2018 Research Day / Journée de la recherche 2018
Douglas Institute Research Centre and McGill Department of Psychiatry
Centre de recherche de l'Institut Douglas et Dépt. de psychiatrie de McGill

Tuesday, June 5, 2018, 8:45 AM - 7:00 PM
Le mardi 5 juin 2018, 8h45 - 19h00

Douglas Hall, Douglas Mental Health University Institute
Pavillon Douglas, Institut universitaire en santé mentale Douglas

8:45 Welcome, opening remarks / Accueil et mots d'ouverture

Session 1 (Chairperson / Présidente de session : Kathleen MacDonald)

9:00 O1 Cocaine Dependence Is Associated with Epigenetic Dysregulation of the Neurodevelopmental Gene Cluster IRX.
Kathryn Vaillancourt, Jennie Yang, Gang G. Chen, Laura Fiori, Carl Ernst, 3, Erin Calipari, Benoit Labonté, Eric Nestler, Deborah C. Mash, Gustavo Turecki


Helen Martin, Megan Pope, Manuela Ferrari, Nicole Pawliuk, Srividya N. Iyer

9:45 Datablitz
List of presentations on page 4 / Liste des présentations à la page 4

10:30-11:15 Coffee break and poster session / Pause-café et session d'affiches
Session 2 (Chairperson / Présidente de session: Polina Ash)

11:15  **O4** The Phase-Shifting Effect of Bright Light on the Human Circadian Transcriptome During Simulated Night Shift Work
Laura Kervezee, Marc Cuesta, Nicolas Cermakian, Diane Boivin

11:30  **O5** CDK5RAP2 gene and Tau Pathophysiology in Late-Onset Sporadic Alzheimer’s disease
Justin Miron, Cynthia Picard, Nathalie Nilsson, Josée Frappier, Doris Dea, Louise Théroux, Jules Poirier

11:45  **O6** Pituitary Volume Mediates the Effect of Prenatal Stress on Internalizing Symptoms: Project Ice Storm
Sherri Lee Jones, James Gazetas, Chloe Anastassiadis, François-Pierre Marcoux, Guillaume Elgbeili, Jens C. Pruessner, David P. Laplante, Suzanne King

12:00  **O7** Driving While Impaired Offenders Show Selective Treatment Responsivity to Brief Motivational Interviewing vs. Information and Advice Based upon Subtype Membership

12:15  **O8** Mapping of Postnatal Neurodevelopment in Response to Early and Late Prenatal Maternal Immune Activation in Mice
Elisa Guma, Chloe Anastassiadis, Jurgen Germann, Daniel Gallino, Gulebru Ayranci, Gabriel Devenyi, M Mallar Chakravarty

12:30-1:30  Lunch/ Dîner

Session 3 (Chairperson / Présidente de session: Elisa Guma)

1:30  **O9** Reduced Resting-State Functional Connectivity of the Basolateral Amygdala to the Medial Prefrontal Cortex in Preweaning Rats Exposed to Chronic Early-Life Stress
Angela Guadagno, Min Su Kang, Gabriel A. Devenyi, Axel P. Mathieu, Pedro Rosa-Neto, Mallar Chakravarty, Claire-Dominique Walker

1:45  **O10** Why We Still Use “Organic Causes”: Results of a Survey of Psychiatrists and Residents
David Benrimoh, Vincent Jetté Pomerleau, Arnaud Demoustier, Stéphane Poulin, Jean- Robert Maltais, Judith Brouillette, Simon Ducharme

2:00  **O11** Genetic and Environmental Factors Are Differentially Related to Aβ Burden in the Presymptomatic Phase of Autosomal Dominant and Sporadic Alzheimer’s Disease.
Julie Gonneaud, Christophe Bedetti, Alexia Pichet Binette, Tammie L.S. Benzinger, John C. Morris, Randall, Bateman, Judes Poirier, John C. Breitner, and Sylvia Villeneuve, for The DIAN Study Group3 and PREVENT-AD Research Group

2:15  **O12** Amphetamine Disrupts DCC-Dependent Dopamine Axon Targeting in Adolescence
Lauren M. Reynolds, Sonia Israel, Santiago Cuesta, Michael Wodzinski, Julia G. Epelbaum, Jose Maria Restrepo-Lozano, Cassandra Fortin-Claes, Bryan Kolb, Cecilia Flores

2:30  **O13** Relationship Between Maternal Antenatal Mood and Child Internalizing Symptoms Is Moderated by Child Genetic Risk for ADHD: A Refined Genome-Wide GxE Approach
2:45-3:30 Coffee break and poster session / Pause-café et session d'affiches

Session 4 (Chairperson / Présidente de session: Lourdes Fernández de Cossío)

3:30 O14 Opening the Minds of American Voters
Jay Olson, Thomas Strandberg, Lars Hall, Amir Raz, and Petter Johansson

3:45 O15 Improving Derivation of a9-Type Dopamine Cells for Cell Transplantation in Parkinson's Disease.
Malvin Jefri, Scott Bell, Huashan Peng, Gilles Maussion, Vincent Soubannier, Hanrong Wu, Heika Silveira, Luc Moquin, Thomas M. Durcan, Alain Gratton, Edward A. Fon, Carl Ernst

4:00 O16 CSF Immune Marker Levels Associate with Ad Symptom Severity and Trajectory
Pierre-François Meyer, Melissa Savard, Judes Poirier, John C S Breitner, for the Alzheimer's Disease Neuroimaging Initiative

4:15 O17 The Relationship Between Molecular Smoking Signature and Cortical Thickness in Children with ADHD: An Epigenetic Neuroimaging Study.
Nellie Fotopoulos, Boris Chaumette, Gabriel A. Devenyi, Sarojini Sengupta, Sherif Karama, Mallar M. Chakravarty, Natalie Grizenko and Ridha Joobber

Keynote lecture / Conférence de prestige (Chairperson / Présidente de session: Lourdes Fernández de Cossío)

4:30 Social Cognition in Schizophrenia: Relevance of Functional MRI to Identify Target Mechanisms and to Develop Improved Measures
Amélie Achim, PhD, Associate Professor, Department of Psychiatry and Neurosciences, Faculty of Medicine, Laval University; Researcher, Clinical and cognitive neurosciences axis, CERVO Brain research centre / Professeure agrégée sous octroi, Département de psychiatrie et neurosciences, Université Laval; Chercheure, Axe neurosciences cliniques et cognitives, Centre de recherche CERVO.

5:15-5:20 Short pause (Jury Deliberations)

5:20-5:40 Award Ceremony / Cérémonie de remise de prix

5:40-7:00 Wine and Cheese Reception / Réception vins et fromages

We wish to thank our generous sponsors / Nous remercions nos généreux commanditaires:
Poster and datablitz presentations / Présentations par affiche et en datablitz

P1  Investigation of the Head Direction Signal in the Anterodorsal Thalamic Nucleus Using Miniaturized Microscopes in Behaving Mice  
Zaki Ajabi, Mark Brandon

P2  LCM-Seq: Single Cell-Type Whole Genome Bisulfite Sequencing and Transcriptomic Profiling in Post-Mortem Brain of Abused Suicides  
Daniel Almeida, Gang Chen, Jean-Francois Theroux, Zahia Aouabed, Maria-Antonietta Davoli, Naguib Mechawar, Gustavo Turecki

P3  Electrophysiological and Morphological Characterization of VIP Cells in the Mouse Entorhinal Cortex  
Saishree Badrinarayanan, Mark Brandon

P4  How Parent-Report and Teacher-Report of Childhood Conduct Problems are Associated with Family Functioning – Lessons About the Rater Effects in a Sample of Children Admitted for Day Hospitalization  
Sahar Balvardi, Noriyeh Rahbari, Mitchell Arnowitz, Ekta Kumar, Jaswant Guzder, Ashley Wazana

P5  Differential Susceptibility to Positive Environments Influences Childhood Emotional Eating According to Genetically Determined Gene Expression of Prefrontal DRD4 Gene  
Barbara Barth, Bizarro L., Nguyen TT., Pokhvisneva I., Miguel PM., Dubé L., Levitan R., Kennedy JL., Meaney MJ., Silveira PP.

P6  Neuropsychiatric Burden Is Related to Increased Amyloid but Not Tau Deposition in Late-Middle-Aged Cognitively Normal Individuals with a Family History of Alzheimer’s Disease  

P7  Correspondences between Plasma Nutrient Levels and DNA Methylation Patterns in Individuals with Anorexia Nervosa  
Jessica Burdo, Esther Kahan, Lea Thaler, Xiaoyan Fang, Mimi Israël, Linda Booj, Luis B. Agellon, Kevin McGregor, Aurelie Labbe, Howard Steiger

P8  Depressed Mood State and Alcohol in Risky Driving  
Nevicia Case, Thomas G. Brown

P9  The Effect of Chronic Altered Lighting Conditions on Motor Coordination, Cognitive Functions and Wheel Running in Aged Mice  
Tara Delorme, Geneviève Dubéau Laramée, Chloé Nobis, Nicolas Cermakian

P10  Walking A Mile In Another’s Shoes: Can Virtual Reality Decrease Prejudice?  
Amanda Dennie, Lauriol Djehounke, Emily Light, Camille W. Chamberlain, Rémi Thériault, Sonia Krol, Amir Raz

P11  What Information Do Fertility Patients Request and Receive During Clinic Visits to Manage the Emotional Burden of Treatment?  
Eden Gelgoot, Margot Kelly-Hedrick, Skye Miner, Phyllis Zelkowitz

P12  Circadian Misalignment in Police Officers After a Week of Night Shifts  
Fernando Gonzales Aste, Laura Kervezee, Diane B. Boivin

P13  Depression and New-Onset Diabetes: Does the Measure of Depression Matter?  
Eva Graham, Sonya Deschenes, Marina Khalil, Sofia Danna, Norbert Schmitz
P14 Maternal High-Fat Diet Alters Leptin Sensitivity and Afferents to Lateral Hypothalamus in Rat Pups
Lyla Kelley, H. Long, S. Verlezza, C.-D. Walker

P15 Myelin-Related Protein Expression and Oligodendrocyte-Lineage Cell Population in the Uncinate Fasciculus of Depressed Suicides with a History of Child Abuse
John Kim, Meghan Shaw, Arnaud Tanti, Maria Antonietta Davoli, Rachel Toope, Naguib Mechawar

P16 Emotion Regulation in Bipolar Disorder Type I: An fMRI Multivariate Analysis
Fumika Kondo, Jocelyne Whitehead, Fernando Corbalan, Serge Beaulieu, Jorge Armony

P17 Small non-coding RNAs in Major Depression and Antidepressant Response
Rixing Lin, Juan Pablo Lopez, Laura Fiori, Cristiana Cruceanu, Raoul Belzeaux, Jane Foster, Sidney Kennedy, Gustavo Turecki

P18 Pathways to Care in Youth Mental Health: A Systematic Review of the Evidence
Kathleen MacDonald, Nina Fainman-Adelman, Kelly K. Anderson, Srividya N. Iyer

P19 Cases, Non-Cases, or Non-Non-Cases: An Examination of Spillover Effects of a Targeted Early Identification Intervention for First Episode Psychosis
Sarah McIlwaine, Gerald Jordan, Marita Pruessner, Miriam Kinkaid, Karen Goldberg, Srividya Iyer, Ridha Joobber, Ashok Malla, Jai Shah

P20 Early Increase in Tau-Pet Signal Is Associated with aβ Burden, CSF P-Tau Levels and Cognition in Cognitively Normal Late-Middle-Aged Adults

P21 Prefrontal Dopamine Transporter Gene Network Interacts with Birth Conditions Influencing Internalizing Problems and Attentional Flexibility in Children
Patricia Miguel, Miguel PM, Pereira LO, Nguyen TT, Garg E, Barth B, Pokhvisneva I, Koh DXP, O’Donnell KJ, Meaney MJ, Silveira PP.

P22 DCC Gene Network in the Prefrontal Cortex Predicts Brain Volume and Impulsivity in Healthy Children
Alice Morgunova, Kieran J. O’Donnell, Michael J. Meaney, Patricia P. Silveira, Cecilia A. Flores

P23 Circadian Control of the CD8 T Cell Response to Antigen Presentation by Dendritic Cells
Chloé C. Nobis, Geneviève Dubeau-Laramée, Laura Kervezee, Nathalie Labrecque, and Nicolas Cermakian

P24 Regional Characterization of Vimentin-Immunoreactive Astrocytes in the Human Brain
Liam O’Leary, Claudia Belliveau, Maria Antonietta Davoli, Naguib Mechawar

P25 Medication Acceptance and Refusal: A Case Study Analysis of Early Neuroleptic Medication Adherence
Matthew Peters, Matthew Isaac Peters, Manuela Ferrari, Katherine A Steger, Ashok Malla, Jai Shah, Srividya Iyer

P26 Selective Melatonin MT2 Receptor Ligands Relieve Neuropathic Pain Through Modulation of Brainstem Descending Antinociceptive Pathways and Opioid Interactions
Luca Posa, Martha Lopez-Canal, Danilo De Gregorio, Sabatino Maione, Vinicio Granados-Soto, Gabriella Gobbi
P27 Differential Effects of High and Low doses of Amphetamine in Adolescence on Dopamine Development
Jose Maria Restrepo, Santiago Cuesta, Lauren Reynolds, Christina Popescu, Susan He, Cassandra Fortin, Julia Eppelbaum, Steven Silvestrin, Cecilia Flores

P28 Hippocampal Subregion CA1 Requires CA3 Input to Encode Novel Space
Isabelle Shank, Shank, I., Brandon, M.

P29 Eating and Sleep Patterns in Eating Disorders
Duncan Sibthorpe, Clément Bourguignon, Asli Buyukkurt, Alexia Della Vecchia, Olivia Crescenzi, Kassandy Kowalyk, Howard Steiger, Mimi Israel, Kai-Florian Storch, Outi Mantere

P30 Volume of Posterior Hippocampus Is Positively Related to Source Memory Accuracy in Healthy Young Adults.
Jamie Snytte, A. Elshiekh, R. K. Olsen and M. N. Rajah

P31 Sex Differences in Brain-Behavior Correlations in Episodic Memory: An Adult Lifespan Study
Sivaniya Subramaniapillai, Charana Rajagopal, Stamatoula Pasvanis, Debra Titone, M. Natasha Rajah

P32 The Gut Microbiome as a Key Regulator of Early Life Stress Induced Depression
J. Kasia Szyszkowicz, S. Barnett Burns, I. Kim, M.-C Audet, G. Turecki, G.N. Luheshi

P33 Discriminating Between Schizophrenia Subtypes Using Clustering and Supervised Learning
Alexandra Talpalaru, Nikhil Bhagwat, Gabriel Devenyi, Mallar Chakravarty

P34 Multivariate Pattern Analysis (MVPA) of Cross-Modal Emotional Processing
Jocelyne Whitehead, Jorge L. Armony

P35 Grid Cell Dysfunction in the Medial Entorhinal Cortex Correlates with Path Integration Deficits in a Mouse Model of Alzheimer's Disease
Johnson Ying, Alexandra Keinath, Mark P. Brandon

Organizing committee / Comité organiseur:
The Douglas Student Committee for Academic Life / Le Comité étudiant pour la vie académique au Douglas: Justin Miron, Lourdes Fernández de Cossío Gómez, Elisa Guma, Weam Fageera, Kathleen MacDonald, Daniel Hoops, Polina Ash, Helen Martin, Nellie Fotopoulos, Ana Elisa Farias de Sousa, Ria Agustina, Christine Laganière and/et Nicolas Cermakian (Directeur des affaires académiques, Centre de recherche de l'institut Douglas)
Abstract title: Cocaine dependence is associated with epigenetic dysregulation of the neurodevelopmental gene cluster IRXA.

Authors: Kathryn Vaillancourt\(^1,2\), Jennie Yang\(^1\), Gang G. Chen\(^1\), Laura Fiori\(^1\), Carl Ernst\(^1,3\), Erin Calipari\(^4\), Benoit Labonté\(^4\), Eric Nestler\(^4\), Deborah C. Mash\(^5\), Gustavo Turecki\(^1,2,3\)

Affiliation(s): 1. McGill Group for Suicide Studies, Douglas Hospital Research Center, Verdun, QC, Canada. 2. Integrated Program in Neuroscience, McGill University, Montreal, QC, Canada. 3. Department of Psychiatry, McGill University, Montreal, QC, Canada. 4. Icahn School of Medicine, Mount Sinai Hospital, New York, NY, USA. 5. Department of Neurology, University of Miami Miller School of Medicine, Miami, FL, USA

Background: Multiple, interacting biological mechanisms are likely to contribute to the development and maintenance of cocaine use disorders. Of particular interest are epigenetic mechanisms as they may mediate the long-term effects of chronic cocaine abuse on brain cell functioning. To date, little is known about the relationship between cocaine dependence, DNA methylation and chromatin remodelling in human cocaine dependence.

Methods: We used RRBS to identify differential methylation, in caudate and nucleus accumbens tissue, from 25 individuals with cocaine dependence and 25 drug-naïve controls. We validated our findings using targeted bisulfite sequencing and fluorescence activated nuclei sorting (FACS). We also used transcriptome sequencing, and chromatin conformation capture (3C) to investigate the relationship between cocaine-related methylation changes and chromatin functioning.

Results: We found altered methylation within two genes of the neurodevelopmental gene cluster, IRXA, in the caudate of the cocaine group. We partially replicated this finding in an independent cohort, and in the neuronal fraction of FACS sorted nuclei. In addition, cocaine dependence is associated with altered co-regulation between the genes within the IRXA cluster. Moreover, we identified a large chromatin loop at this locus in human cells that is likely involved in IRXA regulation.

Conclusions: Chronic cocaine dependence is associated with altered DNA methylation profiles with IRXA. This appears to be associated with dysregulated gene expression, and may be driven by altered chromatin looping. Our ongoing work uses epigenome editing to understand how methylation interacts with chromatin structure to regulate IRX transcription.

Supported by (fellowship and/or granting agency) CIHR, NIDA (DA033684)
Abstract title: Low dose of d-lysergic acid diethylamide (LSD) reverses depressive-like behavior and serotonergic (5-HT) neurotransmission impairments in a murine model of chronic stress.

Authors: Danilo De Gregorio¹², Enns J.¹, Posa L.¹, Aguilar-Valles A.², Lopez-Canul M¹, Sonenberg N.², Gobbi G.¹

Affiliation(s): 1. Department of Psychiatry, McGill University, Montreal, QC, Canada 2. Department of Biochemistry, The Goodman Cancer Centre, McGill University, Montreal, QC, Canada

Introduction: Depression is a disease involving dysfunctions of serotonergic activity in the Dorsal Raphe Nucleus (DRN). D-lysergic diethylamide acid (LSD) is a hallucinogen that has gained popularity based on clinical evidences reporting mood-enhancing properties. Our previous work demonstrated that low doses LSD (5-20 µg/kg) decreased the activity of serotonin (5-HT) neurons in DRN while at higher doses (60-120 µg/kg) it induced a cessation of DA neurons in Ventral Tegmental Area (VTA), suggesting an exclusively low doses effect on 5-HT. Thus, employing a chronic stress (CS) model, our hypothesis is that low doses LSD could reverse depressive symptoms and increase the 5-HT firing activity in the DRN, which is low in depression. Methods: The CS was performed: 8-weeks old male C57BL/6J mice were placed in restrainers for 14 days (2 hours/day). Control mice (CTL) remained undisturbed in their cages. From 7th to 14th day of stress, CTL and CS mice received subcutaneous LSD (30 µg/kg/day) or vehicle and tested on 15th day. In vivo extracellular recordings of 5-HT DRN neurons and behavioral tests (Open Field (OF), Forced Swim (FS) and Novelty Suppressed Feeding (NSF)) were employed. Results: CS mice showed a decreased activity of 5-HT neurons compared to CTL. LSD restored rates to CTL levels. CS mice showed decreased time in the center and frequency of enters in OF, increased immobility time in FS and increased latency to feed in NSF, compared to CTL. LSD normalized these parameters. Conclusions: This study reports that low-dose LSD modulates mood and serotonergic neurotransmission.

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<th>Fonds de recherche du Québec – Santé (FRQS) postdoctoral fellow. MUHC postdoctoral fellow</th>
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Authors: Helen Martin¹², Megan Pope², Manuela Ferrari², Nicole Pawliuk², Srividya N Iyer¹²

Affiliation(s): 1. McGill University, 2. Douglas Mental Health University Institute

Rationale: The benefits of family involvement and interventions in improving outcomes in early psychosis are widely acknowledged. However, their implementation in early intervention (EI) services for psychosis is thought to be impeded by unclear policy/program guidelines. It is therefore important to critically assess and analyze existing EI guidelines with respect to their recommendations regarding family involvement/interventions. The current study addresses this need.

Methods: We conducted a scoping review of existing guidelines for EI services for psychosis published from 2000 to present. The identified guidelines were evaluated using the Guidelines Implementability Appraisal 2.0 instrument comprising of eight quality domains i.e., executability, decidability, validity, flexibility, effect on process of care, measurability, novelty/innovation, and computability. The extracted data were synthesized using quantitative and qualitative techniques.

Results: Most guidelines were developed in Western countries. Preliminary results suggest poor consistency across guidelines with respect to family-focused recommendations, i.e., despite sharing a common vision, guidelines differed on all eight implementation quality domains. Recommendations fared well with respect to flexibility, which permits myriad ways of execution. Guidelines generally lacked in the quality domains of executability, decidability, effect on process of care and measurability. A core issue emerged across guidelines that may at least partially underpin why they fare poorly with respect to implementability: language that although value-driven is not specific (e.g., Families/carers must be involved wherever possible). Implications for improving guidelines and EI service delivery with respect to inclusion of families will be presented.

Supported by (fellowship and/or granting agency) CIHR foundation grant
Abstract title: The phase-shifting effect of bright light on the human circadian transcriptome during simulated night shift work

Authors: Laura Kervezee¹²; Marc Cuesta¹²; Nicolas Cermakian²; Diane B. Boivin¹

Affiliation(s): 1. Centre for Study and Treatment of Circadian Rhythms, Douglas Mental Health University Institute, Department of Psychiatry, McGill University, Montreal, Canada 2. Laboratory of Molecular Chronobiology, Douglas Mental Health University Institute, Department of Psychiatry, McGill University, Montreal, Canada

Misalignment of the endogenous circadian clock with the external environment leads to disruption of physiological rhythms. However, the underlying molecular mechanisms are unknown. The objective of this study was to determine the impact of a simulated night shift work protocol with or without concomitant exposure to bright light on the circadian regulation of the human transcriptome. To this end, transcriptomic analysis was performed on RNA extracted from peripheral blood mononuclear cells (PBMCs) obtained from eleven healthy participants (mean age: 23.6 years old [range: 18-30]; 10 men / 1 woman) at baseline and on the fourth day after a 10-hour delay of the sleep period. Three participants were exposed to bright light (~10,000 lux; bright light group) during the nightly waking period, while eight were exposed to dim light (~10 lux; control group). In the control group, 73% of transcripts rhythmically expressed at baseline remained rhythmic during the night shift protocol with similar phases relative to the habitual bedtimes. In subjects exposed to bright light, phases of rhythmic transcripts were significantly more delayed in the bright light group (mean: 9.3 h, range: 6.2 – 11.8 h) compared to those in the control group (1.3 h, range: 1.1h advance – 3.5 h delay) (F(1,9)=29.4, p < 0.001; circular ANOVA). These results indicate that 4 days of simulated night shifts lead to a loss of temporal coordination of the circadian transcriptome and the external environment and suggest that bright light exposure may facilitate physiological adaptation to night shifts.

Supported by (fellowship and/or granting agency) Canadian Institutes of Health Research (grant MOP-102724 to D.B.B. and N.C.) and Fonds de Recherche du Québec–Santé (fellowship to LK).
INTRODUCTION: Because currently known AD SNPs only account for a small fraction of the genetic variance in this disease, there is a need to identify new variants associated with AD. METHODS: Our team performed a GWAS in the Quebec Founder Population (QFP) isolate to identify novel protective or risk genetic factors for late-onset sporadic AD and examined the impact of these variants on gene expression and AD pathology. RESULTS: The rs10984186 variant is associated with an increased risk of developing AD, as well as with a higher CDK5RAP2 mRNA prevalence in the hippocampus. On the other hand, the rs4837766 variant, which is among the best cis-eQTLs in the CDK5RAP2 gene, is associated with lower MCI/AD risk and conversion rate. DISCUSSION: The rs10984186 risk and rs4837766 protective polymorphic variants of the CDK5RAP2 gene might act as potent genetic modifiers for AD risk and/or conversion by modulating the expression of this gene.
Abstract title: Pituitary volume mediates the effect of prenatal stress on internalizing symptoms: Project Ice Storm

Authors: Sherri L. Jones¹,², James Gazetas³, Chloe Anastassiadis²,⁴, François-Pierre Marcoux³, Guillaume Elgbeili², Jens C. Pruessner⁵, David P. Laplante², Suzanne King¹,²

Affiliation(s): 1. Department of Psychiatry, McGill University, Montreal, Quebec, Canada 2. Douglas Hospital Research Center, Montreal, Quebec, Canada 3. Collège Jean-de-Brébeuf, Montreal, Quebec, Canada 4. Integrated Program in Neuroscience, McGill University 5. University of Constance, Germany

RATIONALE. Animal and human studies have shown that prenatal maternal stress (PNMS) affects the function of the hypothalamic-pituitary axes and is associated with more behavioural problems in the offspring. In Project Ice Storm, our prospective longitudinal study of women exposed to a natural disaster during pregnancy, we have found that more objective hardship (e.g., number of days without electricity) is associated with more internalizing problems in children. Neuroimaging studies have reported larger pituitary volumes to be associated with more internalizing symptoms during adolescence. AIM. The goal of this study was to determine whether pituitary volume mediates the association between objective PNMS and internalizing symptoms. METHODS: Participants were 31 (17M, 14F) 18-year old youth exposed to the January 1998 ice storm prenatally (ICE) and 28 (13M, 15F) community controls born in 1997. Maternal objective hardship experienced during the ice storm was measured by questionnaire. Self-report internalizing symptoms were obtained at 18-years old using the Adult Self-Report. Pituitary volume at 18-years old was manually segmented using T1 and T2 weighted images acquired on a 3T Siemens magnetic resonance imaging scanner. RESULTS: Mediation analyses revealed that higher objective hardship was associated with more internalizing symptoms via smaller pituitary volumes in the ICE cohort, but not in controls. CONCLUSION: Our data suggest that objective PNMS leads to smaller pituitary volume, which in turn explains increased internalizing symptoms, more than 18 years after PNMS exposure. Results are discussed in light of contradictory findings relating pituitary volume to internalizing symptoms.

Supported by (fellowship and/or granting agency) | Fonds de Recherche Québec - Santé, Canadian Institutes of Health Research
Abstract title: Driving while impaired offenders show selective treatment responsivity to brief motivational interviewing vs. information and advice based upon subtype membership

Authors: Nathaniel Moxley-Kelly, M.C. Ouimet, M. Dongier, F. Chanut, J. Tremblay, W. Marcantoni, T.G. Brown

Affiliation(s): Douglas Hospital Research Center, McGill University, University of Sherbrooke, Concordia University, University of Montreal

Background: The persistently modest outcomes from remedial prevention programs in curtailing driving while impaired (DWI) recidivism have fueled interest in matching of intervention to subtypes of DWI offenders to improve outcomes. In past work, we have shown: 1) a greater benefit from exposure to brief (30 min) motivational interviewing (BMI) compared to an information-advice control intervention (IA) in reducing alcohol misuse and driving violations in DWI recidivists; and 2) two subtypes of DWI offenders with distinct behavioural, psychological and neurobiological characteristics: i) offenders who show primary engagement in DWI behaviour and reduced behavioural control (pDWI); and ii) offenders who show a mixed DWI and reckless driving profile, and features consistent with reward deficiency syndrome (MIXED). Accordingly, we hypothesized that the pDWI subtype exhibits selective treatment responsivity to BMI.

Method: DWI recidivists in a randomized controlled trial (Brown et al., 2010; Ouimet et al., 2013) were partitioned into pDWI and MIXED subtypes, and effects from exposure to BMI and AI interventions in each subtype was tested for alcohol misuse over one-year follow-ups, and documented DWI violations over five-year follow-up.

Results: BMI exerted medium-to-high effects in pDWI offenders for reducing alcohol misuse, and small-to-medium effects in the other subgroups. Significantly higher risk of future DWI offence was seen in the MIXED subtype compared to the pDWI subtype.

Conclusions: BMI’s benefit for reducing alcohol misuse in DWI offenders over one year is greater than those commonly seen with BMI and long-term DWI recidivism risk can be predicted by the offender subtypes examined here.

Supported by (fellowship and/or granting agency) Start-up funding from the McGill-Dongier Endowment for Addiction Research. Foundation for Alcohol Research (formerly the Alcoholic Beverage Medical Research Foundation), the Canadian Institutes of Health Research, the Canadian Psychiatric Research Foundation, a career research scholar award to TGB from the Quebec Council for Research into Society and Culture, and a career research scholar award to MCO from the Fonds de recherche de Quebec – Sante.
Abstract title: Mapping of postnatal neurodevelopment in response to early and late prenatal maternal immune activation in mice

Authors: Elisa Guma, Chloe Anastassiadis, Jurgen Germann, Daniel Gallino, Gulebru Ayranci, Gabriel Devenyi, M Mallar Chakravarty

Affiliation(s): McGill University Psychiatry department, and Cerebral Imaging Center of Douglas Research Center

Epidemiological studies have demonstrated that prenatal exposure to infection in mid-to-late gestation is a risk factor for neurodevelopmental disorders. Rodent studies have linked prenatal maternal immune activation (MIA) with neurodevelopmental alterations in offspring mirroring those observed in schizophrenia and autism. This study aims to link precise gestational timing of MIA with neuroanatomical and behavioural phenotypes in offspring.

Pregnant dams (C57BL6) were injected (i.p.) with Poly I:C (POL) (5mg/kg) or vehicle (SAL) at gestational day 9 (E) or 17 (L) - end of first and second trimesters in humans, respectively. Structural MRIs (100um3) were collected on offspring (n= SAL=36, POL-E=21, POL_L=25) in vivo on postnatal day (P)21, 38, 60 and 90. Linear mixed effects modeling was used to investigate voxel-level volume differences in development of SAL, POL_E, and POL_L offspring brains (False Discovery Rate [FDR] corrected). Open field, social preference, marble burying, and prepulse inhibition (PPI) were performed at adolescence (P40) and adulthood (P92).

Local volume differences were observed in the prelimbic cortex, caudate, thalamus, dentate gyrus, and lateral septum in which trajectories for POL_E offspring differed significantly from SAL and POL_L offspring (>1%FDR). POL_E offspring spent less time in the open field center zone (p=0.01), exhibited greater PPI deficits (p=0.006), and buried more marbles (p=0.08) at adolescence.

Early MIA induces greater neuroanatomical and behavioural alterations in the offspring than late MIA. A better understanding of the timing of MIA could help elucidate mechanisms underlying neurodevelopmental disorders.

Supported by (fellowship and/or granting agency) FRQS
Abstract title: Reduced resting-state functional connectivity of the basolateral amygdala to the medial prefrontal cortex in preweaning rats exposed to chronic early-life stress

Authors: Angela Guadagno1,3, Min Su Kang1,3, Gabriel A. Devenyi1, Axel P. Mathieu3, Pedro Rosa-Neto2,3, Mallar Chakravarty2,3, Claire-Dominique Walker2,3

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Early-life stress (ELS) exposure has long-term consequences for both brain structure and function and impacts cognitive and emotional behavior. The basolateral amygdala (BLA) plays an important role in anxiety and fear conditioning through its extensive anatomical and functional connections, in particular to the medial prefrontal cortex (mPFC). However, how ELS affects amygdala function and connectivity in developing rats is unknown. We used the naturalistic limited bedding/nesting (LB) paradigm to induce chronic stress in the pups between postnatal day (PND) 1-10. Male normal bedding (NB, control) or LB offspring underwent structural and resting-state functional MRI (rs-fMRI) on PND18 and in adulthood (PND74-76). Adult male rats were tested for fear conditioning and extinction behavior prior to scanning. Seed-based functional connectivity maps were generated based on four BLA seeds (left, right, anterior and posterior). At both ages, LB induced different effects on anterior and posterior BLA networks, with significant reductions in rs-fMRI connectivity between the anterior BLA and mPFC in LB compared to NB offspring. BLA connectivity was lateralized by preweaning age, with the right hemisphere displaying more connectivity changes than the left. Weak negative volumetric correlations between the BLA and mPFC were also present, mostly in preweaning LB animals. rs-fMRI connectivity and volumetric changes were associated with enhanced fear behaviors in adult LB offspring. Activation of the LB-exposed neonatal amygdala described previously might accelerate the maturation of BLA-mPFC projections and/or modify the activity of reciprocal connections between these structures, leading to a net reduction in rs-fMRI connectivity and increased fear behavior.

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O10

Abstract title: Why We Still Use “Organic Causes”: Results of a Survey of Psychiatrists and Residents

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The diagnostic category of “organic disorders” was officially removed from the psychiatric nosology in DSM-IV, published in 1994. Despite this change, physicians continue to use the term “organic causes” to refer to medical and neurological causes of psychiatric symptoms, and it remains part of the ICD-10 classification. In the context of increasing integration of psychiatric disorders within a medical and neuroscientific framework, the reasons behind the ongoing use of this terminology reminiscent of mind-body dualism have to be clarified. We conducted a survey of 391 Canadian psychiatrists and psychiatric residents to understand attitudes and beliefs related to this terminology. Our results showed that it is used by a majority (55.9%) of psychiatrists and residents for two main reasons: out of a habit that begins in residency training, and because of the belief that other specialties do not fully understand alternative terminology. We found that some psychiatrists are concerned that their patients will not receive adequate investigation unless it is made clear by using the “organic cause” terminology that other medical causes of psychiatric symptoms are suspected. Use of the “organic cause” terminology was predicted by younger age, doing emergency room calls and finding alternative terminology difficult to use. These findings highlight the importance of reflecting upon and discussing the impacts of the terminology used in psychiatry.

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Abstract title: Genetic and environmental factors are differentially related to Aβ burden in the presymptomatic phase of autosomal dominant and sporadic Alzheimer’s disease.

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Background: Autosomal dominant Alzheimer’s disease (ADAD) is considered as a model of preclinical sporadic Alzheimer’s disease (sAD), since estimated years from symptom onset (EYO) can be derived in presymptomatic mutation carriers, taking parental age at symptom onset as a reference. However, whether the preclinical phase of the disease is comparable between the two variants remains unclear. Our objective is to evaluate if factors known to affect Aβ trajectories in presymptomatic ADAD also affect asymptomatic individuals with a parental history (PH) of sAD, and vice-versa. Aβ-PET scans were collected in 114 presymptomatic ADAD mutation carriers (DIAN study; age=35.62±9.30) and 82 asymptomatic individuals with a PH of sAD (PREVENT-AD cohort; age=66.51±4.63). We assessed in each cohort the effect of i) EYO (parent’s age at symptom onset – participant’s age) and ii) apolipoproteinE4 [APOE4], education, and their interaction, on Aβ burden. EYO was related to increased Aβ burden in both cohorts. In asymptomatic individuals with a PH of sAD, we found an effect of APOE4, education, and an APOE4*education interaction, such that the protective effect of education was stronger in APOE4 carriers. In presymptomatic ADAD, APOE4 had no effect, but completing higher levels of education was associated with lower Aβ burden. Our results suggest that a sporadic parental EYO might help to predict Aβ accumulation in preclinical sAD. While APOE4 is highly associated with Aβ burden in people at risk of sAD, it has no impact in ADAD. By contrast, higher levels of education could slow down biomarker progression in both variants of the disease.

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Abstract title: *Amphetamine disrupts DCC-dependent dopamine axon targeting in adolescence*

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**Background**
Initiation of drug use during adolescence enduringly increases addiction vulnerability. The netrin-1 guidance cue receptor DCC controls adolescent dopamine axon growth into the prefrontal cortex (PFC), thereby driving the development of postsynaptic circuitry and cognitive behavior. Interestingly, amphetamine exposure in early adolescence downregulates DCC expression in dopamine neurons. DCC may therefore be a molecular link between adolescent drug use and long-term adverse consequences.

**Methods**
We treated male and female mice with amphetamine (4 mg/kg) or saline during early adolescence (PND 22±1 - 31±1). In adulthood, we measured behavioral inhibition, motivation, and open field behavior. In separate cohorts of male mice, we then assessed how amphetamine affects (1) dopamine axon growth using axon-initiated fluorescent labeling, (2) the organization of PFC dopamine connectivity, and (3) postsynaptic PFC neuron structure.

**Results**
Amphetamine exposure in early adolescence downregulates DCC receptor expression and results in lasting cognitive deficits in male, but not female, mice. In male mice, this amphetamine regimen disrupts the DCC-dependent targeting of mesolimbic dopamine axons. Their ectopic growth to the PFC results in significant alterations to PFC dopamine connectivity and postsynaptic neuronal morphology.

**Conclusions**
DCC signaling in dopamine neurons is a pathway where genetic and environmental risk factors may interact in adolescence to titrate mesocortical dopamine axon growth and, in turn, regulate the maturation of PFC circuitry and cognitive function in a sex-specific manner. We are now investigating whether targeted upregulation of DCC expression during adolescence via CRISPR activation can counteract the long-term effects of early drug use in males.

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NIH/NIDA, CIHR, NSERC, FRQS
**Abstract title:** Relationship between maternal antenatal mood and child internalizing symptoms is moderated by child genetic risk for ADHD: a refined genome-wide GxE approach

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Maternal antenatal depression predicts offspring socio-emotional problems. Its impact varies across the population, as some individuals are resilient. Several attention deficit/hyperactivity disorder (ADHD)-associated genes moderate the susceptibility to antenatal influences. However, genome-wide approaches for GxE interactions have been underexploited. The polygenic risk score (PRS) assesses the genomic risk for a disorder but does not account for GxE effects. We refined the PRS methodology for GxE interactions, examining the polygenic contribution of ADHD in the relationship between maternal antenatal depressive symptoms (MADS) and child socio-emotional outcomes.

MADS and child socio-emotional outcomes were assessed by the Center for Epidemiologic Studies – Depression Scale, and the Child Behavior Checklist, for 187 children in a Canadian birth cohort (MAVAN). We constructed PRS for ADHD from the children’s genotype using conventional PRS (cPRS) methods and applied them in the GxE model. We filtered the contributing SNPs in the best-fit PRS by their independent interaction p-values to refine the PRS (rPRS). The rPRS was re-applied in the GxE model. We replicated the analysis in cohorts from the Netherlands (BIBO, n=132) and Singapore (GUSTO, n=590).

PRS moderated the relationship between MADS and child internalizing problems (p<0.001). A positive association between MADS and internalizing trait was found only in children with high PRS. rPRS interaction model explained 27% of the total variance as opposed to 18% for cPRS. Results were replicated in BIBO (p=0.02) but not GUSTO (p=0.83).

The association between MADS and internalizing problems in children with high genetic risk ADHD is further amplified using the novel rPRS.

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Abstract title: Opening the Minds of American Voters

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Background. American politics has become increasingly polarised. Democrats and Republicans currently dislike each other more than they have for decades, and the majority of voters now report that the opposing party angers, frustrates, and even scares them. Analysts argue that there is a need for open-mindedness in political contexts in order to promote proper debate and critical thinking. Using novel methods from psychology, we tested whether a simple manipulation could make participants believe that they are more open-minded towards competing political candidates. Methods. We asked 136 participants at the 2016 presidential debate in New York to complete a survey rating the leadership traits of Clinton and Trump. Only in the experimental group, we covertly manipulated their survey responses so that the majority of their ratings were neutral rather than favouring a single candidate. No participants noticed this manipulation. Results. When asked to explain the reasoning behind their responses, the majority of the experimental group (86%) accepted and rationalised their (manipulated) neutral position. One participant who was a news reporter, for example, claimed that it was his duty to remain unbiased in political affairs. Participants were able to address the strengths and weaknesses of both candidates, even though they had reported a more polarised view moments earlier. Conclusion. Our study demonstrates the power of suggestion and self-persuasion in shaping one's political values. Further, our results reveal that even the most polarised voters have the potential for open-mindedness.

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Abstract title: Improving derivation of A9-type dopamine cells for cell transplantation in Parkinson's disease.

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Background:

Degeneration of dopamine (DA)-producing cells in the nigrostriatal tract cause Parkinson's disease, a severe movement disorder affecting about 1% of the population over 65. The transplantation of dopamine-producing cells into human striatum has been a major therapeutic objective for over 30 years, but the quality of cells has hindered motor improvement in patients who receive cell therapy. In this study, we demonstrate a new way to enrich for A9 Tyrosine Hydroxylase (TH)-positive DA neurons from disease-free healthy human induced pluripotent stem cells (hiPSC). We test our new method compared to a recent gold standard and demonstrate significant improvement in cell quality including in expression of LMX1A, FOXA2, and OTX2, all important DA cell makers. Live calcium imaging videos and electrophysiological data demonstrate endogenous pacemaker activity and cell currents consistent with an A9 cell phenotype. We also test a novel small molecule identified surreptitiously through cell screening which can improve TH expression by about 30%. We demonstrate enhanced TH mRNA expression after 15 days of differentiation and show consistent results repeated by varying concentrations and length of treatment. HPLC analysis showed large increases in dopamine as well as the downstream catabolites, homovanilic acid (HVA) and 3,4-Dihydroxyphenylacetic acid (DOPAC). Together these data demonstrate a major step forward in cell manufacturing to produce high quality dopaminergic cells to treat humans with Parkinson's disease.

Supported by (fellowship and/or granting agency)  CIHR
Abstract title: CSF immune marker levels associate with AD symptom severity and trajectory

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Background: Immune activation in AD is generally regarded as harmful. However, some investigators suggested that effectiveness of anti-inflammatory treatment may depend on timing of intervention. Thus, we investigated whether and under what circumstances neuro-immune activity affects symptomatic expression of AD pathology.

Methods: Cerebrospinal fluid (CSF) from 297 Alzheimer's Disease Neuroimaging Initiative (ADNI) participants (83 healthy controls [HC], 145 with mild cognitive impairment [MCI], 69 with AD dementia) had been assayed for AD biomarkers and a multi-analyte panel of 83 proteins. Among them, we identified 23 associated with AD biomarker load. A cluster analysis of these 23 identified a class of 13 markers related to immune mechanisms (Immune Class). An Immune Class Summary Score (ICSS, the mean of z-scores for each of the 13 markers) reflected global immune marker activity for each individual. Logistic regression and linear mixed effect models examined whether ICSS associated with clinical diagnostic category and four-year cognitive trajectory in persons with or without amyloid pathology.

Results: In 82 amyloid-negative individuals, ICSS was not associated with either diagnosis or progression. In the 215 amyloid-positive individuals, elevated ICSS portended milder diagnoses and attenuated 4-year cognitive decline. An exploratory mediation analysis suggested that immune activity mitigated an otherwise-strong association between CSF total-tau and diminished cognitive performance.

Conclusions: In persons with established amyloid pathology, increased immune activity predicts attenuation of AD-related symptom expression and cognitive decline. These results suggest a novel avenue for the prevention of AD symptoms, but do not address the possible effects of immune activity in healthy persons.

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Attention-deficit hyperactivity disorder (ADHD) is the most prevalent neurodevelopmental disorder worldwide (5.3%). ADHD is suspected to arise by a complex interplay between genetic and environmental risk factors. Maternal smoking during pregnancy (MSDP) is currently the most associated environmental risk factor of ADHD in the literature. Smoking exposure is linked to epigenetic changes in a specific set of genes giving rise to a particular molecular signature. Since epigenetic factors contribute to fetal brain development, this study investigated the effect of exposure to MSDP on brain structure in children with ADHD. Exposure groups were made according to molecular smoking signature, as determined through epigenetic and cluster analysis (n=35; exposed=14, non-exposed=21). CIVET-1.1.12 and RMINC were used to acquire cortical surface area measurements and perform statistical analyses, respectively. In comparison to non-exposed, children with ADHD exposed to MSDP according to the molecular smoking signature, had significantly smaller cortical surface area measurements in the right prefrontal cortex (t=-3.23; 20% FDR), a region robustly associated with ADHD and involved in executive function. These results suggest that epigenetic changes associated with smoking could alter brain development in regions relevant for ADHD, and thus may represent one of the several epigenetic pathways leading to the development of ADHD. Therefore, understanding the pathophysiology of ADHD is contingent on understanding the underlying epigenetic mechanisms. Ultimately, such studies contribute to the collective understanding of neurodevelopment and warrant further attention.
P1

Abstract title: *Investigation of the head direction signal in the anterodorsal thalamic nucleus using miniaturized microscopes in behaving mice*

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**Background:** Head direction (HD) cells are some of the most abundant spatially tuned neurons in the brain. These cells are found in a series of regions starting in the brainstem and extending through the hypothalamus, thalamus, and up into the cortex areas that govern navigation and spatial memory. One area of interest is the Anterodorsal Thalamic nucleus (ADN), which contains a high concentration of HD cells (~65%). Here, we show calcium imaging of more than 50 HD cells at once and during behaviour using miniaturized microscopes (Miniscopes), in ADN, after we implanted 0.5mm-diameter GRIN relay lenses, in mice that were injected, beforehand, with a non-specific adeno-associated virus (AAV) to express GCaMP6f, in the target region. Calcium transients allowed us to identify HD cells by means of a weighted averaging of the fluorescence changes in different angle bins as well as spike inference algorithms. Our recordings show a stable preferred firing direction of HD cells for more than two months. Interestingly, our data shows a possible clustering of the HD cells with regards to their preferred firing directions and a potential topographical representation of the animal’s head direction in the ADN. This preliminary finding needs to be further investigated. Apart from revealing the physical arrangement of these cells, this technique allowed us to analyze the network dynamics of the HD system using dimensionality reduction methods which can be exploited to assess the credibility of ring attractor network theories that are believed to be governing the HD network.

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Abstract title: LCM-Seq: single cell-type whole genome bisulfite sequencing and transcriptomic profiling in post-mortem brain of abused suicides

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Background: The transcriptome and epigenome of a cell constitutes an essential piece of cellular identity and accounts for the multifaceted complexity and heterogeneity of cell types within the mammalian brain. During neurodevelopment, spatiotemporal control over gene expression through epigenetic regulation of promoters and enhancers leads to precisely defined cellular fates. Each discrete cellular population is differentially influenced by extrinsic signals from their local environments and neighbouring cells. Thus, while some studies have investigated transcriptomic and epigenomic alterations underlying the neurobiology of childhood maltreatment and suicide, the use of bulk-tissue homogenates have masked their ability to determine cell-type specific molecular dysfunctions.

Methods: Here we describe our progress on a pipeline that employs laser capture microdissection, on post-mortem human brain, of prefrontal (BA 10) layer V pyramidal neurons followed by downstream cell-type specific whole-genome bisulfite sequencing (WGBS) and transcriptomic profiling.

Results: Using this method we achieve a 59% mapping rate efficiency, bisulfite conversion rates within the expected rage and optimal coverage of CpG sites for WGBS. RNA sequencing resulted in a mapping efficiency rate of 98% and captured a wide distribution of transcripts that map back to the expected number of genes.

Applications: The major utility of this pipeline is its capacity to allow for the investigation of DNA methylation and expression patterns from the exact same dissected population of cells derived from post-mortem human brain tissue. We next applied these methods to prefrontal layer V pyramidal neurons of suicides with a history of childhood abuse and healthy controls. Abused suicides displayed 85 differentially expressed transcripts; many of which were part of the same expression module, constructed by WGCNA analysis, which in turn associated exclusively with a history of abuse. Future directions include performing a differential methylation analysis of dysregulated transcripts and to follow up genes that are both differentially expressed and methylated with functional experiments.

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Abstract title: Electrophysiological and Morphological characterization of VIP cells in the mouse entorhinal cortex

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Vasoactive Intestinal Peptide (VIP) interneurons have gained interest as they mediate a disinhibitory circuit mechanism in all major neocortical areas. By targeting Parvalbumin (PV) and Somatostatin (SOM) positive interneurons, VIP cells relieve projection neurons from ongoing inhibition. While their role in sensory circuits have been well defined, their influence on the spatial navigation circuit remains elusive. The medial entorhinal cortex (MEC) is an important region necessary for spatial navigation. Recent studies have shown the impact of PV and SOM cell inactivation on spatially tuned cells of various periodicity in the MEC, but whether VIP cells control this periodicity has not been investigated in this structure. To assess the role of disinhibition, we aimed to characterize the electrophysiological and morphological profile of VIP cells in the different cortical layers of the MEC. Using whole cell patch clamp recordings in brain slices, we find that cells in the deep layers of the MEC have a higher input resistance and firing threshold when compared to cells in the superficial layers. Furthermore, the VIP cells in the deep layers have distinct dendritic and axonal morphologies in comparison to the cells in the superficial layers. These intrinsic properties broaden our understanding of a genetically defined interneuron population in a neural structure responsible for navigation.

Supported by (fellowship and/or granting agency) CIHR

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Background: Childhood conduct problems (CP) are associated with severe psychopathology and maladjustment later in life, including adolescence delinquency and depression. Emerging evidences have shown an association between family functioning and early CP. In our earlier study, we examined the association between six dimensions of McMaster model of family function (measured by Family Assessment Device; FAD) and parental report of CP (measured by Strengths and Difficulties Questionnaire; SDQ). Results indicated that both general family function and behavioral control were significantly associated with CP. Purpose: In the present study, we examined the association between FAD and teacher reported CP to avoid the shared-method variance that may occur when a single informant completes two separate measures. Method: A sample of 92 children (76% boys) aged between 5-12 (M=8.64) admitted at the day hospital between years 2015-2016 were included in this cross-sectional study. Teachers at the hospital completed SDQ and parents completed FAD. Results: A descriptive analysis revealed that both parent (M=4.71, SD=2.30), and teacher (M=3.54, SD=2.27) reported CP presented an abnormal average of children’s score on this subscale of SDQ. Consistent with our earlier study, general family function accounted for significant 8.8% and the six dimensions of family function together, accounted for 14% of variance in CP scores reported by teachers. However, while behavior control was significantly associated with parent report of CP in our first study, affective responsiveness was the only dimension significantly predicting CP reported by teachers. More in depth analyses will be used to understand these inconsistencies between two measures.

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Abstract title: Differential susceptibility to positive environments influences childhood emotional eating according to genetically determined gene expression of prefrontal DRD4 gene

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Genetic differential susceptibility states that individuals may vary both by exhibiting poor responses when exposed to adverse environments, and disproportionally benefiting from positive settings. Dopamine-related genes seem to be especially involved in these phenomena. Our group has shown that the differential susceptibility framework can also be applied to obesogenic behaviors (e.g. emotional eating), especially considering the dopamine D4 receptor (DRD4) gene. Here, we explore differential susceptibility to positive environments according to the predicted genetically regulated gene expression of prefrontal cortex DRD4 gene. We analyzed the interaction between a) a score for postnatal environmental “buffer”, that accounts for positive outcomes (adequate birth weight and gestational age, good maternal mental health, income, family function, secure attachment, no marital strains, presence of breastfeeding) and b) the genetically regulated gene expression of prefrontal DRD4, computed using a gene-based association method (PrediXcan), that estimates the component of gene expression determined by the genetic profile, “imputing” gene expression from the genotype information. The outcome measure was the emotional eating domain from the Child Eating Behavior Questionnaire. The interaction between the positive environment and the predicted prefrontal DRD4 gene expression was significant (predicted beta=-0.403, p<0.02), in which the high gene expression group had more or less emotional eating according to the exposure to lower or higher environmental support respectively, showing evidence of differential susceptibility criteria according to Roisman, since regions of significance were inside environmental range (PA=0.46). The genetic differential susceptibility framework can be interesting to guide the development of more effective and cost effective interventions.

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Abstract title: Neuropsychiatric burden is related to increased amyloid but not tau deposition in late middle-aged cognitively normal individuals with a family history of Alzheimer’s disease

Authors: Alexa Pichet Binette¹², Étienne Vachon-Presseau³, Julie Gonneaud¹², Natalie Marchant⁴, Pierre Bellec⁵, John C. S. Breitner¹², Sylvia Villeneuve¹², PREVENT-AD Research Group

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Introduction
Neuropsychiatric factors (NPF) are highly prevalent throughout the course of Alzheimer’s disease (AD). Recent evidence also linked neuroticism, a personality trait associated with negative emotional response, with progression to AD. We investigated whether NPF and/or personality traits were related to AD pathology, brain function and cognition in cognitively normal individuals with a family history of AD dementia.

Methods
82 participants (PREVENT-AD study, age=67±5) underwent PET scanning for Aβ and tau. Resting-state functional connectivity was examined in 13 networks. Cognitive performance was assessed using the RBANS that provides five composite scores. All participants answered questionnaires assessing personality, perseverative thinking, depression, anxiety, stress and apathy. We used partial least squares correlation with permutation tests to assess which combinations of factors (derived as latent variables), if any, were related to Aβ and tau deposition. We also investigated whether this combination of NPF/personality traits was related to 1) functional connectivity and 2) cognitive performance in individuals with and without AD pathology.

Results
One latent variable related NPF and personality traits with Aβ accumulation throughout the cortex (p=0.003). Higher scores on this variable were additionally associated with higher brain connectivity within the dorsal attention and salience networks in Aβ+ subjects, and lower connectivity in Aβ- subjects (both interactions p<0.05). Furthermore, higher scores on this neuropsychiatric component were associated with worse immediate memory (p=0.05). No latent variable related NPF/personality traits with tau accumulation.

Conclusions
Our multivariate approach revealed that NPF/personality traits, especially perseverative thinking, neuroticism and low agreeableness, were associated with Aβ accumulation, altered brain connectivity and lower cognition. Neuropsychiatric burden might be a consequence of AD pathology, or, because personality traits are relatively stable across lifespan, a risk factor.

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Recent findings suggest that people with Anorexia Nervosa (AN) display altered DNA methylation, an epigenetic mechanism postulated to have etiological significance. Methylation is responsive to nutritional factors, and thus implies that nutritional deficits in people with AN may contribute to anomalous methylation patterns. We examined the relationships between global and site-specific methylation levels, and plasma levels of micronutrients involved in the methylation pathway in three groups: AN-Active (n=42), AN-Remitted (n=32) and no eating disorder (NED: n=30). Preliminary analyses suggested that, relative to NED controls, AN-Active people had higher levels of B12 (p=.01) and betaine (p=.02), and AN-Remitted participants had higher levels of B12 (p=.03). We further found that methionine levels were negatively correlated with global methylation; a finding that held for AN-Remitted (r= -.50, p=.02) and NED participants (r=-.47, p=.04) when analyzed separately, but not for AN-Active participants. This relationship may again be attributable to choline influx in blood cells that enables methylation despite the lack of dietary micronutrients. Our preliminary results suggest that people with AN show elevations on some nutrient levels—increases that are paradoxical given their state of malnutrition, but which we speculate may be attributable to choline mobilization from tissue to blood cells. Analyses now-underway examine group-based effects on probe-specific methylation levels, and will help clarify the relationships between micronutrients and methylation levels in AN.

Supported by (fellowship and/or granting agency) Healthy Brains for Healthy Lives (HBHL), Canadian Institutes of Health Research (CIHR)
Abstract title: Depressed mood state and alcohol in risky driving

Authors: Nevicia Case, Thomas G. Brown

Affiliation(s): Douglas Hospital Research Centre; McGill Department of Psychiatry

Background: Human factors are responsible for the majority of road traffic crashes worldwide. This is a randomised, double-blinded, placebo-controlled, between-subjects study seeks to elucidate the cognitive and behavioural influences of both a depressed state and low doses of alcohol on the decision to drive in a driving simulator. We hypothesise that: (1) the frequency of the decision to drive while under the influence of alcohol in participants with both a depressed state and alcohol is greater than participants with alcohol only, participants with a depressed state only, and participants with neither a depressed state nor alcohol, respectively; (2) decision-making is poorer in participants following the same order as Hypothesis 1; and (3) decision-making mediates the relationship between both predictors (depressed state and alcohol) and the decision to drive.

Methods: After assessing baseline characteristics through self-report, healthy male adult participants consume either an alcoholic or a placebo beverage. A decision-to-drive contingency scenario is administered followed by the Iowa Gambling Task, a neuropsychological measure of decision-making.

Results: Recruitment is ongoing and preliminary results will be available for the conference.

Conclusions: Should the results of this study identify dangerous synergistic effects of a depressed state and alcohol, they will advance scientific understanding of their effects on risky driving. Future research may benefit from exploring alcohol dose-dependent interactions with a depressed state or other mood states, such as anxious states. From this research, recommendations for more targeted injury prevention strategies may emerge, ultimately saving lives.

Supported by (fellowship and/or granting agency) CIHR
Brain ageing leads to the degradation of many brain systems, including the suprachiasmatic nucleus, the mammalian master clock. We investigated the link between circadian disruption and neurological ageing, hypothesizing that chronic exposure to altered light cycles would exacerbate aging-related deficits. Three groups of mice were aged for one year under 1) 12h light and 12h dark (12L:12D), 2) 12h light and 12h dim light (12L:12dimL) or 3) week day 9h light and 15h dark and weekend 15h light and 9h dark (irregularL:D). All aged mice and a young mice cohort underwent behavioural testing, before their tissue was collected to examine immune response differences. Compared to each aged group, young mice had significantly higher strength (p<.01) and less anxiety-like behaviour (p<.05). Comparing all aged groups, the 12L:12D mice had significantly less vertical activity (p<.01). All groups performed similarly in the balance beam, Morris Water Maze and prepulse inhibition. Wheel running under 12L:12D showed that young mice were more active over 24h than all groups (p<.05) except the irregularL:D group. Comparing all three aged groups, the irregularL:D group was more active over 24h than the 12L:12D group (p<.05). The 12L:12dimL and 12L:12D groups (p<.01), but not the irregularL:D group, took longer than young mice to re-entrain following a 6-hour advance of the light:dark cycle. No immune response differences were seen between groups. Our data show that year-long lighting alterations result in slight behavioural differences between the lighting conditions. Thus, normal aging can be shaped by chronic aberrant lighting to produce phenotypic differences.

Supported by (fellowship and/or granting agency)

Thank you to the Velux Stiftung, the Schizophrenia Society of Canada Foundation and the Canadian College of Neuropsychopharmacology for funding.
Abstract title: Walking A Mile In Another’s Shoes: Can Virtual Reality Decrease Prejudice?

Authors: Amanda Dennie, Lauriol Djehounke, Emily Light, Camille W. Chamberlain, Rémi Thériault, Sonia Krol, Amir Raz

Affiliation(s): McGill University

Background: Prejudice is a fundamental social problem that can lead to discrimination and violence. It is thus essential to explore, compare, and validate old and new strategies to reduce prejudice.

Methods: We compared two groups who had to take the perspective of a Black confederate to a control group (total N = 81). Participants in the Embodied Perspective-Taking group (EPT) experienced an illusory feeling of embodiment over the body of the Black confederate through virtual reality technology; those in the Mental Perspective-Taking group (MPT) imagined a day in the life of the confederate using a photograph; those in the control group simply imagined a day in their own life.

Results: Although our manipulation checks indicated that our manipulations were on average 60% successful, regression analyses with planned contrasts showed the EPT and EMT groups did not show lower implicit or explicit race bias compared to the control group. However, people from both the EPT and MPT groups showed greater self-other overlap with the confederate compared to those in the control group. The EPT group additionally showed greater empathic concern compared to the control group, with otherwise no other differences on the other subscales of empathy (perspective-taking, fantasy, personal distress, and cognitive and affective empathy).

Conclusions: It seems like short-term prejudice-reduction interventions based on mental perspective-taking or embodiment do not have a reliable impact on race biases, although they may allow one to feel closer to another specific person and to in turn experience greater general concern to help one another.

Supported by (fellowship and/or granting agency) SSHRC
Abstract title: What information do fertility patients request and receive during clinic visits to manage the emotional burden of treatment?

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Background: There is limited research regarding the provision of individualized fertility-related information. This study investigated fertility patients’ distress, their satisfaction with information received, and their preferences for other information.

Methods: 567 patients recruited from fertility clinics completed an anonymous online survey. Patients’ perceived depression levels were measured using the Patient Health Questionnaire (PHQ-2). Patients were asked about the information they received from providers and its helpfulness. When patients did not receive information, they indicated their interest in obtaining it.

Results: Patients frequently received information on tests/procedures, their condition and medications. Topics rated most helpful were: discussing treatment with family/friends, provincial health care coverage, and provincial regulations/laws regarding treatment. Among the topics patients were least likely to be informed about (services offered by different clinics, regulations/laws about treatment in other provinces, discussing treatment with family/friends), 67.9%, 49.6% and 46.3% of individuals wanted this information, respectively. Independent t-tests showed that patients with higher depression levels (PHQ-2) were significantly more likely to desire information on services offered by different clinics (t(206.293)= -2.029, p=0.044) and discussing treatment with family/friends (t(192.207)= -2.073, p=0.040).

Conclusion: Discrepancies may exist between the information provided to patients and its helpfulness. While advice about discussing treatment with family/friends was considered helpful, and was especially desired by patients with more depressive symptoms, it was not often received. Future research should determine what factors limit the discussion of this information with patients. Informing providers about patient needs and preferences for information may facilitate the provision of patient-centered care and reduce patient distress.

Supported by (fellowship and/or granting agency) Canadian Institutes of Health Research (CIHR)
Abstract title: Circadian misalignment in police officers after a week of night shifts

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Introduction: Shift workers have an increased prevalence of adverse health effects, such as obesity, heart disease, and different types of cancer. This may be partly caused by the lack of circadian entrainment to their schedules. The present study aimed to investigate the extent of circadian adaptation of shift workers after 7 consecutive night shifts.

Methods: A total of 25 municipal police officers from Quebec, (17 men, 8 women) aged 31.3 ± 4.5 years (mean ± SD), were enrolled in a 35-day field study during which they worked morning, evening, and night shifts. Participants collected urine samples during three 24-h periods: before 7 consecutive nights, after the series of night shifts, and after 6 subsequent rest days. Circadian phase was determined by calculating the midpoint of 6-sulfatoxymelatonin, a marker for circadian phase, per each period, per participant.

Results: The phase (circular mean ± circadian variance) of 54 urine measurement periods (19 pre-night, 20 post-night, 15 rest-after-nights) was on average 3:48 ± 0:15, 5:06 ± 0:28, and 2:42 ± 0:16 hours, for each period, respectively. There was no effect of shift type on circadian phase (F(2,51)=1.74; p=0.19, circular ANOVA). Circadian phase was delayed by 1.07 ± 1.1 h (mean ± SEM) after the night shifts. After the series of night shifts, melatonin midpoint occurred during nightly working hours (19 - 7h) in most participants (75%).

Conclusion: Our findings indicate that the circadian system of the majority of shift workers was misaligned to their night shift schedule.

Supported by (fellowship and/or granting agency)  Institut de recherche Robert-Sauvé en santé et en sécurité du travail (IRSST)
Abstract title: Depression and New-Onset Diabetes: Does the Measure of Depression Matter?

Authors: Eva Graham, Sonya Deschenes, Marina Khalil, Sofia Danna, Norbert Schmitz

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Background: Previous literature reports that people with depression have an increased risk of incident diabetes. However, this association may differ based on the measure of depression, as it may refer to symptoms, diagnoses, or antidepressant use. The objective of this analysis is to determine whether the association between depression and incident diabetes varies by depression measure in longitudinal studies of participants aged 18+.

Methods: The following databases were searched from inception to July 16, 2017 with no language restrictions: MEDLINE, EMBASE, CINAHL, PsychInfo, Web of Science Emerging Sources Citation Index, Web of Science Conference Proceedings, Proceedings from the Psychosocial Aspects of Diabetes Study Group Meetings, the Cochrane Library, ProQuest Dissertations and Theses, and the Centre for Reviews and Dissemination.

Results: A total of 22,062 records were assessed for inclusion from the title and abstract and 196 were examined in full-text by two independent reviewers. A total of 43 articles met the inclusion criteria, leading to 55 estimates of the association between depression and diabetes. In studies of moderate quality (n=31), the association between depression and incident diabetes was highest among those that assessed depression with antidepressants (pooled RR= 1.34, 95% CI 1.15-1.57) and was similar in studies that used clinical diagnoses (pooled RR = 1.18, 95% CI 0.96-1.46) and depressive symptom scales (pooled RR =1.19, 95% CI 1.12-1.27). There was no statistical difference between associations that used different measures of depression.

Conclusion: The association between depression and diabetes is consistent when measured using symptoms, diagnoses, or antidepressant use.

Supported by (fellowship and/or granting agency)

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The early nutritional environment is critical for the development of neural circuits regulating energy homeostasis and food intake. The lateral hypothalamus (LH) links homeostatic hypothalamic nuclei to the mesocorticolimbic dopamine neurons that modulate food reward. The LH is sensitive to leptin and higher exposure to this hormone in neonates through maternal high-fat feeding might promote neuronal LH afferent projections growth and leptin sensitivity. Here we examined whether a maternal high-fat (HF) diet 1) modifies leptin signaling in identified LH neurons of neonates, and 2) increases the density of projections from the ventromedial (VMH) and dorsomedial (DMH) hypothalamus to LH orexin cells projecting to dopamine neurons. Mothers received either a control (C) or HF diet (60% Kcal from fat) from gestation day 13-14 throughout lactation. The production of second messengers (pERK and pSTAT3) in pup LH neurons (GABA, CART, and orexin cells) was quantified by double immunofluorescence histochemistry after vehicle or leptin challenge (3mg/kg ip). Leptin increased pERK and pSTAT3 on PND16 in different neuronal populations, particularly in HF offspring. To evaluate diet-induced changes in the density LH afferents, fluorescent retrograde microbeads were injected stereotaxically into the LH orexin field on PND5. Preliminary results indicate that HF pups exhibit a greater density of projections from the DMH and VMH compared to C pups. Thus, a maternal HFD might increase both LH afferent fiber density and sensitivity to metabolic hormones in neonates, possibly until adulthood.

Supported by CIHR grant #130323
Major depressive disorder (MDD) is highly associated with suicide, and individuals with a history of child abuse (CA) are strongly predisposed to MDD and suicidality. Imaging studies have shown that MDD and CA may be related to altered myelination and white matter morphology within specific brain regions. Oligodendrocytes, the myelinating cells of the central nervous system, may play a key role in observed differences in myelination.

The uncinate fasciculus (UF) is a corticolimbic white matter tract putatively involved in memory and socio-emotional processing. The UF is unique in that it is the last white matter tract to mature in humans, only reaching full maturity after the third decade of life; this may mean that this tract is particularly vulnerable to the effects of CA and early life adversity. Indeed, diffusion tensor imaging (DTI) has shown that MDD is associated with reduced UF white matter integrity.

In order to assess the impact of CA on UF myelin physiology, we examined myelin-related protein and gene expression, as well as oligodendrocyte morphology and cell density in post-mortem UF tissue. We found no difference in oligodendrocyte-lineage cell density or myelin-related gene expression between groups, but uncovered significant differences in the expression of myelin-constituent proteins PLP and MOG, which were elevated in depressed subjects. These findings may indicate the impaired white matter integrity seen in the UF of patients with MDD or a history of CA may be associated with molecular and cellular changes in the white matter tract.

Supported by (fellowship and/or granting agency) | AFSP Standard Research Grant
Abstract title: *Emotion regulation in bipolar disorder type I: An fMRI multivariate analysis*

Authors: Fumika Kondo, Jocelyne Whitehead, Fernando Corbalan, Serge Beaulieu, Jorge Armony

Affiliation(s): McGill University Integrated Program in Neuroscience, Douglas Mental Health University Institute

Background:
Bipolar disorder type-I (BD-I) patients are known to show emotion regulation abnormalities. In a previous fMRI study using an emotion regulation paradigm, we compared responses from 19 BD-I patients and 17 matched healthy controls (HC). A standard GLM-based univariate analysis revealed that BD patients showed increased activations in VLPFC when instructed to decrease the emotional response elicited by neutral images indicating BD patients engage this region even when emotion regulation is not necessary. Also, BD patients showed sustained amygdala response to all negative images regardless of instruction.

Methods:
We reanalyzed these data using a multivariate pattern recognition approach, as implemented in PRONTO.

Results:
The models were able to accurately classify different task conditions when HC and BD were analyzed separately (65.79% to 96.05%). In addition, although the models were not able to correctly classify HC vs BD subjects with significantly above-chance accuracy using the different conditions, a trend for significant class accuracy p-value for BD (p = .06) was observed when using the condition “Neutral Decrease”.

Conclusion:
Our multivariate analysis successfully reproduced some of the results obtained in our previous univariate analysis, confirming that these findings are not dependent on the analysis approach. In particular, both types of analysis suggest that the different experimental conditions elicited significantly different responses within each subject group. Also, the class accuracy results for HC vs BD classification indicate that BD patients had more consistent responses to the “Neutral Decrease” condition compared to HC.

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Pfizer Psychiatry Research Awards Program, CIHR and NSERC
Abstract title: Small non-coding RNAs in Major Depression and Antidepressant Response

Authors: Rixing Lin¹, Juan Pablo Lopez¹, Laura Fiori¹, Cristiana Cruceanu¹, Raoul Belzeaux¹, CANBIND working group¹, Jane Foster², Sidney Kennedy² and Gustavo Turecki¹

Affiliation(s): 1-McGill Group for Suicide Studies, Douglas Mental Health University Institute, McGill University, Montreal, Quebec, Canada. 2-Department of Psychiatry, University Health Network, University of Toronto, Toronto, Ontario, Canada

Statement of Purpose:
Major depressive disorder (MDD) is a prevalent disorder treated primarily by antidepressants (ADT). Although effective, on average 30%-40% of subjects experience an inadequate response to treatment after several attempts. Thus, there is a great need to identify biomarkers associated with MDD and ADT response. Recent discoveries have pointed towards small non-coding RNAs (sncRNAs) as feasible biomarkers, as they have shown to be stably circulated in peripheral blood and may be associated with a disease state. Here, I profile sncRNAs in MDD pathology, and evaluate their ability to act as candidate biomarkers for diagnosis and/or ADT treatment response. This project addresses these questions with a unique combinatorial approach of using both post-mortem human brain tissue samples and living patient blood samples.

Methods:
Human post-mortem brain samples were obtained the Douglas-Bell Canada Brain Bank. Brain tissue will be collected from individuals who died by suicide during an episode of MDD, and psychiatrically normal individuals who died suddenly. Human peripheral blood samples were collected from a clinical trial using duloxetine (samples provided by Lundbeck). This cohort consisted of depressed subjects treated with duloxetine for 8 weeks. All subjects were assessed for depression severity based on the Montgomery-Asberg Depression Rating Scale (MADRS) at week 0 (pre-ADT treatment) and week 8 (post-ADT treatment). After concluding 8-weeks of ADT therapy, subjects were separated into responders (>50% decrease in MARDs score) or non-responders (<50% decrease in MARDs score) of ADT treatment. Small RNA-sequencing was used to generate expression data on whole sncRNA-transcriptome in post-mortem brain and peripheral blood of MDD subjects.

Results:
37 snoRNAs and 6 piRNAs showed significant up-regulation in MDD brains compared to healthy controls. From this study snoRNAs and piRNAs do not show predictive value for ADT response. snoRNAs and piRNAs only showed differential expression across time-points (i.e. week 0 vs week 8) in responders of duloxetine treatment. 31 snoRNAs showed significant up-regulation in responders of duloxetine. 3 piRNA showed significant up-regulation and 4 piRNAs showed significant down-regulation in responders of duloxetine after treatment. Significant results were specific to responders for both snoRNAs and piRNAs.

Supported by (fellowship and/or granting agency) CIHR
Abstract title: Pathways to Care in Youth Mental Health: A Systematic Review of the Evidence

Authors: Kathleen MacDonald¹, Nina Fainman-Adelman¹, Kelly K Anderson², Srividya Iyer¹

Affiliation(s): 1. McGill University 2. University of Western Ontario

Introduction: The majority of psychiatric conditions emerge before the age of 25, and mental illness is the largest contributor to burden of disease in adolescence. Yet, many youth with mental health problems face lengthy delays prior to accessing services. This systematic review is the first to synthesize findings examining young people’s pathways to care for mental health problems.

Methods: A systematic review was undertaken following PRISMA protocol guidelines. Search terms were generated using expert consultation and a university librarian. Relevant studies were identified through searching five electronic databases (Medline, EMBASE, PsycINFO, HealthStar and CINAHL). 12,458 studies were screened for relevance of study titles and abstracts by two reviewers. Of these, 845 full text studies were independently screened for inclusion.

Results: A total of forty-four studies were identified. The majority stemmed from the field of psychosis, while others investigated pathways to admission to a psychiatric institution, or outpatient settings. Overall, the role of the general practitioner was critical in young people’s help-seeking efforts, across cultures and contexts. Further, friends and family play a key role in the initiation of seeking help. Overall, many gaps remain the assessment of pathways to, notably due to the discrepancies in defining concepts and lack of standardized methodology.

Conclusion: Many youths with mental health problems face delayed detection, long wait-lists and multiple help-seeking contacts before obtaining appropriate mental health services. This review helps to shed light on specific causes of treatment delays in youth mental health.

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Abstract title: Cases, Non-Cases, or Non-Non-Cases: An Examination of Spillover Effects of a Targeted Early Identification Intervention for First Episode Psychosis

Authors: Sarah McIlwaine, Sally Mustafa, Rachel Rosengard, Anne Crawford, Martin Lepage, Srividya Iyer, Ridha Joober, Ashok Malla, Jai Shah

Affiliation(s): 1. Department of Psychiatry, McGill University; 2. Prevention and Early Intervention Program for Psychoses (PEPP-Montreal), Douglas Mental Health University Institute

BACKGROUND: Targeted case identification (TCI) efforts in first episode psychosis (FEP) aim to simplify the referral pathways of people experiencing an FEP, and to provide rapid access to treatment during the illness’ initial phases. Nonetheless, TCIs may have unintended consequences. Here we explore the spillover effects of a TCI for FEP on a) referral pathways for “non-cases” and b) those at clinical high-risk for psychosis (CHR). METHODS: Using a historical control design, referral information from the pre-TCI (from January 2003 to December 2006) and post-TCI (from June 2006 to May 2009) phases was collected via administrative data and clinician notes from a catchment-based early psychosis service in Montreal, Canada. RESULTS: The TCI led to a 17% increase in eligible FEP referrals (“cases”), with a disproportionately large increase (55%) in referrals who were ineligible for FEP services (“non-cases”). Of 334 non-cases, 125 (37%) did not meet FEP diagnostic criteria, and 39 (11%) were eventually referred to an adjacent CHR service. Of these 39, 10 (26%) were lost to follow-up after initial screening for FEP, while 29 (74%) were successfully screened. Twenty-four (83%) of those screened had a CHR state (“non-non-cases”), and were followed for an average of 13 months. CONCLUSIONS: TCIs may have spillover effects, whether for narrowly-defined non-cases or expanded definitions of caseness that include CHR. These findings bring to question whether outreach strategies for psychosis should be specific to disorders and stages, or whether their targets should span across the psychosis spectrum.

Supported by (fellowship and/or granting agency) Canadian Institutes of Health Research (CIHR); Fonds de recherche sante Quebec (FRSQ)
Abstract title: Early increase in tau-PET signal is associated with Aβ burden, CSF p-tau levels and cognition in cognitively normal late-middle-aged adults

Authors: Melissa McSweeney, Alexa Pichet Binette, Pierre-François Meyer, Julie Gonneaud, Christophe Bedetti, Hazal Ozlen, Leslie-Ann Daoust, Ann Labonté, Judes Poirier, Pedro Rosa-Neto, John Breitner, & Sylvia Villeneuve for the PREVENT-AD research group

Affiliation(s): McGill University, Douglas Mental Health University Institute

The role of early cortical tau accumulation and its associations with amyloid-β (Aβ), cerebrospinal fluid (CSF) biomarkers, and cognition in pre-symptomatic stages of Alzheimer’s disease (AD) are unclear. Using PET imaging, we examined these associations in cognitively normal, late-middle-aged adults at increased risk of AD. Ninety-five adults with a family history of AD (PREVENT-AD cohort, mean age=67±5) underwent tau-PET ([18F]AV-1451), Aβ-PET ([18F]NAV4694) and cognitive evaluation (Repeated Battery for Assessment of Neuropsychological Status; RBANS). CSF phosphorylated (p)-tau levels were assayed for 55 subjects. Standardized uptake value ratios (SUVRs) of PET tracers were extracted from 35 Freesurfer Desikan brain atlas regions using the grey matter cerebellum as the reference region. We investigated regional tau SUVR differences between Aβ-positive and Aβ-negative subjects using linear regression. In the identified regions, we assessed whether tau SUVR is related to CSF p-tau, cognition, and cortical thickness using linear regression models. Aβ-positive subjects had higher tau SUVRs than Aβ-negative ones in 14 brain regions (p≤0.05) that are affected by AD-related tau pathology according to post-mortem studies. Tau in 5 of these limbic and temporal regions was positively associated with CSF p-tau (p<0.05). Higher tau SUVR was associated with lower delayed memory, language, and total RBANS index scores (p<0.05). When tau+ subjects were removed from analyses, results remained similar. Overall, these findings suggest that early tau changes in AD-typical regions are clinically meaningful and offers insight on [18F]AV-1451’s utility for identifying preclinical AD.

Supported by (fellowship and/or granting agency) Quebec Bio-imaging Network
Abstract title: Prefrontal dopamine transporter gene network interacts with birth conditions influencing internalizing problems and attentional flexibility in children

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Different genetic variants associated with the dopamine transporter gene (DAT1) were identified as risk factors for attention-deficit hyperactivity disorder (ADHD), and perinatal complications associated with poor oxygenation also affect dopamine function and consequently ADHD risk. We created a novel genetic score reflecting variations in the function of the prefrontal DAT1 gene network, and explored its interaction with the birth conditions associated with the newborn oxygenation on the development of behavioral outcomes related to ADHD in children (socio-emotional and cognitive flexibility). Our polygenic score (ePRS-DAT1) was constructed based on genes co-expressed with DAT1 in the prefrontal cortex, and the birth conditions (type of delivery, APGAR score, birth weight, gestational age, maternal age, use of forceps/vacuum, anesthesia use, intrapartum and newborn complications) were summarized in a score called HICs (hypoxic-ischemic-associated conditions). We observed a significant interaction effect between the ePRS-DAT1 and HICs on the Internalizing problems score of the Child Behavior Checklist at 48 months (p=0.04), in which higher HICs was associated with Internalizing problems only for the high ePRS group ($\hat{\beta}$=1.14, p=0.02). In the Intra-Extra/dimensional task (CANTAB) at 72 months, there was an ePRS vs. HICs interaction in the latency to respond (p=0.001) on stage 8 (extra-dimensional shift), in which higher HICs score was associated with longer latency to respond for the high ePRS group ($\hat{\beta}$=16636, p<0.001). The genetic profile related to prefrontal DA reuptake interacts with perinatal oxygenation, predicting worse ADHD-related outcomes in children. The gene network of the prefrontal DAT1 gene seems to be an important player in modulating these effects

Supported by (fellowship and/or granting agency) CAPES
Abstract title: *DCC gene network in the prefrontal cortex predicts brain volume and impulsivity in healthy children*

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The axon guidance receptor DCC is involved in organizing mesocorticolimbic connectivity during adolescence and its expression is altered in prefrontal cortex (PFC)-related psychopathologies. Here, we created a polygenic score based on the DCC co-expression gene network and hypothesized that discrete differences in behavior and brain structure will emerge. Followed from birth to 12 years of age with multiple behavioral measures (n=260; 131 females), 64 of the healthy volunteers (n=64; 33 females) underwent MRI and had genetic data collected. Under the assumption that coherent gene networks are represented by co-expressed genes, we obtained (from postmortem genetic databases) SNPs in genes co-expressed with DCC, with region (PFC) and age (1.5 to 11 y.o.) specificity. Then, using GTEx regression model of the gene expression we used the slope coefficient as the weight for alleles. The polygenic expression score is created by combining the estimated effects of alleles for the SNPs that each subject carries.

The DCC network expression predicts morphological aspects of a healthy child’s brain. Children with high polygenic score have significantly smaller brain volumes (p=0.016, z=6.22), when adjusted for age, sex and ethnicity. Volumetric thalamus measures are smaller in children with high co-expression scores (p=0.032, z=4.86), especially in boys (p=0.030, z=4.99). Regarding behavioral outcomes, CANTAB Stop Signal test reveals substantial impulsivity of the high polygenic score group (p=0.034, z=4.55).

This novel genomic approach reveals that variations in expression of the DCC gene network predict individual differences in brain structure that are apparent at an early age in a healthy population.

**Supported by (fellowship and/or granting agency)**
Abstract title: Circadian control of the CD8 T cell response to antigen presentation by dendritic cells

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Circadian clocks control various aspects of the immune system but their role in the adaptive immune response remains poorly defined. Our work showed that the CD8 T cell response to vaccination with dendritic cells loaded with the OVA peptide antigen (DC-OVA) varies according to the time of day. In this study, we have identified the clock involved in the in vivo CD8 T cell response and have started to uncover how the circadian clock affects this response. Using tetramer staining, we found that the higher expansion of OVA-specific CD8 T cells in response to DC-OVA vaccination done in the middle of the day is abolished when CD8 T cells are deficient for the essential clock gene Bmal1. Similarly, the rhythm of cytokine production by CD8 T cells was abolished. Moreover, the observed rhythm impacts the ability to control an infectious challenge (by Listeria monocytogenes) as shown by a day/night variation in bacterial load in WT but not CD8 T cell-specific Bmal1 KO mice. In contrast, the rhythm was not affected when Bmal1 KO DCs were used to vaccinate mice, confirming the role of the CD8 T cell clock in this rhythm. Now, we are working on analyzing results from RNA-sequencing data from CD8 T cells (at basal state, without antigen stimulation) harvested every 4 hours over 48 hours to determine the molecular mechanism of this rhythm. These results will help us to understand how the circadian clock controls the immune response to vaccination and to improve therapies based on immunizations.
Abstract title: Regional characterization of vimentin-immunoreactive astrocytes in the human brain

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Introduction: This study aims to characterize the distribution and morphology of astrocytes in various human brain regions. Astrocytes are commonly identified by their expression of glial fibrillary acidic protein (GFAP), an intermediate filament protein. However, GFAP-immunoreactive (GFAP-IR) astrocytes constitute only a subset of astrocytes in the normal, healthy brain, leaving most cells unscrutinized. We hypothesized that vimentin, another intermediate filament protein expressed by glia, would label complementary subsets of astrocytes. To test this hypothesis, we performed fine neuroanatomical analyses on vimentin- and GFAP-immunoreactive (-IR) astrocytes in well-characterized postmortem human brain samples (n=5 healthy individuals) provided by the Douglas-Bell Canada Brain Bank.

Methods: Fresh-frozen tissue from the prefrontal and occipital cortex, caudate nucleus, and mediodorsal thalamus was postfixed and immunostained for brightfield (single labeling) or immunofluorescence (double labeling) using anti-vimentin and anti-GFAP antibodies. Densities and morphometric properties of astrocytes were examined using StereoInvestigator and Neurolucida (MBF Bioscience).

Results: The quantity and morphology of vimentin-IR astrocytes was similar in all examined regions except for the thalamus, in which only a few cells were observed. These cells were generally found to contact vimentin-IR blood vessels. Overall, only a minority (10%) of vimentin-IR astrocytes were also GFAP-IR.

Discussion: Double-labeling immunohistochemical results suggest that in the human brain, vimentin-IR astrocytes are mostly distinct from GFAP-IR astrocytes. This is further supported by the relative inter-regional morphological homogeneity of vimentin-IR astrocytes, which contrasts with previous reports of highly distinct GFAP-IR astrocytic subtypes in the human brain. The functional implications of these findings are currently being investigated.

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Abstract title: Medication acceptance and refusal: a case study analysis of early neuroleptic medication Adherence

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Antipsychotic medication adherence is estimated to be below 50% during the first year of treatment at first-episode psychosis clinics. Treatment alliance, family and social support, symptoms resolution, and side-effects are factors which quantitative studies have identified as contributing to medication adherence. Qualitative studies have explored the experience of people taking antipsychotics. Several questions remain over people’s initial decision to accept or refuse medication and their initial experience of taking medication. To address this gap, we used case studies to explore people’s decision to accept or refuse medication and their associated experiences. Twenty-two in-depth interviews were conducted with people prescribed neuroleptics for a diagnosis of affective or non-affective psychosis, and five representative interviews were chosen for further analysis. Family impressions of mental illness and medication strongly affected initial choices around medications. People from cultural backgrounds with explanatory frameworks other than the Western model of mental health often refused medication when it was first offered. For those who accepted medication, family support was important to continuing to take medication, more so than the support of partners or friends. People experiencing side-effects, which affected their health, or social and professional lives, were more likely to stop taking medication. People were more likely to continue medication if symptoms or sleep were improved by medication. People appreciated doctors who were perceived to be responding to their concerns. Finally, clinicians should be attentive to concerns that people have about medication, whether due to cultural differences, side-effects, or interruption of their social and professional lives.

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P26

Abstract title: Selective melatonin MT2 receptor ligands relieve neuropathic pain through modulation of brainstem descending antinociceptive pathways and opioid interactions

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Aim: Neuropathic pain is a health problem for which few treatments are available. Preclinical studies have shown that melatonin (MLT) and its related MT2 receptor selective agonists have analgesic properties, likely through opioid (OR) receptors. We determined the effects of the selective MT2 receptor partial agonist (UCM924) in two rat neuropathic pain models and examined its supraspinal mechanism of action. Methods: L5-L6 spinal nerve ligation and spared nerve injury models were used to evaluate neuropathic allodynia and in-vivo electrophysiological recordings of ON and OFF cells in the periaqueductal grey-rostral ventral medulla (PAG-RVM) projection were collected to determine the mechanism of action. Results: In both models, UCM924 produced a prolonged antinociceptive effect that is: dose-dependent, superior to a high dose of MLT and comparable with gabapentin, but without motor coordination impairments. Using in-vivo electrophysiology combined with tail-flick, we observed that microinjection of UCM924 into the PAG decreased the tail-flick response, depressed the firing activity of ON cells, and activated the firing of OFF cells. Importantly, non-selective (naloxone) and selective opioid mOR antagonist (CTOP), but not selective dOR antagonist (naltrindole) blocked the antinociceptive effects of UCM924 in the neuropathic model and its effect on ON and OFF cells. Conclusions: Altogether, UCM924 have analgesic properties by modulation of descending antinociceptive pathways and this effect is mediated by mOR. MT2 receptors may represent a target in the treatment of neuropathic pain.

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Abstract title: Differential Effects of High and Low doses of Amphetamine in Adolescence on Dopamine Development

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Introduction: The miR-218/DCC signaling pathway is fundamental to the adolescent development of the mesocorticolimbic dopamine circuitry. Exposure during adolescence to doses of amphetamine similar to those abused by humans, dysregulate miR-218/DCC expression in dopamine neurons, disrupting in turn mesocortical dopamine connectivity and cognitive processing in adulthood. However, amphetamine drugs are commonly prescribed to treat neurodevelopmental conditions. Here we investigated whether low doses of amphetamine, comparable to those used in therapeutic settings, regulate the miR-218/DCC pathway and dopamine development.

Methods: We treated male mice (from PND 22 to PND 31) with saline or with low doses of amphetamine (0.5 mg/kg i.p). First, we measured levels of miR-218 and DCC in the VTA, one week after treatment. Second, we allowed another cohort to reach adulthood (PND 75 ± 15) and assessed performance in the attentional set shifting (ASST) and the Go/No Go tasks. Finally, we performed stereological analyses to measure dopamine connectivity and organization in adulthood.

Results: 1) Low doses of amphetamine in adolescence increased VTA DCC protein expression, without altering miR-218. 2) In comparison to saline groups, amphetamine-treated mice exhibited a small but significant improved performance across the ASST task and greater overall efficiency in the Go/No Go task. 3) There were no detectable group differences in mesocortical dopamine connectivity.

Conclusion: Low doses of amphetamine in adolescence lead to different dopamine and behavioral effects in adulthood, compared to high drug doses. These differences are likely to result from the opposite regulation that these doses exert on miR-218/DCC signaling in the VTA.

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P28

Abstract title: Hippocampal subregion CA1 requires CA3 input to encode novel space.

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Background: Substantial work on the entorhinal-hippocampal circuit has revealed a myriad of spatially tuned neurons, yet the details on how these cell types interact and generate new codes for novel space remain limited. Our prior work has argued against a grid-to-place cell feedforward transfer model. Here, we explore the possibility that the CA1 place code relies on previously generated assemblies, or maps, that are stored within the CA3 auto associative network. Previous work has assessed and rejected this possibility in familiar environments, however we suggest that transfer of information from CA3 to CA1 would be most critical when exploring a novel environment. A chemogenetic approach in Grik4-cre transgenic mice to silence CA3 neurons was used. A cre-dependent AAV that expresses the hM4di inhibitory DREADD receptor, activated upon binding of its ligand, Clozapine-N-Oxide (CNO), was injected into CA3 of Grik4-cre mice. We performed chronic in vivo recordings of CA1 neurons in CA3 hM4di expressing Grik4-cre mice. A baseline recording was first taken in a 90cm² familiar open field (F1). Forty minutes after a 5 mg/kg CNO or saline injection was administered mice were exposed successively to the familiar and novel environment. Recovery recordings were obtained from the familiar and novel environments 12 hours after injection. Preliminary data indicates that CA1 neurons fail to form discrete and stable place fields in the absence of CA3 input in Novel and Familiar environments. These results suggest that information flow from CA3 to CA1 pyramidal cells is a prerequisite to build and sustain CA1 spatial maps.

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Abstract title: Eating and sleep patterns in eating disorders

Authors: Duncan Sibthorpe, Clément Bourguignon, Asli Buyukkurt, Alexia Della Vechia, Olivia Crescenzi, Kassandy Kowalyk, Howard Steiger, Mimi Israel, Kai-Florian Storch, Outi Mantere G

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In this study, we examined the relationship of irregular eating patterns with disrupted sleep in eating disorders (ED).

Consenting ED patients (n=26) from an outpatient, tertiary care clinic completed hourly charts of mood and eating for two weeks, and wore a wrist actigraph for a period of two weeks. To assess the temporal structure of eating, we created eatograms displaying reported eating events across the two-week recording period. To quantify irregularity in the timing of food intake, we computed the standard deviations (SD) of meal frequency (MF), meal-timing (MT), and inter-meal-interval (INT). To quantify sleep, we defined sleep by <50 wrist-angle change for >5min. Quantitative measured used were sleep onset (ON), mid-sleep phase (A) to indicate chronotype, and circadian sleep:wake rhythm strength (R), to indicate rhythm consolidation. Measures of eating regularity were then correlated with descriptors of sleep.

By visual inspection of the eatograms and inactograms, we detected that more disrupted sleep and eating rhythm were present in the same individuals. This was confirmed in the statistical analysis. Later onset of sleep correlated with lower frequency of eating (ON with MF rh=-0.40, p=0.042, A with MF rh=-0.60, p=-0.001), more variation in the timing of meals (A with MT rh=0.55, p=0.003) and in the time between meals (ON with INT 0.51, p=0.006, A with INT 0.66, p=<0.001). More variation in ON correlated with irregular eating (SD of ON with MT rh=0.41, p=0.033).

While causation remains open, both sleep and eating rhythms are strongly and simultaneously disrupted in eating disorders.

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Abstract title: Volume of posterior hippocampus is positively related to source memory accuracy in healthy young adults.

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The relationship between structural parameters of medial temporal lobe (MTL) regions and related cognitive abilities has been examined to a large extent from the perspective of pathology and aging. To determine if individual differences in volume of MTL regions are related to memory, we tested a group of healthy young individuals (N = 18, mean age = 21.41) on a source memory task. Findings from Maguire et al. (2000), and Poppenk and Moscovitch (2011), specify the role of the posterior hippocampus in spatial memory and recollection memory, where memory for the context of episodic events is related to volume and activation of the posterior hippocampus (postHC). High resolution T2-weighted structural MRI images (TR 2500ms, TE 198 ms, 320 slices of 0.60 mm thickness, 0.64 x 0.64 x 0.64 mm voxels, FOV = 206) were obtained from each participant. We used the Multiple Automatically Generated Templates (MAGeT; Chakravarty et al., 2013) brain algorithm to measure the grey matter volume of the perirhinal, entorhinal and parahippocampal cortices, and anterior and posterior hippocampus. Participants also performed a source memory task. Behavioral measures for spatial context memory, recognition memory, misses, correct rejections and false alarms were calculated. Bivariate correlation analyses were conducted to determine if regional volumes correlated with specific mnemonic responses. We found that bilateral posterior, hippocampal volumes were positively correlated with spatial context memory and negatively correlated with misses. This study provides evidence for the role of posterior hippocampus in context memory, and depicts a relationship between volume and cognition mediated by individual differences in healthy young adults.

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Healthy aging is associated with episodic memory decline (i.e., our ability to encode, store and retrieve personally experienced events in rich contextual detail). Prior studies have shown a tendency for women to outperform men on episodic memory tasks. For example, women perform better than men on object-location associative and face memory tasks (Herlitz and Rehman, 2008). Many sociocultural and biological factors likely contribute to these sex differences in performance, which in turn may impact the functional neural networks supporting episodic memory in women, compared to men. This raises the possibility for the presence of sex differences in brain aging, particularly in episodic memory networks. In the current event-related fMRI study, we investigated sex differences in brain activity during face-location associative memory tasks across the adult lifespan. Participants were scanned during encoding and retrieval. Our behavioural results indicate a robust effect of age on memory performance but no sex differences in face-location retrieval accuracy nor reaction time. However, our multivariate behaviour Partial Least Squares fMRI analysis revealed significant interaction between age and sex at encoding and retrieval. Specifically, in women, there was an age-related increase in parahippocampal activity at encoding. In contrast, in men, there was an age-related increase in parahippocampal activity at retrieval. In addition, only in men, there was a generalized pattern of inferior parietal activity across encoding and retrieval with advanced age. Overall, men and women engaged similar brain networks during memory encoding, but sex differences were observed in retrieval-related activity.

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**Abstract title:** The Gut Microbiome as a Key Regulator of Early Life Stress Induced Depression

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**Affiliation(s):** Douglas Mental Health University Insitute (for all authors except MC Audet); School of Nutrition Sciences, University of Ottawa (for MC Audet)

**Background & Hypothesis:** Early life stress (ELS) significantly increases risk of adult psychopathology, including depression and suicide; however, the mechanisms of this vulnerability remain unclear. The gut microbiome (the bacteria, viruses, and eukaryotes in our intestinal tract) may be a key player in this regard as it regulates many physiological processes related to depression including hypothalamic-pituitary-adrenal (HPA) axis homeostasis and brain-immune interactions.

Hypothesis: ELS confers long-lasting changes in gut microbiome composition, intestinal and blood-brain-barrier permeability, and promotes pro-inflammatory brain-immune interactions, ultimately resulting in an increased risk for depression.

Methods: We are exposing male and female C57Bl/6J mice to early life (P2-P9) limited bedding and assessing depressive-like behaviours, HPA axis homeostasis, intestinal and blood-brain barrier permeability, brain-immune interactions, gut microbiome composition, and depressive-like behaviour. Concurrently, we are collecting post-mortem intestinal tissue from depressed suicides or controls in which we will repeat relevant measures of intestinal permeability, cytokine expression, and gut microbiome composition.

Results & Significance: Preliminary results from our animal studies suggest that ELS produces sex-specific deficits in social behaviour along with decreased hypothalamic expression of corticotrophin releasing hormone (CRH) along with decreased expression of claudin-5 in both the hypothalamus and colon of these animals, suggesting altered HPA axis and blood-brain and intestinal barrier disruption respectively. These early observations are indicative of important changes in the multiple systems (brain, immune, gut) targeted for analysis as part of our studies and add support to our hypothesis that ELS triggers an integrative response that may be initiated by fundamental alterations in the microbiome.

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Abstract title: Discriminating between schizophrenia subtypes using clustering and supervised learning

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Schizophrenia affects roughly 1\% of the population, and presents with positive (e.g. hallucinations) and negative (e.g. inability to feel pleasure) symptoms, in addition to cognitive impairments (Sawa & Snyder, 2002). Both symptom burden and associated brain alterations are heterogeneous and intimately linked to prognosis; thus, there is a need for methods that can predict symptom burden at the individual level. This study focuses on characterizing the heterogeneity in a schizophrenia population by defining clinical subgroups, and using neuroanatomical variables as predictors of individual clinical profiles. Data from SchizConnect (http://schizconnect.org) of 104 patients and 63 normal controls was used. Hierarchical clustering was performed on the symptom severity data, resulting in 3 clusters following a stability analysis, representing patients with 1) high-symptomatology, 2) high-positive symptoms, or 3) mild-symptomatology. Demographic variables and the average cortical thickness in 78 brain regions defined by the Automated Anatomical Labeling atlas parcellations were used as input features into three machine learning algorithms (logistic regression, support vector machine, and random forest), and the subgroups as class labels. Random forest performance metrics for predicting the group membership of the high-symptomatology and the mild-symptomatology groups exceeded those of the baseline comparison of all patients versus normal controls (area under the receiver operating characteristic curve (AUC): 0.81 and 0.78 vs. 0.75). Further, the cortical regions that were the most informative predictors in each random forest classification task were different for each subgroup, indicating distinct neuroanatomical impairments in each subtype.

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Abstract title: Multivariate pattern analysis (MVPA) of cross-modal emotional processing

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Functional neuroimaging studies have provided strong evidence for the role of the amygdala in processing fearful information. However, few studies have looked at within-subject cross-modal responses to fear. The current study used fast (TR=0.529s), high-resolution (voxel: 2mm isotropic) functional magnetic resonance imaging (fMRI) to examine the neural response to fearful and neutral auditory and visual information. As the amygdala is a highly connected structure, we employed a multivariate pattern analysis (MVPA) to gain a more comprehensive view of the fear-processing network. Participants (N=30) passively listened to brief auditory stimuli (vocalizations and pseudospeech) or viewed static images (faces and body expressions) that expressed a fearful or neutral emotion. Category-, subject- and run-specific parameter estimates obtained from the univariate GLM were used for pattern analysis, where a classifier was trained to identify voxel activation patterns. Normalized Weights (NW) summarizing the weight of each anatomical region, were computed a posteriori. Using a mask of the cerebrum, which covered 90 anatomical regions, the model could distinguish fear and neutral emotion across all domains, yielding a balanced accuracy of 55.83%, p = 0.023 (1000 permutations), and an area under the curve (AUC) of 0.58. The weight map revealed that the most discriminative voxels were located in the amygdala bilaterally, with a more positive weight contribution dorsomedially and a more negative weight laterally. However, the amygdala alone did not obtain a classification accuracy equivalent to that of the cerebrum, suggesting that fear processing is associated with a distributed pattern of activation across cortical and subcortical structures.

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Abstract title: Grid cell dysfunction in the medial entorhinal cortex correlates with path integration deficits in a mouse model of Alzheimer's disease

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Alzheimer’s disease (AD) is a neurodegenerative disease characterized by spatial memory impairments in the form of disorientation and difficulty navigating. One potential circuit-level mechanistic explanation for these symptoms is a disruption of spatial coding in the brain's navigation system that consists of grid cells, head-direction cells, and border cells in the medial entorhinal cortex (MEC). Here, we employed in-vivo electrophysiological recordings in the freely behaving transgenic J20 mouse model of AD, which expresses an onset of beta-amyloid (AB) plaques in the MEC at four months of age. We demonstrate that grid cells are disrupted in aged J20 animals (months 5-7). Network-level impairments of non-classified cells in the MEC are detectable in young J20 animals (months 2-4), preceding the formation of plaques. To corroborate our physiological findings, we aimed to better characterize the nature of spatial memory impairment seen in AD and to propose a function for the MEC in navigation and memory. J20 mice were tested in a path integration food-foraging task in darkness where they must integrate self-motion cues such as heading direction and movement speed to continuously update their perceived location in space. Without allocentric visual cues, this task provides an opportunity to characterize the role of specific MEC cell types in navigation. Our preliminary data show that aged J20 mice demonstrate impaired path integration behaviour which correlates to the observed physiological dysfunction. Overall, our results suggest that grid cells in the MEC are important targets for future therapies to restore spatial cognitive function in human AD patients.

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