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**DEPARTMENT OF PSYCHIATRY RESEARCH DAY  
2010 ABSTRACTS**

**CLINICAL**

- 1) Social network characteristics and effect on severity of psychosis in a community sample with high prevalence of stimulant use

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Oral	Presenter:	Willough Jenkins R1 Psychiatry Research Track Resident
	Authors	W Jenkins, F Vila-Rodriguez, K Paquet, GW MacEwan, AE Thornton, AM Barr, R Procyshyn, DJ Lang, WG Honer
	Faculty Sponsor	William G Honer

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Background: Urban environments include neighbourhoods with high prevalence of serious and persistent mental illness, substance abuse and communicable infectious disease. Objectives of this study was to collect descriptive information with the goal of identifying strategies for more effective health care intervention and to determine if social network size had a buffering effect on the severity of psychotic symptoms. Methods: Participants were recruited from two single room occupancy hotels in Vancouver and completed structured interviews to provide information on demographics, substance use, mental health and social network characteristics. Results: The study population (n=135) had the following characteristics: 25% female, 74% male and 0.7% transgendered. The substance use characteristics of the population within the month preceding interview are as follows: 95% stimulant use, 54% opiate use, 52% cannabis use. 57% of subjects were determined to be psychotic and 26% depressed at the baseline interview. The mean available network membership was 4.11 (range 0-14) and the mean utilized network membership was 2.98 (range 0-14) people. In contrast to the protective effects of a larger network membership on severity of psychotic symptoms, no such relationships were observed for severity of depression. Discussion: While studies of schizophrenia showed relationships between network size and negative symptom severity, in the present sample network size was related to total, positive and negative symptom severity. Of note, the protective effect of social network size was most prominent in women. In an environment where exposure to stimulant drugs increases the risk of psychosis, social network size appears to be a protective factor that could be a target for future development of interventions.

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2) VANCOUVER INNER CITY YOUTH MENTAL HEALTH PROGRAM:  
CLINICAL EFFECTIVENESS

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Oral	Presenter:	Jennifer Wide Resident, Psychiatry (PGY-4)
	Authors	Jennifer Wide, Tracy Brown, Mitesh Patel, William MacEwan, Steven Mathias
	Faculty Sponsor	Steven Mathias

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Developed in 2007, Vancouver's Inner City Youth Mental Health Program (VICYMP) is a psychiatrist led collaboration between St Paul's Hospital, Covenant House Vancouver, Vancouver Coastal Health and the Ministry of Child and Family Development. The program provides outreach to youth aged 16-24, with or without fixed address, with serious and persistent mental health, many of whom are actively using substances. The VICYMH aims to avoid the stigmatization of chronic care by providing early intervention to an often unrecognized and undertreated population. The program works under a case management model, which includes medication management, therapy, community liaison, crisis management and service referral, with an assertive outreach philosophy. Between July – December 2009, clinicians collected data from over 100 youth (age: 16-24[yr]) self-referred or referred by case management. Outcomes measures examined included housing, education, employment, substance abuse in addition to clinical measures such as mental health diagnoses, medications prescribed, Global Assessment of Functioning, Social and Occupational Assessment Functioning Scale, and compliance with follow-up. Quantitative and qualitative findings from the data, and their implications in treating inner city youth and advancing the program will be discussed.

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3) **Duration of undiagnosed illness as a predictor of clinical outcomes in bipolar disorder**

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Oral	Presenter:	Kevin Wong Resident 1
	Faculty Sponsor	Lakshmi N. Yatham

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Due to the cumulative effect of reduced public awareness of psychiatric disease, limited patient insight during acute mood episodes, and the fluctuating nature of the illness, mean delays to correct diagnosis and treatment in bipolar disorder is 6-13 years. The long-term clinical consequences of prolonged duration of undiagnosed illness or DUI (time between initial symptom onset and correct clinical diagnosis) are still not fully understood in bipolar disorder. In this study, retrospective data from the HOPE.BD study was used to evaluate over two hundred bipolar individuals (types I and II) from across Canada. Participants had initial intake interviews during an acute mood episode and clinical treatment (using the CANMAT guidelines) and follow-up care continued for up to 5 years. Two groups (DUI < 6 years and DUI > 6 years) were compared using numerous illness course variables including length of illness, number of hospitalizations, and psychosocial factors. Results from this study indicate that BP individuals with a DUI of < 6 years were more often BP-I and consequently had more psychotic symptoms and hospitalizations; however, a DUI > 6 years had a significant psychosocial impact. Results from this study illustrate the need for early identification and treatment in bipolar disorder.

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## BASIC SCIENCE

- 1) Early increase in extrasynaptic NMDA receptor signalling and expression contributes to phenotype onset in Huntington's disease mice

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Oral	Presenter:	Austen J Milnerwood Postdoctoral Research Fellow
	Faculty Sponsor	Lynn A Raymond

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N-methyl-D-aspartate receptor (NMDAR) excitotoxicity is implicated in the pathogenesis of Huntington's disease (HD), a late-onset neurodegenerative disorder. However, NMDARs are poor therapeutic targets, due to their essential physiological role. Recent studies demonstrate synaptic NMDAR transmission drives neuroprotective gene transcription, whereas extrasynaptic NMDAR activation promotes cell death. We report specifically increased extrasynaptic NMDAR expression, current, and associated reductions in nuclear CREB activation in HD mouse striatum. The changes are observed in the absence of dendritic morphological alterations, before and after phenotype onset, correlate with mutation severity, and require caspase-6 cleavage of mutant huntingtin. Moreover, pharmacological block of extrasynaptic NMDARs with memantine reversed signalling and motor learning deficits. Our data demonstrate elevated extrasynaptic NMDAR activity in an animal model of neurodegenerative disease. We provide a candidate mechanism linking several pathways previously implicated in HD pathogenesis and demonstrate successful early therapeutic intervention in mice.

Sponsors note: Abnormally enhanced NMDA receptor function is implicated in Huntington's disease (HD). This work, recently published in *Neuron*, demonstrates an abnormal balance between the activity of NMDA receptors at synaptic (prosurvival) and extrasynaptic (proapoptotic) sites in a mouse model of HD, offering hope for treatment with a compound already approved for use in patients.

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2) Detection of brain wiring mechanisms through regional gene expression profiles

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Oral	Presenter:	Leon French Graduate Student
	Faculty Sponsor	Paul Pavlidis

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The wiring diagram of the brain is complex and puzzling. Its self assembly is guided by gradients, activity and guidance signals. Over a hundred neurotransmitters are released and recognized differently across the connections. Neuroscientists have identified many genes that encode such signals in specific contexts. To test the global relationships between gene expression and neuroanatomical connectivity we examine large scale gene expression signatures in the rodent brain.

The analysis approaches whole brain scale by using a wiring diagram containing 962 brain regions and gene expression signatures of 17,530 genes within 141 regions. We find that even after development, adult gene expression signatures have a statistical relationship to connectivity. We extracted a reduced set of genes most correlated with neuroanatomical connectivity. Using Gene Ontology analysis we find this set is enriched for axonogenesis, neuron projection development, axon guidance and neurotransmission.

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- 3) Calcium dependent and independent mechanisms in the control of cerebral blood flow by astrocytes.

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Oral	Presenter:	Grant Gordon Postdoctoral Fellow
	Faculty Sponsor	Dr. Brian MacVicar

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Astrocytes couple changes in neural activity to alterations in cerebral blood flow by eliciting vasoconstriction or vasodilation of arterioles. However, the mechanism for how opposite astrocyte influences provide appropriate changes in vessel tone within an environment that has dynamic metabolic requirements remains unclear. Using two-photon laser scanning microscopy on acute rat brain slices, we show that both Ca<sup>2+</sup> dependent and independent mechanisms operate in the bi-directional control of arteriole diameter. Ca<sup>2+</sup> dependent control relies on the astrocyte enzyme phospholipase A2 (PLA2). Under conditions of low metabolic activity (or low neural activity), PLA2 activity generates arachidonic acid (AA), which diffuses to vascular smooth muscles cells to cause constriction. Under elevated activity, prostaglandin E2 becomes the preferred astrocyte-derived signaling molecule, which acts on smooth muscle cells to cause vasodilation. Ca<sup>2+</sup> independent control of the vasculature occurs when a different enzyme, soluble adenylyl cyclase, becomes active in astrocytes, which ultimately triggers the production of nitric oxide to cause dilation of arterioles. These data show how astrocytes can elicit bidirectional control of the brain vasculature by utilizing different molecular pathways that are dependent on the metabolic state of the tissue.

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**POSTERS - CLINICAL**

1) Error-related potentials in people with early onset schizophrenia and their healthy siblings

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Presenter: Alan T. Bates  
PGY-2 resident

Authors: Alan T. Bates, Madeleine J. Groom, Timothy G. Calton, Debasis Das, Georgina M. Jackson, Chris Hollis, Peter F. Liddle

Faculty Sponsor: Elton Ngan and William Honer

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**Introduction:** Error-related negativity (ERN) is an event-related potential (ERP) that has repeatedly shown abnormality in schizophrenia. Error-related ERPs may be useful intermediate phenotypes for genetic studies. Evaluation of the genetics of schizophrenia may also be aided by focus on subpopulations such as early-onset schizophrenia that appear to be under increased genetic influence.

**Methods:** We studied 35 healthy participants, 30 participants with early-onset schizophrenia (mean onset age 16), and 36 healthy participants with a sibling with schizophrenia. Participants performed a visual go/no-go task (press for X (80%), inhibit response for K (20%)) that induces many errors. ERN, correct-(response)-related negativity (CRN) and Pe (error positivity) were examined. Event-related induced and evoked oscillatory changes were also explored. **Results:** The healthy group showed significantly larger ERN and Pe amplitude, and greater evoked delta and induced theta activity than the schizophrenia group or the sibling group. The sibling group consistently showed ERP amplitudes and oscillatory activity peaks that were intermediate between the healthy group and the schizophrenia group. **Conclusions:** This study extends the finding of ERN and Pe abnormalities in schizophrenia to an early-onset sample. It also demonstrates decreased evoked delta and induced theta activity in young people with schizophrenia and their siblings. Abnormal modulation of low-frequency oscillations may contribute to the functional dysconnectivity of schizophrenia.

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2) White matter cytoarchitecture in the prefrontal cortex in schizophrenia and bipolar disorder

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Presenter: Christa Hercher  
Research Assistant

Faculty Sponsor: Clare Beasley

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**Introduction:** Neuroimaging studies have reported white matter alterations, including reduced volume and changes in fractional anisotropy, in schizophrenia and bipolar disorder. However, the cellular substrates potentially underlying these gross morphological changes remain unclear. Cytoarchitectural evidence suggests abnormalities within the prefrontal cortex in schizophrenia and bipolar disorder, although few studies have examined adjacent white matter. Reductions in oligodendrocytes have been reported in both grey and white matter in schizophrenia, although the data are not consistent. Additionally, the role of astrocyte pathology in the major psychiatric disorders remains inconclusive. **Methods:** We performed a two-dimensional assessment on well-characterized postmortem tissues from subjects with schizophrenia, bipolar disorder and controls (20 subjects per group). **Results:** We will present initial data quantifying the density and spatial distribution of glial fibrillary acidic protein immunoreactive (GFAP-IR) astrocytes as well as nissl stained oligodendrocytes and neurons, in prefrontal (Brodmann area 9) white matter. **Conclusion:** Such data will provide important information on white matter pathology in these major psychiatric conditions.

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3) Schizophrenia patients show differences in activity of neural systems underlying associative memory encoding

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Presenter: Alexander Leung  
 Medical Student

Coauthors: Metzak, P.D., Woodward, T.S.

Faculty Sponsor: Todd S. Woodward

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Introduction: fMRI was used to reveal functionally connected neural networks mediating associative memory in schizophrenia. Method: 26 schizophrenia patients and 26 controls were scanned while completing 90 association trials. A cue word was presented, and subjects were required to choose the more strongly associated of two companion words. Subjects were later asked to free-recall and cue-recall the associated word pairs. Results: Using fMRI-CPCA, three components of neural activity emerged, one involving deactivations in the task negative network regions, including ventral and posterior cingulate cortex, and two others involved activations in task-positive regions, including the visual cortices, dorsal anterior cingulate, and frontal gyri. Observing the estimated BOLD responses, for all components, word-pairs that were later easily recalled were associated with low responses at encoding, and word pairs that were forgotten were associated with high responses at encoding (suggesting memory interference); and this did not differ between patients and controls. However, word pairs that later required a cue to be recalled were associated with relatively little interference-related BOLD response for patients compared to controls. Conclusion: This result gives a biological basis for the observation that, for people with schizophrenia, cues are important for recall even in the absence of interference at encoding.

4) Correlations between behavioural performance and magnitude of hemodynamic response peak in contextual memory tasks in schizophrenia patients and healthy controls.

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Presenter: Metzak, Paul  
 Graduate Student

Coauthors: Liang Wang, Elton Ngan, Todd Woodward

Faculty Sponsor: Woodward, Todd.S

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In the current study, we sought to investigate the neural networks that underlie successful contextual memory performance. While undergoing functional MRI scanning, 21 schizophrenia patients and 21 healthy controls performed the recall portion of a contextual memory task in which they were asked to indicate which of four operations they had previously performed while encoding each word (reading, hearing, semantically associating, or unscrambling letters). Using a Finite Impulse Response (FIR) basis set modelling the peristimulus time points in conjunction with constrained principal component analysis (CPCA) for fMRI data, we extracted 3 functionally interacting but separate components. The first component was characterized by activations in "task positive" regions including occipital cortex, medial supplementary motor /dorsal anterior cingulate cortex, and sensori-motor cortical regions. The second component was characterized by decreased activation in "task negative" regions, including medial prefrontal cortex and precuneus and posterior cingulate cortex. Subsequent analyses revealed that, in the healthy controls, performance accuracy was significantly correlated with the estimated peak hemodynamic response for component 1, whereas, for the schizophrenia patients, performance accuracy was significantly correlated with the estimated hemodynamic response peaks for both component 1 and component 2. The difference between the patient and control samples correlations on component 2 was also found to be significant. This analysis suggests that schizophrenia patients require coordinated activity in these two neural systems in order to successfully complete contextual memory recall tasks.

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5) Who are Chronically Aggressive Inpatients? A sociodemographic, criminological, and clinical profile

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Presenter: Caroline Greaves  
Researcher: BCMHAS  
Co-authors: Nicholls, T. L., Brink, J., Lussier, P., & Verdun-Jones, S.  
Faculty Sponsor: Johann Brink & Tonia Nicholls

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Violent inpatients present considerable challenges for mental health professionals. Problematic behaviours obstruct efforts towards community release for forensic psychiatric patients, and compromise staff and patient safety. Identification of the small minority of chronic aggressors who contribute to the high incidence of violent behaviour in forensic institutions would substantially reduce the rate of inpatient aggression. The entire population of patients (N = 527) assessed or treated in 2004 at a secure psychiatric forensic hospital was eligible for our extensive quantitative file-review. Of all aggressive incidents, 213 involving physical violence against others and/or inappropriate sexual behaviour were retained for analyses, thereby revealing a chronically aggressive subgroup of patients (n = 6.1%) responsible for over three-quarters of these incidents. From a number of risk factors across sociodemographic, criminological, and clinical domains, only age and duration of hospital stay significantly predicted abstainers from incident aggressors. None of the variables under study predicted single from repeat incident aggressors. The number of similarities between the groups highlights the challenge inherent in discerning which patients will be chronically aggressive. This information is essential to violence risk evaluations, and invaluable for furthering integrated treatment efforts and for training front-line staff in effectual inpatient violence prevention strategies.

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6) Exploring their Experiences with Police: A Participatory Action Research Study

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Presenter: Caroline Greaves  
Researcher: BCMHAS  
Co-authors: James D. Livingston, Sarah Desmarais, Johann Brink, Victoria Maxwell, Erin Michalak, Rick Parent, Simon Verdun-Jones, Camia Weaver  
Faculty Sponsor: Johann Brink

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Contact with police is common among the population of individuals living with a severe mental illness. Although the majority of people with mental illness do not commit criminal acts, a significant minority will interact with police for a variety of reasons. Police and people with mental illness' perceptions of one another can influence the nature, quality, and impact of their interactions. However, there is a dearth of research focusing on the perceptions of people with mental illness regarding the police. Utilizing a Participatory Action Research (PAR) approach, this research works with people who have severe mental illness to understand their perceptions of and interactions with the police. The PAR elements of our study – engaging people with mental illness as co-investigators and peer-interviewers, developing consumer-informed research materials, and involving people with mental illness in the process of interpreting the research finding – will be featured in this poster. Our multi-component study involves focus groups, in-depth interviews, and community surveys to consult with and learn from people with severe mental illness. Recommendations generated by this research are intended to inform police training and guidelines for interacting with people who have severe mental illness.

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7) Aberrant fronto-temporal connectivity underlying self vs. other source monitoring in schizophrenia

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Presenter: Wang, Liang  
Postdoctoral Fellow  
Coauthors: Metzak, P.D., & Woodward, T.S.  
Faculty Sponsor: Woodward, Todd S.

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Introduction: The anterior medial prefrontal cortex (amFC) is a critical region for understanding of neural substrates of mentalizing and/or self-reflection, and may play a role in the manifestation of the positive symptoms of schizophrenia. In this study, we used an effective connectivity approach to explore the neural substrates related to aberrant source monitoring in schizophrenia.

Methods: 37 healthy controls and 27 schizophrenia patients underwent fMRI scanning while performing a source monitoring paradigm that was designed to evaluate the ability to use contextual memory processes that were self and other generated. Probabilistic independent component analysis was employed to locate the amFC. Then, a psychophysiological interaction was used to investigate a casual influence that one region exerts on another, modulated by the goal-directed experimental conditions.

Results: Significantly increased effective connectivity from the amFC to left superior temporal gyrus (LSTG) was observed in patients compared with controls ( $p < 0.05$ , cluster-based correction) when recalling that information was self-generated, whereas in healthy people this connectivity was increased when recalling that it was other-generated..

Conclusions: This finding suggests that the amFCàLSTG connection may be involved in the inner-outer or self-other confusion that manifests in schizophrenia as positive symptoms such as hallucinations or Schneiderian delusions.

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8) Successful community reintegration among Female Forensic Psychiatric Patients

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Presenter: Simone Viljoen, Caroline Greaves  
Research Assistants  
Faculty Sponsor: Tonia Nicholls and Johann Brink

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Introduction: Research on resilience- related factors, including desistance from offending behaviour and maintaining mental and emotional stability, presently remains limited. Information pertaining to successful community reintegration would contribute to a more comprehensive assessment of functioning and informed treatment planning that fits within a recovery model of service provision. Thus far, no studies have examined resilience factors related to successful reintegration into the community among female forensic psychiatric patients. The present study investigated the rate of successful/unsuccessful community reintegration, examined protective and risk factors, and evaluated the Short-Term Assessment of Risk and Treatability's (START) predictive validity in female forensic psychiatric patients.

Methods: This study was conducted with 45 female forensic patients using a prospective file review design. Results: Of the 45 participants included in this study, 48.9% qualified as successful and 51.1% as unsuccessful. We found that the successful reintegrators had significantly more protective factors and significantly less risk factors than the unsuccessful reintegrators. Additionally, the START showed good predictive validity with regard to successful community reintegration. Conclusions: Our findings indicate that both risk and protective factors were influential in the recovery process.

Furthermore, findings support the utility of strength-based measurements in risk assessment and treatment planning.

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- 9) A bias against disconfirmatory evidence (BADE) in schizophrenia is associated with reduced activation in a task-negative network involving the ventral anterior cingulate cortex
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Presenter: Katie M. Lavigne  
M.Sc. Student

Authors: Katie M. Lavigne, Jennifer, C. Whitman, Paul D. Metzack, Patrick Carolan, & Todd S. Woodward

Faculty Sponsor: Todd S. Woodward

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A bias against disconfirmatory evidence (BADE) has been proposed to be present in schizophrenia, and may underlie the fixedness aspect of delusions. In the current study, we investigated neural regions involved in the processing of disconfirmatory evidence using event-related functional magnetic resonance imaging (fMRI). Twenty healthy controls and fifteen schizophrenia patients performed a perceptual integration task, in which they rated the degree to which a morphed image composed of two different animals appeared to be an image of one animal or the other. Following a backward mask and delay, they rated a second image composed of the same animals morphed at a different ratio. Constrained principal components analysis (CPCA) revealed two neural networks, one task-positive network involving primarily activation in the dorsal anterior cingulate cortex (dACC) and a task-negative network involving deactivation in the ventral anterior cingulate cortex (vACC). Patients showed greater deactivation in the vACC system relative to controls, but no differences emerged for the dACC system. These results suggest that the BADE observed in schizophrenia patients may result from reduced deactivation in a task-negative network involving the vACC and are consistent with previous research finding an association between impairments in the default network and cognitive dysfunction in schizophrenia.

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- 10) Internalized Stigma in a Population of Chronic Residential Patients with Severe Mental Illness
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Presenter: Karen L. Petersen  
Graduate Student

Faculty Sponsor: Tonia L. Nicholls

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Tertiary psychiatric services in British Columbia are currently undergoing redevelopment and the provision of psychiatric care is being transferred to smaller community-based facilities. The PATHWAYS project is a prospective study designed to assess the impact of this change on the provision of care to patients. As part of an holistic effort to assess quality of life, the study considers the internalization of the stigma of mental illness pre and post transfer using the Internalized Stigma of Mental Illness Inventory (ISMII). Prior to being transferred to a community-base facility, participants generally endorsed ISMII items less than 50% of the time. However, there were several items with which participants frequently identified. For example, one of the most strongly endorsed items was “mentally ill people tend to be violent”. One of the important goals of moving patients from a large-centralized hospital into smaller community-based facilities is to increase patients’ contact with family, friends, and their community. Caregivers should consider if patients’ internalization of mental illness stereotypes and stigma may limit their willingness to re-engage with their family, friends, and community. For example, patients who endorse statements such as “being around people who don’t have a mental illness makes me feel out of place or inadequate” or “I stay away from social situations in order to protect my family or friends from embarrassment” indicate possible psychological barriers to reengagement. This represents an important area to target in transition programming and planning.

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11) The Relationship Between Level of Care in a Civil Psychiatric Population and Short-Term Assessment of Risk and Treatability (START) Scores

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Presenter: Karen L. Petersen  
Graduate Student

Faculty Sponsor: Tonia L. Nicholls

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The Short-Term Assessment of Risk and Treatability (START) Scores. The Short-Term of Assessment of Risk and Treatability (START) has not been validated in a civil psychiatric setting. As part of a larger project to evaluate the redevelopment of psychiatric services in British Columbia, the current study will evaluate the relationship between level of care received at Riverview Hospital and patients' strengths and vulnerabilities as measured by the START. 50 psychiatric inpatients underwent baseline assessments at Riverview Hospital. This assessment included psychosocial and mental health characteristics as well as START. Patients receiving tertiary residential care demonstrated mean START vulnerability scores significantly higher than patients receiving tertiary rehabilitation care. START strength scores were not significantly different. An understanding of dynamic risks and strengths in persons with mental illness is invaluable for assessing appropriate levels of care with regard to risk for aggression to self and others, as well as identifying targets for treatment, risk reduction, and management. START provides a framework for supporting decisions regarding levels of care and management required for patients in a civil psychiatric setting. These findings contribute to a growing body of literature documenting the utility of START, in community, civil psychiatric and forensic settings.

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12) Profiling the postmortem human brain: A meta-analytic approach

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Presenter: Meeta Mistry  
PhD Candidate

Faculty Sponsor: Paul Pavlidis

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Expression profiling of post-mortem human brain tissue has been widely used to study molecular changes associated with neuropsychiatric diseases as well as normal processes such as aging. Changes in expression associated with factors such as age, gender or postmortem interval are often more pronounced than changes associated with disease. Therefore, in addition to being of interest in their own right, careful consideration of these effects are important in the interpretation of disease studies. We have performed a large meta-analysis of genome-wide expression studies of normal human cortex to more fully catalogue the effects of age, gender, postmortem interval and brain pH, yielding a "meta-signature" of gene expression changes for each factor. This presentation will discuss the results of our meta-analysis, the different methods used in extracting the meta-signatures, and the validation of our results. Importantly, we will comment on genes in the profiles that are only identified through meta-analysis. Finally, we will show that many schizophrenia candidate genes appear in the meta-signatures, reinforcing the idea that studies must be carefully controlled for interactions between these factors and disease.

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13) A New Scale for Assessing Perceived Cognitive Impairment in Patients with Depression

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Presenter: Kyle E. Ferguson  
Postdoctoral Fellow

Authors: Grant L. Iverson, Diane McIntosh, Kyle E. Ferguson, Kevin Kjernisted, Allan H. Young,

Faculty Sponsor: Allan Young

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Introduction: Perceived cognitive impairment is a cardinal feature of depression. Unfortunately, there are no well-validated and widely available tests for measuring symptoms of cognitive impairment. The purpose of this study is to examine the clinical utility of a new cognitive scale for use as an outcome measure in clinical practice and research. Methods: Participants were 23 outpatients with depression (age=40.1years, SD=12.7; education=13.9 years, SD=2.1; 56.5% women; 69.6% employed, 78% with at least one past episode of depression, and 43.5% were prescribed antidepressants). Their average score on the 21-item version of the Hamilton Depression Rating Scale (HAM-D) was 28.5 (SD=5.7). The cognitive scale consists of 24 items extracted from the 243-item Ruff Neurobehavioral Inventory (RNBI) and is comprised of four subscales with six items each. The subscales are Attention & Concentration, Speech & Language, Learning & Memory, and Executive Functioning. All completed the scale twice separated by 6 days (SD=2.3). Results: The patients had elevated scores, relative to the normative sample, on Attention & Concentration (T=76.7, SD=13.3, Cohen's d=2.3, very large effect size), Speech & Language (T=76.0, SD=17.7, d=1.9), (3) Learning & Memory (T=71.9, SD=16.5, d=1.7), Executive Functioning (T=78.2, SD=9.8, d=2.8), and the Total Score (T=76.7, SD=11.9, d=2.4). Pearson correlations with the HAM-D were as follows: Attention & Concentration (r=.48), Speech & Language (r=.59), (3) Learning & Memory (r=.54), Executive Functioning (r=.41), and the Total Score (r=.66). The Pearson test-retest reliabilities were as follows: Attention & Concentration (r=.86), Speech & Language (r=.91), (3) Learning & Memory (r=.88), Executive Functioning (r=.56), and the Total Score (r=.86). Discussion: This is the first study utilizing this new cognitive scale in patients with mood disorders. The scale was sensitive to perceived cognitive impairment, moderately correlated with symptoms of depression, and it had good test-retest reliability.

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14) Development of a New Neurocognitive Screening Battery for Depression

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Presenter:	Kyle E. Ferguson Postdoctoral Fellow
Authors:	Grant L. Iverson, Brian L. Brooks, Kyle E. Ferguson, Allan H. Young
Faculty Sponsor:	Allan Young

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Objective: Subjectively-experienced problems with concentration memory, and problem solving are cardinal diagnostic features of major depressive disorder. To date, neurocognitive test batteries have not been systematically evaluated for use in depression, they are mostly idiosyncratic, and they are not co-normed. The purpose of this study is to develop a new time- and cost-effective neurocognitive screening battery for use in clinical practice and research with patients suffering from depression. Methods: Participants were 1,269 healthy adults between 18 and 79 years old (mean age=55.1, SD=17.8) selected from the Neuropsychological Assessment Battery (NAB; Stern & White, 2003) normative sample. The full NAB requires 3-3.5 hours of testing. The new screening battery requires approximately 1 hour of testing. It includes co-normed measures of attention, speed of processing, expressive language, learning, memory, and executive functioning that were selected based on a review of the depression literature. Results: Sixteen individual test scores are derived from this screening battery. The base rates of low scores, stratified by intelligence, are presented for different cutoff scores. For those with average intelligence, it is common to have 1-3 scores below 1SD from the mean, but uncommon to have six or more low scores. For those with high average intelligence, it is common to have 0-2 scores below 1SD, but uncommon to have four or more low scores. Conclusions: This one-hour battery, which includes data on the base rates of low scores, is designed for evaluating cognition in patients with depression. A case series of patients with depression will be presented.

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15) Assessing Inpatient Aggression Across Different Follow-up Periods using the START

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Presenter:	Cathy Wilson M.A., Ph.D. Candidate
Authors:	Wilson, C. M., Nicholls, T. L., Desmarais, S. L., Brink, J.
Faculty Sponsor:	Nicholls, T. L.

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The Short-Term Assessment of Risk and Treatability (START; Webster et al., 2004, 2009) is a relatively new structured professional judgment guide for assessment and management of short-term (i.e., weeks to months) risk of problematic behaviours through the differential coding of 20 dynamic strength and vulnerability factors. This paper will present findings of a study that investigates the START's ability to predict aggression (verbal aggression, physical aggression toward objects, physical aggression toward others) over shorter (i.e., up to six months) and longer (i.e., six to 12 months) follow-up periods. START assessments were completed from file for 120 male forensic psychiatric inpatients by graduate-level research assistants. Outcome data were collected from file for a one-year period. Preliminary analyses indicate that patients who are involved in an aggressive incident during the first six months have significantly lower START strength scores and higher vulnerability scores than those who are not aggressive at all during the 12-month follow-up. Although differences did not reach significance, patients who were aggressive within six months of the assessment have noticeably lower strength scores and higher vulnerability scores than those who are aggressive 6-12 months after the assessment. Discussion will focus on the utility of START for short-term clinical assessments.

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16) Can valproate reopen a critical period of learning in the adult human brain?

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Presenter:	Bradley W. Vines Research Associate
Co-authors:	Rubo Seo, Holly MacPherson, Tatiana Ramirez
Faculty Sponsor:	Allan H. Young

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Valproate inhibits histone deacetylase (HDAC), which is an enzyme that closes the critical period of development. Studies have shown that inhibiting HDAC can reopen critical-period learning in adult mice. Our experiment employs behavioral measures and epigenetic analysis to investigate the potential for valproate to reopen critical-period neuroplasticity in the adult human brain. The study has a randomized, double-blind, placebo controlled, cross-over design. Subjects are healthy young males, whom we randomize to the valproate- or placebo-first group in counterbalanced blocks of four. Subjects undergo two identical treatment series, each comprising 1) a baseline assessment, 2) taking capsules for two weeks (valproate or placebo), and 3) a post-treatment assessment. Subjects complete daily online training activities during the second week of taking capsules. A washout period of two to four weeks separates the two treatment series. For each assessment, subjects complete a cognitive and mood battery, and computerized tasks that are either associated or not associated with a critical period of learning, and they give a blood sample. The analysis will compare the effects of placebo and valproate on the change in behavioral performance from baseline to post-treatment, and on epigenetic factors in the blood samples, including DNA methylation state, and RNA expression.

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17) Longitudinal study of NAA levels in the hippocampus of first mania bipolar patients.

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Presenter:	Alexandre Gigante Fellow
Faculty Sponsor:	Lakshmi Yatham and L. Trevor Young

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Introduction: N-acetyl aspartate (NAA) is considered a putative marker of neuron integrity. Decreased levels of this metabolite have been found in patients with bipolar disorder, which has been associated with neuron degeneration in this disease. This MRS study investigates NAA levels longitudinally in the hippocampus of first episode manic patients. Methods: 15 euthymic bipolar I patients ( $22.4 \pm 3.9$  years; 7 male) and 10 controls ( $22.6 \pm 4.3$  years; 7 male) underwent 1H MRS at three different times: within one month of the first episode of mania (baseline), one and three years later. A single voxel was placed in left and right hippocampus and absolute values of NAA were obtained. Results: No significant difference for NAA levels was found at baseline, year one and year three between BD patients and controls. However, a tendency to decreased levels was found at year three. No correlation was found between NAA levels and days with a mood episode. NAA at year three had an inverse correlation with the duration of the first episode of mania and severity of mania. Conclusion: Neuron integrity seems to be preserved in patients after the first episode of mania. The potential decrease in NAA might be associated with the severity of the first episode of mania. More time of follow up is needed to confirm the tendency for decrease with time observed in this study.

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18) Functional Impact of Major Depressive Disorder in an Employee and Family Assistance Program

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Presenter: Cindy Woo  
Research Associate

Authors: Cindy Woo, Paula Cayley, Anne Bowen Walker, Melady Preece,  
Raymond W. Lam.

Faculty Sponsor: Raymond W. Lam

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**Objective:** This study assessed the effects of depression on clients' functional outcomes within an Employment Assistance Program (EAP). These employer-subsidized programs offer confidential counselling services for employees with problems affecting work performance. Although employees often present to EAPs with depression, anxiety, and stress, little research has investigated the impact of depression on outcomes after EAP intervention.

**Methods:** Data were obtained from 10,794 consecutive, self-referred clients of Interlock PPC, a large EAP serving 350+ organizations across Canada. Assessment measures included the Patient Health Questionnaire 9 (PHQ-9) and the Global Assessment of Functioning (GAF) Scale. A PHQ-9 score of  $\geq 10$  has been shown to indicate major depressive disorder (MDD).

**Results:** Of all clients, 37% met PHQ-9 criteria for MDD. Compared to non-depressed clients, clients with MDD received more hours of service from Interlock, had lower baseline GAF scores, and showed significantly greater impairment in routine work-related tasks.

**Conclusions:** A significant proportion of Interlock's clients were clinically depressed by PHQ-9 criteria. These clients also showed poorer outcomes following EAP intervention, suggesting a need for more intensive services than those available within the usual EAP structure. EAP providers should emphasize early recognition of MDD in clients and targeted strategies to optimize client outcomes.

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19) A Systematic Review of the Treatment Effects of Antidepressants on Occupational Functioning

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Presenter: Jane McLeod  
MEd

Authors Jane McLeod; Cindy Woo; Lakshmi N. Yatham; David J. Bond;  
Raymond W. Lam.

Faculty Sponsor: Raymond W. Lam

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**Objectives:** The focus of clinical trials of antidepressant medications has been on symptom remission. However, functional recovery (including occupational functioning) is an important aspect of treatment, especially for patients, and psychosocial functioning is not well correlated with symptom improvement. However, less than 5% of clinical trials in depression include measures of psychosocial functioning (McKnight and Kashdan, 2009). This presentation focuses on the methodology for a systematic review of treatment effects of antidepressants on occupational functioning (work absence and productivity). **Methods:** Electronic databases will be searched using appropriate search terms. The bibliographies of relevant publications will be scanned for additional citations. Inclusion criteria are 1) diagnosis of MDD by prospective criteria, e.g., DSM-IV or ICD-9, 2) randomized controlled trials, with or without a placebo condition, 3) involvement of one or more antidepressants, and 4) a specific outcome related to occupational functioning (work absence, disability, or work functioning scale). Data will be abstracted by two reviewers and double-entered for accuracy. **Results:** An example of an antidepressant clinical trial will be presented to illustrate how improvement in depressive symptoms and work functioning are not necessarily related. **Conclusions:** Occupational and work functioning are important outcomes for treatment of MDD. More clinical trials of antidepressants (and other depression treatments) should incorporate work functioning measures as primary or secondary clinical outcomes.

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POSTERS - BASIC SCIENCE

1) Slow cortical oscillations and muscle twitches in the neonatal rat

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Presenter: David McVea  
 PhD Student  
 Faculty Sponsor: Tim Murphy

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Remarkably, most of the activity of the brain is unrelated to ongoing motor or sensory tasks. Understanding the function of this activity has emerged in the past decade as a major aim of neuroscience research.

One crucial role played by spontaneous activity is promoting correct network development early in life. Unlike in adults, sleep-related spontaneous brain activity in neonates is often prompted by peripheral activity such as muscle twitches. To understand how such twitches drive cortical activity in developing rat pups, we have combined high speed video recordings of the body with voltage-sensitive dye imaging of neural activity from large regions of the cortex. We have found that relatively fast spontaneous cortical bursts usually follow twitching of the peripheral limbs, but these twitches are in turn preceded by very slow cortical oscillations. We propose very slow oscillations may drive peripheral twitches and subsequent fast cortical bursts as a mechanism for calibrating and connecting the sensorimotor system during development. This may serve as a model for activity-dependent network development in early life that underlies social and mental development and their related disorders.

2) Hypothermia does not prevent ischemia-induced dendritic damage but does improve structural recovery in reperfusion

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Presenter: Sherri Tran  
 Graduate student (MSc Candidate)  
 Faculty Sponsor: Tim Murphy

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**Introduction.** Following ischemia, dendrites exhibit a dramatic structural alteration known as blebbing, taking on a “beads on a string” appearance. Here, we examine recovery of dendritic blebbing in reperfusion following global forebrain ischemia under hypothermic and normothermic conditions. **Methods.** Bilateral occlusion of the common carotid arteries was used to produce global forebrain ischemia in GFP and YFP transgenic C57Bl/6 mice (2-4 months). Two-photon imaging was used to visualise dendritic blebbing and recovery and monitor blood flow dynamics. Cortical temperature was regulated either under normothermic (37°C) or moderate hypothermic (32°C) conditions and mice were given strokes either 6, 4, or 2 minutes in duration. In all cases, core body temperature was maintained at 37°C. **Results.** With long periods (6 min) of global ischemia, a significant improvement ( $p < 0.001$ ) in blebbing recovery is seen by 30 minutes of reperfusion with hypothermia treatment compared to normothermic conditions. Under normothermic conditions, recovery from blebbing is also observed by 30 minutes ( $p < 0.01$ ) with short (2 min) but not longer periods (4-6 min) of global ischemia. **Conclusion.** Structural recovery from dendritic blebbing is improved under hypothermic conditions, and for normothermic conditions, occurs with short periods of ischemia.

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3) Investigating altered NMDAR localisation and signalling in a Huntington Disease mouse model

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Presenter: Dr. Clare Gladding  
Postdoctoral Fellow

Co-authors: Austen J. Milnerwood, M. R. Hayden, L. A. Raymond

Faculty Sponsor: Lynn Raymond

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**Introduction:** Huntington disease (HD) is a neurodegenerative disease characterised by mood, cognition and movement abnormalities. It is caused by a polymorphic CAG repeat expansion in the HD gene that results in the mutant huntingtin protein (mhtt), that is linked to selective striatal medium spiny neuron (MSN) degeneration. HD is also associated with excitotoxicity as a result of altered NMDA receptor (NMDAR) signalling and trafficking. Survival or apoptotic pathways can be preferentially triggered by activation of synaptic or extrasynaptic NMDARs (eNMDARs), respectively. HD pathogenesis can be investigated using yeast artificial chromosome (YAC) transgenic mice expressing full-length human htt with 18 (normal), 72 or 128 (pathological) polyglutamine repeats. Electrophysiological and biochemical studies indicate that YAC128 MSNs have increased eNMDAR expression and activity and elevated calpain cleavage compared to YAC18 MSNs. **Materials and Methods:** Striatal nuclear, cytosolic and synaptosomal fractions were isolated from 4-month old WT and YAC128 mice that had been treated for 2 months with the eNMDAR antagonist, memantine. **Results:** Nuclear activation of the neuroprotective transcription factor CREB was significantly reduced in YAC128 mice but was increased to WT levels after memantine treatment. Furthermore, memantine reduced elevated calpain activation (reflected in cleavage of spectrin, NR2B and the tyrosine phosphatase, STEP) in YAC128 mice. **Conclusion:** Consistent with the hypothesis that eNMDAR signalling triggers apoptotic cascades, this study provides an important link between neuronal degeneration and NMDAR excitotoxicity associated with HD.

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4) Synaptic versus extrasynaptic N-methyl-D-aspartate receptor signaling in corticostriatal co-culture

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Presenter: Alexandra (Ali) Kaufman  
Graduate Student

Faculty Sponsor: Lynn A Raymond

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The subcellular localization of the N-methyl-D-aspartate receptor (NMDAR) profoundly affects its signaling. Extrasynaptic NMDAR activation triggers death-related processes, while synaptic NMDARs trigger pathways associated with synaptic plasticity and survival. These results have been reported in cortical and hippocampal neurons; however, it is unknown whether striatal medium-sized spiny projection neurons (MSNs) that bear the brunt of degeneration in Huntington disease, follow the same pattern. Studies suggest that NMDAR-activated cell death signaling pathways are different in striatal MSNs compared with cortical and hippocampal pyramidal neurons. Here, we test the hypothesis that NMDAR-mediated cell death vs. survival signaling occurs via distinct pathways in striatal MSNs compared to cortical pyramidal neurons. Striatal MSNs and cortical pyramidal cells are co-cultured and allowed to create synaptic connections. Results indicate that MSNs grown in coculture show spine-like processes not seen in monoculture, indicating the formation of synaptic connections. Synaptic NMDARs are selectively activated by network disinhibition, as previously described in hippocampal cells. Extrasynaptic NMDARs are stimulated by network inhibition in the presence of MK-801, an irreversible open-channel NMDAR blocker, followed by exposure to NMDA. Assays include immunohistochemical analysis of the Cre-response element binding protein (CREB). Results indicate that synaptic stimulation causes an increase in nuclear pCREB, while extrasynaptic stimulation causes a decrease in nuclear pCREB. This research may help provide targets for interventions in the treatment of Huntington disease.

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 5) P38 MAPK is involved in enhanced NMDA receptor-dependent excitotoxicity in YAC transgenic mouse model of Huntington disease
 

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Presenter: Jing Fan  
 Ph.D Student  
 Authors: J. Fan, L. Zhang, L. A. Raymond  
 Faculty Sponsor: Lynn Raymond

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Huntington disease (HD) is a dominantly inherited neurodegenerative disease, which is caused by polyglutamine (polyQ) expansion in the protein huntingtin (htt). Our lab has previously shown enhanced NMDA-induced excitotoxicity in cell and neuronal models of HD (Zeron et al. 2001; Zeron et al. 2002; Shehadeh et al. 2006). N-methyl-D-aspartate receptor (NMDAR) NR2 subunits interact with the postsynaptic density protein-95 (PSD-95) (Kornau et al. 1995), while PSD-95 also binds downstream signalling proteins such as the neuronal nitric oxide synthase (nNOS) (Brenman et al. 1996). More interestingly, PSD-95 binds to huntingtin in a polyQ-dependent manner (Sun et al. 2001), and we have recently found increasing PSD-95/NR2B binding in striatal tissue from YAC transgenic mice with increasing htt polyQ length. By using a TAT-fused NR2B C-terminal peptide (Tat-NR2B9c) to disturb this interaction (Aarts et al. 2002; Cui et al. 2007), we found that the enhanced interaction of NR2B with PSD-95 plays a key role in mediating potentiation of NMDAR excitotoxicity by mutant htt (mhtt) in cultured striatal neurons. A recent publication shows that NMDA-induced cell death in cultured cortical neurons is mediated by two distinct excitotoxicity pathways: the p38 mitogen-activated protein kinase (MAPK) and the c-Jun N-terminal protein kinase (JNK) (Soriano et al., 2008). It has been found recently that the p38 death pathway is downstream of NMDAR-PSD-95 signaling either through nNOS or synaptic Ras-GTPase activating protein (SynGAP) (Kim et al., 1998; Rumbaugh et al., 2006), and can be disrupted by Tat-NR2B9c without impacting prosurvival signaling (Soriano et al., 2008). We have found that the basal levels of both activated p38 and JNK MAPK were elevated in YAC128 (HD) mice striatal tissues compared with YAC18 at 8-weeks of age. By using TUNEL-Hoechst staining assay, we found that p38 inhibitor (SB-239063) reduced NMDA-induced cell death in cultured MSNs of YAC128 to the level of WT, and occluded the Tat-NR2B9c peptide protective effect. In contrast, JNK inhibitor (SP-600125) at 20  $\mu$ M had no effect on NMDA-induced cell death in cultured MSNs of either WT or YAC128. Preliminary data on NMDA-induced activation of p38 MAPK and JNK with or without Tat-NR2B9c pretreatment in corticostriatal slices of WT and YAC128 mice at 8-weeks of age indicated that NMDA treatment significantly activated p38 in both WT and YAC128 striatum; this activation was blocked by Tat-NR2B9c only in YAC128 tissue. NMDA also elevated JNK activity in both genotypes and was not blocked by Tat-NR2B9c. Our results suggest that altered activation of p38 but not JNK MAPK contributes to mutant htt-mediated enhancement of NR2B-PSD-95 toxic signaling. However, the JNK pathway may also contribute to increased sensitivity of YAC128 striatal neurons to excitotoxicity.

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- 6) Decreased levels of glutathione, the major brain antioxidant, in *post-mortem* prefrontal cortex from patients with mood disorders
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Presenter: Jeremy W. Gawryluk  
Postdoctoral Fellow

Authors: Gawryluk, J.W., Wang, J.F., Shao, L., Young LT

Faculty Sponsor: L. Trevor Young

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Background: Glutathione is the body's major free radical scavenger. Diminished glutathione levels elevate cellular vulnerability toward oxidative stress; characterized by accumulating reactive oxygen species. Accruing data suggest that oxidative stress underlies the pathophysiology of bipolar disorder (BD), major depressive disorder (MDD), and schizophrenia (SCZ). The purpose of this study is to (1) measure levels of oxidized and reduced glutathione; (2) analyze the synthetic and utilization enzymes for glutathione. Methods: Post-mortem prefrontal cortex from individuals with BD, MDD, SCZ, and from non-psychiatric comparison controls were provided by the Stanley Foundation Neuropathology Consortium. We utilized an enzymatic recycling methodology for the quantitative determination of oxidized and reduced levels of glutathione. To examine glutathione synthesis, we performed Western blot analyses for the rate-limiting catalytic subunit of glutamate-cysteine ligase. To determine the use of glutathione, we measured via Western blot analyses: glutathione reductase, glutathione peroxidase-1, and glutathione s-transferases mu-1 and pi. Results: The levels of reduced, oxidized, and total glutathione were significantly decreased in all psychiatric conditions as compared against control. Though the levels of glutamate-cysteine ligase were unaltered in any of these disorders, the levels of glutathione reductase, peroxidase-1, and s-transferase mu-1 were significantly reduced in MDD and SCZ as compared to control subjects. Conclusion: These findings indicate that glutathione levels are reduced in psychiatric illness and these decreases are due to glutathione usage and not hindered synthesis. These results suggest that psychiatric patients may benefit from compounds, such as N-acetyl cysteine, that increase glutathione's levels.

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- 7) Mood stabilizing drug lithium inhibits amphetamine-increased oxidative damage in rat brain.
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Presenter: Hua Tan  
Postdoctoral Fellow

Faculty Sponsor: Jun Feng Wang

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Previous study in our laboratory has shown that chronic treatment with lithium at therapeutically relevant concentration inhibits oxidative damage in primary cultured rat cerebral cortical cells in vitro. Amphetamine-induced hyperactivity is a well-established animal model for mania. It has been reported that repeated amphetamine stimulation induces oxidative damage. 4-hydroxynonenal (4-HNE), a major product of lipid peroxidation, is able to exert cytotoxicity and disturb cellular function by forming protein adducts. In the current study, we determined whether repeated amphetamine stimulation and chronic lithium treatment regulate 4-HNE-protein adducts in rat brain. The level of 4-HNE-protein adducts was analyzed by using immunohistochemistry. We found that repeated amphetamine stimulation significantly increased locomotor activity and also increased levels of 4-HNE-protein adducts in rat brain. Though lithium treatment alone has no effects on locomotor activity and 4-HNE-protein adducts, this treatment significantly inhibited amphetamine-increased locomotor activity and levels of 4-HNE-protein adducts. This finding suggests that the process of oxidative damage may be a target for the treatment of bipolar disorder.

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8) Lithium prevents nitration and oxidation in mitochondrial but not in non-mitochondrial proteins.

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Presenter: Ana Cristina Andreatza  
Post-Doctoral Fellow

Authors: Andreatza AC, Gigante AD, Shao L, Young LT, Wang JF

Faculty Sponsor: L. Trevor Young

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Summary: There is an emerging body of data suggesting that mitochondrial dysfunction and oxidative stress damage contribute to the pathophysiology of bipolar disorder. Recent data from our group showed decreased complex I activity and increased oxidation and nitration of mitochondrial protein in postmortem prefrontal cortex from patients with bipolar disorder. Interestingly, accruing data suggests that mood stabilizers, especially lithium, may reduce the oxidative stress damage by increasing expression and activity of antioxidant enzymes. Thus, the purpose of this study was to evaluate whether lithium can prevent the oxidative and nitrosative damage to mitochondrial and non-mitochondrial proteins. Methods: Adolescent male Wistar rats received 1mg/kg of d-amphetamine or saline for 14 days, with or without concurrent administration of lithium in their diet (0.24%). Mitochondrial proteins-enriched extracts (MTC) were prepared using sucrose-tris method and non-mitochondrial proteins (N-MTC) were kept for future analysis. Immunoblotting analysis was used to measure the levels of 3-nitrotyrosine (tyrosine-nitration induced damage) and carbonyl groups (protein oxidation). Results: Protein oxidation and nitration levels in MTC and N-MTC proteins were significantly increased in animals treated with d-amphetamine. Concurrent lithium administration reduces the protein oxidation and nitration caused by d-amphetamine in MTC but not in N-MTC proteins. Conclusion: These findings indicate that lithium is able to prevent oxidative and nitrosative damage in mitochondrial, but not in non-mitochondrial proteins. These results support that lithium may be an important compound to prevent the mitochondrial dysfunction and consequent oxidative stress damage observed in bipolar disorder patients.

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9) A critique of gene function prediction in neuropsychiatric disorders: Reassessing the significance of coexpression and protein interaction

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Presenter: Jesse Gillis  
Postdoctoral Fellow

Faculty Sponsor: Paul Pavlidis

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Multigene Neuropsychiatric disorders often involve many of the same genes. For example, the AZ Database (AZgene) of Alzheimer's associated genes shares approximately half of its genes with the Parkinson's (PDgene) or Schizophrenia (SZgene) lists. In fact, these "disease candidate genes" are often just genes related to the brain, as opposed to being truly specific candidates for a particular disease. Our work characterizes this source of bias and its effects (e.g., problem genes). We specifically focus on a form of "placebo effect" present in gene function prediction which allows problem genes to appear significantly relevant to many different disorders. We show that the genes most strongly related to a disorder are typically not the genes most specifically related to a disorder. Since many attempts to determine genetic causes of psychiatric diseases focus on the former, they may draw flawed conclusions. We employ a variety of genetic association data (protein interaction and coexpression) to show the problem is pervasive and can be understood in the context of gene function prediction methods (e.g., "guilt by association"). We discuss methods and strategies for correction and control.

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10) In Vivo Voltage Sensitive Dye Imaging Reveals Bi-hemispheric Functional Changes Following Focal Infarct to the Forelimb Somatosensory Cortex of Rehabilitated Mice.

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Presenter: Khatereh Aminoltejari  
M.Sc. Student

Authors: Khatereh Aminoltejari, Matthew Fingas, Craig E. Brown, Majid H. Mohajerani, Timothy H. Murphy

Faculty Sponsor: Tim Murphy

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Normally, most sensory activity is processed within the contralateral cortex through crossed pathways. However, there is ample evidence for ipsilateral (uncrossed pathway) maps of tactile stimuli within mirrored cortical regions. Functional recovery after stroke has been associated with plasticity not only at the lesion site but also at remote brain areas. It is, therefore, important to identify the circuits that undergo plasticity to facilitate functional and behavioral recovery in order to tailor rehabilitation and pharmacological interventions to enhance recovery. In the present study, we investigated ipsilateral representation of tactile information before and after stroke and examined the effect of lesion size on the contribution of the ipsilateral hemisphere to recovery after stroke. We also rehabilitated mice with large strokes, using a single-pellet reaching task, the Montoya staircase task with acclimatization to a running wheel. We used voltage sensitive dye (VSD) imaging, which is more sensitive to ipsilateral responses due to its ability to detect subthreshold activity. C57Bl/6 mice were given small or large (~1mm<sup>2</sup>, and 3mm<sup>2</sup> of cortical surface area respectively), unilateral targeted infarct using photothrombosis directed to the right forelimb somatosensory cortex. Urethane anesthetized animals were imaged through a large, bilateral cranial window encompassing both hemispheres. Our results demonstrate that ipsilateral (unaffected) circuits are actively remodeled following stroke. Additionally, the size of intact somatosensory cortex following focal stroke determines the laterality of sensory processing. Rehabilitation after a large stroke facilitates more contralateral (ipsilesional processing) in comparison to non-rehabilitated animals. Simultaneous VSD imaging of both hemispheres suggests widespread bilateral functional reorganization of the brain following a unilateral ischemic insult and increased contralesional processing of ipsilesional tactile stimuli.

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11) A novel form of regenerative glutamate release by NMDA receptors causes spreading depression

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Presenter: Ning Zhou  
PhD Student

Faculty Sponsor: Brian MacVicar

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Spreading depression (SD) is a slowly propagating wave of neuronal depolarization which underlies certain neurological conditions such as migraine with aura. The pattern of propagation and the involvement of glutamate suggests that SD arises from an unusual form of neuronal communication. We used enzyme based glutamate electrodes and electrophysiological recordings to show that NMDA receptors (NMDAR) likely at presynaptic sites, trigger SD by evoking glutamate release via vesicular exocytosis. The SD evoked glutamate release and DC shift were blocked by both the NMDAR antagonist and the vacuolar H<sup>+</sup>-ATPase (V-ATPase) inhibitor; however, they were still present when action potentials and voltage gated calcium channels (VGCC) were blocked with TTX and Cd<sup>2+</sup>. Interestingly, SD and glutamate release still occurred when Ca<sup>2+</sup> was removed from the extracellular solution, but was blocked by inhibition of the mitochondrial Na<sup>+</sup>/Ca<sup>2+</sup> exchanger (NCXmito). Additionally NMDAR stimulation itself was capable of initiating an SD wave and vesicular glutamate release which was also blocked by NCXmito inhibitors. These data suggest that sodium influx evoked by NMDAR activation can act via NCXmito to release calcium from mitochondria in presynaptic terminals and thereby trigger vesicular release of glutamate. Through this mechanism NMDAR stimulation evokes a vicious cycle of glutamate-induced glutamate release, causing SD.

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12) Acute Modulation of Synaptic Plasticity by LPS and Hypoxia

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Presenter: Jingfei Zhang  
PhD student

Faculty Sponsor: Brian MacVicar

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Objectives: Our study is aimed to investigate how the acute inflammatory stimulation can modulate synaptic function by microglia activation. Hippocampal slices were obtained from 18-24 days SD rats. Evoked field potentials were recorded in CA1 region. Two photon imaging was performed to measure the reactive oxygen species (ROS) level. Results: We combined inflammation and hypoxia, two stressors in the brain, to investigate a new short-term modulation of synaptic function. We perfused hypoxic gas (8% O<sub>2</sub>) saturated ACSF on slices for 15min. fEPSP shrank to 0mV in 10min, but fully recovered 30min after reperfusion of normal ACSF. LPS application during and after hypoxia triggered long term depression (LTD) (66.8±3.7% of baseline), and was not rescued by NMDAR inhibitor APV. ROS is involvement in both inflammation and hypoxia pathways and has been shown to modulate synaptic plasticity. Apocynin blocking of NADPH oxidase (major source of ROS) resulted in a total LTD blockage. ROS level was measured by 2 photon imaging. No significant change was found in either LPS or hypoxia experiment. However, LPS and hypoxia together triggered a significant and steady increase of ROS (109.6±1.4%) in CA1, which was blocked by apocynin. Conclusion: Acute exposure to LPS together with hypoxia generated LTD in rat hippocampal slices. This LTD is triggered by ROS generated from NADPH oxidase. ROS level significantly increased during hypoxia and LPS treatment, which can be blocked by apocynin.

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13) Oxidative stress & astrocyte control of the vasculature

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Presenter: Clare Howarth  
Postdoctoral Fellow

Faculty Sponsor: Brian MacVicar

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Elevations in astrocytic  $Ca^{2+}$  levels, evoked by neural activity, can lead to vasoconstriction or dilation. Both of these responses originate with a calcium induced activation of cPLA2 and arachidonic acid (AA) formation. Conversion of AA to 20-HETE in smooth muscle cells results in constriction whereas conversion of AA to prostaglandin E2 (PGE2) in astrocytes induces vasodilation. The formation of PGE2 from AA requires glutathione, a cofactor for the enzyme PGE2 synthase. We tested whether a decrease in glutathione leads to reduced PGE2-mediated vasodilation. Hippocampal slices were incubated in BSO (a glutathione synthesis inhibitor) and loaded with the calcium indicator dye Rhod-2/AM. An increase in astrocytic calcium levels was evoked either by applying tACPD or by photolysis of caged IP3. Lumen diameter, PGE2 release and glutathione levels were measured. In hippocampal slices, downstream of  $Ca^{2+}$ -evoked AA release in astrocytes, the component of functional hyperaemia mediated by PGE2 release from astrocytes requires glutathione. When the level of glutathione was reduced PGE2 release was inhibited and functional hyperaemia was reduced. After stroke glutathione becomes depleted, and these data would predict that this should inhibit prostaglandin-mediated vasodilation. This may contribute to the long-lasting failure of vasodilatory mechanisms that is known to occur after stroke and that contributes to increasing neuronal damage.

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14) MRM-based quantitation of SNAP-25 protein isoforms in cells and human brain samples

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Presenter: Viltė Barakauskas  
Graduate Student

Faculty Sponsor: William Honer

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SNAP-25 is one of three neuronal SNARE proteins essential for regulated neurotransmitter release. SNAP-25 occurs in two isoforms (A and B) in the brain. Isoform expression at the mRNA level is developmentally regulated, and the two protein isoforms confer different properties on neurotransmitter release. SNAP-25 has been shown to be altered in schizophrenia, including reductions in protein expression in the ventromedial caudate (VMC). Previous studies did not distinguish between the two isoforms, and SNAP-25A and B expression in brain is known only at the mRNA level in rodents. To better understand the functional implications of SNAP-25 protein reductions in schizophrenia, we have developed a means of measuring SNAP-25A and B at the protein level in post-mortem human brain. Using a quantitative proteomic approach, we have developed and characterized a multiple reaction monitoring (MRM)-based isoform assay that is able to detect known changes in SNAP-25 isoform expression. Using this assay we now report that SNAP-25A protein levels are significantly reduced in the VMC in schizophrenia. Striatal dysfunction in schizophrenia may be due, in part, to changes in the properties of neurotransmission due to a change in the expression pattern of SNAP-25 protein isoforms.

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