CIMR.ca
Centre for Integrative Mood Research
Quarterly Newsletter

Volume 1, Issue 3
Fall 2010

In this issue

Contact: The Centre for Integrative Mood Research
Department of Psychiatry
Toronto General Hospital
University Health Network
EN8-222 - 200 Elizabeth St
Toronto, Ontario M5G 2C4
www.cimr.ca

Editor: Susan Rotzinger, PhD
416-340-4800 x 6040
susan.rotzinger@uhn.on.ca

Founding Members of CIMR:
Dr. Sophie Grigoriadis
Dr. Sidney Kennedy
Dr. Roger McIntyre
Dr. Sagar Parikh
Dr. Franco Vaccarino

University Health Network

The Centre for Integrative Mood Research (CIMR)

The CIMR is established at University Health Network to promote the understanding of depression and mood disorders; to develop innovative evidence-based therapeutic interventions, and to disseminate and apply this knowledge to the general public, the health care community, and policy makers.

Upcoming Events

WORKSHOP

- **Women's Mental Health and Substance Use** is a one-day workshop that will provide practical tips on psychotherapy, medication, and community resources for women with mental illness and substance use issues during various life stages.

Featured Speakers:

- **Dr. Gail Robinson**, MD, FRCPC, Head, Women's Mental Health Program
- **Dr. Sophie Grigoriadis**, MD, FRCPC, Fellowship Director
- **Dr. Leslie Buckley**, MD, FRCPC, Medical Director, Addictions

November 5, 2010 at the University of Toronto Faculty Club

Contact: for further details please contact sia.maro@uhn.on.ca

CONFERENCE

ISAD 2011 Regional Conference Toronto: Mood Disorders—From Neuroscience to Treatment

- The International Society for Affective Disorders and the Canadian Network for Mood and Anxiety Treatments present a joint meeting in Toronto April 8-9, 2011:

Featured symposia include:

- **Chronobiology**
- **Stress Biology**
- **Atypicals in the Treatment of Mood Disorders**
- **The Neurocircuitry of Depression: Application to Psychotherapy**

Featured Speakers Include:

- **Dr. Allan Young**, University of British Columbia
- **Dr. Robert Levitan**, Centre for Addiction and Mental Health, Toronto
- **Dr. Roger McIntyre**, University Health Network, Toronto
- **Dr. Pierre Blier**, University of Ottawa
- **Dr. Lakshmi Yatham**, University of British Columbia
- **Dr. Jan Scott**, Institute of Psychiatry, London
- **Dr. Zindel Segal**, Centre for Addiction and Mental Health, Toronto

Contact: susan.rotzinger@uhn.on.ca for more information

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Neurostimulation for Psychiatrists

In April we held our first CIMR Educational Event, "Neurostimulation for Psychiatrists: A Practical Guide to Neuroimaging, TMS, ECT and DBS". The event was held at the University of Toronto Faculty Club, April 30 and May 1, 2010, and was attended by psychiatrists from across Canada.

The two days were very rich in information and interaction.

In this issue of the newsletter, we provide a summary of the day.

> *"Excellent workshop! One of the best workshops I have been to in while. Thank you. – quote from participant"*

Neurocircuitry and Neuroimaging

The day began with a session on Neurocircuitry and Neuroimaging. **Dr. Sherese Ali** gave a detailed review of neurocircuitry and neuroanatomy of depression, with a view to highlighting the limbic system and its cortical connections. This information forms the rationale for the choice of targets in for the various neurostimulation techniques and their proposed mechanisms of action.

Highlights of her talk include:

The **prefrontal cortex** is of critical importance in executive function, memory, preparation for meaningful action, and inhibitory control of inappropriate impulses and reflexes.

The **anterior cingulate cortex** is a key region that integrates emotional, sensory, cognitive and motor information to produce cognitive

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and motor responses. It is a key integrative and regulatory area for mood, motivation and cognition, and has important connections with structures such as the amygdala, hippocampus, and nucleus accumbens.

Frontal-subcortical circuits can be dysregulated in depression, anxiety and obsessive compulsive disorder. The dysregulation often relates to impaired frontal inhibition of limbic activity, and poor top-down regulation of subcortical structures. Both medications and psychotherapy attempt to restore normal function in these circuits. New interventions such as neurostimulation techniques act to exogenously modulate limbic activity and restore normal top-down modulation.

The next presenter was **Dr. Omar Ghaffar** of the Neuropsychiatry Program at Sunnybrook Health Sciences Centre. Dr. Ghaffar presented an overview of structural magnetic resonance imaging (MRI), and the major structural abnormalities that have been identified in mood disorders, and how MRI data can complement neurostimulatory treatments.

Four brain areas have been particularly studied and identified in brain volume abnormality studies: the subgenual cingulate, orbitofrontal cortex, striatum, and hippocampus.

Subgenual anterior cingulate:

- Reduced grey matter volume in many studies of major depression and bipolar disorder, particularly on the left.
- Important for emotional regulation and appropriate motivated behaviour.

Orbitofrontal cortex:

- Volume reductions bilaterally in major depression and bipolar disorder
- Important for flexible cognitive strategies, and appropriate decision making on risk/reward tasks.

Striatum:

- Reduced volume bilaterally in major depression
- Important structure for mood, cognition, motor control, and motivation.

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Hippocampus:

- One of the most studied regions in major depression, but is also the most heterogeneous structure and therefore methodological differences between studies have made it difficult to determine consistent effects.
- Evidence suggests that there is reduced hippocampal volume in depression, and that it is associated with duration of depression, as well as early life trauma.

Dr. Jonathan Downar presented on functional neuroimaging techniques, and how they help researchers visualize how neurostimulation therapies work. Dr. Downar gave a detailed discussion of how the brain processes and integrates external and internal sensations, and how these sensations influence cognition. Successful affect regulation depends upon properly functioning prefrontal-subcortical pathways. Failure of appropriate regulation can lead to depressed moods and major depressive disorder. Neurostimulation techniques artificially disrupt networks with the goal of restoring normal function. Dr. Downar presented PET images of brains before and after ECT, DBS and TMS, demonstrating functional changes in brain activity in key regions, which were associated with clinical improvement. Dr. Downar hopes to use these techniques in his own work to develop more targeted neurostimulation therapies on the basis of functional imaging information.

Transcranial Magnetic Stimulation

Dr. Roumen Milev of Queen's University, Kingston, Ontario, presented a lecture on transcranial magnetic stimulation (TMS). TMS is generally safe and well tolerated, with headache being the most common side effect. TMS is not appropriate for individuals with a history of seizures or epilepsy, or for individuals with ferromagnetic metal anywhere in the head. A course of TMS treatment is typically one session per day for 2 weeks, but many other treatment courses have been described. TMS has been approved in Canada since 2002 but is not currently covered by OHIP. Major studies in the area have found response rates of around

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25% and remission rates of approximately 15%, although methodological differences between studies have resulted in some discrepancies. It appears to be a safe and well-tolerated alternative to ECT.

Deep Brain Stimulation

The next day began with a presentation on Deep Brain Stimulation (DBS) by Dr. Sidney Kennedy, a founding member of the DBS team at University Health Network. Dr. Kennedy's lecture described the rationale for neurostimulation therapies, and for DBS in particular. In psychiatry, DBS has been investigated mostly for depression, but also shows promise in Obsessive Compulsive Disorder (OCD) and Tourette's syndrome. Dr. Kennedy reviewed the neurocircuitry

Refractory Depression Deep Brain Stimulation

This clinical trial is investigating the safety and antidepressant effects of Deep Brain Stimulation (DBS) in refractory depression.

This study is the third trial of DBS to the subcallosal cinguate gyrus for treating depression. This site is similar to that used in the surgical management of depression, but the DBS procedure is reversible, more anatomically selective, and can be post-operatively modulated.

To be in the study, participants must be between the ages of 35 and 70, have refractory unipolar major depressive disorder, and have failed to respond to multiple treatments for depression.

For more information on this study, please call the study coordinator at 416-340-3466

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of depression, and discussed in detail the subcallosal cingulate gyrus, a key region identified through neuroimaging methods as being involved in depression and mood regulation. Dr. Kennedy reviewed data from a number of studies showing efficacy of DBS in patients who had been resistant to all other forms of treatment. The hour ended with a discussion of scientific and ethical issues and the future of DBS.

A Deep Brain Stimulation Study for the Treatment of Obsessive Compulsive Disorder

This clinical trial is investigating the safety and efficacy of Deep Brain Stimulation (DBS) for the treatment of chronic and severe OCD.

DBS delivers mild pulses of electrical current from a surgically implanted device to a targeted area of the brain.

To be in the study, participants must be at least 18 years of age and have failed to respond to multiple treatments for OCD.

For more information on this study, please call the study coordinator at 416-340-4800 ext.8839

Electroconvulsive Therapy

Dr. Peter Giacobbe presented the latest evidence for electroconvulsive therapy (ECT) for depression. Despite negative portrayals of ECT in the media, and the associated stigma, ECT remains a very effective treatment for major depression, with response rates of 80-90% reported. ECT is also very effective in patients who have failed to respond to one or more antidepressant medication trials. Relapse prevention is important following ECT, and Dr. Giacobbe presented data on the efficacy of both pharmacotherapy and continuous ECT for relapse prevention. Cognitive effects can occur, and are more common with bilateral ECT and more frequent ECT. However, many people also experience an

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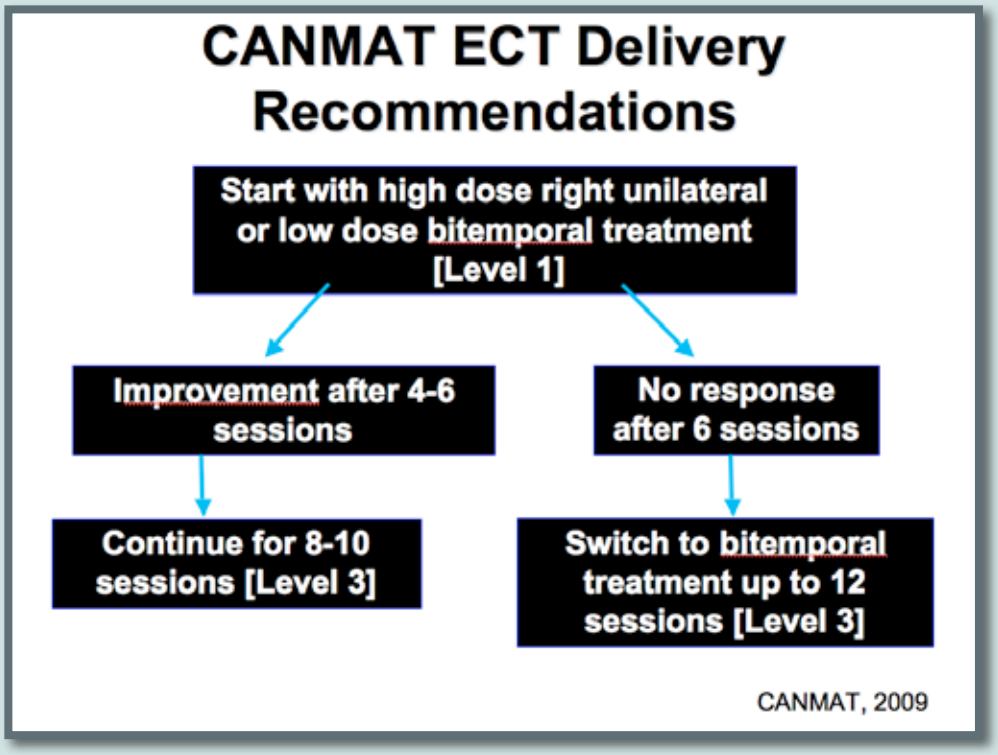
improvement in memory following ECT. Recommendations for ECT as a first line treatment are for cases of acute suicidal ideation, major depressive episode with psychotic features, treatment resistant MDD, or medication intolerance. Recommended parameters to begin with are high dose right unilateral or low dose bitemporal treatments.



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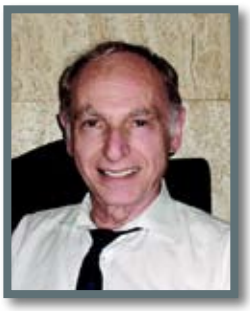
Interview: Dr. Philip Seeman



In 1975, Dr. Philip Seeman discovered the target of antipsychotic action in the human brain. This antipsychotic receptor target is now known as the dopamine D2 receptor.

Q 1: What is your new strategy in searching for a new and more effective way to treat depression?

A 1: The two main natural chemicals in the brain that influence mood are serotonin and dopamine. These two substances, when released from nerve terminals act on receptors to control mood. The new strategy is to increase the sensitivity of dopamine receptors so that the released dopamine will have a greater effect in improving mood. Such an increase in receptor sensitivity can be easily and safely obtained in a few days, after which the mood improves. The drug being tested is a different form of an old drug that has been used for another illness on a long-term daily basis. For this depression trial, it is being taken at a very low dose for a limited period.*

Q 2: How is it possible to increase the sensitivity of neurotransmitter receptors in a person so that the person becomes more responsive to his own natural neurotransmitter substance?

A 2: Neurotransmitter receptors in the human brain are constantly switching back and forth every few minutes between a state of high sensitivity and a state of low sensitivity to neurotransmitters such as serotonin, dopamine and others. Each receptor is a protein that can change its shape and sensitivity just like hemoglobin in the blood - for example, red hemoglobin has a high sensitivity to attach oxygen, while blue hemoglobin has a low sensitivity to attach oxygen. It is possible to enhance a person's receptor sensitivity to dopamine or serotonin by giving a safe, well-established medication.

Q 3: Which state of receptor sensitivity controls a person's mood?

A 3: Extensive basic science has found that when there are more neurotransmitter receptors in a state of high sensitivity to dopamine for example, then the person is more active, energetic, curious, engaging, and outgoing.

* This study is currently underway at UHN. For more information, please call 416-340-4800 ext. 8839.

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Clinical Trial Opportunities:

Patients with a diagnosis of Bipolar Disorder may participate in one of our upcoming medication trials.

To find out more, please contact Hanna at (416) 603-5133 or visit www.mdpu.ca

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Mood Disorders Psychopharmacology Unit
medicine | research | technology | education

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