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Thank you for joining us!

JANUARY 22, 2021

5TH ANNUAL RESEARCH DAY
BRAIN, BEHAVIOUR & DEVELOPMENT

BC Children's Hospital Research Institute

https://www.bcchr.ca/BBD-research-day

E-Poster Gallery

Please visit https://www.bcchr.ca/BBD-research-day/poster-gallery to browse the e-posters and audio recordings. In addition to the e-poster gallery, there will be opportunities to speak with the poster presenters via individual zoom rooms (see poster session schedule on page 2).

Zoom Meeting Links

All links are also available on Google docs at http://bit.ly/bbdzoom

Main Sessions (Opening, Keynote, Lightning Talks, Awards, Closing):

https://ubc.zoom.us/j/67248959420?pwd=ZnlsWktwcmlDOGk1cjhtQXVySU4rUT09
Meeting ID: 672 4895 9420 Passcode: 202020

The main sessions will be recorded and uploaded to Research Day website following the event.

Town Hall for BB&D PIs:

A separate zoom meeting link has been sent to all BB&D PIs.
Please contact bb&d@bcchr.ca if you have not received the link.

Poster Session (Individual Zoom Rooms):

Visit http://bit.ly/bbdzoom or see poster session schedule on page 2.

Slido for Q&As & Best Poster and Talk Voting

Go to www.sli.do and enter the event code: **BBD**

For Q&As

- Click on the "Q&A" icon and submit your questions during the talk
- The moderator will deliver to the submitted questions to the presenter following the talk
- During the lightning talk round, please identify the speaker the question is addressed to

Vote for the Best Posters & Talk:

- Click on the "Polls" icon during the voting period from **8:45am - 12:20pm**
- Fill out the survey – Pick your TOP two favourite talk and favourite poster from each category

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Poster Session – Zoom Info

Interested in a poster and want to talk with the presenter? Join during their time slot to have a conversation!

	11:30AM-11:45AM	11:45AM-12:15PM	12:00PM-12:15PM	12:15PM-12:30PM
ROOM 1 https://ubc.zoom.us/j/67184738534?pwd=UnFxaFNLd2paZU9CRFE2R0gvaGI3UT09 Meeting ID: 671 8473 8534 Passcode: 1111	**Helena Biasibetti Brendler** PRENATAL ALCOHOL EXPOSURE IN BXD EMBRYONIC MICE INDUCES HISTONE AND APOPTOSIS-RELATED CHROMATIN CHANGES IN A STRAIN-DEPENDENT MANNER	**Jessica Khangura** ANALYSIS OF BRAIN NETWORKS EVOKED DURING A LANGUAGE PROCESSING TASK IN SCHIZOPHRENIA PATIENTS	**Emma Karwandy** INVESTIGATION OF VARIANTS IN NON-CODING REGIONS THAT MAY INFLUENCE LINGO2 GENE EXPRESSION IN A FAMILY WITH AUTISM SPECTRUM DISORDER.	**Alexis Dawson** CUMULATIVE BURDEN OF ADOLESCENT PSYCHOPATHOLOGY: YOUNG ADULT OUTCOMES AND MENTAL HEALTH SERVICE UTILIZATION
ROOM 2 https://ubc.zoom.us/j/66857294460?pwd=SGJWNkNIM1pJR0dtQzh6eXRBUXZ4UT09 Meeting ID: 668 5729 4460 Passcode: 2222	**Sarah Dada** INTEGRATION OF GENOMIC AND PHENOMIC DATA FOR PRECISION DIAGNOSIS AND TREATMENT WITHIN AUTISM SPECTRUM DISORDER	**Laura Chan** DEVELOPMENT OF A CELLULAR ASSAY FOR HUNTINGTIN'S PRO-SURVIVAL FUNCTION	**Robert Selles** INTENSIVE COGNITIVE BEHAVIORAL TREATMENT FOR YOUTH WITH OBSESSION COMPULSIVE DISORDER: IDENTIFYING OPTIMAL SETTING AND DOSE	**Judy Cheng** CHARACTERIZATION OF A NOVEL BRAIN NETWORK DERIVED FROM TASK-BASED FUNCTIONAL MAGNETIC RESONANCE IMAGING: AUDITORY ATTENTION FOR RESPONSE
ROOM 3 https://ubc.zoom.us/j/69758822439?pwd=SVhLYVNSUXk0TTNHTG5tV0ZCNFcyOT09 Meeting ID: 697 5882 2439 Passcode: 3333	**Jennifer Coelho** BODY CHECKING IN YOUTH: ASSOCIATION WITH EATING PATHOLOGY	**Erin Klein** THE IMPACT OF DEVELOPMENTAL COORDINATION DISORDER: PARENT PERSPECTIVES	**Katelynn Boerner** THE ROLE OF PRENATAL EXPOSURE TO SEROTONIN REUPTAKE INHIBITOR ANTIDEPRESSANTS, CHILD SEX, AND SEROTONIN-RELATED GENOTYPE ON PAIN-RELATED SOMATIC SYMPTOMS AND GLOBAL PHYSICAL HEALTH IN YOUNG CHILDREN	**Yuka Obayashi** EXAMINING THE ROLE OF H3K4 METHYLATION IN THE HIPPOCAMPAL MEMORY FORMATION AND IN THE PATHOGENESIS OF ALZHEIMER'S DISEASE
ROOM 4 https://ubc.zoom.us/j/62248989500?pwd=UG5lcGhIMmFodlFuYVY1NGlpSnI3dz09 Meeting ID: 622 4898 9500 Passcode: 4444	**Alison Lui (unable to attend)** THE MIND BODY CONNECTION GROUP: YOUTH AND CAREGIVER PERSPECTIVES ON MULTI-FAMILY GROUP THERAPY FOR YOUTH AFFECTED BY SOMATIZATION ***Questions can be directed to Amrit.Dhariwal@cw.bc.ca***	**Catherine Hsu** DIFFERING LEVELS OF UBIQUITYLATED PROTEINS AND UBIQUITIN GENE EXPRESSION IN THE PREFRONTAL CORTEX IN SCHIZOPHRENIA AND BIPOLAR DISORDER		**Hannah Phillips** EARLY PAIN-STRESS AND ARITHMETIC SKILLS: INVESTIGATING FUNCTIONAL CONNECTIVITY DURING VISUOSPATIAL PROCESSING AT AGE 8 YEARS IN CHILDREN BORN VERY PRETERM
ROOM 5 https://ubc.zoom.us/i/63490049802?pwd=dkV2RU1NUFdVeFpOWUkrblR5aUhFUT09 Meeting ID: 634 9004 9802 Passcode: 5555	**Chantal Percival** CHARACTERIZATION OF A NOVEL TASK-BASED FMRI FUNCTIONAL BRAIN NETWORK: FOCUS ON VISUAL FEATURES			**Ben Life** INVESTIGATING PROGRANULIN OVEREXPRESSION IN FRAGILE X SYNDROME
ROOM 6 https://ubc.zoom.us/j/68796649742?pwd=VVc3VkhDUzBRaDY1dkd3cDhGa3Mwdz09 Meeting ID: 687 9664 9742 Passcode: 6666	**Lara Bartels** ORIENTATION DEPENDENCY OF T2 IN NEWBORN WHITE MATTER SHOWS DIPOLE-DIPOLE INTERACTION EFFECTS	**Zahra Nasseri Moghaddam** SATISFACTION OF CLINICAL GENETICS PROFESSIONALS WITH TELEHEALTH DURING THE COVID-19 PANDEMIC	**Robert Stowe** METABOLIC AND GENETIC EXPLORATIONS IN REFRACTORY SCHIZOPHRENIA PROJECT: FINDINGS FROM WHOLE GENOME AND RNA SEQUENCING IN THE FIRST 10 PARTICIPANTS.	**Sarah Thomson** DESIGN OF LIPID NANOPARTICLE SYSTEMS FOR BRAIN GENE THERAPY

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Program at a Glance

8:45 AM Opening & Introduction

Dr. Evelyn Stewart

9:00 AM BB&D Research Day Keynote & BCCHR Hot Topics in Research Seminar Speaker

Dr. Daniel Pine

"Advancing Psychiatric Care through Clinical Neuroscience: Lessons from Research on Anxiety"

10:00 AM Townhall for BB&D PI's

- *A separate zoom meeting link has been sent to all BB&D PIs. Please contact bb&d@bcchr.ca if you do not have the link.*
- Other attendees are encouraged to browse the e-Poster gallery during this time

11:00 AM Lightning Talks

1. Jennifer Coelho, Psychologist, Provincial Specialized Eating Disorders Program for Children & Adolescents
"Why is it hard to love yourself? The role of self-compassion and fear of self-compassion in predicting eating pathology and psychological distress"

2. Hilal Al-Shekaili, Postdoctoral Fellow | Leavitt Research Team
"Using a mouse model to understand the pathogenesis and improve the cognitive deficits in children affected with pyridoxine-dependent epilepsy due to antiquitin deficiency"

3. Clara Westwell-Roper, PGY3/4 Resident | Stewart Research Team
"*Salivary biomarkers in childhood-onset obsessive compulsive disorder: Preliminary analyses of pro-inflammatory cytokines*"

~~**4. Mia Mclean,** Postdoctoral Fellow | Grunau Research Team~~
~~*"Early life stress is related to neonatal structural brain subnetworks and internalizing behaviours at 4 years"*~~

Speaker is unable to present at the Research Day but is scheduled for the next BB&D Research-in-Progress seminar on Wed, Feb 3, 12-1pm

5. Olivia Campbell, Co-op Student | Weber Research Team
"Fractal-based analysis of movie watching vs. eyes-open resting state reveals widespread differences in fMRI signal complexity"

11:30 AM Poster Session, Vote for Best Posters & Lightning Talk

12:45 PM Awards & Closing

Keynote Speaker
Hot Topics in Research

DR. DANNY PINE, MD

Chief, Emotion and Development Branch, National Institute of Mental Health Intramural Research Program

"Advancing Psychiatric Care through Clinical Neuroscience: Lessons from Research on Anxiety"

Dr. Daniel Pine is Chief, Emotion and Development Branch in the National Institute of Mental Health Intramural Research Program. Dr. Pine moved to this position in 2000, after 10 years of training, teaching, and research at Columbia University. Since graduating from medical school at the University of Chicago, Dr. Pine has been engaged continuously in research on pediatric mental disorders, as reflected in more than 600 peer-reviewed papers. Currently, his group examines the degree to which pediatric mood and anxiety disorders are associated with perturbed neural circuitry function.

Dr. Pine served as the Chair of the Psychopharmacologic Drug Advisory Committee for the Food and Drug Administration, Chair of the Child and Adolescent Disorders Work Group for the DSM-5 Task Force, and President of the Society of Biological Psychiatry. He is a member of the National Academy of Medicine, a Distinguished Investigator indicating stature as among the 1-2% most impactful National Institute of Health intramural scientists and has received many other awards.

Learning Objectives

This presentation will begin with a review of the complexities that challenge attempts to integrate neuroscience and clinical data. The presentation will introduce pediatric anxiety disorders as an area where these challenges might be met. The presentation will then provide two examples where research addresses clinically-relevant questions. In the first example, novel therapy will be described. In the second example, a developmental aspect of anxiety disorders will be described. Both examples provide novel insights on the ways in which neuroscience can address clinically-relevant questions.

Objective	Content
Understand the types of data that inform translational neuroscience research	Research on RDoC, executive function, and neuroscience will be reviewed
Understand how attention relates to anxiety	Research on biases in attention will be reviewed
Understand how appraisals of emotion changes with development	Research on memory as it relates to appraisal will be reviewed

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Abstracts: LIGHTNING TALK

Jennifer Coelho, Dzung Vo

SELF-COMPASSION AND PSYCHOLOGICAL RESILIENCE IN INDIVIDUALS WITH EATING-RELATED CONCERNS

This project examines the role of self-compassion on eating pathology in youth.

Study 1 will examine self-compassion and fear of self-compassion as predictors of treatment outcome in youth with eating disorders.

Study 2 will explore the interaction between self-compassion, psychological well-being and use of social media in a community sample of youth. The results of the project are expected to inform how self-compassion protects against the development and exacerbation of eating and body image concerns.

Lightning Talk

Hilal Al-Shekaili, Terri Petkau, Izabella Pena, Tess Lengyell, Nanda Verhoeven-Duif, Jolita Ciapaite, Marjolein Bosma, Martijn van Faassen, Ido Kema, Gabriella Horvath, Colin Ross, Elizabeth Simpson, Jan Friedman, Clara van Karnebeek, Blair Leavitt

A NOVEL MOUSE MODEL FOR PYRIDOXINE-DEPENDENT EPILEPSY DUE TO ALDH7A1 DEFICIENCY

SUPERVISOR: Blair Leavitt

Pyridoxine-dependent epilepsy (PDE) is a rare autosomal recessive disease caused by mutations in the ALDH7A1 gene which codes for an enzyme that functions within the cerebral lysine catabolism pathway. PDE is characterized by recurrent seizures that are resistant to conventional anticonvulsant treatment but are well-controlled by pyridoxine (PN). Most PDE patients also suffer from neurodevelopmental deficits despite adequate seizure control with PN.

To investigate potential pathophysiological mechanisms associated with ALDH7A1 deficiency, we generated a transgenic mouse strain with constitutive genetic ablation of Aldh7a1. We undertook extensive biochemical characterization of Aldh7a1-knockout (KO) mice consuming a low lysine/high PN diet.

Results showed that KO mice accumulated high concentrations of upstream lysine metabolites including Δ1-piperideine-6-carboxylic acid (P6C), α-aminoadipic semialdehyde (α-AASA), and pipecolic acid (PIP) both in brain and liver tissues along with a widely deranged amino acid profile, accurately recapitulating the biochemical picture in ALDH7A1-deficient patients. We also observed preliminary evidence of novel pathobiochemical mechanisms including increased levels of methionine sulfoxide, an oxidative stress biomarker, and saccharopine, a lysine metabolite of known cellular toxicity, in the brains of KO mice. KO mice lacked epileptic seizures when fed a low lysine/high PN diet. Switching mice to a high lysine/low PN diet led to vigorous seizures and a quick death in KO mice. Treatment with PN controlled seizures and improved survival of high-lysine/low PN fed KO mice.

This study expands the spectrum of biochemical abnormalities that may be associated with ALDH7A1 deficiency and provides a proof-of-concept for the utility of the model to study PDE pathophysiology and to test new therapeutics.

Lightning Talk

Clara Westwell-Roper, Zainab Naqqash, Antony Au, Boyee Lin, Cynthia Lu, Li Shao, Clare Beasley, Evelyn Stewart

SALIVARY BIOMARKERS IN CHILDHOOD-ONSET OBSESSIVE COMPULSIVE DISORDER: PRELIMINARY ANALYSES OF PRO-INFLAMMATORY CYTOKINES

SUPERVISOR: **Evelyn Stewart**

Background/Objectives: Previous studies suggest an association between obsessive-compulsive disorder (OCD) and immune dysregulation. Saliva may provide a minimally-invasive tool for assessing mucosal immunity and neuroendocrine-immune interactions in psychiatric disorders. This study will compare inflammatory mediators in saliva from participants with childhood-onset OCD and healthy controls and evaluate their associations with OCD phenotype.

Methods: Saliva was collected from 42 children and youth attending the BCCH Provincial OCD Program and 52 controls. All participants completed an oral health survey and medical questionnaire. Clinician-rated OCD severity was assessed with the Child Yale-Brown Obsessive Compulsive Scale. C-reactive protein (CRP) and selected pro-inflammatory cytokines were measured by multiplex immunoassay in the first 20 patient samples and age-matched controls.

Results: Tumour necrosis factor-α (TNF-α), interleukin-1β (IL 1β), IL-6, IL-8, and CRP were detectable in saliva. There were significant bivariate correlations among all cytokines ($rs=0.671$-0.748, $p<0.0005$ for all). Analyte concentrations were higher in participants who were younger and female. Fewer participants with OCD flossed daily compared to controls (41% versus 90%; $n=61$, $p<0.0005$). Linear regression models including age, gender, oral health measures, and OCD severity explained a large proportion of the variance in IL-6 (63%, $p=0.002$), IL-1β (46%, $p=0.059$), and TNF-α (37%, $p=0.015$). Use of braces or a retainer and presence of severe OCD were significant predictors for levels of all three salivary cytokines.

Conclusions: These data point to the feasibility of analyzing soluble immune mediators in the saliva of children and youth with OCD. Disease- or stress-associated salivary changes may ultimately aid in identifying subgroups for prognostic or treatment purposes. Because this fluid reflects both systemic and local mucosal factors, evaluation of oral health is essential. Additional proteomic profiling is ongoing.

Lightning Talk

Mia McLean, Cecil Chau, Lynne Williams, Colin Brown, Ghassan Hamarneh, Joanne Weinberg, Anne Synes, Steven Miller, Ruth Grunau

(WITHDRAWN) EARLY-LIFE STRESS IS RELATED TO NEONATAL STRUCTURAL BRAIN SUBNETWORKS AND INTERNALIZING BEHAVIORS AT 4 YEARS

SUPERVISOR: Ruth Grunau

INTRODUCTION: Internalizing behaviors (anxiety, depressive symptoms) are prevalent in children born very preterm (≤ 32 weeks gestation). Across a period of rapid neurodevelopment, these neonates are vulnerable to procedural pain/stress during hospitalization. Neonatal pain/stress is associated with regionally-specific neonatal brain microstructure alterations, hypothalamic-pituitary-adrenal (HPA) axis functioning (cortisol), and internalizing behaviors in childhood. The interplay between early pain/stress, structural brain organisation, and cortisol dysregulation in relation to internalizing behaviors has not been studied.

HYPOTHESES: 1. Greater NICU pain-related stress will be related to neonatal structural network alterations, beyond clinical factors associated with prematurity 2. Structural brain organisation will be related to child internalizing behaviors at 4 years 3. Cortisol levels age 4 will moderate relationships between structural brain networks and internalizing behaviors.

STUDY POPULATION: N=49 infants born very preterm recruited from the BC Women's Hospital Level III Neonatal Intensive Care Unit (NICU) with neuroimaging (MRI/DTI) at term-equivalent age and developmental assessments at 4 years. Exclusions: major impairment or IQ <70. Food/drink or medication affecting cortisol.

METHODS: Neonatal chart review (e.g. pain/stress [number of invasive procedures], illness severity, infection). Whole-brain connectivity networks using DTI at term (MRI). At age 4-years 3 saliva samples across cognitive assessment were assayed for cortisol and parents completed Child Behavior Checklist (CBCL 1½-5).

RESULTS: In progress.

IMPLICATIONS FOR BB&D THEME: This study will advance understanding of the effects of early life stress on brain circuitry during a critical developmental window of early life, and how such alterations impact internalizing behaviors, considering the role of neuroendocrine stress regulation.

Lightning Talk

Olivia Campbell, Tamara Vanderwal, Alexander Weber

FRACTAL-BASED ANALYSIS OF MOVIE WATCHING VS. EYES-OPEN RESTING STATE REVEALS WIDESPREAD DIFFERENCES IN FMRI SIGNAL COMPLEXITY

SUPERVISOR: Alexander Weber

Introduction: It has been suggested that the conventional functional magnetic resonance imaging (fMRI) resting-state condition, fixating on cross-hairs, does not capture the natural state of the brain. However, a continuous and ecologically valid stimulus, such as a movie, may better reflect this endogenous state.

Hypothesis: As measured by the Hurst exponent (H), movie-watching, compared to rest, will reveal more persistent fractal (scale-invariant) phenomena in whole-brain greymatter, visual network, and default-mode-network (DMN), reflecting a more natural brain state. **Study**

Population: 7T fMRI data (TR=1ms) from 55 subjects (ages=22-35; mean 29.33 years; 20M/35F) was downloaded from the Human Connectome Project (https://www.humanconnectome.org/). Each subject was scanned: with eyes fixed on a cross-hair ("Rest": ~10mins), and viewing a short film ("Movie": ~10mins).

Methods: Fractal analysis (Welch's Method) was performed. H values were compared with a Paired Student's T-Test between the two paradigms in three regions-of-interest: whole-brain greymatter, a combined visual network, and the DMN.

Results: Compared to Rest, Movie expressed more persistent fractal scaling behaviour in all three regions analyzed: whole-brain greymatter (adj_p.=0.014, Cohen's_D=0.34), DMN (adj_p.=2.55x10-8, Cohen's_D=0.90), and visual network (adj_p.=6.44x10-10, Cohen's_D=1.05). The effect size is small in the greymatter, and large in the DMN and visual network.

Implications for BB&D Theme: This study provides evidence for the use of: 1) movie-viewing to better capture the brain's natural state; and 2) fractal-analysis to reveal and quantify inherent brain dynamics. This may be extremely valuable in experimental and clinical settings, where deviations in H values from a network's endogenous state can reflect enhanced or impaired functioning.

Lightning Talk

Abstracts: INVESTIGATOR & RESEARCH STAFF

Nichole Fairbrother, Fanie Collardeau, Sheila Woody, David Wolfe, Cora Keeney

(WITHDRAWN) POSTPARTUM THOUGHTS OF INFANT-RELATED HARM AND OBSESSIVE-COMPULSIVE DISORDER: RELATION TO MATERNAL PHYSICAL AGGRESSION TOWARDS THE INFANT

Introduction: Unwanted intrusive thoughts (i.e., thoughts, images and impulses; UITs) of harm coming to one's infant are a common postpartum experience, with UITs of accidental harm reported by most, if not all, new mothers, and UITs of intentional harm reported by approximately one half. UITs of infant-related harm are also a core characteristic of postpartum OCD. Nonetheless, little is known about whether women who experience UITs of infant-related harm (in particular UITs of harming one's infant on purpose) are more likely to behave violently towards their infant compared with those who do not. This purpose of this research was to investigate the relationship between new mothers' UITs of intentional infant-related harm with physical aggression towards the infant.

Hypotheses: We hypothesized that women who report UITs of intentional harm will be no more likely to behave violently towards their infant compared with women who report UITs of accidental harm only. Study Population: English-speaking, pregnant women, aged 19+, and living in British Columbia were eligible to participate (N = 34).

Methods: Interviews to assess postpartum harm thoughts and OCD diagnostic status were administered at approximately 9 and 21 weeks postpartum. Questionnaires were completed at approximately 7 and 25 weeks postpartum, and included assessment of child harming behavior.

Results: Overall, few (2.8%; 95% CI 1.5-5.2) of participants reported behaving aggressively towards their infant. Participants who reported UITs of intentional, infant-related harm (44.4%) were not more likely to report aggression toward their newborn, compared with women who did not report this ideation: 2.7% [95% CI 0.9-7.1] and 3.2% [95% CI 1.3-7.1] respectively. The same was true for women with and without OCD: 1.6% [95% CI 0.1-9.5] and 3.6% [95% CI 2.0-6.7] respectively.

Implications for BB&D Theme: The findings from this study provide critical and reassuring information regarding the relation between new mothers' UITs of intentional harm and the risk of physical violence towards the infant.

Investigator

Robert Stowe, Guillaume Poirier-Morency, Sanja Rogic, Adrienne Elbert, Kennedy Borle, Ashley DeGraaf, Prescilla Carrion, Pedram Laghaei*

METABOLIC AND GENETIC EXPLORATIONS IN REFRACTORY SCHIZOPHRENIA PROJECT: FINDINGS FROM WHOLE GENOME AND RNA SEQUENCING IN THE FIRST 10 PARTICIPANTS.

Introduction: We aimed to identify candidate genetic drivers of psychosis using whole genome and RNA sequencing and intensive genotype-phenotype correlation.

Hypotheses: Whole genome sequencing (WGS) will identify rare genomic variants relevant to the neurobiology of psychosis

Study Population: 10 deeply phenotyped participants with highly treatment-resistant schizophrenia or schizoaffective disorder

Method: Genomic DNA (gDNA) and whole blood RNA was sequenced at BC's Genome Sciences Centre. Variants were filtered and prioritized using a customized Michael Smith Labs pipeline. After QC, variants were prioritized by pathogenicity prediction, allele frequency and conservation; reviewed in the IGV in association with RNA-Seq data; and manually curated using databases (e.g. SCHEMA, Varsome, SZGR2, OMIM, UniProt) and literature review. RNA-seq data and phasing from linked-read WGS sequencing enabled identification of allelic expression imbalances. Missense mutations mapping to intrinsically disordered protein regions were analyzed for predicted binding to functional domains of their interaction partners. 5.

Results: Participants harbored between 12 and 42 prioritized sequence variants (mean ~19.5). 15 loss-of-function (LoF) mutations impacted genes including SETD1A (the schizophrenia risk gene most significantly enriched in LoF variants to date), the neurodevelopmental risk gene FOXP1, and ATP7B (heterozygous; biallelic ATP7B mutations cause Wilson's disease). Protein-altering variants were found in many mutation-intolerant genes relevant to the neurobiology of schizophrenia, including MDGA1, GGA1, GRK2, KCNV1, LPHN1, NCDN, and PI4KA. 6.

Implications for BB&D Theme: While individually rare, as a class, potentially potent genomic drivers of psychosis are not uncommon in individuals with extreme phenotypes and may pinpoint tractable treatment targets.

**Jessica Jun, Michelle Lisonek, Natasha Verzosa, Olga Leonovo, Clara Westwell-Roper, Clare Beasley, Mahesh Menon, Ivan Torres, Jennifer Li, Harish Neelekant, Veerle Willaeys, Randall White, Eric wong, Joerg Gsponer, Willian Honer, Andrew J. Mungall, Monica Hrynchak, Agata Minor, Christine Tyson, Patrick Macleod, Patrick Sullivan, Paul Pavlidis*

Investigator

Jennifer Coelho, Rachelle Pullmer, Shannon Zaitsoff

BODY CHECKING IN YOUTH: ASSOCIATION WITH EATING PATHOLOGY

Background. Eating disorders (EDs) involve unhealthy eating behaviours and attitudes, such as food restriction, binge-eating, and over-emphasis on body weight and shape. Frequently checking one's body shape and weight (e.g., via frequent weighing, scrutinizing body parts in mirrors, checking clothes for fit, and measuring body parts) is believed to perpetuate these maladaptive patterns of eating and over-evaluation of shape and weight. However, it is not clear whether body checking precedes the development of eating pathology.

Hypotheses. We expected a reciprocal relationship between body checking and eating pathology. Study Population. We investigated body checking and eating behaviours in high school students (n=104 males and n=134 females) over a 4-month period.

Methods. Adolescents provided informed consent, and completed questionnaires assessing body checking and eating disorder symptoms at baseline and approximately 4 months later. Hierarchical linear regressions were performed to assess the relationship between body checking and eating symptomatology.

Results. Body checking predicted increases in eating pathology for both males and females. In contrast, eating pathology predicted increased body checking behavior for males, but not females. Body checking appears to be a risk factor for the development of eating pathology. Implications. Assessment of body checking behaviours, in addition to eating behaviour, can provide insight into eating disorder symptomatology. These findings support cognitive-behavioural models of eating disorders, yet suggest divergent relationships across males and females. This study adds to research conducted by our group (Coelho et al., 2019) relating to the role of body checking in etiological models for eating disorders and obsessive-compulsive disorder.

Investigator

Jessica Khangura, Sofia Eickhoff, Linda Chen, Nicole Sanford, Todd Woodward

ANALYSIS OF BRAIN NETWORKS EVOKED DURING A LANGUAGE PROCESSING TASK IN SCHIZOPHRENIA PATIENTS

SUPERVISOR: Todd Woodward

Introduction and Study Population: Schizophrenia is characterized by extensive cognitive dysfunction. The functional brain networks underlying the thought generation task (TGT) are examined and compared between schizophrenia patients (n=29) and healthy controls (n=32).

Hypothesis: Schizophrenia patients should exhibit abnormal activity in task-evoked brain networks.

Methods: During the TGT participants were presented with a noun and its respective image, and asked to listen to a definition or mentally generate a definition. Functional brain networks were extracted using Constrained Principal Component Analysis for fMRI. Component loadings were classified by correlating positive and negative loadings in select brain slices with previously established prototype brain networks. Analysis of estimated hemodynamic response was performed using ANOVA.

Results: Functional brain networks retrieved include: response (RESP), focus on visual features (FVF), default-mode (DMN), cognitive evaluation (CEN) and primary auditory networks (AUD). While no significant differences were observed between the groups, patterns emerged in the FVF, CEN and AUD when averaged over groups. Specifically, the FVF and CEN displayed greater activity in both groups during the generating (inner speech) condition compared to the hearing (external speech-perception) condition. Contrarily, the AUD displayed greater activity during the hearing (external speech-perception) condition. FVF and AUD peaked at 7seconds while the CEN peaked later between 8-9seconds.

Implications: These results provide new information about functional interpretations of brain networks. We confirmed that (1) sensory-based (FVF and AUD) networks peak early in the trial, and are differentially sensitive to their respective sensory demands, and (2) the internal-thought-based network (CEN) peaks later, and is thought to be involved in reflecting on performance. Comparing the functionality of task-evoked brain networks allows for a greater understanding of fMRI-detectable cognitive super-processes.

Other (Staff)

Chantal Percival, Todd Woodward

CHARACTERIZATION OF A NOVEL TASK-BASED FMRI FUNCTIONAL BRAIN NETWORK: FOCUS ON VISUAL FEATURES

Introduction: Task-based fMRI can detect a limited number of cognitive super-processes, each with their own brain configuration. This cross-task comparison examines the function of the focus on visual features (FVF) functional brain network, identified in multiple previously analyzed datasets. FVF displays activation in the medial occipital and parietal cortex, with reciprocal suppression in the lateral occipital cortex.

Hypothesis: FVF network activates when attending to visual stimuli, but deactivates below baseline when this focus is not beneficial.

Study Population: Participants included 185 controls and 24 bipolar patients across five separate task-based fMRI studies.

Methods: Functional brain networks were extracted with 9constrained principal component analysis for fMRI (fMRI-CPCA). FVF networks were identified by characteristic activation and suppression patterns, and voxel-wise region-specific correlation with previously identified FVF networks. Corresponding estimated hemodynamic responses were examined across conditions to test the cognitive super-function associated with FVF.

Results: FVF activation occurred upon hearing and generating word and image definitions, distracter image presentation, and a Raven's Progressive Matrices test. FVF suppression occurred throughout a working memory task, when determining if presented letters form words, and in word incongruent conditions of a Stroop task.

Implications: Results suggest that the FVF network activates both when intensive attention to visual stimuli is required, and in the presence of an image. FVF deactivates below baseline when this focus is not beneficial, such as the requirement to focus on semantic meaning of words or encoding and maintaining in working memory. This research consolidates one of the cognitive super-processes detected by fMRI.

Other (Staff)

Abstracts: DOCTORAL STUDENTS & POST-DOCTORAL FELLOWS

Robert Selles, Zainab Naqqash, John Best, Evelyn Stewart

INTENSIVE COGNITIVE BEHAVIORAL TREATMENT FOR YOUTH WITH OBSESSION COMPULSIVE DISORDER: IDENTIFYING OPTIMAL SETTING AND DOSE

SUPERVISOR: Evelyn Stewart

Introduction: Cognitive behavioral therapy (CBT) is a well-established treatment for pediatric OCD; however, efforts to optimize individual outcomes remains a priority.

Hypotheses: The present study hypothesized that: 1) intensive CBT would be associated with significant improvements in OCD symptoms and functioning; 2) families would utilize differing levels of service in order to achieve benefits; and 3) providing treatment within home settings would enhance outcomes.

Study Population: The study included 23-OCD affected youth (7-19 years old) and their families.

Methods: Youth were randomized to receive treatment at the hospital (n = 11) or within their home (n = 12). All youth received 3x3 hour treatment sessions in Phase I, following which they could receive up to four additional 3-hour sessions in Phase II. All youth were evaluated 1-month following their last session. Primary outcomes include session utilization, measures of OCD-severity and impairment, and satisfaction.

Results: At follow-up, 70% of youth (n = 16) were treatment responders (> 35% reduction in symptoms), with 35% (n = 8) in remission (> 55% reduction). Families utilized an average of 5 sessions, with 22% of families (n = 5) utilizing the minimal dose and 39% (n = 9) using all 7 sessions. Session utilization was comparable across setting. The home condition demonstrated small advatanges in reducing impairment and satisfaction.

Implications for BB&D Theme: Intensive CBT is a feasible and efficacious treatment format. Flexibility in treatment dosing optimizes the level of care to individual families while conserving resources. Incorporating home-based sessions appears to offer additional benefits.

Post-Doctoral

Katelynn Boerner, Melissa Glier, Ursula Brain, Amrit Dhariwal, Ruth Grunau, Tim Oberlander

THE ROLE OF PRENATAL EXPOSURE TO SEROTONIN REUPTAKE INHIBITOR ANTIDEPRESSANTS, CHILD SEX, AND SEROTONIN-RELATED GENOTYPE ON PAIN-RELATED SOMATIC SYMPTOMS AND GLOBAL PHYSICAL HEALTH IN YOUNG CHILDREN

SUPERVISOR: Tim Oberlander

Introduction: Somatic symptoms and poor health in childhood may be a precursor to the emergence of chronic pain in later stages of development. Little is known about what early life factors predisposes certain children to develop symptoms. The present study investigated the impact of prenatal exposure to serotonin reuptake inhibitor (SRI) antidepressants on childhood somatic symptoms and global physical health.

Hypotheses: As sex-specific effects of prenatal exposures have been described in a number of areas relevant to child health, we expected a greater impact of SRI exposure in girls.

Study Population: A longitudinal cohort of women followed from pregnancy and their children.

Methods: Analysis of variance was used to examine the effects of prenatal exposure to SRIs, variations in serotonin levels associated with the serotonin transporter gene polymorphism (5-HTTLPR), and child sex on child health outcomes at 3 (n=143) and 6 (n=107) years.

Results: At 3 years, more somatic symptoms were reported amongst children exposed prenatally to SRIs compared to non-exposed children (p=.016, ηp2=.043). At 6 years, SRI-exposed girls were reported to have worse health than non-exposed girls (p=.014, ηp2=.105), while no difference was observed for boys. Additionally, SRI exposed children with the S or LG genotype (lower levels of 5HTT transcription), were reported to have worse health compared with non-exposed (p=.012, ηp2 =.080), while no difference was observed based on SRI exposure for children with the LALA genotype.

Implications for BB&D Theme: These findings further our understanding of the emergence of sex differences in children's pain and health concerns.

Post-Doctoral

Helena Biasibetti Brendler, Cheryl Tan, Kristin Hamre, Dan Goldowitz

PRENATAL ALCOHOL EXPOSURE IN BXD EMBRYONIC MICE INDUCES HISTONE AND APOPTOSIS-RELATED CHROMATIN CHANGES IN A STRAIN-DEPENDENT MANNER

SUPERVISOR: **Michael Kobor**

Prenatal alcohol exposure (PAE) has been linked to brain development alterations leading to lasting physiological and behavioural outcomes. Moreover, ethanol has been shown to alter the epigenetic landscape following PAE at later developmental stages.

Here we examined histone modifications and DNA damage mark in the brain of B6 (high susceptibility) and BXD60 (low susceptibility) mice exposed to an ethanol challenge on embryonic day (E) 9.5. Females were mated with the males of the same genotype with the day of conception termed E0. Two groups of mice were exposed via gavage: 1) ethanol treated given a total of 5.8 g/kg ethanol in 2 equal doses or 2) controls given isocaloric and isovolumetric maltose-dextrin. Mice were sacrificed 7 hours after the first exposure. Histone modifications H3K9ac, H3K27ac, H3K27me2, H3K27me3 as well as γH2AX (DNA damage marker) were analysed by Western blot.

We found that prenatal ethanol exposure significantly increased the levels of di and tri methylation at H3K27 in the B6 embryos only. Furthermore, there was an increase in the levels of γH2AX in the B6 strain indicating that prenatal ethanol exposure may impact double-strand DNA breaks. These results are consistent with those found using immunocytochemistry.

Together, these findings demonstrate that the levels of ethanol-induced effects on the expression of epigenetic marks occur in a strain-dependent manner and highlight the role of genetics in the epigenetic response to PAE. These results provide new insights into the epigenetic landscape underlying ethanol-induced changes in the developing brain.

Doctoral

Sara Dada

INTEGRATION OF GENOMIC AND PHENOMIC DATA FOR PRECISION DIAGNOSIS AND TREATMENT WITHIN AUTISM SPECTRUM DISORDER

SUPERVISOR: Steven Jones, Suzanne Lewis

Autism Spectrum Disorder (ASD) is the most common childhood developmental disability, affecting 1 in 58 Canadian school-aged children. ASD is defined by deficits in communication and relationship interactions, as well as restricted and repetitive behaviours. Although it is known that early intervention substantially improves patient outcome, oftentimes children are not diagnosed until 3-4 years of age. Alongside the emotional and social burden on the individual and their family, the financial burden upon the Canadian healthcare system is substantial, averaging 5-8 million dollars per person's lifetime.

ASD diagnosis is complex, derived from the presence of a highly variable pattern of behavioural and developmental symptoms. Co-morbidities, including seizures and intellectual disability can occur as clusters of symptoms, suggesting syndromic relationships to each other and ASD. These symptoms are representative of an underlying genetic or environmentally associated developmental abnormality in the embryo.

This project aims to integrate genotypic (common and rare genetic changes) and phenotypic (symptom-based) data to improve diagnosis and treatment of persons with ASD. I will identify common and rare genetic variants in the ASD population for an initial cohort of 500 patients and their parents (n=1418 subjects) using Whole Genome Sequencing (WGS) data. I will integrate this with phenotypic data that has been clustered based on ASD symptoms and co-morbidities.

This project will increase the clinical utility of WGS results by providing a stable and defined ASD view of the patient; this will allow us to provide an individualized and cost-effective treatment in an anticipatory, rather than a reactive way.

Doctoral

Sarah Thomson, Jayesh Kulkarni, Terri Petkau, Pieter Cullis, Blair Leavitt

DESIGN OF LIPID NANOPARTICLE SYSTEMS FOR BRAIN GENE THERAPY

SUPERVISOR: **Blair Leavitt**

INTRODUCTION: The majority of genetic neurological diseases are caused by toxic gain-of-function of a mutant protein or loss-of-function of a wild-type protein. The treatment of these disorders, either by knockdown of gene products or by gene replacement therapy, is a viable strategy provided gene therapy agents can be delivered to the affected cells and regions of the central nervous system. Many current approaches to brain gene therapy are limited by functionality, potency, and safety, leaving ample opportunity for innovation of gene therapy drugs.

HYPOTHESES: Lipid nanoparticle (LNP)-mediated gene therapy, enabled by the same technology as the first Health Canada-approved COVID-19 vaccine, is a promising alternative approach for the treatment of genetic brain diseases. The safety of LNP systems is well-established, and neurons, the primary cells of interest in the brain, are highly amenable to transfection by LNPs. We hypothesize that LNP systems can be designed and optimized to efficiently deliver gene therapy agents to neurons.

STUDY POPULATION: Not applicable (animal study data).

METHODS: We developed a screening strategy to evaluate LNP formulations of nucleic acid in vitro using primary cortical neurons. This iterative approach utilizes a reporter system to identify optimal formulation parameters while minimizing disruption of endogenous gene expression.

RESULTS: We demonstrate that LNP-mediated delivery of nucleic acids significantly impacts neuronal reporter gene expression, and show that efficacy and toxicity vary with lipid composition and dose.

IMPLICATIONS FOR BB&D THEME: This work will enable the comparison of LNP-based gene therapy methods to current approaches and support the development of target-specific treatments for genetic brain disease by the BB&D community.

Doctoral

Ben Life, Terri Petkau, Luis Bettio, Brian Christie, Blair Leavitt

INVESTIGATING PROGRANULIN OVEREXPRESSION IN FRAGILE X SYNDROME

SUPERVISOR: Blair Leavitt

Introduction: Fragile X Syndrome (FXS) is the most common cause of heritable intellectual disability and autism, affecting 1 in 4000 males and 1 in 6000 females in Canada. FXS is caused by loss of expression of the protein FMRP, a negative regulator of many brain-expressed transcripts. There are currently no approved therapies for FXS and the specific mechanisms that cause disease remain elusive. Recently, a protein called progranulin was found to be increased in a mouse model of FXS. When progranulin levels were reduced in these mice, FXS-associated phenotypes were ameliorated. However, progranulin's role in FXS remains poorly understood.

Hypotheses: 1) Progranulin expression is upregulated in FXS mice because FMRP is a negative regulator of progranulin translation. 2) Increased progranulin expression during development is sufficient to cause FXS-associated phenotypes.

Methods: To determine if FMRP is a regulator of progranulin translation, we use RNA immunoprecipitation to probe for an interaction between FMRP and progranulin mRNA. To evaluate the role of progranulin overexpression in FXS-associated neurodevelopmental abnormalities, we developed mice that overexpress progranulin without the loss of FMRP expression.

Results: We detected an interaction between FMRP and progranulin mRNA, suggesting that progranulin mRNA is a target of FMRP. Progranulin overexpressing mice recapitulate the hyperactivity of FXS mice but do not exhibit any other FXS-associated behavioural or electrophysiological phenotypes.

Implications for BB&D Theme: This research project seeks to understand the role of progranulin in FXS and determine if progranulin reducing therapies can improve the lives of children with Fragile X Syndrome.

Doctoral

Abstracts: MASTERS STUDENTS

Alexis Dawson, Isaac Rhew, Elizabeth McCauley, Robert McMahon, Ann Vander Stoep

CUMULATIVE BURDEN OF ADOLESCENT PSYCHOPATHOLOGY: YOUNG ADULT OUTCOMES AND MENTAL HEALTH SERVICE UTILIZATION

SUPERVISOR: Robert McMahon

Little research has investigated potential specificity of the effects of different adolescent mental health disorders on young adult outcomes and patterns of mental health service utilization.

We employed data from the Developmental Pathways Project (DPP), a longitudinal study of the development of comorbid depression and conduct disorders. The DPP cohort was recruited from Seattle Public Schools at middle school entry. Utilizing the Diagnostic Interview Schedule for Children, we estimated the cumulative burden of adolescent psychopathology measured across 6th-12th grade.

416 participants were interviewed at age 21 using the Young Adult Milestones Timeline. Logistic regression models showed those with elevated adolescent comorbid psychopathology had a higher likelihood of homelessness in young adulthood ($p<0.001$, OR: 9.34). Youth with elevated ODD/CD symptoms were more likely to be financially self-supporting since the age of 18 ($p<0.01$, OR: 4.99), while both adolescent depression and ODD/CD symptoms were uniquely associated with young adult pregnancy ($p<0.01$, OR: 3.78, $p<0.001$, OR: 4.16). Patterns of mental health service utilization during young adulthood varied across type of adolescent psychopathology. Adolescent depressive symptoms were associated with a higher likelihood of meeting with a mental health professional ($p <0.01$, OR: 3.60), seeing a medical doctor for emotional or behavioral concerns ($p < 0.05$, OR: 4.33), and being in residential treatment or having an inpatient psychiatric hospitalization as a young adult ($p<0.01$, OR: 10.86). Comorbid psychopathology was associated with seeing a medical doctor for emotional or behavioral concerns including at an ER ($p<0.05$, OR: 4.18). Adolescents with elevated ODD/CD symptoms did not experience more service utilization as young adults than adolescents with low psychopathology.

How an adolescent with mental health problems functions in young adulthood depends upon what type of psychopathology the adolescent has experienced. Implications of our findings for how to support vulnerable adolescents as they transition into adult roles will be highlighted.

Masters

Hannah Phillips, Mia McLean, Lynne Williams, Bruce Bjornson, Cecil Chau, Anne Synnes, Steven Miller, Ruth Grunau

EARLY PAIN-STRESS AND ARITHMETIC SKILLS: INVESTIGATING FUNCTIONAL CONNECTIVITY DURING VISUOSPATIAL PROCESSING AT AGE 8 YEARS IN CHILDREN BORN VERY PRETERM

SUPERVISOR: Ruth Grunau

Introduction: Children born very preterm (24-32 weeks gestational age [GA]) are vulnerable to neurodevelopmental problems. Poorer academic performance compared to children born full-term is particularly evident in math skills. Essential care during the neonatal intensive care unit (NICU) stay necessitates exposing neonates to possible pain and stress. Neonatal pain-stress exposure from invasive procedures (~10 per day) is associated with altered brain structure and function in childhood. Deficits in visual-spatial processing are also highly prevalent, and closely related to acquisition of early arithmetic skills.

Hypotheses: Neonatal pain-stress, above and beyond known neonatal risk factors, will be associated with arithmetic skills at school age. Functional brain networks during visual-spatial processing (mental rotation) will relate to both neonatal factors and arithmetic skills.

Study Population: N=103 children born very preterm (GA mean 28±2.4 weeks, 54% boys) in a prospective longitudinal cohort study attended 8-year follow-up (8.3±0.4 years). Excluded: major brain injury (cystic PVL, IVH grade 3/4), visual, hearing, cognitive (IQ<70), motor (non-ambulatory CP) impairments.

Methods: Participants completed a mental rotation task during fMRI at 8-year visit. Arithmetic skills were assessed by experienced psychology staff on the KTEA3. Regression and Partial Least Squares (PLS) analysis will be used. PLS analysis will provide salience maps of activation patterns in the brain during visual-spatial processing.

Results: In progress.

Implications for BB&D Theme: Our findings will contribute to understanding impacts of neonatal clinical factors on altered brain networks at age 8 years in very preterm children, and associations between networks engaging visual-spatial processing in relation to arithmetic skills.

Masters

Lara Bartels, J. Doucette, C. Birkl, Y. Zhang, A. Weber, A. Rauscher

ORIENTATION DEPENDENCY OF T2 IN NEWBORN WHITE MATTER SHOWS DIPOLE-DIPOLE INTERACTION EFFECTS

SUPERVISOR: Alexander Rauscher

Introduction & Hypotheses: In MRI, T2 signal relaxation shows significant dependence on the orientation between ordered tissues and the magnetic field. In adult White Matter (WM), tissue orientation effects on the R2 relaxation are best described by diffusion within field inhomogeneities created by the myelin sheath. It is not clear, however, whether dipole-dipole interaction effects, are absent in brain tissue or whether they are overshadowed by the magnetic susceptibility effects. We hypothesized that in the absence of myelin the orientation dependence of R2 would exhibit a pattern of dipole-dipole interaction. To address this question we measured the R2 orientation dependency in the unmyelinated human newborn brain in vivo.

Study Population & Methods: Eight healthy subjects (gestational age 40.1 pm 1.1 weeks) were scanned at 3T. R2 data were acquired with a 32-echo 3D GRASE sequence (1st TE=10ms, Delta TE=10ms, TR=4300ms). Fiber orientation was mapped with diffusion tensor imaging (DTI).

Results & Implications for BB&D: R2 was plotted as a function of fiber angle pooling voxels according to their orientation. Models of dipole-dipole interaction, diffusion related dephasing and the model of diffusion and field gradients were fitted to R2(angle). We found that the orientation dependency is very different from adults and best described by a model of dipole-dipole interaction. In the absence of myelin, this finding suggests the alignment of water with neurofilaments or microtubuli. Measuring tissue orientation dependent R2 may therefore allow researchers to probe brain development in infants on a microstructure level.

Masters

Yuka Obayashi, Timothy O'Leary

EXAMINING THE ROLE OF H3K4 METHYLATION IN THE HIPPOCAMPAL MEMORY FORMATION AND IN THE PATHOGENESIS OF ALZHEIMER'S DISEASE

SUPERVISOR: **Brad Hoffman**

Introduction: Alzheimer's disease (AD) is the leading cause of dementia affecting 50 million people worldwide. Despite this, how patients lose cognitive abilities is still not clear. We believe a deeper understanding of how hippocampal neurons become dysfunctional is essential to facilitate the development of new strategies to prevent cognitive declines in AD.

Hypotheses: Histone H3 lysine 4 methylation (H3K4me) is required for transcriptional activation of memory-associated genes and subsequent consolidation of hippocampal memory. Moreover, the loss of H3K4 methylation is involved in a pathophysiology of AD.

Methods: We generated a transgenic mouse model with conditional elimination of H3K4me in the post-mitotic excitatory neurons of hippocampus [immunohistochemistry/behavioural studies/single-cell-RNA sequence]. Furthermore, we obtained age- and sex-matched healthy and AD patient brain tissue sections and homogenates from the Douglas Bell Brain Bank [histology/immunoblotting].

Results: The significant reduction of H3K4me appeared in the hippocampal proper by 3 months of age. However, we did not observe abnormalities in the hippocampal morphology and neurogenesis. The knockout mice exhibited several intellectual abnormalities [anxiety-like behaviour/deficits in spatial navigation and recognition memory] with normal locomotory coordination. We observed significant reduction of H3K4me from the hippocampal tissue homogenate of AD donors.

Implications: This study employed a combination of patient samples and rodent disease models to determine if loss of H3K4me affect hippocampal neuronal activities and subsequent memory formation. The successful completion of this research will help extend our understanding of the AD pathogenesis, which may contribute to identifying a novel therapeutic intervention against cognitive decline in patients with AD.

Masters

Laura Chan, Christy Opina, Terri Petkau, Blair Leavitt

DEVELOPMENT OF A CELLULAR ASSAY FOR HUNTINGTIN'S PRO-SURVIVAL FUNCTION

SUPERVISOR: Blair Leavitt

Background: Huntington's disease is caused by the expansion of a CAG trinucleotide repeat within the huntingtin gene. This mutation causes a toxic gain of function in the protein huntingtin. Huntingtin function is required for normal neurodevelopment and huntingtin has pro-survival effects in a number of model systems, but the mechanisms involved are not well understood. Our study aims to develop a cellular assay of huntingtin function utilizing anoikis, a specific form of apoptosis important in oncogenesis. The development of an in vitro model for the pro-survival function of huntingtin will allow us to dissect critical steps involved in this important neurodevelopmental process.

Hypothesis: We hypothesize that altering the pro-survival function of huntingtin will modulate cell death in anoikis. Methods: To assess huntingtin's pro-survival function a human carcinoma cell line was transfected with various huntingtin constructs and anoikis induced. Transfection of huntingtin constructs of varying lengths, with induced mutations, addition of a nuclear localization signal, and the usage of conditioned media from transfected cells were assessed. A human umbilical vein endothelial cell line will be used to reproduce, extend, and validate these previous findings.

Results: A pro-survival effect on anoikis was seen with huntingtin constructs >1955 amino acids, but was decreased by preventing huntingtin phosphorylation, or adding a nuclear localization signal. Conditioned media from huntingtin-transfected cells replicates this effect.

Implications for BB&D Theme: This study has direct implications for huntingtin in neuronal development and will provide novel insights into human neurodevelopmental disorders.

Masters

Erin Klein, Melissa Licari, Skye Barbic, Jill Zwicker

THE IMPACT OF DEVELOPMENTAL COORDINATION DISORDER: PARENT PERSPECTIVES

SUPERVISOR: Jill Zwicker

Introduction: Affecting one in 20 children, developmental coordination disorder (DCD) is a common but under-recognized neurodevelopmental disorder that impedes motor function and interferes with tasks of daily living. There is no standard of care in British Columbia (BC) for diagnosis of and treatment for children with DCD. To advocate for change, it is necessary to understand parents' perspectives of the impact of DCD and the needs of their children.

Hypotheses: We expect that parents will face many barriers to support their child with DCD. We hypothesize that these challenges can have physical, mental, and financial implications for the family.

Study Population: We targeted parents/caregivers in BC whose children were ≤18 years of age, with a confirmed or suspected diagnosis of DCD.

Methods: The impACT for DCD questionnaire was distributed online across the province using convenience, purposive, and snowball sampling. Descriptive data analysis was conducted for close-ended questions, while content analysis was used for open-ended questions.

Results: A total of 244 questionnaires were analyzed. Families reported waiting 1-4 years for a diagnosis. Access to school-based therapy was inconsistent, with 75% choosing to pay out-of-pocket for therapy. Limited educator knowledge of DCD and few classroom supports were reported. Parent-identified priorities include: (1) funded, coordinated, and timely diagnostic services; (2) publically-funded therapy that addresses physical, social, and emotional function; and (4) education of teachers about DCD and classroom support for their children.

Implications for BB&D Theme: Results of this study will support advocacy efforts to improve support and services for children with DCD.

Masters

Abstracts: UNDERGRADUATE & MEDICAL STUDENTS

Alison Lui, Shanlea Gordon, Amrit Dhariwal

THE MIND BODY CONNECTION GROUP: YOUTH AND CAREGIVER PERSPECTIVES ON MULTI-FAMILY GROUP THERAPY FOR YOUTH AFFECTED BY SOMATIZATION

SUPERVISOR: Amrit Dhariwal

Introduction & Hypothesis: Pediatric somatization is a common psychiatric presentation. Psychological treatments showing promise focus on addressing maladaptive cognitions. However, several treatment factors remain unknown, including: the application of care in groups, the role of caregivers in treatment, and the relevance of focusing on emotions. This qualitative study articulates the narratives of youth and their caregivers who attended a multi-family group treatment for adolescent somatization that focuses on emotions, the Mind Body Connection Group (MBCG). We hypothesized that focusing on the role of emotions and the group social connection would help participants better understand and accept the mind-body-connection.

Study Population: 21 post-therapy interviews (10 youth aged 12-17, 11 caregivers) were conducted through purposeful sampling. Participants were recruited as nine youth-caregiver dyads, two single caregivers, and one single youth.

Methods: Participants engaged in a 6-week (once a week) multi-family group therapy focused on educating families about somatization, improving family communication, and exploring the role of emotions. Youth and caregivers were interviewed separately and interviews were transcribed and inductively coded using thematic analysis.

Results: Three themes, expressed by both youth and caregivers, were identified: (1) group therapy provided social connection, (2) including caregivers improved youth-caregiver dynamic and communication, and (3) discussing emotions and providing education helped participants better understand and accept the mind-body-connection.

Implications: Our research suggests multi-family group therapy helps families accept embodied emotions which can support recovery from somatic symptoms. This study lays the groundwork for future quantitative studies evaluating the efficacy of the MBCG in a larger sample.

Undergraduate/Medical Student

Judy Cheng, Chantal Percival

CHARACTERIZATION OF A NOVEL BRAIN NETWORK DERIVED FROM TASK-BASED FUNCTIONAL MAGNETIC RESONANCE IMAGING: AUDITORY ATTENTION FOR RESPONSE

SUPERVISOR: Todd Woodward

Task-based functional magnetic resonance imaging (fMRI) techniques have provided further insight into the reverse inference challenge, which proposes conclusions about active cognitive processes inferred from observation of brain activity. Several prototype task-based functional brain networks have previously been identified by averaging over replicating studies that performed constrained principal component analysis for fMRI. However, the specific cognitive function associated with each network remains undefined.

The current study aimed to characterize the specific functions of the Auditory Attention for Response (AAR) network by comparing hemodynamic response (HDR) patterns across studies where the AAR configuration emerged, including activation in the superior temporal gyrus, supplementary motor area and thalamus. Based on cognitive tasks that revealed engagement of the AAR network, it is hypothesized that the AAR shows activation when an individual attends to auditory sounds and a motor response to a specific auditory stimulus is expected, and that AAR suppression is associated with intensive monitoring of visual details. An example is when an individual that is visually monitoring their phone is less likely to hear what someone else is saying to them.

AAR activation was compared across 6 studies for which its activation has already been identified, and interpretation of the network involved comparing anatomical patterns and HDR plots to determine an interpretation that fits all studies. While the results support the hypothesized function of the AAR, an overlap was revealed between the AAR and the Auditory Attention network, and future studies are needed to tease apart the exact differences between these two networks.

Undergraduate/Medical Student

Helen Hsiao, Todd Woodward

(WITHDRAWN) FMRI ANALYSIS OF FUNCTIONAL BRAIN NETWORKS INVOLVED IN THREE MEMORY TASKS IN HEALTHY INDIVIDUALS

SUPERVISOR: Todd Woodward

Studies have shown that certain processes tend to be specialized to one side of the human brain or the other. However, many of these studies are limited to measurements of cerebral lateralization for a single task, and only examine specific regions in the brain, as opposed to the entire brain. We investigate task-based brain networks and patterns in whole-brain activation in the fMRI Midnight Scanning Club dataset.

We hypothesized that brain networks involved in scene and face memory will demonstrate right hemisphere dominance, and networks involved in language memory will demonstrate left hemisphere dominance.

10 healthy subjects completed three tasks: Memory faces, Memory scenes, and Memory words. In faces, subjects indicated whether the face presented was male or female. For scenes, subjects indicated whether an indoor or outdoor picture was presented. For words, subjects judged whether the word presented was an abstract or concrete noun.

Constrained Principal Component Analysis for fMRI (fMRI-CPCA) was used to determine functional brain networks and associated hemodynamic responses engaged in the memory tasks. Statistical significance was determined with ANOVAs. The four-component hrfmax rotation solution will be classified into brain networks based on differences in estimated HDR, location of anatomical peaks and cluster shapes, and comparison to networks in literature for similar tasks.

This study will improve our understanding of the lateralization of functional brain networks, and contribute to the future use of neuromodulation to increase or decrease activation of brain networks as an intervention to treat brain disorders affecting a certain hemisphere of the brain.

Undergraduate/Medical Student

Zahra Nasseri Moghaddam, Heather MacRitchie, Chieko Chijiwa, Suzanne Lewis

SATISFACTION OF CLINICAL GENETICS PROFESSIONALS WITH TELEHEALTH DURING THE COVID-19 PANDEMIC

SUPERVISOR: Suzanne Lewis

The COVID-19 pandemic has affected clinical genetics services significantly. Clinical genetics professionals have had to rely on telehealth to provide over-the-phone or virtual (e.g. Zoom for Health) genetic counselling services. Research regarding the impact of telehealth has focused primarily on issues such as accessibility, patient satisfaction, and patient demographics.

This investigation aims to focus on a less explored topic within this discourse, which is the overall satisfaction of clinical genetics professionals with telehealth and whether this method of service delivery should be used more frequently, particularly for initial appointments. Qualitative data will be obtained by conducting virtual interviews with experienced clinical genetics counsellors and medical geneticists, who practice at the Autism Integrated Medical Services (AIMS) clinic in Richmond, BC, and/or the Provincial Medical Genetics Program (PMGP) at B.C. Children's and Women's Health Center in Vancouver, BC.

Our hypothesis is that there is a general trend towards increased satisfaction, efficiency and productivity. Interview questions have been selected based on relevance, importance and the depth of information that they will reveal. Further structured interviews and feedback will be collected in January, eight months into providing regular telephone consults due to the pandemic. All participants will have a chance to review the questions prior to the interview for a more in-depth reflection.

This preliminary study will highlight all noted strengths, challenges, and potential implications of remote clinical genetics appointments as compared to in-person appointments. Findings of this study can aid in determining the best method to deliver clinical genetics services to patients and ultimately improve their clinical management.

Undergraduate/Medical Student

Emma Karwandy, Kristina Calli, Chieko Chijiwa, Ying Qiao, Angela Cullen, Suzanne Lewis

INVESTIGATION OF VARIANTS IN NON-CODING REGIONS THAT MAY INFLUENCE LINGO2 GENE EXPRESSION IN A FAMILY WITH AUTISM SPECTRUM DISORDER.

SUPERVISOR: Suzanne Lewis

Autism Spectrum Disorder (ASD) is marked by deficits in social-communication skills and atypical behaviours and development. It is commonly accepted that genetic factors can contribute to the presentation of ASD; however, genetic etiologies are not determined for a majority of patients.

Our subject presents with ASD, Intellectual Disability (ID), Epilepsy and deficits in expressive language. Chromosomal Microarray (CMA) detected a maternally inherited copy loss at 9p21.1 of uncertain clinical significance that overlaps with the LINGO2 gene. LINGO2 encodes for a transmembrane protein in neuronal tissue, and while the function remains largely unknown, it has been suggested that this gene is involved in the regulation of neurite outgrowth based on its homology to LINGO1 and results from mouse studies. Mutations in the LINGO2 gene have been associated with severe autism and intellectual disability (ID), as seen in our proband, as well as neurodegenerative diseases such as Parkinson's disease (PD) and Essential Tremor (ET), indicating a possible link between the subject's mutation and phenotype. Whole exome sequencing (WES) performed through Blueprint Genetics did not identify any single nucleotide variants associated with the participant's ASD phenotype. Recent studies have highlighted the importance of non-coding regions on gene regulation concerning ASD, and specifically for LINGO2.

We hypothesize that further investigations using Whole Genome Sequencing (WGS) could identify smaller mutations in non-coding regions that may impact the altered expression of LINGO2 in the proband resulting in the subjects' ASD/ID phenotype, yet incomplete expression and penetrance in neuro-typical carrier members of this family.

Undergraduate/Medical Student

Catherine Hsu, Li Shao

DIFFERING LEVELS OF UBIQUITYLATED PROTEINS AND UBIQUITIN GENE EXPRESSION IN THE PREFRONTAL CORTEX IN SCHIZOPHRENIA AND BIPOLAR DISORDER

SUPERVISOR: Clare Beasley

Introduction: Ubiquitylation is a post-translational modification in which one or more ubiquitin molecules are covalently attached to lysine residues on the substrate protein. Ubiquitylation orchestrates targeted degradation of proteins as part of the ubiquitin-proteasome system (UPS) but can also exert proteasome-independent effects, including regulation of endocytosis, inflammation, signal transduction and DNA repair. As such, dysregulation of ubiquitylation is well placed to link the disparate cellular and molecular abnormalities previously reported in schizophrenia (SCZ). Evidence for the involvement of ubiquitin in SCZ comes in part from transcriptomic studies that have identified the UPS as one of the top canonical pathways associated with this disorder. Additional targeted investigation at the gene and protein levels may help elucidate the role of ubiquitylation in SCZ. In this study we quantified mRNA expression of genes that encode ubiquitin or polyubiquitin precursors, levels of free ubiquitin protein and presence of K48- (proteolytic) and K63- (non-proteolytic) linked polyubiquitin chains in postmortem brain tissue from SCZ, bipolar disorder (BD) and control subjects.

Methods: Postmortem dorsolateral prefrontal cortex from 104 subjects (35 control, 35 SCZ, 34 BD) was obtained from the Stanley Medical Research Institute. Levels of free ubiquitin and K48 and K63-linked ubiquitin chains were quantified by immunoblotting. Gene expression of the ubiquitin and polyubiquitin precursors UBA52, UBB and UBC was quantified by qPCR.

Results: UBC gene expression was significantly lower in both SCZ and BD, relative to controls. Immunoreactivity for two K48-linked bands was lower in the BD group. Sex by diagnosis effects were observed for several measures. Psychotropic medications did not significantly impact gene or protein levels.

Conclusions: Our findings of lower UBC expression suggest that protein ubiquitinylation is dysregulated in both SCZ and BD. UBC contributes to maintenance of ubiquitin levels under cellular stress conditions. Further investigation of mechanisms underlying dysregulation of ubiquitylation and the UPS in SCZ may inform the discovery of future therapeutic interventions in this disorder.

Undergraduate/Medical Student