an antipsychotic medication used to treat schizophrenia.

Another aspect of this work will characterize new PET imaging agents before they are used in humans. One of the latest developments in our PET neuroscience program is a new method that uses positron sensitive microprobes, surgically implanted in the brain of rodents, to measure drug-induced occupancy of neuroreceptors in vivo. This technique is of great interest, as the brain of rodents is too small for accurate imaging with human PET scanners. Dedicated small-animal scanners are available, but they are expensive, and their use is still being validated. Our new method has already delivered exciting results that will benefit our human research.

Investigation of the Neurochemical Sequelae of Ecstasy Use

The effects on the brain of MDMA, better known as ecstasy and widely used by young adults in Canada, remain controversial. Dr. Stephen Kish is using [C-11]-DASB to find definite evidence about the presence or absence of ecstasy's effects on the serotonin transporter.

This work also illustrates the translation of PET research into public policies, as it will establish the extent to which ecstasy is harmful to the human brain. Current policies on ecstasy were influenced by the results of a PET study carried out in the United States. This study has now been shown to be wanting technically, particularly because of the lack of a suitable PET radiotracer.

Using a meticulous approach and our superior PET imaging agent, we are carrying out a study (preliminary data already obtained) to determine definitively if ecstasy and a more potent related drug, MDA (which is often sold as "ecstasy" to drug users), are actually toxic to human brain cells. The results of this study will be important to the general public, governmental agencies involved in drug policy and the judiciary. The results will also provide, for the first time in this controversial area, accurate information for drug education and awareness programs about recreational drugs.

Clinical Research Department

DIRECTOR: R. Michael Bagby

The Clinical Research Department continues to support clinical research activities by producing publications, making presentations to the community and academic audiences, funding specific research proposals and providing start-up funds to "clinician-scientists" located in various clinical and research sections at CAMH.

During 2002/2003, the department funded studies by Dr. Carolina Cristi (Interpersonal Therapy Clinic, Mood and Anxiety Disorders Program), Dr. Christine Wekerle (Child Psychiatry) and Dr. Peter Farvolden (Personality and Psychopathology Research Section). Dr. Beth Sproule has received continued research "start-up" funds.

Ms Justine Joseph, a student in the Mood and Anxiety Disorders Program, also received funding, to examine race-related stressors, non-race-related stressors and the relation of these stressors to depression in Canadians of African descent.

Drs. Tony Toneatto and Bruna Brands received travel funds to attend international and national conferences on addiction. Dr. Brands has also received "bridge funding" for her work in a variety of areas related to addiction.

We collaborated with the Law and Mental Health and Child Psychiatry programs to support a conference at CAMH on risk assessment across the

lifespan, addressing the probability of antisocial behaviour and violence across the lifespan. Dr. Nasreen Khatri, a post-doctoral fellow funded by the Canadian Institute of Health Research, also received support from our department to advance her training in the area of depression and women.

Following previous investment in "between-program initiatives," Drs. Peter Farvolden, R. Michael Bagby and Tony Toneatto received renewed funding from the Ontario Problem Gaming Foundation to study personality variables in people who gamble.

The Personality and Psychopathology Research Section underwent an external review during the Fall of 2002. The review was conducted by Dr. Joel Paris, from the Department of Psychiatry at McGill University, and Dr. Paul T. Costa, Jr., from the National Institute of Health (USA). This review produced uniformly positive appraisal, citing our section as one of the top personality disorder programs on the international stage and arguing for its expansion.

Dr. L. Trevor Young was appointed Acting Head of the Mood and Anxiety Research Section. Dr. R. Michael Bagby, who was the Acting Director of the department, was appointed Director in 2002.

Addictions

SECTION HEAD: Dr. Tony Toneatto

THE ADDICTION SECTION CONDUCTS CLINICAL research, experimental and applied, in all aspects of addiction. Drs. Bruna Brands, Beth Sproule and Tony Toneatto are the Section's scientists. Our research activities focus on four areas: gambling, psychopharmacology, treatment outcomes and clinical services.

Gambling Research

In our gambling research (Dr. Tony Toneatto), we aim to develop effective treatments for pathological gambling.

Within the past year, we have completed two studies, one on the effectiveness of naltrexone for people with concurrent alcohol and gambling problems, and a second comparing several brief cognitive-behavioural treatments. We are now in the follow-up stages with both studies.

During the next year, we will conduct two treatment studies. The first will evaluate manual-assisted tele-counselling for gambling problems. The second, in collaboration with Dr. Nigel Turner and Mr. Warren Spence, will evaluate the effectiveness of acupuncture as a treatment for problem gambling.

Dr. Toneatto is also studying thinking processes in people who have gambling problems; results show a high correlation between irrational beliefs (such as thinking that efforts to regain gambling losses are justified) and the development of problem gambling.

Psychopharmacology Research

Our psychopharmacology research (Drs. Bruna Brands, Beth Sproule, Peter Selby, David Marsh) focuses on the care of opioid addiction.

Drs. Brands and Marsh have co-authored *Best Practices in the Design and Delivery of Methadone Maintenance Treatment Programs*. This publication offers information that can help opioid-treatment programs become more effective and encourage the establishment of new programs.

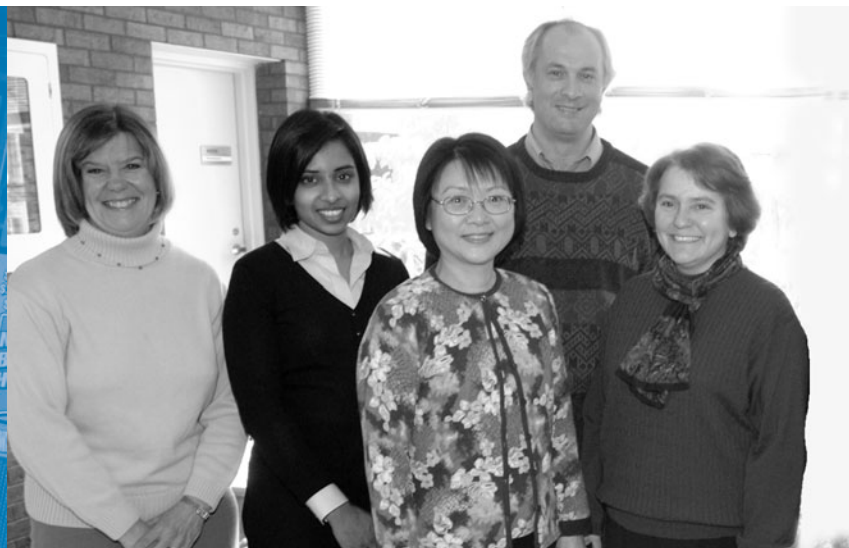
Dr. Brands (with Drs. Joan Blake, Beth Sproule, Douglas Gourlay and Usoa Busto) is studying the expansion of methadone maintenance treatment (MMT) availability to patients with dependence on opioids other than heroin, to increase access to treatment that previously would have been unobtainable.

Dr. Brands is also studying the effectiveness of treatment programs specifically designed for adolescents who are dependent on heroin, among whom multiple drug use is common. We found that, among adolescents who use heroin, the mean age of first use was 15 years. In this population we also saw an association between heroin use and significant comorbidity, including mental health issues and physical health risks.

Dr. Sproule is developing a novel approach to statistical analysis, using "fuzzy logic" to evaluate the relationships between patient characteristics and medication outcomes. We are conducting an ongoing and extensive evaluation of this approach, including comparisons to other methodologies.

In another study, Dr. Sproule has compared the attitudes and professional interactions of community pharmacists toward patients taking mental health–related medications and those taking cardiovascular medications. Despite the generally positive attitudes expressed by community pharmacists, we found that pharmacists interacted less with, and offered fewer professional activities to, patients using mental health medications. This pattern needs to be improved; more interaction could optimize the prevention, detection and management of drug-related problems in these patients.

In collaboration with colleagues in the Clinical Neuroscience Section, Dr. Sproule is also evaluating the effects of hypnotic medications in older adults.



Treatment Outcome Research

Treatment outcome research consists of three clinics, headed by psychologists who are developing empirically based treatments for addictive disorders.

Dr. Shelley McMain, head of the Dialectical Behaviour Therapy Unit, is conducting a five-year, CIHR-funded study evaluating the clinical and cost effectiveness of dialectical behaviour therapy (DBT) for people who have borderline personality disorder, including many who have concurrent substance use problems.

The Anger and Addiction Clinic, headed by Dr. Lorne Korman, is evaluating an integrated treatment for people who have concurrent anger, substance use and gambling problems. The researchers are testing a DBT-based treatment that targets emotion dysregulation, thought to underlie both anger and addiction problems.

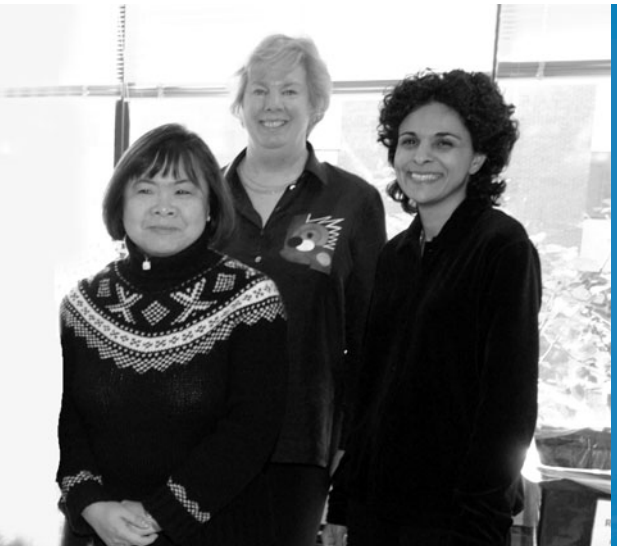
The Eating Disorders and Addiction Clinic, headed by Dr. Christine Courbasson, has developed (with Lauren Dixon) a manualized treatment, rooted in DBT, that targets the emotion regulation problems that are common to both eating disorders and problem substance use. This treatment is the first to tailor DBT to treat concurrent eating and substance use problems simultaneously.

Clinical Service Research

Our clinical services research area conducts effectiveness and process research in collaboration with CAMH addiction programs and services.

We are about to complete a study evaluating the outcome and process of brief treatment for addictions. This study will identify the key treatment interventions that produce therapeutic benefit.

Other projects in progress include studies evaluating the delivery of treatments for problem gambling, addiction in youth and addiction in women.



Mood and Anxiety

SECTION HEAD: Dr. L. Trevor Young

MEMBERS OF THE MOOD AND ANXIETY DISORDERS Program continue to undertake multidimensional research in mood and anxiety disorders. Our work has ranged from studying molecular mechanisms to developing and evaluating new treatments, such as therapies based on meditation. In addition to population-based research methods, we use basic science methodologies, brain imaging techniques, family studies and clinical trials.

Mood Disorders

Dr. Robert Levitan has identified a particular subgroup of women who have chronic depression and who also have a cluster of symptoms such as obesity and attention problems; these women may have an abnormal variance of a dopamine receptor gene.

Dr. Jeffrey Meyer found increased prefrontal serotonin receptor binding potential in people who were depressed and who also showed negativistic thinking. These results may be related to the findings, by other groups, of increased serotonin receptor bindings, in the same brain region, in people who completed suicide.

At the laboratory level, Dr. Jun-Feng Wang used DNA arrays to find new patterns of gene expression after administering drugs such as lithium and antidepressants to cultured brain cells.

Dr. Jerry Warsh has identified specific signal transduction abnormalities related to calcium, using blood cells from people with bipolar disorder.

Dr. Sagar Parikh has started a Canada-wide study of the effectiveness of psychoeducation and cognitive therapy for people with bipolar disorder.

Investigations, led by Drs. R. Michael Bagby and Helen Mayberg, continue to compare 1. brain functioning of people with depression and 2. brain functioning of people whose personality types are thought to make them vulnerable to depression, but who have never developed a depressive episode. Results indicate that the brain functioning in never-depressed, but vulnerable, people was similar to that of people who had previously had a depressive episode.

Dr. Bagby is also examining how changes in personality during treatment may predict outcome in different types of psychotherapies.

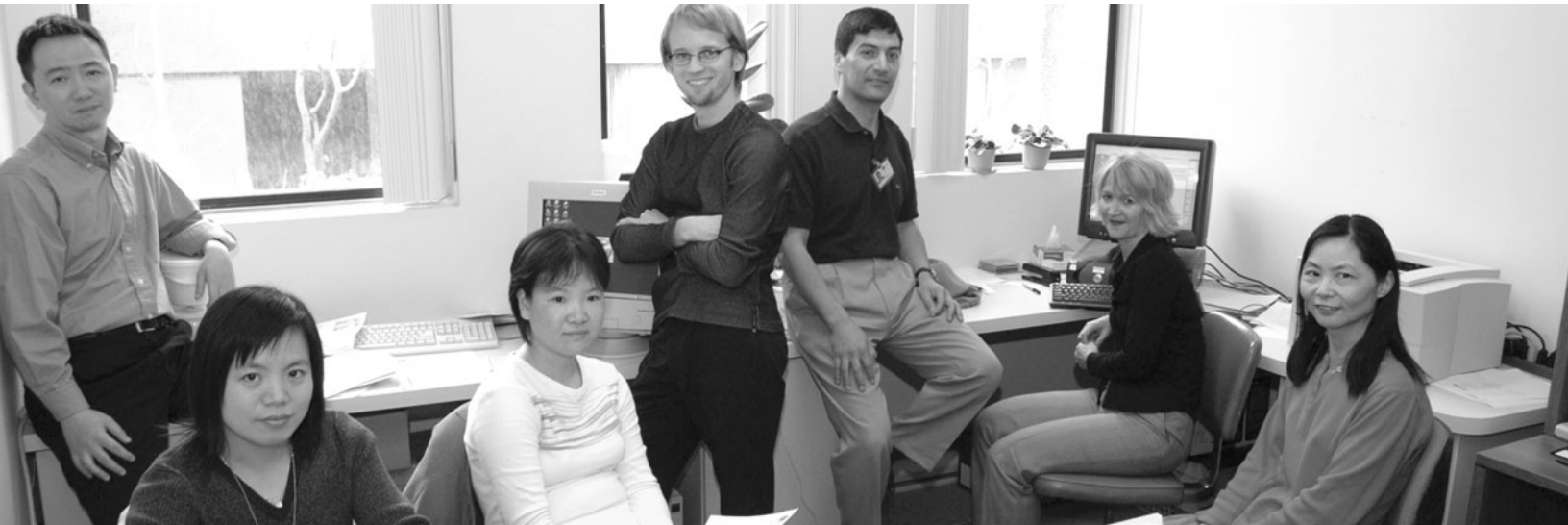
In the Cognitive Behaviour Therapy Unit, Dr. Zindel Segal and Dr. Mayberg collaborated on a study comparing cognitive therapy to antidepressant medication. Using PET scans, they found patterns of changes in brain metabolism in patients who responded to cognitive therapy; these patterns differed from those of people who responded to antidepressant treatment.

Dr. Mark Lau has shown interesting differences in vulnerability to depression using psychological tests in people with depression. His team also continues their internationally recognized trials comparing the effectiveness of cognitive therapy and medications for relapse prevention.

Anxiety Disorders

In the Anxiety Disorders Clinic, the OCD group has been very busy developing a new brief cognitive therapy treatment for people who have concurrent obsessive-compulsive disorder (OCD) and depression, and testing the efficacy of cognitive therapy for medication-refractory OCD.

In collaboration with Dr. Jim Kennedy, Dr. Richter's group have also replicated their earlier finding about the possible role of a serotonin receptor gene in OCD, which conceivably may lead to improved diagnosis and treatment in the future.



Personality and Psychopathology

SECTION HEAD: Dr. R. Michael Bagby

RESEARCH IN THE PERSONALITY AND PSYCHOPATHOLOGY

Research Section examines a broad range of themes related to personality and psychopathology. We also develop tests and instruments to assess personality and related constructs, and develop strategies to assess and treat mental disorders using the Internet.

Our current projects explore: alternative structures of personality psychopathology; the effects of personality traits in treatment outcomes for disorders such as depression, anxiety and problem gambling; the influence of personality on the development of mental disorders; the influence of acute distress on personality and its assessment; and the role of neurotransmitter mechanisms in personality.

Personality and Cognitive Vulnerability and Problem Gambling

Surprisingly little is known about the personality and cognitive characteristics of people with gambling problems. Drs. R. Michael Bagby and Peter Farvolden are attempting to identify personality and cognitive factors that distinguish people who remain "social gamblers" from those whose gambling activities escalate into a dysfunction or problem gambling.

Results to date suggest that, in contrast to people with gambling problems who seek treatment, people with gambling problems who do not seek treatment and social gamblers are not characterized by high levels of psychopathology or alterations in cognitive functioning. This finding challenges conventional thinking about problem gambling.

Behavioural Inhibition, Behavioural Activation, Personality and Novelty

Based mainly on research on how animals learn, Gray's influential motivational model (1994) proposes biological systems that mediate all of our different motivations and emotions: the behavioural inhibition system (BIS), the behavioural activation system (BAS) and the flight-fight system. Gray's BIS and BAS offer promise for explaining a variety of normal and psychopathological behaviour.

We are developing novel paradigms to study the relations between BIS and BAS sensitivity, other systems of personality and preference for novelty. We are tentatively exploring connections to psychopathology by examining these relationships in different patient groups.

Panic Disorder, Agoraphobia, Anxiety Sensitivity and Attachment

According to current explanations of panic disorder and agoraphobia (PD/AG), panic attacks are the result of a "false alarm" combined with an over-attentiveness to internal bodily sensations and/or a tendency to catastrophize. Although there is considerable support for the current explanations of PD/AG, there is also some evidence that increased vulnerability to separation distress and/or an "insecure" attachment style may also have an important role in PD/AG.

Results to date suggest that neuroticism and attachment style predict anxiety sensitivity, which in turn predicts severity and intensity of panic symptoms. These results suggest some benefit from using personality and attachment dimensions to better understand the onset and maintenance of PD/AG.

Personality, Positive Mood and Attentional Biases in Depression

Major depressive disorder (MDD) is an extremely prevalent mental health problem with vast socio-emotional and economic costs. A continuing challenge in the treatment of MDD is the high rates of relapse and recurrence.

This project examines the potential role of "positive" traits such as behavioural activation sensitivity, extraversion, ability to experience positive mood and "positive" cognitive biases in predicting response to treatment and relapse in depression.

Results to date suggest that response to a positive mood induction may help predict treatment response.

Internet Assessment and Treatment

Considerable data suggest that the Internet can be a powerful tool for delivering collaborative assessment and treatment.

We have recently presented data supporting the potential utility of a Web-based tool for assessing depression and anxiety disorders in primary care. In addition, we have presented data supporting the reach, patterns of use and potential efficacy of a free Web-based smoking cessation program.

Application of the Five-Factor Model of Personality to Psychopathology

Recognition of the limitations associated with the categorical approach to personality psychopathology has led to the development of several new dimensional models of personality psychopathology.

Our ongoing research attempts to find if the dimensions of personality represented by the Five-Factor Model of Personality can be applied successfully to a variety of patient samples and used to better understand the relevant neurobiology, psychopharmacology and structure of personality psychopathology.

Personality, Limbic-Cortical Function and Vulnerability to Major Depression and Other Imaging Studies

This project attempts to unify two parallel lines of research examining vulnerability to depression. One line shows that PET scans in patients with depression display specific patterns to induced sad mood; the other shows that individuals who have a high score on "neuroticism" are vulnerable to develop depression.

Our research examines whether never-depressed "normal" subjects with high neuroticism scores show the same response as people who are depressed or were previously depressed. These results have recently been published in *Neuroimage*.

Personality as a Mediator of Treatment Outcome

This ongoing project, now in its third year, examines whether different types of personality traits (dependency and self-criticism) moderate and/or mediate treatment outcome differently in three standard and empirically established effective interventions for depression (interpersonal therapy, cognitive-behavioural therapy and pharmacotherapy). Previous studies have shown that all these treatments are about equally effective, but no study has systematically examined whether targeting depressive symptoms related to personality traits mediates outcome differently.

Personality, Life Stress and Recurrent Major Depression

More than half of all people with major depression will have multiple recurrent episodes throughout their lives; the impact is often devastating. Recurrence of depression is also an ongoing burden on the public health system. For these reasons, we are trying to understand the mechanism that perpetuates the recurrence of depression.

Several risk factors for recurrent depression include childhood adversity, personality style and poor social support. But what is the mechanism that underlies the relationship between these risk factors and recurrence?

In collaboration with Dr. Kate Harkness (Queen's University), Dr. Bagby is conducting research to see if people who have both depression and a history of childhood adversity, disrupted personality and poor interpersonal functioning are generating stressful events that precipitate new episodes of depression. If this is found to be true, treatments that target stress generation may ultimately help prevent depression from becoming a lifelong disorder.

Drs. Harkness and Bagby have recently received an operating grant from the Ontario Mental Health Foundation to examine this causal model of depression recurrence, with clear targets for treatment and prevention.

Psychobiology of Aggression and Antisocial Behaviour across the Lifespan

SECTION HEAD: Dr. Leslie Atkinson

AGGRESSION AND ANTISOCIAL BEHAVIOUR POSE tremendous risks to individuals, families and society. The Psychobiology of Aggression and Antisocial Behaviour across the Lifespan Section incorporates researchers from the Law and Mental Health and Child, Youth and Family Programs, facilitating lifespan research. In the past year, we have conducted research into risk, intervention/management and knowledge transfer.

Infant Stress

Dr. Leslie Atkinson and others are investigating genetic and environmental influences on infants' response to stress. This group is examining normal infants at 12 to 18 months of age to determine their response to mild stressful events, such as maternal separation.

Chemical analysis of the saliva of the children will determine the levels of important stress hormones in these children. Investigators in the Neuroscience Research Department will then be able to investigate a variety of factors in the hormones and blood samples of these children that may contribute to our understanding of how humans develop both adaptive and maladaptive responses to stress. In addition, these stress hormones are involved in a variety of other behaviours throughout the lifespan, including aggression.

Risk Factors for Aggressive and Antisocial Behaviour

Drs. Joe Beitchman and James Kennedy and colleagues have been focusing on the role of select serotonin genes and family and personality factors in aggression.

This year, they found that one form of serotonin transporter gene was less common in aggressive children than in non-aggressive children. A second variant of this gene was not significantly linked with aggression, but was linked to a diagnosis of ADHD. These findings could have implications, in future, for assessing risk of aggression and implementing early intervention strategies.

Dr. Martin Lalumiere and colleagues showed that, among sex offenders, number of older brothers is positively related to a greater interest in coercive and violent sexuality. Number of older sisters, or younger brothers or sisters, is unrelated to sexual interest. Dr. Lalumiere and colleagues speculate that the link involves maternal immunoreactivity to something involved in sexual differentiation of the brain.These findings may eventually contribute to early identification of risk and intervention strategies.

Dr. Fiona Miller and colleagues studied the risks of childhood disturbance associated with low socioeconomic status (SES) and harsh, inconsistent parenting practices. They found that, although the absolute risk of children developing disorders associated with low SES and harsh parenting is low, the relative risk is high.

For example, relative to his or her mid-SES peers, a child eight or nine years old from a low-SES family is five times more likely to develop conduct disorder, while a child eight or nine years old who experiences harsh parenting is four times more likely to show symptoms of conduct disorder.

Dr. Christine Wekerle is surveying teenagers who have been maltreated by their caregivers; question topics include health risk behaviours (problem substance use, dating violence, risky sexual practices, mental health problems) and resiliency factors (school achievement, leisure activity). The primary hypothesis of the study is that maltreated youth have a high prevalence of risk behaviours and a greater number of overlapping problems.

The survey will also measure mediators (e.g., cognitive expectancies, motives for risky sexual practices), enhancing the study's potential for identifying targets for intervention.

In another study, of reported child abuse, Dr. Wekerle is studying the association of caregiver substance use and maltreatment. Dr. Wekerle found that parents with substance use

problems are more likely than parents without substance use problems to neglect and emotionally abuse their children and less likely to sexually abuse them. No relation was found between substance abuse and physical abuse.

In a third survey, Dr. Wekerle and colleagues identified a small group of adolescent males whose behaviour was broadly antisocial, whose activities included, for example, gambling, weapons possession, stealing, frequent physical violence and bullying. These youths had more difficult backgrounds, a higher rate of depression, more frequent suicidal ideation and reported more problem substance use than other youths.

These findings highlight the unmet mental health needs of antisocial male youth and the challenges to getting help for substance use problems.

Dr. Michael Seto and colleagues compared young people who had been charged with a juvenile sex offence with young people who had been charged with other, non-sexual, juvenile offences. They found a meaningful distinction between juvenile sex offenders who have few conduct problems but engage in sexual misconduct and those who engage in non-sexual forms of criminal behaviour. These findings will help target and focus interventions to better treat the sexual aspects of juvenile delinquency.

Dr. Seto reviewed the literature on pornography's effects on attitudes, aggression in the laboratory and sexual arousal. He concluded that there is an interaction between individual characteristics and the effects of pornography exposure. These findings have relevance to an ongoing debate about the impact of pornography—again, that the impact of pornography depends on the individual involved with it. Students within the section have also been active. Ms Karen Milligan, under the supervision of Dr. Leslie Atkinson, explored how attachment security and maternal sensitivity relate to children's aggressive behaviour. Studying typically developing best-friend pairs, Ms Milligan found that children who were less securely attached exhibited higher levels of aggression.

In a second study of children with Down syndrome, Ms Milligan found that the effect of child intellectual level on aggressive behaviour is moderated by maternal sensitivity. This finding is important, because it had previously been assumed that aggression in this population was entirely due to intellectual factors, which are difficult to change. Interventions focused on the mother-child relationship may reduce later incidents of aggression between the child and his or her peers.

Mr. Calvin Langton (now Dr. Langton), under the supervision of Dr. Howard Barbaree, completed a doctoral dissertation contrasting approaches to risk assessment and violence prediction among adult offenders.

The findings confirmed the validity of actuarial devices but also suggested that structured clinical approaches hold promise. Additional findings indicated that information about offenders' completion of and response to institutional treatment improves the accuracy of sexual recidivism predictions. Drs. Langton and Barbaree are now studying which treatment components are most important for this purpose.

Mr. Mark Watson, Mr. Mark Levi, Ms Carey Sturgeon and Ms Sandy Greenberg, under the supervision of Dr. David Nussbaum, successfully applied a neurobiological model to the prediction of violence and also demonstrated the need to carefully match predictive instrumentation to the population being studied (e.g., different predictors may be necessary when studying people who carry out planned acts of aggression as opposed to people who aggress in reaction to some stressor).

Aggressive and Antisocial Behaviour Interventions and Management

Dr. Wekerle studied the effectiveness of a dating violence prevention and dating health promotion program for

Investigating a variety of factors in the hormones and blood samples of children may contribute to our understanding of how humans develop both adaptive and maladaptive responses to stress.

youth who have experienced childhood maltreatment. The program reduced incidents of physical and emotional abuse in dating and symptoms of emotional distress. Dr. Wekerle and colleagues are extending their studies to incorporate an intervention for substance use problems into the program.

Dr. Joe Ducharme and student Ms Kimberly Harris are evaluating innovative interventions to improve child compliance with teacher requests and on-task behaviour. The interventions, referred to as errorless remediation, are based on the sophisticated use of learning strategies. In this type of intervention, maladaptive responses are treated like errors, and the environment is rearranged to ensure that low levels of these errors occur. Gradually, conditions associated with problem behaviour are introduced at a rate that ensures that these behaviours remain at low levels. This approach has produced gains in compliance, on-task behaviour and peer relationships.

Conducting the largest quantitative review of studies evaluating sex offender treatment outcome published to date, Dr. Seto and colleagues found that treated sex offenders repeated their crimes significantly less often than non-treated sex offenders.

Knowledge Transfer

Ms Joanna Henderson (now Dr. Henderson), under the supervision of Dr. Sherri MacKay, conducted a provincial study of factors affecting the adoption and use of TAPP-C, a community-based children's mental health program for juvenile firesetting. This study revealed that adopter, innovation, dissemination and organizational characteristics are all important in understanding knowledge-transfer from academic settings to community-based settings.

In addition, analyses to examine the relative importance of each group of variables revealed that different variables are particularly important at different stages of program dissemination. For example, innovation characteristics were important in the adoption process, but not at the utilization stage. This study provides preliminary data that will help close the research-practice gap in children's mental health.

A dating violence prevention and dating health promotion program, for youth who have experienced childhood maltreatment, reduced incidents of physical and emotional abuse in dating and symptoms of emotional distress.

Schizophrenia

SECTION HEAD: Dr. Shitij Kapur

THE SCHIZOPHRENIA RESEARCH PROGRAM IS dedicated to understanding the causes and mechanisms of recovery of schizophrenia, with the hope of improving the lives of people and families affected by the illness. In pursuit of this goal, our methods range from molecular studies to community-based research.

Genes and Schizophrenia: Animal Models of Schizophrenia
Dr. Albert Wong and colleagues are using animal models to identify candidate genes for schizophrenia. The team has discovered that two genes, 14-3-3eta and syntaxin1a, are associated with schizophrenia (*Molecular Psychiatry*, 2003). Now, we ask the question of how these genes lead to schizophrenia; studies are under way to test how these genes affect the release of brain chemicals and are involved in brain development.

Genetic Subtypes of Schizophrenia
Drs. Anne Bassett and Eva Chow lead the Clinical Genetics Research Program team, focusing their research on genetic subtypes of schizophrenia. Drs. Bassett and Chow have been instrumental in showing that 22qDS (deletion syndrome of 22q) represents an identifiable genetic subtype of schizophrenia.

With support from the W. Garfield Weston Foundation, our team is following over 70 adults with 22qDS to determine the developmental, psychiatric and medical features, as well as the molecular genetic make-up, of this complex subtype. We have also started a study of children and adolescents with 22qDS, who have a high risk of developing schizophrenia. (Supported by NARSAD and Bill Jeffries Schizophrenia Endowment Fund).

Dr. Chow reported in 2002 (*Biological Psychiatry* 51: 208– 215, 2002) that brain structure in 22qDS-schizophrenia resembles that of other forms of schizophrenia; this is leading us to study whether brain structural features may predict who will develop schizophrenia in young people with 22qDS.

Tackling Schizophrenia Before It Begins
Drs. Robert Zipursky, Irvin Epstein and colleagues have been leading the Prevention through Risk Identification, Management & Education (PRIME) research clinic in early detection strategies and treatment, using psychological tests and brain imaging. These approaches are already showing promise (*Biological Psychiatry*, Woods et al, 2003).

Recently, the team of Drs. Jean Addington, Zipursky, Epstein and colleagues has begun a five-year project, in collaboration with the Universities of North Carolina and Yale, to improve early identification of people who are likely to develop schizophrenia. Early and accurate identification of risk for schizophrenic psychosis may be the field's best hope for developing more effective treatment strategies, including secondary prevention of this typically devastating disorder. (Funded by NIMH).

Drugs and Therapy Go Hand-in-Hand
For many years, we have known that antipsychotic drugs work on the dopamine neurotransmitter. However, we do not understand how drug action on this neurotransmitter takes away the delusions and hallucinations that are a symptom of psychosis.

Dr. Shitij Kapur and colleagues have proposed a new theory to link dopamine to psychosis and to antipsychotic treatment (*American Journal of Psychiatry*, 2003). According to this theory, drugs provide a background of dampened salience of symptoms; this background makes it easier for the person to give up his or her delusions and hallucinations. Our theory predicts how drugs and therapy may actually work hand in hand. Studies are now under way to test this new theory.

Cognitive Behavioural Treatments: A Focus on Functional Recovery

While antipsychotic treatment takes away symptoms of schizophrenia, not everyone returns to their original level of functioning. Recently, the field of schizophrenia research and treatment has not focused on individual psychotherapies, but the last few years have seen a growing interest in this area.

Dr. Jean Addington, a leader in psychological interventions for psychosis, is currently leading the development of new types of psychotherapies for people who are in the early stages of schizophrenia, and is examining if these therapies lead to improvement in functional outcome (funded by the NIH, USA).

Understanding and Managing Side-Effects

Drugs have side-effects. This cannot be avoided. In the Schizophrenia Research Program, we strive to understand antipsychotic side-effects, to help people manage them.

Dr. Tony Cohn, in association with Dr. Gary Remington, runs a research-treatment clinic focusing on weight gain and diabetes problems for people taking antipsychotics. This clinic has led to several new discoveries.

We find that the medication-induced weight gain observed in young people experiencing a first episode of psychosis is substantially higher than previously reported (presented by Dr. Cohn at the International Congress on Schizophrenia Research, 2003).

In people who have experienced chronic psychosis over many years, we found a two- to three-fold increase in rates of type 2 diabetes, abdominal obesity and a syndrome of insulin resistance and abnormalities in cholesterol and glucose metabolism, both in hospitalized and community patients with schizophrenia. (Presented by Dr. Cohn at the International Congress on Schizophrenia Research, 2003).

These factors, combined with the very high rates of cigarette smoking (70 to 80 per cent) in this population, suggest a markedly increased risk for coronary heart disease.

In screening for diabetes among this same group of people with chronic psychosis, we have found that the recommended fasting glucose procedure is only 20 per cent reliable in detecting undiagnosed diabetes and five per cent reliable for determining if persons are at risk for diabetes, compared with a different screen test, the glucose challenge.

This has led us to develop new guidelines for testing for diabetes and risk for diabetes in people with schizophrenia.

Beyond Drugs and Psychotherapy: Magnetic Stimulation as a Treatment

Drs. Jeff Daskalakis and Bruce Christensen have been conducting studies using a new research technique called transcranial magnetic stimulation (TMS). Our studies have shown, for the first time, that people having an active psychotic episode of schizophrenia show abnormal inhibition of neuronal activity of the front part of the brain (*Archives of General Psychiatry,* 2003).

These studies show the path to possible new treatments. We are now working to see if magnetic stimulation can be used to treat these inhibition deficits and lessen hallucinations for people with schizophrenia that does not respond to conventional treatments.

Neuropsychology: Exploring How the Brain Works

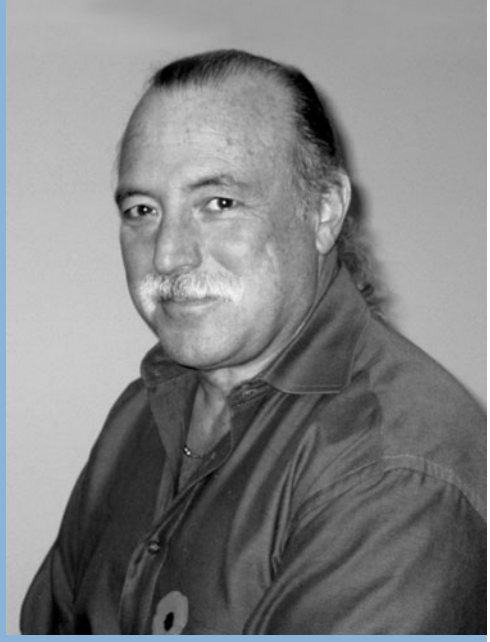
Working in the Neuropsychology Lab, Dr. Christensen and colleagues focus on the cognitive and neurobiological effects of schizophrenia. One of the challenges in this area has been to understand the wide variety of cognitive changes associated with this illness in terms of a unified reason.

We have proposed that schizophrenia-related cognitive impairment may be associated with one of two major developmental brain pathways: the pathway that controls goal-directed activity.

As part of our ongoing work in this area, we have completed a study using a visual discrimination paradigm and a visually guided reach paradigm, both of which support this hypothesis—both of these studies have been presented at international conferences and we are currently preparing manuscripts for each.

We are also interested in understanding the prominent memory deficit that is associated with schizophrenia; for example, in people with schizophrenia who do not use memory strategies to improve recall, such as mentally grouping items that belong to the same category (e.g., apple, pear and banana are all fruits).

In a recent study, we have shown that, although patients are able to learn category strategies, having the skill does not improve their recall. This type of problem has been termed a "utilization deficit" and may reflect how general intellectual deficits interfere with using new skills. Our findings also suggest the need for repeated practice in skills training for people with schizophrenia.



Social, Prevention and Health Policy Research Department

DIRECTOR: Dr. Louis Gliksman

The Social, Prevention and Health Policy Research Department contains six research units; while each has different mandates, they often collaborate on research projects with each other and with other programs at CAMH. Our department staff have diverse professional backgrounds in fields such as, among others, criminology, epidemiology, history, nursing, psychiatry, psychology and sociology.

This multidisciplinary team environment provides a synergy of ideas, theories and approaches that is both exciting and creative. All scientists in the department have university affiliations, and many are actively engaged in teaching.

Our research ranges from surveys of the general population and sub-populations (e.g., school children, women, immigrant populations) to policy interventions, community studies and health systems delivery. The information that we produce informs the research community, the public, policy makers and program developers; we disseminate this knowledge through reports, papers, conference presentations, peer-reviewed publications, position papers and media releases. Our end goal is to develop and disseminate resources and services that will improve the lives of people with mental health and addiction problems.

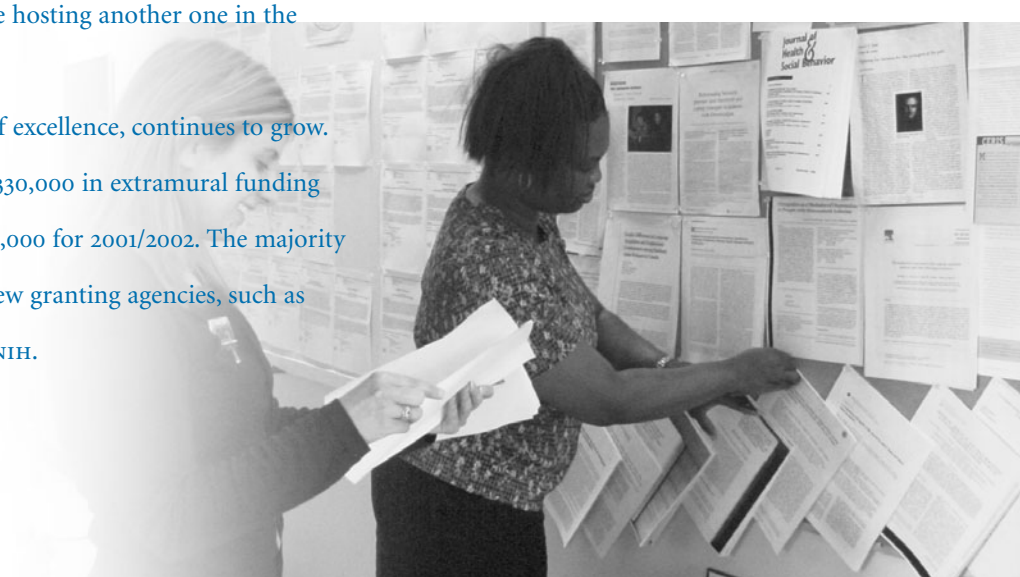
We are committed to working with our community partners, and all the research units are actively involved with government, agencies and special interest groups. In addition, we have resources dedicated to help agencies

and community groups develop and evaluate resources and services in which these community groups may be engaged.

We continue to pursue and be involved in international research. In addition to North American collaborations, our staff have worked with the World Health Organization and Swiss, Norwegian, British, Brazilian and Mexican researchers on various projects.

As CAMH is a designated World Health Organization (WHO) Collaborating Centre, we expect that our internationally recognized scientists will continue to be asked to undertake or collaborate on international research projects in the areas of mental health and substance use. We have committed to being part of the WHO mhGAP program, which is designed to train researchers in developing countries, and we have created the CAMH/WHO Centre of Excellence for training in research as part of our agreement with the WHO. We have accommodated one international fellowship scientist this past year and will be hosting another one in the coming year.

Our extramural funding, an indicator of excellence, continues to grow. Researchers in the Department received $9,330,000 in extramural funding during the 2000/2001 fiscal year and $10,600,000 for 2001/2002. The majority of this funding has come through peer-review granting agencies, such as CIHR, SSHRCC, Robert Woods Johnson and NIH.



Culture, Community and Health Studies

ACTING SECTION HEAD: Dr. Louis Gliksman

AN INTEGRATED RESEARCH, TRAINING AND consultation unit, the Culture, Community and Health Studies (CCHS) Research Section takes a psychiatric epidemiology perspective to understanding cultural and social determinants of population health, with a focus on immigrant and refugee populations.

The team includes scholars from psychiatry, sociology, clinical and developmental psychology, social epidemiology, anthropology, demography, medicine, nursing and public health. Detailed project and staff information may be found at www.camh.net/research/research_ar2000/culture_comm_health.html or at http://www.utpsychiatry.ca/programs/cchs.cfm.

Research

The CCHS attracts funding through the Canadian Institutes of Health Research, the Social Sciences and Humanities Research Council, Citizenship and Immigration Canada, Health Canada, Human Resources and Development Canada and Canadian Heritage in support of its research programs.

Faculty and scientists of the CCHS section are leading 25 different research initiatives. The ongoing research activities of the CCHS include a national longitudinal study of the health and development of immigrant and refugee children; epidemiological studies in Toronto's Ethiopian and Tamil communities; youth acquisition of ethnocultural identity; the mental health effects of discrimination; long-term mental health impact of exposure to traumatic stress; multicultural meanings of social support; the development of a community resource guide to assist newcomers to Canada; stress and tuberculosis; depression and suicide among people from Pakistan living in the UK; and a randomized double-blind trial on raloxifene as an adjunct in the treatment of psychosis.

Recent research highlights include: (1) Although immigrant families are three times more likely to have low income than non-immigrant families, immigrant children have fewer mental health and behavioural problems than their non-immigrant counterparts; (2) The prevalence of depression among Ethiopians in Toronto roughly equals that found among the general population of Ontario, but it is three times higher than the rates in Ethiopia; (3) Approximately one-quarter of people who are visible minority immigrants experience discrimination, and those experiences jeopardize mental health.

Education, Training and Clinical Initiatives

The CCHS educates and trains future generations of health researchers and health care providers in appropriate policy and practice responses to the challenges of diversity and equity.

The CCHS offers an Inter-Faculty Research Seminar series, with topics such as immigrant and refugee mental health, cross-cultural research, economic and social determinants of health and general topics of mental health and addictions. The seminars are open to researchers, staff and students at the University of Toronto and the Centre for Addiction and Mental Health.

Faculty of the CCHS research section also contribute to the development, implementation and delivery of graduate and post-graduate courses offered by the Department of Psychiatry, the Institute of Medical Sciences (IMS) and other university departments. Dr. Ted Lo conducts a cultural competence training program for residents, psychiatrists and mental health staff.

The CCHS also offers resident and medical student training, clinical service consultations and public education on culture and mental health, including training in research methodologies for doctoral students and post-doctoral fellows through thesis supervision.

Dr. Lisa Andermann's completed post-doctoral work,

Approximately one-quarter of people who are visible minority immigrants experience discrimination, and those experiences jeopardize mental health.

jointly sponsored by the CCHS and the Psychological Trauma Clinic at Mt. Sinai Hospital, focused on cross-cultural perceptions of mental health. Rani Srivastava, Director of Clinical Resources in the Faculty of Nursing at the University of Toronto, continues PhD studies at the IMS through the CCHS section, with her research focusing on institutional and individual cultural competence. Through the CCHS, Dr. Kenneth Fung completed a study of alexithymia among Chinese people, in fulfilment of master's degree requirements in IMS, and continues to expand this research area.

Finally, research institutions and universities are increasingly recognising an obligation to provide information about their scholarship and its implications for improved clinical practices. Members of the CCHS section participated in the development of an ethno-racial initiative in the Joint General Psychiatry Program; implementing a Cultural Consultation Program that provides clinician training in cultural issues relevant for patient assessment and management. The CCHS also created partnerships with settlement agencies, public health units and CAMH to develop a community education program on mental health and addiction for ethno-racial groups.

Consultations and Review Panels

The CCHS provides community, policy and scientific consultations at national and international levels. Through affiliations with the Joint Centre of Excellence for Research on Immigration and Settlement–Toronto, a tri-university centre supported by SSHRC through agreements with eight departments of the federal government, the CCHS contributes to a national agenda of policy-oriented research, focusing on immigration and mental health.

As part of a Canadian Heritage initiative, Dr. Anneke Rummens continues to develop a database on identities in Canada. Dr. Ted Lo provides cultural consultation to hospitals and education on integrative medicine. In collaboration with professionals in China, he is also planning an international conference on traditional medicines. Dr. Lo also serves on the Toronto/Peel Mental Health Reform Implementation Task Force.

Dr. Violet Kaspar is a member of the Canadian Institutes of Health Research peer review committee for Strategic Programs—Reducing Health Disparities and Promoting Equity for Vulnerable Populations.

Visiting Scholars

Dr. Francis Lu, Professor of Clinical Psychiatry and Director of the Cultural Competence and Diversity Program, Department of Psychiatry, San Francisco General Hospital and University of California, San Francisco, visited CAMH as the 2002–03 Beverley Professor. This visit was hosted by the CCHS section, through support from CAMH's Beverley Professorship fund. The Professorship brings distinguished researchers and clinicians to CAMH to promote and participate in academic discussion on a topic relevant to research, clinical care and teaching activities.

As the 2002–03 Beverley Professor, Dr. Lu provided lectures, workshops and consultation groups on cultural competence in academic research, clinical care and teaching, focusing on the role of systems' cultural competence in understanding mental health disparities.

International Initiatives

The CCHS has developed a memo of understanding involving the University of Port Harcourt, the University of Toronto and CAMH, and is continuing this initiative to establish a Centre for Stress and Health in the Niger Delta region of Nigeria. This work is being expanded to include methods of enhancing capacity to combat health hazards in the Niger Delta.

Another initiative is an ongoing collaboration between the University of Toronto, CAMH and the American University of Beirut, for a comparative study of adolescent mental health.

Finally, the CCHS has created an education elective in Addis Ababa, Ethiopia. The elective will allow two staff psychiatrists and one resident from the University of Toronto to travel to Addis Ababa three times per year, for one month per visit, to teach in the newly formed Ethiopian psychiatry residency program.

Health Systems Research and Consulting Unit

SECTION HEAD: Dr. Paula Goering

INFORMING AND IMPROVING SYSTEMS OF MENTAL health and addiction service delivery—this is the goal of the CAMH Health Systems Research and Consulting Unit (HSRCU), the base of the University of Toronto Department of Psychiatry's Health Systems Program. Our interdisciplinary team draws on the expertise of other jurisdictions, reviews current literature, interviews and consults with local stakeholders, analyzes data in existing administrative databases and gathers information through epidemiological and program evaluation studies.

Our goal is to have research disseminated and translated into policy and practice. Our section head, Dr. Paula Goering, also holds a CIHR/CHSRF (Canadian Health Services Research Foundation) health services chair; this supports knowledge transfer and exchange activities and emphasizes training.

HSRCU members work in close collaboration with the Ontario Substance Abuse Bureau and the Mental Health and Rehabilitation Reform Branch on system-related issues, such as performance measures and planning. We are affiliated with the Department of Health Policy, Management and Evaluation at the University of Toronto and have developed a collaborative relationship with the Institute for Clinical Evaluative Studies.

Our staff have cross-appointments with other departments at the University of Toronto, including the Faculty of Nursing, Department of Public Health Science and the Institute for Medical Science.

Education and Training

We had over 16 trainees supervised by scientists on the unit in the last year, three of whom won awards for the excellence of their work. Our summer studentship program has shown great success, attracting 80 applications this year for four positions. Three fellows have learned about health services research, as have graduate students from various disciplines.

We are involved in two CIHR Training Centres that will provide stipends for trainees as well as opportunities to connect with broader networks. Our scientists are teaching several new university courses, and our unit offers an educational series for trainees and staff.

Linkage and Exchange

Our knowledge and exchange activities are well-established; we have helped develop a knowledge transfer plan for best practices in concurrent disorders; organized a research education series for our policy partner; evaluated and disseminated the research transfer training series and worked with our provincial evaluation project to implement innovative communication strategies.

A paper describing our relationship with the provincial policy branch has been accepted for publication. We are also developing a knowledge translation research program and a university course.

Consultation

Our consultation service is busy transferring knowledge and keeping research staff in touch with front-line service delivery issues and problems. We have added an evaluation component to all of our projects, which in the last year have included a review of Toronto's mental health court support services, an evaluation of a lead agency in northern Ontario and a study of use of inpatient services in southwestern Ontario.

Community Mental Health Evaluation Initiative

The HSRCU is the co-ordinating centre for a multi-site evaluation research project to advance understanding of the roles played by case management, assertive community treatment, crisis services and consumer and family initiatives.

We are collecting common outcomes data on a cohort of over 600 people at baseline, nine and 18 months. The outcome protocol was designed to be brief and comprehensive; portions of it have been incorporated into other studies and monitoring initiatives. Projects are in the final stages of data collection and are now focusing on analyzing and interpreting results.

We conducted a half-day plenary at the "Making Gains" conference in Fall 2003 to engage Ontario stakeholders in discussion around the implications of the research for practice, programs and policy.

Profile of Ontario Methadone Recipients and Providers

Until recently, the availability of methadone treatment in Ontario and elsewhere in Canada has been restricted. In 1996, Ontario introduced a series of policy changes aimed at increasing the availability and uptake of methadone therapy.

Using registry data from the College of Physicians and Surgeons of Ontario, we are assessing the five-year impact of these policy changes on the patient and physician populations. Between 1996 and 2001, the total number of methadone clients in treatment in Ontario increased substantially, from 1,595 to 7,787. Over this time period, the number of physicians prescribing methadone increased from 60 to 161.

However, the estimated low proportion of opioid users in contact with the methadone treatment system shows that more efforts are needed to address the potential demand for treatment.

Drug and Alcohol Treatment Information System

Drug and Alcohol Treatment Information System (DATIS) is a provincial information system that collects, summarizes and reports information on the volume and characteristics of people being treated for alcohol, other drug and gambling problems in Ontario. Unit staff help select performance measures within DATIS and analyse and interpret trends that are useful for planning, accountability and research.

This year we completed a provincial report and three research papers using the provincial data: 1. a study looking at the high rate of referral into the treatment system of clients with legal/correctional systems involvement; 2. a study showing the numbers and characteristics of clients in treatment for problem gambling; and 3. a study describing the volume and characteristics of clients seeking help for problems related to their use of cannabis.

Depression in the Workplace

In response to a request from the Ontario Roundtable on Appropriate Prescribing, we designed a study called Depression in the Workplace: Examining Antidepressant Use and Worker Characteristics and Their Associations with Disability. Three Canadian companies with national employee bases were recruited as project participants, representing over 65,000 workers.

Results showed that approximately 58 per cent of employees who were receiving depression-related short-term disability benefits had made at least one antidepressant claim. mployees who did not use antidepressants typically reported significantly fewer symptoms at baseline on average than those who did use antidepressants.

The results of this study represent an important first step in exploring the question of how antidepressants are used among workers who are most affected by depression and who use disability benefits.

Comprehensive Assessment Projects

This series of needs-based planning projects originated in Ontario's psychiatric hospitals and expanded into the community system. We used a consistent methodology to assess current and recommended levels of care for people who use mental health services and to determine how well care received matched the level of need.

This series of needs-based planning projects is now completed; we created a database that merges results from projects across the province. There are about 42,000 clients of community mental health services and 13,000 clients of provincial psychiatric hospital services represented in this provincial database. Plans are under way to transfer the database to the Ontario Ministry of Health and Long-Term Care so researchers and planners can have full access to it.

Between 1996 and 2001, the total number of methadone clients in treatment in Ontario increased substantially, from 1,595 to 7,787.

Ontario Tobacco Research Unit

SECTION HEAD: Dr. Roberta Ferrence

SINCE ITS INCEPTION IN 1993 AS THE RESEARCH component of the Ontario Tobacco Strategy, the Ontario Tobacco Research Unit (OTRU) has been a focal point for an active, tobacco-control research network in Ontario. The principal sponsor of OTRU is the Department of Public Health Sciences, University of Toronto. CAMH is one of three co-sponsors of the unit, making in-kind contributions of investigator and staff time, facilities and administrative support. Funding comes from the Ontario Ministry of Health and Long-Term Care, in-kind contributions from sponsoring institutions and various external grants and contracts.

The OTRU network is a university-based, multi-disciplinary team of six principal investigators, 32 co-investigators, 24 collaborating investigators, many affiliates, consultants and Ontario Tobacco Strategy partners.

Following our external review in 2002, we began an extensive strategic planning process to review activities in the five functional areas based on our mandate (Program and Policy Research and Development, Monitoring and Evaluation, Teaching and Training, Information Analysis and Dissemination, and Networking and Communications) and to develop a research agenda for tobacco control in Ontario.

Program and Policy Research and Development

We continue to support tobacco control research in Ontario by informing and supporting our investigator base. In the past year, we developed and implemented the OTRU Investigator Award Program for research in tobacco control. Through this program, we earmarked funds for four awards of up to $7,500 to OTRU-affiliated co-investigators and collaborating investigators.

New Research

We presented findings from OTRU research projects at several conferences. These included results from a national study on second-hand smoke in the home, a study of pharmacists' role in advising clients about smoking and cessation and an examination of connections between the tobacco industry and universities in Canada.

Based on an analysis of data from the *Ontario Student Drug Use Survey*, we reported that students who perceived themselves as overweight and engaged in weight-control behaviours were two to six times more likely to smoke than those who didn't have this perception. The findings were stronger for young women than for young men.

In our second-hand smoke study, we found that having at least one non-smoker and having children in the home reduced the likelihood of exposure to second-hand smoke by almost half and increased attitudes favourable to controlling it. Further, we found that a majority of Canadians support banning smoking in vehicles carrying children, and about 40 per cent support banning smoking in homes where children live.

Monitoring and Evaluation

This year, our Monitoring and Evaluation group issued our Annual Monitoring Report as a four-part Monitoring and Evaluation Series that examined progress of the Ontario Tobacco Strategy.

This series relies on qualitative and quantitative evidence to document changes in the province's tobacco control climate, including policy and program initiatives and tobacco-related knowledge, attitudes and behaviours. Two principal sources of data for our series are the annual *CAMH Monitor* and the biennial *Ontario Student Drug Use Survey*.

Teaching and Training

Involving students and graduates early in their careers is an essential strategy for developing a future generation of researchers and practitioners with interests and skills in tobacco control.

In the past year, our student-related initiatives included individual thesis research and field practica under the supervision of OTRU investigators. We expanded the University of Toronto graduate-level course, "Tobacco and Health: From Cells to Society," developed by Drs. Roberta Ferrence and Joanna Cohen.

We also continue to video-conference the course through our Eli Lilly Learning Centre; in the past year, we offered this option to students at the Universities of Toronto and Waterloo, McGill University and the University of British Columbia.

This course gives students a comprehensive overview of tobacco and tobacco-related issues from a public health perspective. Topics include patterns of tobacco use, nicotine addiction, genetic factors, determinants of smoking, health effects, social and economic impacts, treatment issues, prevention, and program and policy issues.

OTRU is now a collaborator on two CIHR strategic transdisciplinary tobacco training program grants, including one with three partners—the University of Waterloo, the University of British Columbia and the University of Toronto—that focuses on tobacco control research, and another training program grant, funded this spring through CAMH and the University of Toronto, that focuses on training clinicians in tobacco research on special populations, such as people with mental health and substance use problems.

Through the OTRU Graduate Studentships for Research in Tobacco Control Program, initiated in 2001 to increase tobacco research capacity in Ontario, we offered 10 studentships of $7,000 each in the 2002/2003 academic year.

Information Analysis and Dissemination

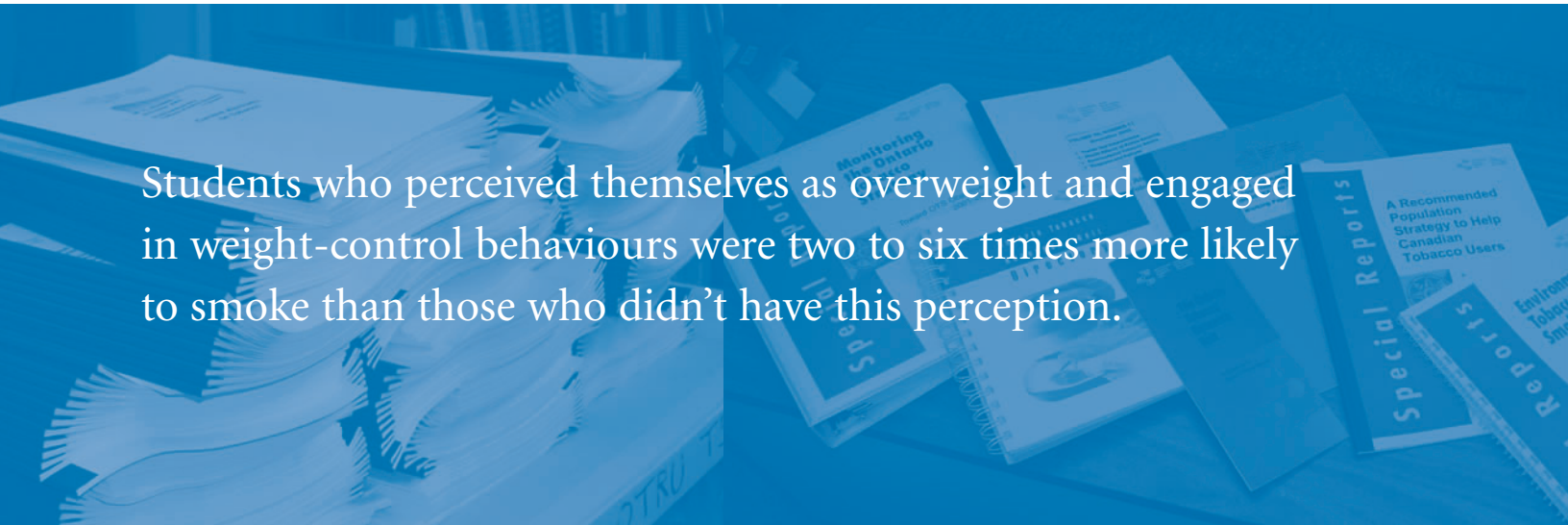
We continue to disseminate working papers and current abstracts on tobacco control to other researchers, public health professionals and policy makers in Ontario, through our library services and monthly mailings.

Networking and Communications

This year, OTRU investigators and staff continued to present new research findings at scientific conferences, workshops, seminars and lectures.

We held networking events and provided conference displays, media and electronic communication; we developed and disseminated various OTRU products, including several working papers, research and information updates and issues of current abstracts on tobacco. We presented several papers at the National Conference on Tobacco or Health held in Ottawa in December, 2002; at this conference, we held a reception for investigators and partners to honour our studentship recipients.

Our Web site and listserv continue to provide key information on funding and research events, as well as discussion on research issues for 152 investigators and practitioners across the province and beyond. In 2002/2003, we reviewed and updated the content and look of our Web site, which receives 2,000 to 3,000 visits per month.



Students who perceived themselves as overweight and engaged in weight-control behaviours were two to six times more likely to smoke than those who didn't have this perception.

Population and Life Course Studies

SECTION HEAD: Dr. Edward Adlaf

THE OVERALL GOAL OF THE POPULATION AND LIFE Course Studies Unit is to describe the extent of addiction and mental health indicators in the population and to monitor trends. This includes: providing and disseminating accurate and timely data about alcohol use, other drug use and mental health indicators among general and special populations; and monitoring and identifying risk and protective factors for alcohol use, other drug use and mental health indicators.

By measuring addiction and mental health indicators, we provide the knowledge base for health professionals, program planners and municipal, provincial and national government bodies. This information can also help us target prevention and other programs and evaluate existing programs, policies and health objectives. The result is an information base that helps ensure needed programs are established in a timely and cost-effective manner.

Our team of investigators includes epidemiologists, sociologists, psychologists, criminologists and historians. Investigators also serve as experts for international agencies such as the World Health Organization and the United Nations Drug Control Programme. Unit staff hold appointments with University of Toronto departments, including Public Health Sciences, Psychology, Psychiatry, Sociology and History.

Survey Research

In the past year, we prepared the 14th cycle of the *Ontario Student Drug Use Survey* (OSDUS), the longest ongoing school survey in Canada, and began the fieldwork in February. We expect that almost 6,000 students from over 100 schools will participate in the survey.

Some of the new issues that will be covered include work activity and related injuries, Internet gambling, non-medical use of Ritalin® and the use of ketamine. The final report was released in November 2003.

In addition to monitoring addiction and mental health indicators among Ontario adults, the *CAMH Monitor*, our ongoing telephone survey of adults, investigates areas such as road rage among drivers, stigma related to mental health and the role of pharmacists in smoking cessation.

Along with Dr. Louis Gliksman and colleagues from the Universities of Montreal and Alberta and Dalhousie and Harvard universities, we have begun a three-year study of Canadian university undergraduates. This study, funded by the Canadian Institutes for Health Research, will survey some 10,000 undergraduates throughout Canada. The study will investigate the determinants of outcomes such as heavy drinking, illicit drug use, mental health problems and gambling behaviours.

Internet Resources

We published seven *eBulletins*, our ongoing series of brief data overviews of substance use and mental health trends among Ontario students and adults. Topics included issues such as trends in rave attendance, binge drinking, student exposure to illicit drugs and suicide ideation. Among the results, we found that 11 per cent of Ontario students reported that they had seriously considered suicide during the past year.

We also completed and released our electronic monitoring report: *CAMH Monitor eReport: Addiction and Mental Health Indicators among Ontario Adults in 2001, and Changes Since 1977*. The report describes the extent of alcohol use, drug use, mental health indicators and gambling problems, and provides a knowledge base for health professionals.

Visitors to our Web page (www.camh.net/research/population_life_course.html) will find highlights of our survey research.

International Activities

Our staff have also been active in international research and training. We continue to train graduate students from the Faculty of Public Health, University of Applied Sciences (Hamburg, Germany), consult with and train staff at the National Drug Council of the Cayman Islands regarding their Cayman Islands Student Drug Use Survey, and collaborate with the DAVI (Drugs Alcohol and Violence International) study, a multi-site study involving researchers from Philadelphia, Montreal and Amsterdam.

Gin Use in 18th Century London

Dr. Jessica Warner's *Craze: Gin and Debauchery in an Age of Reason*, a book about the gin epidemic in eighteenth century England, received critical acclaim in both North America and Britain.

The book has been reviewed in the *Globe and Mail*, the *Toronto Star*, the *Washington Post*, the *New York Times*, the London *Times*, the *Daily Telegraph*, the *Guardian*, the *London Review of Books*, *BBC History Magazine* and *Forbes Magazine*, among others, and it has also been featured on CBC Radio, BBC Radio and National Public Radio.

Natural History Telephone Survey

Dr. John Cunningham completed a representative, general population telephone survey of 3,006 respondents, exploring the natural history of alcohol problems.

The survey contains a detailed assessment of current and prior alcohol problems, use of treatment and other social services, and demographic factors thought to be associated with recovery from alcohol problems. The survey also includes a qualitative interview component, asking people who have recovered from a drinking problem about their reasons for change.

By measuring addiction and mental health indicators, we provide the knowledge base for health professionals, program planners and municipal, provincial and national government bodies.

Public Health and Regulatory Policy

SECTION HEADS: Drs. Benedikt Fischer & Jürgen Rehm

LATE IN 2002, THE PUBLIC HEALTH AND REGULATORY Policy Section was established with a broadened focus, emerging from the former Legal Controls and Regulatory Policy Section. The section is co-headed by Drs. Benedikt Fischer and Jürgen Rehm. Over the past few years, our investigators have secured substantial funding for several areas of research, highlighted below.

Social and Epidemiological Studies

Exemplary projects of the section include the CIHR-funded multi-year Interdisciplinary Health Research Team (IHRT) on Illicit Opiate Addiction Research, Treatment and Policy. Led by Dr. Benedikt Fischer, the IHRT convened its first annual all-projects' meeting in September 2002; this meeting offered a forum in which all of the IHRT projects represented by research investigators, staff and students presented research results or plans.

One of the IHRT projects—the OPICAN multi-site cohort study, headed by Dr. Fischer, on untreated illicit opioid use in five cities across Canada—featured results from its baseline component.

As select key information, the majority of people from the total OPICAN baseline sample (679 subjects) featured the following characteristics: non-permanent housing, cocaine or crack use in conjunction with opioid use, physical and depression problems, similar use of health or social services and unmet treatment needs. The investigators will follow up with this cohort; our results will inform research and development of more effective interventions.

Drs. Reginald Smart and Robert Mann have received funding from the AUTO21 Network of Centres of Excellence to study antisocial driving behaviour. The Networks of Centres of Excellence program is funded by the Natural Sciences and Engineering Research Council (NSERC), the Canadian Institutes of Health Research (CIHR) and the Social Sciences and Humanities Research Council (SSHRC), in partnership with Industry Canada.

One study focused on the emerging problem of road rage in the Ontario adult population. The investigators found that experiences as a victim or perpetrator of road rage are common; about half of Ontario drivers had such an experience in the past year. More serious road rage cases involving threats or injuries affected nearly one person in ten. Road rage is more common among young, male drivers and people living in larger, urban centres.

The investigators identified a small group of frequent road ragers, with elevated levels of psychiatric distress, who are involved in most of the serious cases. Future studies will focus on ways to prevent road rage, particularly among people who have the most severe problems.

Preliminary results of the Canadian Alcohol Experiences and Nordic Perspectives project, led by Dr. Norman Giesbrecht, indicate that commercial and policy measures that promote drinking and increase overall alcohol consumption (e.g., extended liquor store operations, increased density of liquor outlets and/or liquor price reductions) are not benign. In fact, such measures are associated with risks and costs for the general population.

As a result of such risks, the research team is recommending the promotion of policies that favour low-risk drinking and prevent an increase in aggregate drinking rates.

Activities to promote better policies could include, for example: promoting a better balance between control and trade agendas; developing a monitoring system of changes in alcohol policy; including health and safety experts at the table when plans for changes in retailing are considered; conducting impact assessments before introducing changes in access to alcohol; and increasing public awareness of the risks of higher drinking rates and the relevance of alcohol policies for public health and safety.

Developing and Evaluating Interventions to Reduce Substance-Related Harm

An important area of our research has been to evaluate policies in Ontario and Canada that aim to reduce alcohol-related motor vehicle collisions. This year, Dr. Mann and his team completed the first long-term evaluation of the effects of the legal blood alcohol limit for driving (.08%) in Canada since the limit was introduced in 1969.

The investigators analysed alcohol-related driver fatalities in Ontario that occurred between 1962 and 1996, controlling for long-term fatality trends.

They found that the introduction of the legal limit has had a very strong impact on the number of alcohol-related fatalities; the legal limit law has been associated with a sustained reduction of 18 per cent in alcohol-related driver fatalities in the province. Additionally, the analysis demonstrated the impact of other factors on drinking driving fatality rates. In particular, a strong relationship with population alcohol consumption levels was observed, with drinking driving deaths increasing as consumption increased.

Dr. Scott Macdonald and colleagues recently also compiled data on motor vehicle collisions, in which collision rates of people who received treatment for problems with alcohol, cannabis or cocaine were compared with rates of population controls. Both the alcohol and cocaine groups had significant declines in "at fault collisions" after receiving treatment, compared to a control group.

Dr. Jürgen Rehm led the Comparative Risk Analyses for Alcohol within the Global Burden of Disease Study under the umbrella of the World Health Organization. The aim of the study was to quantify and compare the impact of 26 health risk factors on global burden of disease (see graph).

Alcohol was found to be the most important risk factor in developing countries with overall low mortality, such as China, and the third most important risk factor in established market economies, such as Canada (after tobacco and high blood pressure).

Based on these results, in part published in the 2002 *World Health Report,* several countries have initiated interventions to reduce alcohol-related harm.

Knowledge Transfer: From Research to Policy

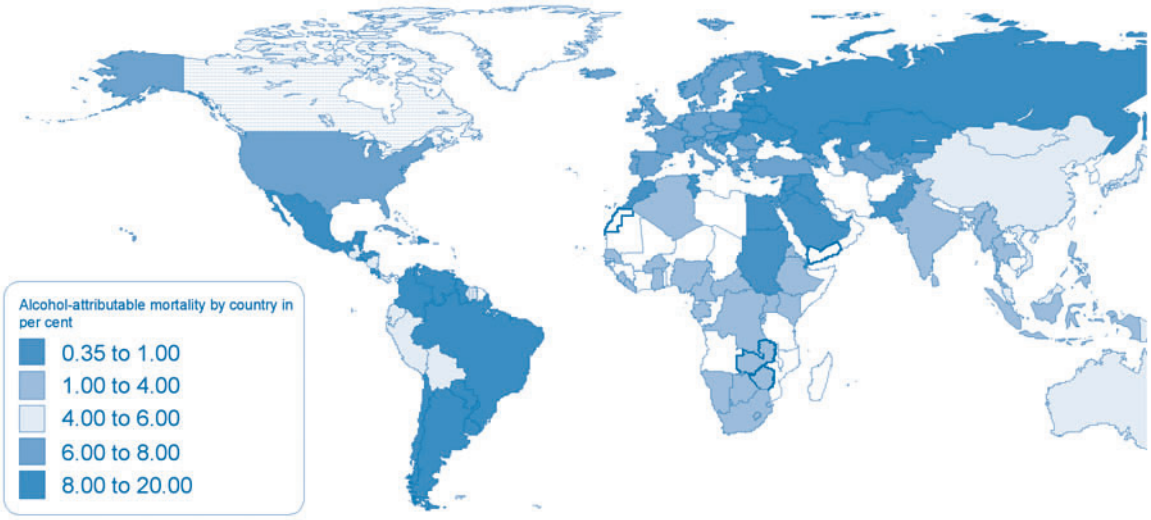
Dr. Norman Giesbrecht, as head of a large team studying Canadian alcohol policy, has submitted a book manuscript, *Alcohol, Commerce and Public Health—Agendas in Recent Canadian Policy Experiences*, to McGill-Queens University Press for publication. The manuscript has received very favourable reviews, and the author team expects that the manuscript will go forward to publication in 2004.

The book compares seven case studies, showing that a public health and safety agenda is not prominent in most national and provincial alcohol policy deliberations; these deliberations tend to favour commerce, revenue generation, vested interests and ideology.

Research findings and public opinion play some role, but not a critical one, in alcohol policy deliberations. The final chapter of the monograph notes the implications of these developments for research, prevention practice and effective policy.

Commissioned by Health Canada and its project partner organization UNAIDS, Jürgen Rehm and Benedikt Fischer led the development of an international compendium with the working title: "Reducing the Risks, Harms and Costs of HIV/AIDS and Injection Drug Use (IDU): A Synthesis of the Evidence Base for Development of Policies and Programs."

This compendium, the basis for an international policy dialogue co-organized by Health Canada, comprises special topic chapters on the evidence of and best intervention practices for HIV/AIDS and IDU from some 21 expert contributor teams from four continents.



Social Factors and Prevention Interventions

SECTION HEAD: Dr. Kathryn Graham

IN THE SOCIAL FACTORS AND PREVENTION INTERventions Section, our research identifies environmental factors (e.g., social, physical, cultural) and individual factors (e.g., personality, predisposition, risk, protection) that are associated with mental health and substance use problems. We then use this knowledge to develop and evaluate research-driven interventions to reduce the occurrence and severity of such problems.

Current programs of research in this section focus on gender and alcohol, preventing barroom aggression, alcohol-related aggression among students and other young adults, school-based and workplace-based prevention programs, healthy psychosocial development and childhood risk and preventive factors, parenting and school culture, and preventing and treating problem gambling.

A National Survey on Alcohol and Gender: the GENACIS Project

The Canadian Institutes of Health Research have funded Dr. Kathryn Graham's national survey on gender and alcohol. This survey, co-led by Dr. Andrée Demers from the University of Montreal and involving collaboration with researchers from across Canada, is part of a multinational collaboration known as the GENACIS (Gender, Alcohol and Culture, an International Study) Project, involving about 30 countries from around the world.

In this study, we will examine the relationship between gender and drinking patterns, as well as the interaction of gender and alcohol consumption related to issues such as social and health consequences of drinking, partner violence, depression and social roles, both at the national level and as part of cross-national comparisons.

Families Working Together

Led by Dr. David DeWit (CAMH) and Drs. Thomas Nochjaski and Andrew Safyer (University at Buffalo), the Families Working Together Project, funded by the U.S. National Institute on Alcohol Abuse and Alcoholism (NIAAA), has completed its third year.

The goal of the project is to evaluate the effectiveness of the *Strengthening Families Program*, a program designed to build resiliency among families struggling with alcohol problems. We have recruited families from 10 alcohol and drug treatment agencies (five in Ontario and five in New York); 277 of our target of 360 Ontario families are already enrolled. Preliminary results—of the impact of the program on children's social and coping skills—were presented at an international conference this past June.

Reducing Aggression and Injury in Bars

Dr. Kathryn Graham heads an international team of investigators conducting a randomized control study, funded by the NIAAA, to evaluate the effectiveness of the *Safer Bars* program on reducing aggression and injury related to drinking in licensed premises.

The impact of the *Safer Bars* program was assessed by teams of trained observers, who conducted over 1,300 nights of observation in study bars and clubs before and after the intervention.

The study found that bars and clubs that participated in the *Safer Bars* program showed a significant decrease in physical aggression, especially more severe aggression such as punching and kicking, when compared with bars and clubs in the control group.These results have generated international interest leading to a number of invited presentations around the world.

Promoting Healthy Childhood and Adolescence

Dr. DeWit and collaborators from CAMH, and from universities and programs across Canada, have been funded by the Hospital for Sick Children Foundation (Innovative Grants Competition) to study the feasibility of conducting a national evaluation of the Big Brothers/Big Sisters adult mentoring program.

In 2002, Dr. DeWit and his colleagues published a report summarizing the results of the *School Culture Project*. This project included a survey of over 2,400 students at 22 high schools in Ontario to study the impact of school culture on academic achievement, behavioural functioning and mental health of high-school students.

Findings revealed that a positive social environment at school contributes to feelings of belonging and acceptance among students, and these feelings, in turn, are associated with strong academic performance, positive mental health and minimal behavioural problems.

Fairness and the Human Spirit at Work

Dr. Martin Shain and Ms Helen Suurvali have completed the development and preliminary evaluation of the *Neighbour at Work Project*. As part of this project, employees volunteer to participate in exercises that help them revisit the fundamental promises of their employment relationships.

The test site for this project was the federal department of Human Resources (HRDC) in Prince Edward Island. Our preliminary evaluation shows that the concept and practice of the *Neighbour at Work* idea have great appeal for all levels of staff and that the surveys and workshops can successfully

raise and resolve issues about the quality of the employment relationship. This idea needs the full support of senior management and unions if it is to have credibility and power.

The project is now entering a quasi-experimental phase, in which staff in several worksites will be trained to conduct surveys and workshops themselves. We will then be able to compare the effectiveness of their interventions with worksites that do not adopt the program. Outcome measures will include indicators of improved mental health.

In this area, we have also prepared an extensive review of the scientific literature on mental health in the workplace for Bill Wilkerson's Global Business and Economic Roundtable on Addictions and Mental Health.

Understanding and Preventing Problem Gambling

Over the past several years, Dr. Nigel Turner has led a program of research into the development of gambling problems and applying this knowledge to prevention and treatment.

Two completed studies (*Winners* and *Pathways*) have shown that problem gambling results from a combination of impulsivity, pre-existing unhappiness, over-reliance on escape as a means of coping with stress, erroneous beliefs about one's ability to win and the experience of winning early in one's gambling career. Our research suggests that none of these factors is necessary for development of a gambling problem; however, the more these factors are present, the higher the risk of gambling problems.

This knowledge on the causes of problem gambling is also being applied to the development of a problem gambling prevention curriculum. In collaboration with CAMH's Problem Gambling Service, Dr. Turner has helped develop and evaluate a curriculum resource of information on problem gambling. Dr. Turner has recently completed an evaluation of the retention of information from this curriculum in a school setting, which found significant improvements in the students' understanding of randomness and coping skills.

Dr. Turner's work has also included developing new psychometric tools to measure erroneous beliefs about random events (*Random Events Knowledge Test*), gambling experiences (*Winning Experiences Questionniare*) and experiences of mood across the lifespan (*Life Charts*).

Alcohol-Related Aggression among University Students and Other Young Adults

Dr. Paul Tremblay has been funded by the Canadian Institutes of Health Research to conduct a study at four universities, looking at alcohol and aggression among students.

Using a Web-based questionnaire, our researchers will study students' perceptions about the effects of alcohol intoxication on aggression, and determine if these perceptions are influenced by dispositions toward aggression and various socio-environmental factors within the drinking environment.

A pilot study, conducted by Ms Laura Ewart under Dr. Tremblay's supervision as part of her fourth-year honours thesis, revealed that students think intoxication affects aggression in certain situations and that their likelihood of becoming aggressive is influenced by motivational factors, such as self-confidence, in provoking situations and level of anger.

Ms Samantha Wells is conducting secondary analyses of data from young adults who participated in the U.S. National Longitudinal Survey of Youth. The main focus of her analyses will be to explore the roles of drinking patterns, drinking contexts, social roles adopted during young adulthood and individual characteristics, including early anti-social behaviour and risk-taking, in terms of their association with alcohol-related aggression.

This extension of Ms Wells's previous research on alcohol-related aggression is part of her PhD dissertation in the Department of Epidemiology and Biostatistics at the University of Western Ontario. She presented preliminary results at a recent international conference.

Personality, Provoking Situations and Aggression

Dr. Paul Tremblay, with others at CAMH and the University of Western Ontario, is investigating the role of personality in responding to provoking situations. In this work, researchers will develop a taxonomy of aggression-provoking situations, covering domains such as workplace aggression, schoolyard bullying, intimate conflict and driver aggression.

Our research papers and reviews have been presented at conferences and submitted for publication; Ms Mirjana Belchevski has completed an empirical study on this topic as part of an honours thesis.

Women's Mental Health and Addiction

SECTION HEAD: Dr. Brenda Toner

THE WOMEN'S MENTAL HEALTH AND ADDICTION

Research Section continues to focus on multidisciplinary research collaboration at international and local levels. This year, we have strengthened our section by recruiting two outstanding research scientists, Drs. Lori Ross and Nili Benazon. The following represent selected highlights of our new and ongoing research programs.

Mental Health Issues in Marginalized Populations of Women

In a new program, Dr. Ross has fostered collaborations with researchers and clinicians across disciplines and fields of study, including community partners, to study mental health issues in marginalized populations of women.

Examples of pilot projects in this program include studies on the role of culture in postpartum mood problems and mental health in lesbian biological mothers and co-parents.

This research seeks to examine potential relationships between experiences of discrimination (including racism and homophobia) and mental health. We also aim to determine whether existing mental services for new mothers meet the unique needs of women who are immigrants and/or identify as lesbian.

Psychosocial Issues in Medical Disorders

Dr. Benazon's area of expertise is the role of affective and anxiety disorders, as well as the family environment, on recovery from physical health conditions. A CIHR investigator, Dr. Benazon is principal investigator on a new study evaluating the quality of care for depression among cardiac patients.

Functional Gastrointestinal Disorders in Women

We completed a study, funded by the U.S. National Institute of Heath, of a multicentre trial of functional bowel disorders. We are pleased to say that that the first paper to come out of this work, "Cognitive-behavioral therapy versus education and desipramine versus placebo for moderate to severe functional bowel disorders," has recently been published in *Gastroenterology*, a high-impact journal in the field.

This study, a collaboration between mental health professionals and gastroenterologists from the University of Toronto (Drs. Toner and Nick Diamant) and the University of North Carolina (Drs. Bill Whitehead and Doug Drossman), aimed to improve understanding and treatment of these chronic and debilitating illnesses, which are diagnosed mainly in women.

This study is the first to take a holistic view of these disorders, assessing both the biological and psychosocial impact of cognitive behaviour therapy (CBT) versus antidepressant medication. We have continued, and expect to continue, to produce papers, abstracts and presentations from this rich database over the past five years.

We are pleased to report that we have had a large grant approved from CIHR (funds released contingent on NIH funding for U.S. collaborators) to continue this very productive program of research. Our new grant will focus on comparing the effect of combination treatment (CBT and antidepressants) versus monotreatment (CBT or antidepressants) for women with functional gastrointestinal disorders.

Development of a Gender Role Scale for Women

Theorists suggest that many mental health problems experienced by women are influenced by socialization into the female gender role. We are one year into a three-year study, funded by the Social Sciences and Humanities Research Council of Canada, to develop and validate a scale to measure gender role socialization in women.

This year, we recruited over 800 research participants from local universities, the community, and health and mental health clinics to complete the candidate items for our scale

together with other questionnaires that will help us validate the scale.

Gender Role Messages for Women: An Intervention
Feminist researchers and clinicians have agreed on the need to develop interventions that expose and challenge gender role messages for women. During this year, we have further developed and refined a manual for such an intervention. We continue to look for a publisher for our prospectus for this work, *Exposing and Challenging Gender Role Messages for Women: Theoretical, Empirical and Clinical Perspectives*.

Complex Post-traumatic Stress Disorder
Dr. Linda McLean's study (co-supervised by Drs. Brenda Toner and Noreen Stuckless), "The development of a complex posttraumatic stress disorder, dissociation, somatization, childhood trauma, and alexithymia in an outpatient sample of women," funded by an Eli Lilly Canada Fellowship in Women's Mental Health Research, is proceeding as planned. Participant recruitment is almost complete.

Life Role Changes that Contribute to Well-Being among Immigrant Chinese Women
Ms Taryn Tang leads this longitudinal program of research that examines the transitional life event of immigration and the changes in Chinese women's roles.

This year, she has recruited 50 Chinese women using a semi-structured interview protocol. This study incorporates quantitative and qualitative research methods and analyses to examine sources of coping and support that are associated with mental health and well-being.

Trichotillomania
Ms Josee Casati is developing a research proposal to further identify themes involving women's experiences with trichotillomania, or compulsive hair pulling.

Ms Casati's previous work in this area was a qualitative study that investigated psychosocial concerns for women with trichotillomania. Critical to this was the need to understand how women with trichotillomania conceptualized their condition and what feelings and concerns were associated with their hair-pulling.

The study identified several concerns, including negative affects, control and triggers. This timely study addressed the importance of identifying and integrating psychosocial concerns into current treatment protocols.

Her current research project will examine factors that may contribute to the development of trichotillomania and affect the quality of life for women with this condition. While providing a foundation for future research, findings from this study will help to define the relationship between early life events and trichotillomania.

Feminist researchers and clinicians have agreed on the need to develop interventions that expose and challenge gender role messages for women.

HONOURS, APPOINTMENTS AND AWARDS

Addington, Jean: was elected Vice President–North America of the International Early Psychosis Association.

Arnold, Paul: received a Travel Award from the American Psychiatric Association to attend and present at the American Psychiatric Institute for Research and Education Colloquium for Junior Investigators.

Ballon, Bruce: was chosen in competition for a slot in the CMA Leaders Forum. He also received the Origins Award from the Game Manufacturers Association and the Outie Award from Gamers Realm for his book *Unseen Masters*.

Barankin, Tatyana: received the Joint Council of Psychiatric Continuing Education–Canadian Psychiatric Association Award for the most outstanding continuing education activity in psychiatry in Canada for continuing education planners affiliated with medical schools.

Bassett, Anne: was appointed as a Consultant to the Yale University Human Behavioral Genetics Research Clinic.

Beitchman, Joseph: was called as an expert witness on Children's Mental Health to the Senate Standing Committee on Science, Technology, and Social Affairs.

Buckley, Leslie: was awarded the Prize for Best Research Day Poster by a Resident, Department of Psychiatry, University of Toronto for her poster, "How to Evaluate a Research Transfer Course and Learn More Than You Expected." This poster also received Best Poster honours at the International Association for Psychosocial Rehabilitation Services annual meeting.

Butterill, Dale: was a member of the MOHLTC Advisory Committee On Mental Health Accountability Framework.

Butters, Jennifer: was awarded the Edie Yolles Award for Dissertation Excellence from the Department of Sociology, University of Toronto.

Cheung, Amy: was a Faculty Member, Adolescent Depression Collaborative Institute for Healthcare Improvement, Bureau of Primary Care, USA. She also received the Robin Hunter Traveling Fellowship Award from the Department of Psychiatry, University of Toronto.

Cheung, Amy & Rodgers, Jennifer: were awarded first prize for their poster presentation at the Department of Health Policy Management and Evaluation, University of Toronto, Research Day and Best Paper honours at the Canadian Psychiatric Association's Annual meeting. Both projects were titled "Cost-Effectiveness of Assertive Community Treatment Teams."

Christensen, Bruce: received the CAMH Research in Psychiatry Award for his study, Regional Analysis of Hippocampal Function in Schizophrenia.

Cohn, Tony: received the CAMH Research in Psychiatry Award for his study, The Effect of Atypical Antipsychotic Medication on Glucose Homeostasis and Blood Lipids: A Prospective Study in First Episode Psychosis.

Cooke, Robert: was promoted to Associate Professor, University of Toronto.

Crawford, Allison: received the University of Toronto Department of Psychiatry Paul E. Garfinkel Caversham Booksellers Prize for Excellence in Resident Leadership.

Cristi, Carolina: was promoted to Assistant Professor, Department of Psychiatry, University of Toronto.

Cunningham, John: received a CAMH Research in Psychiatry Award for his study, Self-Help Materials for Cannabis Users: A Feasibility Trial.

Daskalakis, Jeff: received the Mary Earky Fellow, which is awarded to the highest ranked grant application of the Canadian Psychiatric Research Foundation. He also received the Brain Star Award from the Institute of Neurosciences, Mental Health and Addiction, Canadian Institutes of Health Research (CIHR), and the Laidlaw Prize Award from the Institute of Medical Science, University of Toronto. He received a PhD from the Institute of Medical Sciences at the University of Toronto for his research using transcranial magnetic stimulation to investigate schizophrenia.

Dewa, Carolyn: was a member of the Canadian Health Services Research Foundation Postdoctoral Awards Merit Review Panel, the Canadian Institutes of Health Research's (CIHR) Institute of Population and Public Health (IPPH) and the Institute of Neurosciences, Mental Health and Addiction (INHMA) mental health and work advisory group.

DeWit, Davis: was promoted to Associate Professor, Department of Epidemiology and Biostatistics, University of Western Ontario and was appointed a member of the Research Alliance for Children with Special Needs (RACSN).

Erickson, Patricia: was appointed a member of the Gender & Health special competition review committee, CIHR. She was also appointed Chair of the Gender, Sex & Health Operating Grants Committee, CIHR.

Fischer, Benedikt: received the 2002 IVO Award (IVO Institute, Netherlands), for international research excellence award in addiction/substance use studies and the 2003 Anthony Miller Award (Dept. of Public Health Sciences, University of Toronto), for excellence in research in public health.

Fornazzari, Luis: was appointed by the government of the Republic of Argentina to review and comment on the program, "Elderly and Dementia," by participating in the "Analysis of the Mental Health Program of the Republic of Argentina."

Graham, Kathryn: received the Queen's Golden Jubilee Medal.

Jain, Umesh: received the Dalhousie Prize for Best Poster by a Member of the Canadian Academy of Child Psychiatry at its annual meeting.

Kapur, Shitij: was appointed to the editorial board of *Neuropsychopharmacology*.

Kaspar, Violet: received a CAMH Research in Psychiatry Award for her study, Racial and Ethnic Disparities in Adolescent Mental Health: A Preliminary Project to Establish Community Collaboration and a Sampling Strategy.

Katzman, Martin: received the first annual CAMH Award for Excellence in Undergraduate Education.

Kurdyak, Paul: was awarded the Cleghorn Prize for Best Research Day Presentation by a Resident, Department of Psychiatry, University of Toronto for his presentation, "Quality of Depression Care in Populations with Chronic Medical Conditions."

Langton, Clavin: received the John M. Cleghorn Newly Established Researcher Prize.

Lau, Mark: became a fellow of the Academy of Cognitive Therapy.

Lin, Elizabeth: was a member of the Canadian Institutes for Health Research 2003 Grant Review Panel and the National Institutes for Health 2003 Grant Review Panel.

Lofchy, Jodi: received the Bruce Tovee Best Lecturer Award.

Lunsky, Yona: received a CAMH Research in Psychiatry Award for the study, Psychotic Disorders in Patients with Developmental Disabilities: Diagnostic Concerns.

Manassis, Katharina: received the University of Toronto Department of Psychiatry Award for Excellence in Continuing Mental Health Education.

Mann, Robert: was a member of the National Board of Directors of MADD Canada.

Marsh, David: received the Council Award of the College of Physicians and Surgeons of Ontario.

McLean, Linda: received the University of Toronto Department of Psychiatry Award for Best Accomplishment for a Fellow.

McNeely, Heather: Received a CAMH Research in Psychiatry Award for her study, The Functional Neurobiology of Major Depression.

Meyer, Jeffrey: received an honourable mention for the Klerman award from NARSAD. This award is for research done by people holding NARSAD young investigator awards; honourable mentions were given to six out of 150 investigators.

Oskin, Alec: was selected as an American Psychiatric Association/ GlaxoSmithKline Fellow for a two-year term. He also received the University of Toronto Department of Psychiatry Paul E. Garfinkel Caversham Booksellers Prize for Excellence in Resident Leadership.

Ravitz, Paula: was promoted to Assistant Professor, University of Toronto.

Rehm, Jürgen: received the Jellinek Memorial Fund Award for outstanding contributions to the advancement of knowledge on alcohol/ alcoholism.

Richter, Peggy: was promoted to Associate Professor, Department of Psychiatry, University of Toronto.

Ross, Lori: won the 2003 Junior Investigator Travel Award for Women and Gender Differences Research, National Institute on Drug Abuse.

Rush, Brian: was a member of the British Columbia Advisory Committee for Addictions Framework and Best Practices.

Sadavoy, Joel: was appointed President-Elect of the International Psychogeriatric Association.

Seeman, Mary: was awarded the Queen's Golden Jubilee Commemorative Medal, was named a Distinguished Fellow of the American Psychiatric Association and was awarded an honorary Doctor of Science degree from the University of Toronto.

Segal, Zindel: was appointed as a reviewer for the National Institute of Mental Health's panel on treatment interventions for psychiatric disorders.

Siu, Maurice: received the University of Toronto Department of Psychiatry Juan C. Negrete Award in Addiction Psychiatry.

Smith, Patrick: was appointed Vice-President of the Canadian Executive Council on Addictions (CECA).

Strauss, John: was awarded the CINP Pfizer Best Research Poster Award at the 13th CINP Congress, in Montreal.

Strike, Carol & Rush, Brian: received a CAMH Research in Psychiatry Award for their study, Therapist Attitudes Towards Cannabis-Related Drug Problems.

Sylvestre, John: received a CAMH Research in Psychiatry Award for his study, Is a Job Enough? Developing a Conceptual Model of the Working Careers of Consumer/Survivors.

Tomkins, Denise: received a CAMH Research in Psychiatry Award for her study, Sex Differences in Susceptibility to Alcohol-Induced Cognitive Deficits.

Toner, Brenda: received a Research Scientist Award for outstanding clinical research in brain-gut interactions, Functional Brain Gut Group, American Gastrointestinal Association.

Toplak, Maggie: was the co-recipient of the Fellowship Award of Merit at the Hospital for Sick Children.

Turner, Ed: received the Queen's Golden Jubilee Commemorative Medal for his contributions to psychiatry and the Anglican Church of Canada. He was also designated a Distinguished Life Fellow by the American Psychiatric Association.

Tyndale, Rachel: received the American Society for Clinical Pharmacology and Therapeutics Leon Goldberg Young Investigator Award, was appointed to the editorial board for *Drug Metabolism Reviews* and chaired the session on Genetics of Addiction for the WHO International Conference on Neuroscience and Addictions, in Mexico City.

VanderSpek, Suzi: received the University of Toronto Department of Psychiatry Award for Best Overall Poster Presentation.

Wittenberg, Jean: was chosen to be a Member of the Advisory Committee for Human Resources Development Canada. He was also invited to be a Visiting Professor at the University of Tel Aviv and received the University of Toronto Department of Psychiatry Psychotherapy Award for Academic Excellence.

Wolfe, David: was appointed the inaugural RBC Investments Chair in Children's Mental Health and Developmental Psychopathology.

Zipursky, Robert: received the John M. Cleghorn Memorial Award for Excellence and Leadership in Clinical Research from the Canadian Psychiatric Association. He was appointed Vice-Chair, Research for the Department of Psychiatry, University of Toronto, and Chair of the Professional Advisory Board of the Canadian Psychiatric Research Foundation. He also received the Paul E. Garfinkel Award for Best Fellowship Supervisor.

Adlaf, E. *Cayman Islands student drug use survey consulting.* National Drug Council of the Cayman Islands.

Adlaf, E., Gliksman, L., Poulin, C., Wild, C., Demers, A. & Kairouz, S. *Social determinants of hazardous drinking and other health outcomes.* Canadian Institutes of Health Research.

Adlaf, E. & Turner, N. *Schools, students and adolescent gambling in Ontario.* Ontario Problem Gambling Research Centre.

Alda, M., Turecki, G., Groff., P., Rouleau, G. & Young, T. *Genetic studies of lithium responsive bipolar disorders.* Canadian Institutes of Health Research.

Allison, K., Adlaf, E., Dwyer, J. & Goodman, J. *Physical activity promotion among youth.* Heart and Stroke Foundation of Ontario.

Arnold, P. & Kennedy, J. (supervisor). *Investigation of serotonin-dopamine interaction in obsessive-compulsive disorder: An innovative strategy combining genetics and neuroimaging.* Ontario Mental Health Foundation.

Ashley, M.J., Cohen, J. & Ferrence, R. *On the front line: Exploring the expanding roles of pharmacists in smoking cessation.* National Cancer Institute of Canada.

Atkinson, L., Goldberg, S., Levitan, R., Matthews, S., Macciardi, F., Basile, V. & Masellis, M. *Development of the HPA axis in infants: Environmental and genetic influences.* Canadian Institutes of Health Research.

Bagby, R.M. *Patient dimensions as predictors of response, relapse and recurrence following cognitive-behavioral therapy, interpersonal psychotherapy and pharmacotherapy treatment of patients with major depression.* Ontario Mental Health Foundation.

Bagby, R.M. & Christi, C. *Patient dimensions as predictors of response, relapse and recurrence following cognitive-behavioral therapy, interpersonal psychotherapy and pharmacotherapy treatment of patients with major depression.* Ontario Mental Health Foundation.

Bagby, R.M., Farvolden, P., Toneatto, T. & Oakman, J. *Personality and vulnerabilty in problem gambling.* Ontario Problem Gambling Research Centre.

Bagby, R.M. & Taylor, G. *Development of a structured interview to assess the alexithymia construct.* Social Sciences and Humanities Research Council of Canada.

Barbaree, H., Langton, C. & Seto, M. *Toward a model of risk management: The contributions of actuarial risk, institutional treatment, dynamic risk factors, and community supervision in the prediction and prevention of sex offender recidivism.* Ontario Mental Health Foundation.

Barr, C. & Kennedy, J.L. *Investigation of genetic factors in attention deficit hyperactivity disorder.* Canadian Institutes of Health Research.

Barr, C., Lovett, M., Beitchman, J., Humphries, T., Tannock, R. & Macciardi, F. *Genetics of reading disabilities.* Canadian Institutes of Health Research.

Bassett, A. *Canada research chair (Tier I).* Canadian Institutes of Health Research.

Bassett, A.S., Chow, E., Weksberg, R., Zipursky, R., Bryustowics, L. & Siu, S. *A screening strategy for a genetic subtype of schizophrenia.* Canadian Institutes of Health Research.

Bassett, A.S., Husted, J. & Chow, E. *Identifying predictive factors for familial schizophrenia.* Bill Jeffries Schizophrenia Endowment Fund.

Beiser, M. *Online development project.* Citizenship and Immigration Canada.

Beiser, M., Amrhein, C., Rocha, C., Kilbride, K., Lo, L., Ali, M., Doucet, M., Siemiarycki, M., Khanlou, N., Anisef, P., Murdie, R., George, U., Ratanshi, F., Kwong, W., Troper, H., Shields, J. & Wortley, S. *Joint Centre of Excellence for Research on Immigration and Settlement (CERIS).* Social Sciences and Humanities Research Council of Canada.

Beiser, M., Kaspar, V., Simich, L., Rummens, A., Hamilton, H. & Khanlou, N. *New Canadian children and youth study.* Canadian Institutes of Health Research.

Beiser, M., Noh, S., Simich, L. & Rummens, A. *A community in distress: Mental health in the Tamil community.* Canadian Institutes of Health Research.

Beiser, M., Simich, L., Rummens, A. & Hamilton, H. *Enhancing capacity to combat health hazards in the Niger delta.* Canadian Institutes of Health Research.

Beiser, M., Zakus, D., Briggs, N. & Simich, L. *Chronic conflict and the health of exposed populations.* International Development Research Centre.

Beitchman, J. *Tele-psychiatry service contract.* Ministry of Community, Family, and Children's Services.

Beitchman, J., Johnson, C., Young, A., Atkinson, L., Adlaf, E., Escobar, M. & Vohra, S. *The Ottawa language study: The moderating effects of transitional age variables on psychological outcomes: A 20 year follow-up study.* Canadian Institutes of Health Research.

Bishop, S.R., Anderson, N.D., Abbey, S.E., Devins, G.M., Segal, Z.V. & Lau, M.A. *Toward a program of research in mindfulness-based stress reduction: Validating and specifying the construct of mindfulness and the development of self-report measure.* Canadian Institutes of Health Research.

Blanchard, R., Christensen, B., Zipursky, R., Mikulis, D., Klassen, P., Dickey, R. & Barbaree, H. *Brain structure and function in pedophiles.* Canadian Institutes of Health Research.

Blomqvist, J., Cunningham, J., Koski-Jannes, A. & Wallander, L. *Solutions to alcohol problems: The significance of treatment and other influences.* The Bank of Sweden Tercentenary Foundation.

Boydell, K. & Trainor, J. *CMHEI project: A longitudinal evaluation of family initiatives in Ontario.* Ontario Mental Health Foundation.

Brzustowicz, L., Bassett, A. & Cox Matisse, T. *Molecular genetics of a schizophrenia locus on 1q21-22.* National Institutes of Health.

Buskard, P. & Lavigne, P. *Development of training and education curriculum for service providers on issues related to hep C, HIV and substance use.* Health Canada.

Busto, U., Naranjo, C., Mayberg, H. & Cardenas, L. *Brain reward system, depression, and nicotine dependence.* National Institute on Drug Abuse.

Busto, U., Streiner, D., Herrmann, N. & Sproule, B. *The comparative pharmacological effects of temazepam, diphendydramine, and valerian in elderly subjects.* Canadian Institutes of Health Research.

Calzavara, L., Strike, C., Millson, M., Major, C., Myers, T., Fischer, B. & Remis, R. *Rapid assessment of injection drug use in Peel region.* Region of Peel Public Health Department.

Castel, S., Kennedy, S.H. & Rush, B. *The assessment of the role of concurrent substance use and mental health disorders in the utilization abuse and community services and associated outcomes.* Canadian Institutes of Health Research.

Castel, S., Rush, B. & Toneatto, T. *Screening and assessment of concurrent disorders among clients with substance use disorders: The pilot project of the validation of a self-assessment instrument.* Canadian Institutes of Health Research.

Christensen, B., Zipursky, R. & Kapur, S. *Schizophrenia as a neurodevelopmental disorder: Selective dorsal pathway impairment.* Canadian Psychiatric Research Foundation.

Cohen, J., Abernathy, T., Adlaf, E., Ashley, M.J. & Ferrence, R. *Support for tobacco control policy measures: Multi-level analysis.* Social Sciences and Humanities Research Council of Canada.

Cohen, J., Ashley, M.J., Ferrence, R. & Steward, D. *Institutional addiction to tobacco: Defining links between the tobacco industry and academic and health institutes.* National Cancer Institute of Canada.

Cohen, J., Brown, S., Campbell, S., Adlaf, E., D'Avernas, J., Ferrence, R. & Garcia, J. *Tobacco control policies: A program of research: Canadian tobacco control research initiative.* National Cancer Institute of Canada.

Cooke, R. *A multicentre, pivotal, safety and efficacy study of the neurocybernetic prosthesis in patients with depression.* Cyberonics Inc.

Corrigall, W. & Rahman, S. *Cholinergic and opiate mechanisms in drug reinforcement.* National Institute on Drug Abuse.

Court, J. & Khouri, E. *Hannah archives internship.* Associated Medical Services Inc./ Hannah Institute for the History of Medicine.

Cunningham, J.A. *The impact of self-help materials for problem drinkers: Population studies.* Canadian Institutes of Health Research.

Daskalakis, Z., Kapur, S., Chen, R. & Christensen, B. *A study of cortical inhibition and plasticity in schizophrenia using transcranial magnetic stimulation.* Canadian Institutes of Health Research.

Daskalakis, Z., Kapur, S., Christensen, B. & Chen, R. *A study of cortical inhibition in schizophrenia using TMS transcranial magnetic stimulation.* Canadian Psychiatric Research Foundation.

Devins, G., Beiser, M., Siu, L., Rodin, G., Lee, R. & Mah, K. *Cultural syndromes, coping, and the psychosocial impact of illness intrusiveness in cancer.* Canadian Institutes of Health Research.

Dewa, C. *Career scientist award.* Ontario Ministry of Health and Long-Term Care.

Dewa, C., Hoch, J. & Goering, P. *The impacts of drug benefit co-payments on the guideline recommended use of antidepressants.* Canadian Institutes of Health Research.

Dewa, C., Zipursky, R., Collins, A., Doan, R., Goering, P., Sylvestre, J. & Tolomiczenko, G. *Examining the cost-effectiveness and effectiveness of a mobile treatment approach to delivering care for first-episode psychosis.* Canadian Institutes of Health Research.

Drossman, D.A., Toner, B.B., Whitehead, W. & Diamant, N.E. *Multicenter trial of functional bowel disorders.* National Institutes of Health.

Duffy, A. & Young, T. *A longitudinal study of the children of bipolar parents.* Canadian Institutes of Health Research.

Erickson, P., Harrison, L. & Adlaf, E. *A cross national study of the youth drugs violence nexus.* National Institute on Drug Abuse.

Farvolden, P. & Oakman, J. *Behavioural inhibition, behavioural activation, personality, and novelty.* Social Sciences and Humanities Research Council of Canada.

Ferentzy, P., Skinner, W. & Antze, P. *Exploring mutual aid pathways to recovery from gambling problems and co-occuring gambling and substance abuse problems.* Ontario Problem Gambling Research Centre.

Ferrence, R., Ashley, M.J., Bull, S., Cohen, J., Lovato, C. & Potvin, L. *A national study on environmental tobacco smoke in the home.* National Cancer Institute of Canada.

Ferrence, R., Cohen, J., Ashley, M.J., Selby, P., Tremblay, P. & Broadway, T. *Protecting children's health: The role of primary care physicians addressing environmental tobacco smoke (ETS) in home environments.* The Hospital for Sick Children Foundation.

Ferrence, R., Cohen, J., Kaufman, P., Perkins, N., Perley, M. & Poland, B. *Smoking in outdoor public places: A study of socio-spatial relationships.* Canadian Tobacco Control Research Initiative, National Cancer Institute of Canada.

Ferrence, R., Rootman, I., Ashley, M.J., Brown, K.S., Cohen, J., McDonald, P. & Stephens, T. *Ontario tobacco research unit (sub-grant University of Toronto).* Ontario Ministry of Health and Long-Term Care.

Ferrence, R., Rootman, I., Ashley, M.J., Brown, K.S., Cohen, J., McDonald, P. & Stephens, T. *Plans for enhanced surveillance, evaluation and research.* Ontario Ministry of Health and Long-Term Care.

Fischer, B. *Illicit opiate addiction (IHRT): Training grant.* Canadian Institutes of Health Research/Institute of Neurosciences, Mental Health and Addiction.

Fischer, B. *New investigator award: Illicit drug use, treatment and policy.* Canadian Institutes of Health Research.

Fischer, B., Adlaf, E., Anis, A.H., Brochu, S. & Bruneau, J. *The socio-environmental determinants of substance use and health: Epidemiology, prevention and treatment.* Canadian Institutes of Health Research.

Fischer, B., Brissette, S., Brochu, S., Bruneau, J., El-Guebaly, N., Lauzon, P., Marsh, D., O'Shaughnessy, M., Poulin, C., Rehm, J., Schechter, M., Single, E., Stewart, J., Tyndall, M. & Wild, C. *Illicit opiate addiction treatment, research and policy.* Canadian Institutes of Health Research.

Fischer, B. & Rehm, J. *Evaluation framework proposal for supervised injection sites.* Health Canada.

Fischer, B. & Rehm, J. *Policy framework: Reducing risks, harms, and costs of injection drug use and HIV/AIDS.* Health Canada.

Fischer, B., Rehm, J. & Krajden, M. *HCV: Socio-behavioural research priorities workshop.* Canadian Institutes of Health Research.

Fitzmaurice, P. & Kish, S. (supervisor). *Brain glutathione in Friedreich's ataxia.* Friedreich's Ataxia Research Alliance.

Fletcher, P. *The role of the ventral pallidum in mediating drug reinforcement.* Natural Sciences and Engineering Research Council.

Fletcher, P. *Serotonin-dopamine interactions and reward related behaviour.* Canadian Institutes of Health Research.

Fornazzari, L., Simard, M., St. George-Hyslop, P., Wherret, J., Keren, R., Sauthier, S. & Feldman, H. *Multi-site collaborative study for genotype-phenotype associations in Alzheimer's disease.* GlaxoSmithKline Inc.

George, S. *Canada research chair (Tier I).* Canadian Institutes of Health Research.

George, S. *Regulation and function of neuropeptide receptors.* Canadian Institutes of Health Research.

George, S.R. & O'Dowd, B.F. *The biology of dopamine and other amine binding receptors.* Canadian Institutes of Health Research.

George, S.R. & O'Dowd, B.F. *Receptors mediating drug dependence.* National Institute on Drug Abuse.

Gerald, D. & Beiser, M. *Gender and ethnocultural moderators of illness-instrusiveness across the life span.* Canadian Institutes of Health Research.

Ginovart, N., Kapur, S. & Houle, S. *Can dopamine D2 receptor upregulation by antipsychotics be avoided by a different regimen of occupancy kinetics? A longitudinal [11C]-raclopride PET study.* National Alliance for Research on Schizophrenia and Depression.

Ginovart, N., Kapur, S. & Houle, S. *Imaging endogenous dopamine levels with in vivo [11C] raclopride displacement studies: Understanding the true mechanism.* Canadian Institutes of Health Research.

Gliksman, L. *FOCUS program needs assessment (Ontario stroke strategy).* Ministry of Health and Long-Term Care.

Gnam, W. *Profiling the mental health and service utilization of WCB claimants.* Workers' Compensation Board of British Columbia.

Gnam, W., Mustard, C., Lin, E., Dewa, C. & Rush, B. *The economic costs of mental disorders, alcohol, tobacco, and illicit drugs in Ontario.* Ontario Mental Health Foundation.

Goering, P. *Canadian Health Services Research Foundation chair award.* Canadian Institutes of Health Research.

Goering, P. *Community Mental Health Evaluation Initiative coordinating centre.* Ontario Mental Health Foundation.

Goering, P., Butterill, D., Macfarlane, D., Cripps, M.J., Baranek, P., Beseau, K., Koegl, C., Durbin, J. & Aitchison-Drake, C. *Toronto–Peel comprehensive assessment project.* Ministry of Health and Long-Term Care.

Goering, P., Butterill, D., Macfarlane, D., Cripps, M.J. & Prendergast, P. *Collingwood community mental health services review.* Community Mental Health Services, Collingwood (MOHLTC).

Goering, P., Macfarlane, D., Palmer, H. & Higgins, C. *Evaluation of Muskoka–Parry Sound community mental health service.* North East Mental Health Implementation Task Force.

Goering, P., Macfarlane, D., Tolomiczenko, G., Bullock, H., Robins, S.L., Doob, A., Blackburn, J., Haber, S. & Pyke, J. *A review of Toronto's mental health court support services.* Canadian Mental Health Association.

Goering, P., Rogers, J. & English, R.A. *Grey Bruce health services: An examination of inpatient utilization patterns at the psychiatric unit.* Grey Bruce Huron Perth District Health Council.

Graham, K., Demers, A., Nadeau, L., Poulin, C., Wilsnack, S., Bloomfield, K. & George, A. *Multi-national study on alcohol and gender.* Canadian Institutes of Health Research (University of Alberta).

Graham, K., Osgood, D.W. & Gliksman, L. *Safer bars: Evaluating an intervention to reduce barroom violence.* National Institute on Alcohol Abuse and Alcoholism.

Graham, K., Rehm, J., Demers, A., Nadeau, L., Poulin, C., Dell., C.A. & Kairouz, S. *A multinational perspective on gender, alcohol and health: GENACIS Canada: A national survey to be done in collaboration with the international GENACIS project.* Canadian Institutes of Health Research.

Guttman, M. *PREDICT-HD (neurobiological predictors of Huntington's disease).* National Institutes of Health.

Hodgins, D.C., Toneatto, T., Makarchuk, K., Skinner, W. & Vincent, S. *Minimal treatment approaches for concerned significant others of problem gamblers.* Ontario Problem Gambling Research Centre.

Holden J., Garcin, N., Lewis, M.E.S., Minnes, P., Bradley, E., Hennen, B., Lunsky, Y., Ouellett-Kuntz, H., McCreary, B. & Rajcan-Separovic, E. *HEIDI: Healthcare equity for intellectually disabled individuals.* Canadian Institutes of Health Research.

Honer, W.G., Phillips, A.G., Thornton, A. & Kennedy, J. *Interactions of development, early life experience and genetic predisposition in schizophrenia.* Canadian Institutes of Health Research.

Houle, S. & McIntosh, R. *BRAIN (Behavioural Research and Imaging Network).* Ontario Research and Development Fund.

Jain, U., Turner, N. & Spence, W. *Special populations in gambling: Attention deficit hyperactivity disorder (ADHD) and pathways to problem gambling.* Ontario Problem Gambling Research Centre.

Kan, P. & Petronis, A. (supervisor). *Epigenetic analysis of multicopy DNA elements in major psychosis.* Ontario Mental Health Foundation.

Kapur, S. *Canada research chair (Tier II).* Canadian Institutes of Health Research.

Kapur, S. *Characterisation of PS003 (including anti-avoidance test, catalepsy, and binding to brain tissue).* Clera Inc.

Kapur, S. & Allison, F. *The effect of antipsychotics on maternal behaviour: Identifying the underlying behavioural and neurobiological mechanisms.* National Alliance for Research on Schizophrenia and Depression.

Kapur, S., Apiquian, R., Ulloa, E., Fresan, A. & Nicolini, H. *Amoxapine as an atypical antipsychotic: A comparative study vs. risperidone.* Stanley Research Foundation.

Kapur, S., Fletcher, P. & Nobrega, J. *Animal models of schizophrenia: What do they predict and what to make of it?* Eli Lilly Canada Inc.

Kapur, S., Fletcher, P., Tallerico, T., Becker, S. & Seeman, P. *Decoding schizophrenia: Putting the pieces together: Linking genes, neurochemistry, cognition, affect and neural networks.* Ontario Mental Health Foundation.

Kapur, S., Lanctot, K., Herrmann, N. & Black, S.E. *PET study of 5-HT1A receptors in Alzheimer's disease.* Alzheimer's Association.

Kapur, S., McClelland, R.B., Nobrega, J.N. & Rompre, P.P. *The pharmacological basis of atypical antipsychotic activity: A new hypothesis.* Canadian Institutes of Health Research.

Kapur, S. & Sellers, E. *A single centre PET study to determine the occupancy of different doses of EMD 281014 at cortical 5-HT2A receptor.* Merck KGaA.

Kapur, S. & Zipursky, R. *PET investigations of endogenous dopamine and clinical response in schizophrenia.* Canadian Institutes of Health Research.

Kaspar, V. *Health and development of immigrant and minority children and youth.* Canadian Institutes of Health Research.

Kaspar, V., Noh, S., Hou, F. & Wickrama, K.A.S. *Racial and ethnic disparities in adolescent mental health.* Canadian Institutes of Health Research.

Katzman, D., Zipursky, R., Christensen, B., Young, A. & Mikulis, D. *Neurobiologic determinants of cognitive outcome in adolescent-onset anorexia nervosa.* Ontario Mental Health Foundation.

Keating, D.P., Miller, F.K., Sagar, A., Landy, S., Atkinson, L., Bradley, S. & Wittenberg, J.V. *Aggression problems in young children: Early intervention in a community based approach.* Change Foundation.

Kennedy, J., Macciardi, F., Wong, A., Muglia, P. & Masellis, M. *Strategies for gene discovery in schizophrenia.* Canadian Institutes of Health Research.

Kennedy, J., Muglia, P. & Jain, U. *ADHD in adulthood: Identification of genetic risk factors.* Ontario Mental Health Foundation.

Khatri, N. *Coping, thinking, and personality factors of women with depression: A relapse prevention treatment program.* Canadian Institutes of Health Research.

King, G., DeWit, D., LaPorta, J., MacDougall, J., Meyer, K., Miller, L. & Offord, D. *Predictors of Canadian children's mental health and competence: A structural equation modelling approach using the national longitudinal survey of children and youth.* National Health Research and Development Program (CIHR).

Kish, S.J., Guttman, M., Warsh, J., Saint-Cyr, J., Houle, S., Blake, J., Schapiro, C. & Wilson, A. *PET neuroimaging study of the brain serotonin transporter in Parkinson's disease.* Michael J. Fox Foundation.

Kish, S.J., Mundo, E. & Houle, S. *Does ecstasy damage brain serotonin neurones in young, chronic users of the drug? A pilot study.* Canadian Psychiatric Research Foundation.

Kish, S.J., Mundo, E., Warsh, J., Saint-Cyr, J., Houle, S., Blake, J., Schapiro, C. & Wilson, A. *Do serotonin transporter gene polymorphisms influence transporter expression in human brain?* Canadian Institutes of Health Research.

Kocovski, N. *Cognitive models of social anxiety: Postdoctoral fellowship award.* Social Sciences and Humanities Research Council of Canada.

Korman, L., Collins, J., McMain, S., Skinner, W. & Toneatto, T. *Concurrent gambling, substance use and anger: Development of a brief integrated treatment.* Ontario Problem Gambling Research Centre.

Kovaks, M., Vetro, A., Kennedy, J.L., Barr, C.L. & Devlin, B. *Risk factors in childhood onset depression.* National Institutes of Health (Subgrant Agreement with U. of Pittsburgh)

Krank, M.D., Stacy, A., Wall, A.M., Wekerle, C. & Lai, D. *A longitudinal study of social context, cognition, risk-taking behaviour, and health outcomes.* Social Sciences and Humanities Research Council of Canada.

Lalumière, M.L. & Coté, K. *The influence of birth order on development: A study of adoptees.* Social Sciences and Humanities Research Council of Canada.

Lau, M., Christensen, B., Gemar, M. & Segal, Z. *Inhibitory deficits in persons with major depressive disorder: Risk factor or correlate?* Canadian Institutes of Health Research.

Lê, A.D. *Role of serotonin in stress-induced relapse to alcohol.* Ontario Mental Health Foundation.

Lê, A.D. & Fletcher, P. *Role of serotonin in stress-induced relapse to alcohol.* National Institute on Alcohol Abuse and Alcoholism.

Levitan, R., Masellis, M., Kaplan, A., Basile, V., Macciardi, F., Kennedy, S. & Lam, R. *Polymorphism in serotonin system genes: Putative role in increased food intake in bulimia nervosa (BN) and seasonal affective disorder (SAD).* Ontario Mental Health Foundation.

Levitan, R.D. *Serotonin genetic variation and increased eating behaviour in bulimia nervosa and seasonal affective disorder.* Ontario Mental Health Foundation.

Levitan, R.D. *Serotonin-induced Ca+2 mobilization in platelets: A biochemical phenotype to study bulimia nervosa and seasonal affective disorder.* National Alliance for Research on Schizophrenia and Depression.

Li, M. & Kapur, S. (supervisor). *The disruptive effects of antipsychotics on maternal behavior: Identifying the underlying mechanisms.* Ontario Mental Health Foundation.

Li, P. & Warsh, J. *Pathophysiological significance of altered cAMP signaling in bipolar affective disorder.* Ontario Mental Health Foundation.

Liu, F. *Dopamine D1-NMDA: Receptor protein: Protein interactions: Implications for schizophrenia.* Canadian Psychiatric Research Foundation.

Liu, F. *Ligand-gated GABA-A and dopamine D5 receptor protein-protein interaction in post-mortem schizophrenia brain.* National Alliance for Research on Schizophrenia and Depression.

Liu, F. *Novel model of g-protein coupled receptor and ligand gated ion channel cross-talk.* Canadian Institutes of Health Research.

Liu, S.C.I. & Nobrega, J. (supervisor). *Altered gene expression in schizophrenia.* Canadian Institutes of Health Research.

Lunsky, Y., Goering, P. & Bradley, E. *Dual diagnosis in the provincial psychiatric hospitals: A population-based study.* Ontario Mental Health Foundation.

Macciardi, F. *Haplotype transmission disequilibrium test (H-TDT) of candidate genes for the susceptibility to schizophrenia on chromosome 22q11.* National Alliance for Research on Schizophrenia and Depression.

Macciardi, F. *Molecular genetic epidemiology of complex psychiatric disorders.* Canadian Foundation for Innovation.

Macciardi, F. *Molecular genetic epidemiology of complex psychiatric disorders.* Ontario Innovation Trust.

Macciardi, F.M., Bradwejn, J., Kennedy, J.L. & Koszycki, D. *Genetic factors in panic disorders.* Canadian Institutes of Health Research.

MacDonald, J. & Van Tol, H.H.M. *Calcium-sensing in hippocampal neurons.* Canadian Institutes of Health Research.

MacDonald, J.F., Atwood, H.L., Bouilianne, G.L., Charlton, M.P., Roder, J., Trimble, W.S., Van Tol, H.H.M., Wang, Y.T. & Wang, L.T. *The synapse.* Canadian Institutes of Health Research.

MacDonald, J.F. & Turner, N. *Life skills, mathematical reasoning and critical thinking: Curriculum for prevention of problem gambling.* Ontario Problem Gambling Research Centre.

MacDonald, S., Csiernik, R.P., Wild, C. & Durand, P. *Understanding approaches to address alcohol and drug problems in the Canadian workforce.* Social Sciences and Humanities Research Council of Canada.

MacDonald, S., Mann, R., Chipman, M., Erickson, P. & Hathaway, A. *Factors related to traffic collisions, violence and injury risk among cannabis and cocaine clients in treatment.* Canadian Institutes of Health Research.

MacQueen, G. & Young, T. *Functional and structural hippocampal changes in major depression.* Canadian Institutes of Health Research.

Martucci, L. & Kennedy, J. (supervisor). *Pharmacogenetics of antipsychotic medication response in schizophrenia.* Canadian Institutes of Health Research.

Mayberg, H. & Segal, Z. *Limbic-cortical metabolic changes as a final common pathway of depression remission: A comparison of venlafaxine and cognitive behavioural therapy.* Canadian Institutes of Health Research.

McMain, S., Gnam, W., Links, P., Cardish, B., Korman, L., Dawe, I. & Quastel, A. *Hope for chronically suicidal patient: Evaluating the clinical and health services impact of dialetical behaviour therapy in individuals with borderline personality disorder.* Canadian Institutes of Health Research.

McNeely, H. *Neurophysiology of emotion processing in major depressive disorder.* University of Toronto.

Meyer, J. *5-HT2A receptors in suicidality and impulsivity (fellowship).* Canadian Institutes of Health Research.

Meyer, J., Houle, S., Ginovart, N. & Wilson, A. *The assessment of the reproducibility and specificity of [11C] harmine as a PET radioligand for the investigation of MAO-A in humans.* GlaxoSmithKline Inc.

Meyer, J., Houle, S. & Wilson, A. *Occupancy of the serotonin transporter by fluoxetine in healthy Japanese subjects.* Eli Lilly Canada Inc.

Meyer, J., Kennedy, S.H., Mayberg, H. & Houle, S. *5-HT2A receptors and treatment responsiveness during depression.* National Alliance for Research on Schizophrenia and Depression.

Meyer, J.H., Kennedy, S.H. & Houle, S. *5-HT2A receptors in suicidality and impulsivity.* Canadian Institutes of Health Research.

Millson, M., Strike, C., Calzavara, L. & Myers, T. *Understanding injection drug using in Toronto: Injection drug users' descriptions of their experiences and perceptions of HIV risk and prevention.* The Ontario HIV Treatment Network.

Millson, M., Strike, C., Fischer, B., Myers, T. & Calzavara, L. *Assessing the impact of low threshold methadone programs on HIV risk taking behaviours.* National Health Research and Development Program (CIHR).

Muglia, P., Kennedy, J., Jain, U. & Turner, N. *Identification of genetic risk factors for pathological gambling.* Ontario Problem Gambling Research Centre.

Muller, D. & Kennedy, J. (supervisor). *Molecular genetic studies on weight gain in antipsychotic treatment.* Canadian Institutes of Health Research.

Mundo, E. *In vivo expression of the serotonin transporter gene in bipolar disorder patients with antidepressant-induced mania.* National Alliance for Research on Schizophrenia and Depression.

Myers, T., Bullock, S., Calzavara, L., Fischer, B. & Millson, M. *Dual risk for HIV? Drug use and sexual behavior among MSM in Toronto.* Ontario HIV Treatment Network.

Naranjo, C., Busto, U., Mayberg, H. & Herrmann, N. *Brain reward system dysfunction in major depressive disorder: An f-MRI study.* Canadian Institutes of Health Research.

Naranjo, C., Hermann, N. & Busto, U. *Central serotonin dysfunction and alcohol dependence.* Ontario Mental Health Foundation.

Ni, X. & Kennedy, J. (supervisor). *Searching for major susceptibility genes for bipolar disorder differential screening of gene initiation sequences.* Canadian Psychiatric Research Foundation.

Nobrega, J. *Brain substrates of side effect vulnerability after long-term neuroleptic treatment.* National Alliance for Research on Schizophrenia and Depression.

Nochajski, T., DeWit, D., Macdonald, S., Maguin, G. & Safyer, A. *Family-based prevention for children of alcoholics.* National Institute on Alcohol Abuse and Alcoholism.

Nussbaum, D. *Ministry of Health (correctional services) agreement.* Ministry of Correctional Services.

O'Dowd, B. & George, S. *Identification and characterization of novel human GPCR genes.* Merck Frosst Canada & Co.

O'Dowd, B. & George, S. *Proof of principle: Drug screening for agonists of G protein coupled receptor function using a cell-based assay.* Canadian Institutes of Health Research.

O'Loughlin, J., Paradis, G., Hanley, J., DiFranza, J., Tyndale, R.F., Clarke, P., Sacks-Silver, G., Tremblay, M., Heneman, B., Dupuis, G., Bujold, M., Band, P. & Dery, V. *A prospective study on the natural history of nicotine dependence.* National Cancer Institute of Canada.

Palmour, R.M., Vaccarino, F.J., Bateson, A.N., Baker, G.B., Ervin, F., Gutkowska, J. & Chaudhuri, A. *CCK and anxiety: Neurobiological characterization.* Canadian Institutes of Health Research.

Parikh, S. & Zaretsky, A. *Cognitive-behavioral therapy versus psycho-education in bipolar disorder.* Stanley Research Foundation.

Parikh, S., Zaretsky, A., Streiner, D., Yatham, L., Beaulieu, S., Siotis, I.P., Levitt, A.J. & Young, T. *Psychoeducation versus cognitive-behavioural therapy in bipolar disorder.* Canadian Institutes of Health Research.

Petronis, A. *Epigenetic regulation of the tumor necrosis factor gene in Crohn's disease.* Crohn's and Colitis Foundation of Canada.

Petronis, A. *Epigenetic studies of the serotonin receptor 2A gene in schizophrenia.* National Alliance for Research on Schizophrenia and Depression.

Petronis, A. *Epigenetics of "junk" DNA: Insights for finding the genes of major psychosis.* Canadian Psychiatric Research Foundation.

Petronis, A. *Epigenetics of schizophrenia.* Ontario Mental Health Foundation.

Petronis, A., Singh, S., Wong, A., Vincent, J. & Macciardi, F. *Epigenetic studies of chromosome 22 in major psychosis.* Ontario Mental Health Foundation.

Rahman, S. *Dopamine and non-dopamine mechanisms of nicotine addiction: A microdialysis study.* University of Toronto, Dean's Fund.

Rector, N.A., Richter, M., Gemar, M. & Denisoff, E. *Cognitive-behavioural therapy for co-morbid OCD and major depression.* Ontario Mental Health Foundation.

Rector, N.A., Richter, M., Gemar, M. & Denisoff, E. *Cognitive and behavioural treatment of obsessive-compulsive disorder: The role of cognitive factors in treatment response and relapse prevention.* Canadian Institutes of Health Research.

Remington, G. *Antipsychotic medication extended closing study.* National Alliance for Research on Schizophrenia and Depression.

Remington, G. & Kapur, S. *Augmentation of clozapine partial responders with tetrabenazine.* Stanley Research Foundation.

Richter, M.A. *Obsessive-compulsive disorder: An innovative genetic study.* Ontario Mental Health Foundation.

Rootman, I. & Ferrence, R. *Plans for enhanced surveillance, evaluation and research under the renewed Ontario tobacco stategy.* Ontario Ministry of Health and Long-Term Care.

Rootman, I., Ferrence, R., Ashley, M.J., Brown, K.S., Cohen, J., McDonald, P. & Stephens, T. *Ontario tobacco research unit.* Ontario Ministry of Health and Long-Term Care.

Ross, B. *Abnormal phospholipid dependent signaling in schizophrenia: Potential for novel therapeutic approaches (new investigator fellowship).* Ontario Mental Health Foundation.

Rotzinger, S. & Vaccarino, F. (supervisor). *The role of glutamate and CRF projections in the amygdala in anxiety.* Alberta Heritage Foundation for Medical Research.

Rummens, J. *The Canadian identities database (CID).* Public Works and Government Services Canada.

Rummens, J. *Who are I? Identity formation and negotiation among new Canadian youth.* Canadian Heritage (Multiculturalism).

Rush, B., Norman, R., Kirsch, B. & Wild, C. *Assessing the critical characteristics of community support programs for people with severe mental illness.* Ontario Mental Health Foundation.

Schaffer, A. & Young, T. *A randomized double blind study comparing add-on treatment with a second mood stabilizer or an antidepressant to depressed bipolar patients on mood stabilizer monotherapy.* Ontario Mental Health Foundation.

Schechter, M., Anis, A., Brissette, S., Brochu, S., Fischer, B., Hankins, C., Lauzon, P., Marsh, D., O'Shaughnessy, M. & Rehm, J. *Multi-centre, randomized controlled trial of heroin assisted therapy for treatment-refractory injection opiate users.* Canadian Institutes of Health Research.

Segal, Z. *Predicting depressive relapse through cognitive changes following mood induction.* Ontario Mental Health Foundation.

Segal, Z., Gemar, M. & Kennedy, S.H. *Predicting depressive relapse through cognitive changes following mood challenge.* Canadian Institutes of Health Research.

Shain, M. *Reconnecting health and the promise of employment: Development and evaluation of a resource.* Health Canada.

Shain, M. & Weil, S. *Evaluating an alternative to long-term suspension programs.* Ontario Trillium Foundation.

Simard, M., Fornazzari, L., Van Reekum, R. & Conn, D. *An open-label trial of olanzapine for psychosis in dementia with Lewy bodies.* Eli Lilly Canada Inc.

Skinner, W. & Ferentzy, P. *Exploring mutual aid pathways to recovery from gambling problems and co-occuring gambling and substance abuse problems.* Ontario Problem Gambling Research Centre.

Smart, R.G., Mann, R.E., Beirness, D., Chipman, M., Dussault, C., Tasca, L., Mercer, W., Solomon, R. & Vingilis, E. *Anti-social behaviour and the automobile.* Networks of Centres of Excellence Program.

Smith, P. *Drug treatment court project: Crime Prevention Investment Fund.* Department of Justice, National Crime Prevention Centre.

Smith, P., Dempster, R., Ingber, E., Munn, E. & Chaim, G. *Development of substance abuse program.* Public Works and Government Services Canada.

Sproule, B., Shulman, K., Naranjo, C. & Turksen, I. *Fuzzy logic modelling of lithium kinetics and dynamics.* Canadian Institutes of Health Research (Transferred from Sunnybrook).

Stewart, M., Beiser, M. & Simich, L. *Multicultural meaning of social support among immigrants and refugees.* Social Sciences and Humanities Research Council of Canada.

Strauss, J. *Brain derived neurotrophic factor: A candidate for childhood-onset depression.* Canadian Institutes of Health Research.

Strike, C. & Fischer, B. *HCV and cocaine/crack use: Literature review.* Health Canada.

Strike, C., Millson, M., Fischer, B., Myers, T. & Villeneuve, P. *Methadone programs in non-traditional settings: Programs, policies, and prevention.* Ontario HIV Treatment Network.

Sum, C. & Van Tol, H. (supervisor). *Mechanisms of dopamine receptor: Mediated receptor tyrosine kinase activation.* Ontario Mental Health Foundation.

Sylvestre, J., Trainor, J., Ilves, P., Aubry, T., George, L. & Nelson, G. *An evaluation of housing programs in Ontario.* Ontario Mental Health Foundation.

Tenn, C. & Kapur, S. (supervisor). *An amphetamine sensitized-state model that links neurochemical, cognitive and behavioural changes to schizophrenia psychosis.* Ontario Mental Health Foundation.

Tolomiczenko, G. & Dewa, C. *Mental health court diversion evaluation project.* Ontario Mental Health Foundation.

Tomkins, D., Nobrega, J. & Tyndale, R. *Influence of genetic and neuroadaptations in alcohol drinking: A role for $GABA_A$ receptors.* Ontario Mental Health Foundation.

Tomkins, D. & O'Neil, M. *Ethanol reinforcement: The role of 5-HT1B receptors.* National Institute on Alcohol Abuse and Alcoholism.

Toneatto, T. *A controlled evaluation of cognitive therapy for problem gambling.* Ontario Problem Gambling Research Centre.

Toneatto, T., Brands, B., Selby, P. & Sinclair, D. *A randomized, double-blind, placebo-controlled trial of naltrexone in the treatment of concurrent alcohol dependence and pathological gambling.* Ontario Problem Gambling Research Centre.

Toneatto, T., Wynne, H., Skinner, W. & Littman-Sharp, N. *Development and testing of a telephone-based treatment program and delivery model for problem gamblers.* Ontario Problem Gambling Research Centre.

Toner, B., Ali, A., Esplen, M.J., Rolin-Gilman, C. & Stuckless, N. *Development of a gender role socialization scale for women.* Social Sciences and Humanities Research Council of Canada.

Toner, B. & Tang, T. *Transition and engagement of life roles: Impact on mental health of Chinese immigrant women.* Social Sciences and Humanities Research Council of Canada.

Turner, N., Horton, K. & Fritz, B. *Implicit learning and problem gambling: Is there a connection?* Ontario Problem Gambling Research Centre.

Turner, N., Jain, U. & Toneatto, T. *A research pilot study to evaluate the effects of acupuncture on gambling behaviour and anxiety in problem gamblers.* Ontario Problem Gambling Research Centre.

Tyndale, R.F. *Canada research chair (Tier II).* Canadian Institutes of Health Research.

Tyndale, R.F. *Drug metabolism in the brain: Expression and regulation of cytochromes P450.* Canadian Institutes of Health Research.

Tyndale, R.F. & Sellers, E.M. *Pharmacogenetics: CYP2A6 genetic variants alter smoking.* Canadian Institutes of Health Research.

Vaccarino, F.J. *GRF Behavioural and physiological characterization.* Natural Sciences and Engineering Research Council.

Vaccarino, F.J., Arifuzzaman, A., Vichnevetski, K., Rayfield, C. *Intellectual property management program.* Canadian Institutes of Health Research.

Vaccarino, F.J., Palmour, R.M. & Ervin, F. *CCK and anxiety: Neurobehavioral characterization.* Canadian Institutes of Health Research.

Vaccarino, F.J. & Rotzinger, S. *Neurobiology of the opposing motivational effects of stress on psychostimulant self-administration.* Canadian Institutes of Health Research.

Van Tol, H.H.M. *Canada research chair (Tier I).* Canadian Institutes of Health Research/Canada Research Chairs Program.

Van Tol, H.H.M. *SH3 domain interactions in dopamine receptors.* Canadian Institutes of Health Research.

Van Tol, H.H.M., Niznik, H.B. & Kennedy, J.L. *Dopamine and psychomotor disease.* Canadian Institutes of Health Research.

Vincent, J. & Petronis, A. *Investigating the role of the SCA8 locus in major psychosis.* Ontario Mental Health Foundation.

Vingilis, E., Mann, R., McLeod, A., Seeley, J., Beirness, D., Girling, S., Gliksman, L., Lane, P., Lamble, R., Single, E., Stoduto, G. & Voas, R. *Health/safety impact of Ontario's drinking hours.* National Institute on Alcohol Abuse and Alcoholism.

Wang, J.-F. & Young, T. *Mood stabilizers and neuroprotection.* Ontario Mental Health Foundation.

Warner, J. & Adlaf, E. *Narratives of gender and aggression in a Maritime town.* Social Sciences and Humanities Research Council of Canada.

Warsh, J. *Calcium homeostasis and g protein-coupled cAMP signaling disturbances in bipolar affective disorder.* Canadian Institutes of Health Research.

Warsh, J. *Diagnostic specificity of B lymphoblast calcium abnormalities to bipolar disorder.* Ontario Mental Health Foundation.

Warsh, J. & Li, P. *Effect of antipolar medications on cellular and molecular mechanisms modulating intracellular calcium signalling.* Canadian Institutes of Health Research.

Warsh, J. & Li, P. *Fluorescence microplate reader for high throughput analysis of intracellular calcium dynamics.* Canadian Institutes of Health Research.

Wekerle, C. & Wall, A.M. *Canadian incidence study on child abuse and neglect: Substance abuse analysis.* Health Canada.

Wekerle, C., Wall, A.M., MacMillan, H. & Trocme, N. *Maltreatment and adolescent pathways (MAP) project.* Canadian Institutes of Health Research.

Wherret, D., Zucker, K.J., Bradley, S.J. & Nielson, B. *Psychosocial adjustment and gender identity in genetic males born with ambiguous genitalia.* The Hospital for Sick Children Research Institute.

Wilson, A. *Norepinephrine transporter occupancy by duloxetine in rats.* Eli Lilly Canada Inc.

Wilson, A., Houle, S. & Meyer, J. *Imaging of the norepinephrine transporter (NET) in the living human brain by positron emission tomography (PET) with (11C) - MeNER: Safety and efficacy evaluation.* Eli Lilly Canada Inc.

Wong, A. *Genetic studies with candidate genes in schizophrenia.* Ontario Mental Health Foundation.

Wong, A. & Van Tol, H. *Candidate genes and linkage disequilibrium studies in schizophrenia (clinician scientist award).* Canadian Institutes of Health Research.

Wong, A., Van Tol, H. & Kennedy, J. *Schizophrenia and developmental changes in gene expression.* National Alliance for Research on Schizophrenia and Depression.

Wu, Z., Kaspar, V., Noh, S. & Chen, J. *Immigrants, selectivity and mental health.* Canadian Population Health Initiative.

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