



OCTOBER 4, 2021

6<sup>TH</sup> ANNUAL RESEARCH DAY

BRAIN, BEHAVIOUR & DEVELOPMENT



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

Thank you for joining us!

### E-Poster Gallery

Please visit the [Research Day website](#) to browse the e-posters and audio recordings (gallery sub-page will be available by Wednesday, September 29<sup>th</sup>). In addition to the e-poster gallery, there will be opportunities to speak with the poster presenters via zoom breakout rooms (see poster session schedule on page 2).

### Zoom Meeting Links

#### Town Hall for BB&D PIs (9-10am):

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

#### Research Day (10am-3pm):

<https://ubc.zoom.us/j/66363173668?pwd=UjdLeUZPeGtldENJRWZ5dEtTR2pqdz09>  
Meeting ID: 663 6317 3668 Passcode: 605942

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

### Slido for Q&As & Best Poster and Talk Voting

On October 4<sup>th</sup> go to [www.sli.do](http://www.sli.do) and enter the event code: **BBD**

#### For Q&As

- In Slido, click on the “Q&A” icon and submit your questions during the talk
- The moderator will deliver the submitted questions to the presenter following the talk

#### Vote for the Best Posters & Talk:


- In Slido, Click on the “Polls” icon during the voting period from **11:30am – 1:50pm**
- Fill in the surveys – Pick your favourite trainee lightning talk and favourite posters from each of the three categories: 1.) Post-Doctoral Fellows 2.) Graduate/Medical Students 3.) Undergraduate Students
- Please vote based on the quality of work and contribution to their field

# Poster Session Breakout Room Schedule

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

	1:00PM-1:15PM	1:15PM-1:30PM	1:30PM-1:45PM	1:45PM-2:00PM
<b>ROOM 1</b> Post-Doctorates	<b>Katelynn Boerner- Oberlander Team</b> An Intersectional-Biopsychosocial-Developmental Model for Understanding the Contributions of Sex and Gender to Pediatric Pain	<b>Maryam Rahimi Balaei- Goldowitz Team</b> Investigating the Role of Novel MicroRNAs on Granule Cell Development During Mouse Cerebellar Development	<b>Hilal Al Shekaili- Leavitt Team</b> Dietary Lysine is a Key Phenotypic Modifier of Pyridoxine-Dependent Epilepsy (PDE-ALDH7A1): Evidence from a Mouse Model	<b>Sarah Hutchison- Oberlander Team</b> 12 Year Longitudinal Study: Maternal Depressive Symptoms and Prenatal Antidepressant Treatment on Internalizing and Anxiety Behaviors in Children
<b>ROOM 2</b> Graduate/ Medical Students	<b>Melika Kangarani-Farahani- Zwicker Team</b> Brain Similarities and Differences in Children with Autism Spectrum Disorder, Developmental Coordination Disorder, and/or Attention Deficit Hyperactivity Disorder	<b>Jessica Sevick- Panenka Team</b> Evaluating Neuroimaging Sensitivities to Alterations in Structural Connectivity Following Mild Traumatic Brain Injury	<b>Anna Zhu- Weber Team</b> Brain Health in Preterm Infants: Cerebral Metabolic Rate of Oxygen (CMRO2) Using Advanced MRI	
<b>ROOM 3</b> Graduate/ Medical Students	<b>Jonathan Lim- Lewis Team</b> Identification of X-Linked Missense Variants in TAF1 in 4 Unrelated Families with Autism Spectrum Disorder (ASD)	<b>Bethany Adair- Simpson Team</b> Optimizing a CRISPR Gene Therapy for Aniridia Employing a Humanized Cellular Model		
<b>ROOM 4</b> Undergraduates	<b>Sangeetha Kasturi- Beasley Team</b> Density, Morphology and Distribution of Interlaminar Astrocytes in Prefrontal Cortex in Bipolar Disorder, Schizophrenia and Controls	<b>Helen Hsiao- Woodward Team</b> fMRI Analysis of Functional Brain Networks Involved in Memory Tasks and Visual and Verbal Discrimination Tasks in Healthy Individuals	<b>Julia Askew- Panenka Team</b> The Effect of TBI on Symptoms of Depression and Psychosis in Homeless and Precariously Housed Individuals	<b>Jenn Huo- Woodward Team</b> Functional Assessment of the fMRI-Derived Auditory Attention-For-Response Network
<b>ROOM 5</b> Undergraduates	<b>Ava Momeni- Woodward Team</b> Functional Assessment of the fMRI-Derived Maintaining Network	<b>Johann Peter Drayne- Weber Team</b> Fractal Analysis of Preterm Infants Scanned at Birth and at Term Equivalent Age: Implications for Brain Development and Sucrose Administration	<b>Crystal Han- Woodward Team</b> EXT Network Function	<b>Nima Toussi- Woodward Team</b> Functional Assessment of the fMRI-Derived Extraction of Meaning Network

## Joining breakout rooms/switch between rooms:

1. Click **Breakout Rooms**  in your meeting controls.  
This will display the list of open breakout rooms created by the host.
2. Hover your pointer over the number to the right of breakout room you wish to join, click **Join**, then confirm by clicking **Join**.
3. Repeat as necessary to join other breakout rooms, or click **Leave Room** to return to the main session.

# Program at a Glance

- 9:00 AM**      **Townhall for BB&D PI's**
- 10:00 AM**      **Introduction & Welcome**  
**Dr. Evelyn Stewart**
- 10:15 AM**      **Keynote Discovery Talk**  
**Dr. Staci D. Bilbo**  
*"Microglia, microbes, and development: implications for neurodevelopmental disorders"*
- 11:15 AM**      **Short Break**
- 11:30 AM**      **Lightning Talks**
- 1. Todd Woodward**, Professor, Department of Psychiatry, University of British Columbia  
*"Pain-Responsive Brain Networks During Naturalistic Viewing: A Pilot fMRI Study in Adults and Children"*
  - 2. Anita Datta**, Clinical Assistant Professor, Division of Neurology, BC Children's Hospital  
*"Determining The Impact of Epileptiform Discharges on Cognitive and Emotional Function in Children with Epilepsy"*
  - 3. Hayley Wroot**, Medical Student | Richardson Research Team  
*"Examinations Under Anesthesia: Quality Improvement for Children with Severe Behavioural Complexity"*
  - 4. Mia McLean**, Postdoctoral Fellow | Grunau Research Team  
*"Associations Between Neonatal Pain-Related Stress, Neonatal Brain Structural Connectome, and Behavior at School Age in Children Born Very Preterm"*
  - 5. Alexis Dawson**, Masters Student | McMahon Research Team  
*"Childhood Abuse History among Adolescent Mothers and Their Children's Adjustment in Elementary School: Examining Indirect Effects"*
- 12:30 PM**      **Lunch**
- 1:00 PM**      **Poster Session & Vote for Best Posters**
- 2:00 PM**      **Trainee Awards & Closing Remarks**



## Keynote Discovery Talk

# DR. STACI D. BILBO, PH. D

*Professor, Psychology and Neuroscience, Neurobiology, and Cell Biology at Duke University*

“Microglia, microbes, and development: implications for neurodevelopmental disorders”

Dr. Staci Bilbo is a Professor of Psychology and Neuroscience, Neurobiology, and Cell Biology at Duke University whose research is broadly focused on the mechanisms by which the immune and endocrine systems interact with the brain to impact health and behavior, particularly during critical developmental windows. Her research program is primarily aimed at exploring the mechanisms by which innate central nervous system immune cells - microglia - and signaling molecules such as cytokines and chemokines, influence both normal and abnormal brain development, and the implications for (mal)adaptive behavioral outcomes later in life, including a focus on neurodevelopmental disorders such as autism spectrum disorder.

Dr. Bilbo was on the faculty at Duke University from 2007-2015 before she joined the faculty at Harvard where she served as the Lurie Family Associate Professor of Pediatrics and Neuroscience at Harvard Medical School and as the Director of Research for the Lurie Center for Autism at Massachusetts General Hospital for Children. She returned to Duke in 2019 as the Haley Family Professor of Psychology and Neuroscience, and maintains an appointment at Harvard to continue her research collaborations in Boston and beyond.

### Keynote Presentation

Gestational exposure to environmental toxins, infections, and stressors are epidemiologically linked to neurodevelopmental disorders with strong male-bias, such as autism spectrum disorder. This talk will discuss findings from modeling some of these prenatal risk factors in mice, consisting of co-exposing pregnant dams to an environmental pollutant and limited-resource stress, which robustly dysregulated the maternal immune system. Male but not female offspring displayed long-lasting behavioral abnormalities and alterations in the activity of brain networks encoding social interactions, along with disruptions of gut structure and microbiome composition. Cellularly, prenatal stressors impaired microglial synaptic pruning in males during early postnatal development. Precise inhibition of microglial phagocytosis during the same critical period mimicked the impact of prenatal stressors on the male-specific social deficits. Conversely, modifying the gut microbiome rescued the social and cellular deficits, indicating that environmental stressors alter neural circuit formation in males via impairing microglia function during development, perhaps via a gut-brain disruption.

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\*Catalyst Grant updates—not eligible for voting



**Todd Woodward, Tamara Vanderwal**

**“Pain-Responsive Brain Networks During Naturalistic Viewing: A Pilot fMRI Study in Adults and Children”**

The repeated experience of pain during infancy and childhood can have long-lasting effects on development, often resulting in altered pain thresholds and significant brain changes. To date, studies of pain in children have focused on brain structure, as studying the functional neural underpinnings of pain in young children—particularly children who have endured repeated pain—is complex and procedurally challenging. This project develops the methodological advances required to study pain-related neural circuitry in children without the need to evoke physical pain. Previous work has shown that the networks recruited when participants watch someone experience physical pain involve essentially the same brain regions as when participants actually experience physical pain. Watching movies in the scanner has recently enabled researchers to study complex brain processes in young children because it helps them to remain still during scans. This project will use two existing data sets in which children (N=122) and adults (N=34, two scans each) watch movies during functional MRI. The goal is to identify a network that is active when children watch movie characters who are experiencing physical pain. Identifying a pain-responsive network that can be studied in this reliable, childfriendly way would provide a foundational tool to objectively measure how children modulate their experience of pain, including during real-time functional MRI scanning. It could also reveal new brain regions not previously implicated in pain circuitry, and provide a network of developmental interest to study in children with altered pain thresholds.



**Anita Datta, William Panenka, Kirstina Gigas, Mary Connolly, Alasdair Barr**

**“Determining the Impact of Epileptiform Discharges on Cognitive and Emotional Function in Children with Epilepsy”**

Epilepsy, even if well controlled, is commonly associated with learning, attention, behaviour and psychiatric problems that may have a significant impact on the function of the child and family. These problems are not always identified and as a result the child may not get appropriate help to address these issues. As with most other epilepsy clinics, access to appropriate neuropsychological and psychiatric assessment is limited in the BC Children’s Hospital Seizure Clinic.

In this study, we will systematically screen patients with epilepsy for cognitive problems using a specialized new “Toolbox” that assesses multiple domains of cognitive functioning. It will be administered via iPad and is user friendly for children and parents/caregivers. We will also screen for psychological problems, such as depression and anxiety. We will describe the frequency and severity of emotional and cognitive problems in children with various forms of epilepsy. The primary goal of the study is to determine the impact of inter-ictal epileptiform discharges (IEDs) on cognitive and emotional functioning. IEDs are defined as discharges on the EEG during seizure-free periods. We believe that frequent IEDs have a negative impact on learning and emotions, above and beyond other risk factors. In addition, we believe that IEDs involving both sides of the brain have a greater negative impact than those restricted to one side. Ultimately, identifying and addressing the modifiable risk factors that impact psychosocial psychological functioning is critically important to improving outcomes for children with epilepsy.





**Hayley Wroot, Anamaria Richardson, Aaron Ooi, Annemarie Hansen, Natasha Broemling, Randa Ridgway**

**“Examinations Under Anesthesia: Quality Improvement for Children with Severe Behavioural Complexity”**

**SUPERVISOR: Anamaria Richardson**

**Introduction:** Many children with neurodevelopmental conditions in BC are unable to access medical investigations due to behavioural complexity, necessitating examinations under anesthesia (EUA). Difficulties in coordinating care between providers results in fragmented service provision and inequitable care.

**Hypotheses:** A retrospective chart review will establish the current state and provide intervention points for improving EUA in children with behavioural complexity.

**Population/Methods:** All patients aged 2-18 undergoing an elective procedure requiring anaesthesia were identified from the Operating Room (OR) slate from a week in January 2021 (n=185). An in-depth retrospective chart review was conducted for patients who were identified to have specific tags indicating behavioural complexity, to identify missed opportunities for optimization of care.

**Results:** 31/185 patients (17%) were identified to have behavioural complexity (mean age 9.1years). 58%, 52% and 32% were diagnosed with autism spectrum disorder, developmental delay/intellectual disability and were non-verbal respectively. On average, children were on 2 medications (range 0-15) and involved with 3 specialties. On review of 25/31 available clinical records, 20% received an examination/add-on procedure while under anesthesia, while 24% had examinations/procedures done in the Anesthesia Care Unit prior to emergence. 39% had not had bloodwork done for over a year. Despite the extensive review of clinical records, it was impossible to determine if patients had outstanding medical evaluations at time of anesthesia.

**Implications:** A significant proportion of children seen in the OR have behavioural complexity. The lack of a centralized coordinated system resulted in challenges identifying missed opportunities, and presents as a significant inequitable service gap.



Mia McLean, Lynne Williams, Jeremy Kawahara, Colin Brown, Ghassan Hamarneh, Joanne Weinberg, Anne Synnes, Steven P Miller, Ruth E Grunau

## “Associations Between Neonatal Pain-Related Stress, Neonatal Brain Structural Connectome, and Behavior at School Age in Children Born Very Preterm”

**SUPERVISOR:** Ruth Grunau

**Introduction:** Internalizing behaviors (anxiety, depressive symptoms) and executive function difficulties are prevalent in children born very preterm ( $\leq 32$  weeks gestation). Procedural pain/stress during neonatal intensive care unit (NICU) stay is associated with regionally-specific neonatal brain microstructure alterations, hypothalamic-pituitary-adrenal (HPA) axis functioning (cortisol), and behavior problems in childhood.

**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 cortisol levels, internalizing behaviors and executive functioning at 4 years.

**Study Population:** N = 50 infants born very preterm recruited from the BC Women's Hospital Level III NICU.

**Methods:** Neonatal chart review (e.g. pain/stress [number of invasive procedures], infection), and whole-brain tractography in early life and term equivalent age (MRI/DTI), parent report of internalizing behaviors, executive functioning, and salivary cortisol at 4-years.

**Results:** Whole-brain network integration (global efficiency) and segregation (transitivity) decreased with greater neonatal pain/stress. Partial-Least Squares Correlation analysis showed clinical factors including neonatal pain/stress were related to change in 128 region-pair connections (normalized streamline count; 69% intrahemispheric, 82% cortico-cortical) across the neonatal period. Relative to weeks between scans, smaller increases in connectivity were primarily related to frontal-limbic (25%) regions, with less decrease in frontal-limbic (14%) and frontal-temporal (15%) regions. Analyses to 4-year behavior and cortisol are in progress.

**Implications:** Our study advances understanding of the effects of early life pain/stress on brain circuitry during a critical developmental window. Findings will elucidate associations of such alterations with behavior and physiological stress regulation.



**Alexis Dawson, Robert J. McMahon, Natalie Goulter, Susan Spieker**

**“Childhood Abuse History among Adolescent Mothers and Their Children's Adjustment in Elementary School: Examining Indirect Effects”**

**SUPERVISOR: Robert J McMahon**

**Introduction:** A history of abuse during childhood is associated with significant challenges for adolescent mothers. However, existing research is limited regarding intergenerational effects of adolescent mothers' abuse histories on their offspring and the developmental pathways by which transmission of risk occurs. Given that adolescent mothers have experienced exceptionally high rates of childhood maltreatment, it is critical to more closely examine the association between adolescent mothers' abuse history and their children's adjustment across multiple domains.

**Hypotheses:** The current study examined whether a history of child abuse victimization in adolescent mothers is directly related to offspring psychosocial adjustment in the context of the elementary school setting. In addition, potential mediators of this relationship were examined: (a) infant attachment security and (b) child preschool externalizing behaviour.

**Methods:** The study included a community-based sample of 114 adolescent mother-child dyads recruited to be part of a longitudinal evaluation of early parenting. Mothers reported their own childhood abuse history; infant attachment security was measured using the Strange Situation procedure at 12 months and coded by independent observers; child externalizing behaviour was reported by mothers when the children were age 4.5 years; child externalizing/internalizing behaviour and social competence were reported by teachers; and academic achievement was assessed using standardized assessments when the children were in grade 3. Path analyses were conducted to: (a) evaluate the direct effects between maternal history of abuse and child internalizing/ externalizing behaviour, social competence, and academic achievement in elementary school; and (b) evaluate the indirect effects of infant attachment security and child preschool externalizing behaviour on child functioning in grade 3.

**Results:** Maternal childhood abuse directly predicted teacher-reported child internalizing problems and social competence in Grade 3. In addition, mother-infant attachment mediated the relationship between maternal childhood abuse and teacher-reported child externalizing problems as well as social competence.

**Implications for BB&D Theme:** Clinical implications for families with trauma histories will be highlighted.

# Abstracts: POST-DOCTORAL FELLOWS

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**Katelynn Boerner, Edmund Keogh, Hadas Nahman-Averbuch**

**“An Intersectional-Biopsychosocial-Developmental Model for Understanding the Contributions of Sex and Gender to Pediatric Pain”**

**SUPERVISOR: Tim Oberlander**

**Introduction:** Pain in childhood is a common, debilitating, and costly public health problem. After mid-/late-adolescent, there is a clear female predominance in chronic pain. This has led to the hypothesis that sex hormones are primary contributors to this emergence of male-female differences in pain.

**Hypotheses:** A comprehensive understanding of sex and gender contributions to the pain experience should start as early as conception and take a biopsychosocial perspective.

**Study Population:** Pain is a nearly ubiquitous experience of childhood, as a frequent everyday experience (e.g., minor injuries), a component of routine medical care (e.g., vaccination), a feature of nearly every childhood illness or disease (e.g., arthritis, cancer), and a condition in its own right (e.g., migraine, musculoskeletal pain, recurrent abdominal pain). This presentation will incorporate research on all forms of pediatric pain across the developmental spectrum.

**Methods:** The literature on the biopsychosocial mechanisms implicated in sex and gender differences in pediatric pain was reviewed, situated within a developmental context, considering the role of intersecting identities.

**Results:** A conceptual model will be presented, with an agenda for the future of equity-driven patient-oriented research in pediatric pain.

**Implications for BB&D Theme:** Pain has known consequences for typical child development: impairing the ability to engage in recreational, academic, and social activities, increasing risk for the development of mental health conditions and persistent pain into adulthood.

Understanding what early factors influence sex differences in pain may offer the opportunity to develop more personalized approaches to the prevention and management of pain.

**Post-Doctoral**



**Maryam Rahimi Balaei, Miguel Ramirez**

**“Investigating the Role of Novel MicroRNAs on Granule Cell Development During Mouse Cerebellar Development”**

**SUPERVISOR: Daniel Goldowitz**

The cerebellum is involved in a key motor and non-motor functions. Gene mutations and/or environmental perturbations during cerebellar development can alter the pattern of gene expression via deregulation of epigenetic factors and result in cerebellar dysfunction and a wide range of neurodevelopmental and psychiatric disorders. miRNAs are key regulators of gene expression in cerebellar granule cell development and perturbations of these key miRNAs will perturb that development. miRNAs, (and their cognate DNA sequences) important for granule cell development from early postnatal day (P) are identified to study how miRNAs control this delicate developmental process. Step 1, To distinguish candidate miRNAs in developing cerebellar granule cell population: I isolated granule cells at P0, P3, P6, and P9 and extracted their m- and mi-RNAs. After RNA-Sequencing, a bioinformatics exploration of the time-course transcriptional data is completed to create a catalog of miRNAs in the granule cell precursors at the comparison of these time points. The focus was on miRNAs that are granule cell-specific and expressed in a dynamic pattern over time. Step 2, To validate the candidate miRNAs that are specific to the developing cerebellar granule cell: The miRNAs will be further filtered for those that are quantitatively replicated with qRT-PCR and spatially validated with in situ hybridization. Step 3, To perturb the best validated candidate miRNAs and understand the importance of these miRNAs in cerebellar granule cell development and disease: I will perturb gene expression in granule cell cultures, and mice by stereotaxic surgery to knockdown or over-express these miRNAs. The deliverable will be novel roles of miRNAs and their sequences from which they are transcribed to show their importance in granule cell development and disease.

**Post-Doctoral**



## Hilal Al Shekaili

### “Dietary Lysine is a Key Phenotypic Modifier of Pyridoxine-Dependent Epilepsy (PDE-ALDH7A1): Evidence from a Mouse Model”

**SUPERVISOR: Blair Leavitt**

**Introduction:** Pyridoxine-dependent epilepsy (PDE) is a rare autosomal recessive disease characterized by recurrent perinatal-onset seizures that are resistant to conventional anticonvulsant treatment but show remarkable response to pyridoxine (PN). PDE is caused by mutations in ALDH7A1 and subsequent inactivation of antiquitin, a dehydrogenase enzyme that functions within the cerebral lysine catabolism pathway. Blockade of the antiquitin-catalyzed step leads to the accumulation of lysine catabolites. About 75% of PDE patients suffer neurodevelopmental disabilities even with adequate seizure control with PN treatment, which is likely caused by the build-up of lysine catabolites. Adjunct dietary therapies like lysine-restricted diet have been tested in PDE patients and led to an improvement in the clinical outcome.

**Hypotheses:** We hypothesized that increasing the level of lysine in diet will induce a more robust clinical phenotype in a mouse model of PDE.

**Methods:** We have generated a mouse model for PDE by targeted ablation of *aldh7a1* in embryonic stem cells. To test the effect of lysine on the clinical phenotype, mice were fed different types of diets with varying levels of lysine (0.9%, 3.5% and 4.7%) at pre-natal and postnatal timepoints. The outcome was assessed by biochemical (measurement of lysine metabolite levels) and clinical (EEG, behavioral tests) analyses.

**Results:** Mice showed variable phenotypes which was dependent on the dietary levels of lysine and pyridoxine. The most severe phenotype (strong seizures and quick death) was observed in knockout (KO) mice fed a diet that contains high lysine and minimal pyridoxine. This phenotype was rescued by supplementing KO mice with high dose pyridoxine. Restricting lysine to a low level of 0.9% abolished the seizure and death phenotype in KO mice indicating the importance of lysine in determining the phenotypic outcome in PDE.

Post-Doctoral



**Sarah Hutchison, Louise C. Mâsse, Ursula Brain, Boris Kuzeljevic, Mike Irvine, and Tim F. Oberlander**

**“12 Year Longitudinal Study: Maternal Depressive Symptoms and Prenatal Antidepressant Treatment on Internalizing and Anxiety Behaviors in Children”**

**SUPERVISOR: Tim Oberlander**

**Introduction:** Approximately 10-20% of women experience depression and/or anxiety during the perinatal period and are commonly treated with a selective serotonin reuptake inhibitor antidepressants (SSRI). To inform clinical practice, the current study assessed associations between maternal depressive symptoms, prenatal SSRI antidepressant treatment, and internalizing and anxiety behaviors in children at 3, 6, and 12 years.

**Hypotheses:** We expected that across childhood and into early adolescence, prenatal maternal mood would be associated with persistently higher levels of internalizing and anxiety, even when accounting for prenatal SSRI treatment and concurrent maternal depressive symptoms.

**Study Population:** 191 mothers with and without SSRI prenatal treatment and their children

**Methods:** Maternal reports of internalizing and anxiety behaviors in children were obtained at 3, 6, and 12 years.

**Results:** Multilevel mixed effects models revealed that prenatal maternal depressed mood, not prenatal SSRI exposure, was associated with longitudinal patterns of higher levels of internalizing and anxiety behaviors across childhood from 3 to 12 years of age. At each age, hierarchical regressions showed that prenatal maternal depressed mood, compared with concurrent maternal depression or prenatal SSRI exposure explained a greater proportion of the variance in internalizing and anxiety behaviors.

**Implications for BB&D Theme:** Regardless of maternal prenatal SSRI treatment, development in children of depressed mothers remain disproportionality at risk.

**Post-Doctoral**



# Abstracts:

## GRADUATE & MEDICAL STUDENTS

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Melika Kangarani-Farahani

**“Brain Similarities and Differences in Children with Autism Spectrum Disorder, Developmental Coordination Disorder, and/or Attention Deficit Hyperactivity Disorder”**

**SUPERVISOR: Jill Zwicker**

**Introduction:** Children diagnosed with a neurodevelopmental disorder often have one or more other neurodevelopmental conditions. Commonly co-occurring conditions include autism spectrum disorder (ASD), developmental coordination disorder (DCD), and attention deficit hyperactivity disorder (ADHD). While altered brain development is suspected across conditions, how the brain differs between conditions has not been systematically evaluated.

**Objective:** To explore similarities and differences in brain structure and function in children with ASD, DCD, and/or ADHD.

**Methods:** This systematic review included articles from four databases meeting the following criteria: (1) peer-reviewed studies published in English; (2) children  $\leq 18$  years of age with one or more diagnoses of ASD, DCD, and/or ADHD compared to children with one or more of these neurodevelopmental conditions; (3) brain MRI involving structural MRI, diffusion tensor imaging (DTI), and/or resting-state fMRI.

**Results:** Twenty-nine included articles compared brain structure and function of children with the following conditions: DCD to ADHD (n=6), DCD to ASD (n=1), ASD to ADHD (n=15), and various combinations of co-occurring conditions (n=7). Structural neuroimaging was the most commonly reported MRI modality (n=14), followed by resting-state (n=8), DTI (n=4), and multi-modalities (n=3). Evidence suggests that the neural correlates of co-occurring conditions were more widespread and distinct compared to a single diagnosis. The majority of findings indicate that each neurodevelopmental disorder had more discrete than common neural correlates, suggesting that each disorder is distinct despite commonly co-occurring with each other.

**Conclusion:** While neurodevelopmental disorders often result from altered brain development, findings suggest that brain structure and function differ across disorders.



**Bethany Adair, Andrea Korecki, Nina Chiu, Siu Ling Lam**

**“Optimizing a CRISPR Gene Therapy for Aniridia Employing a Humanized Cellular Model”**

**SUPERVISOR: Elizabeth Simpson**

Aniridia is a rare, panocular disorder characterized by malformation or absence of the iris, and underdevelopment of other ocular tissues. At birth, patients have limited vision, which eventually progresses to blindness by young adulthood. Aniridia is a dominant haploinsufficiency disorder caused by mutations in the transcription factor paired box 6 (PAX6) gene. Current interventions aim to slow the progression of the disease, but none exist to correct the underlying causal variant. One exciting approach is to utilize the gene-editing capabilities of CRISPR/Cas9 to correct the variant and restore gene function. Here, I hypothesize that a CRISPR therapy developed and optimized in minimally humanized mouse embryonic stem cells (ESCs) will be a suitable strategy to differentiate between wild-type and patient variant chromosomes, in order for a CRISPR therapy for aniridia to be effective in humans. We have generated humanized mouse ESC lines and tested therapeutic conditions by transfection of CRISPR reagents to ESCs by electroporation. Characterization of cell lines and therapeutic correction are assayed by PCR, RFLP, and Sanger sequencing. To date, I have found the most successful therapeutic strategy corrected the variant at a frequency of 30%. Beyond my contribution to this research, the optimized CRISPR strategy will be tested on a humanized mouse model of aniridia to determine if the strategy can restore expression of Pax6 and prevent blindness in mice. Most importantly, the innovative humanized models will allow for the development of a CRISPR therapy on human DNA, making it directly translatable to human cells, and eventually patients.



[Anna Zhu](#)

## “Brain Health in Preterm Infants: Cerebral Metabolic Rate of Oxygen (CMRO2) Using Advanced MRI”

**SUPERVISOR: Alexander Weber**

**Introduction:** Cerebral metabolic rate of oxygen (CMRO<sub>2</sub>) is a measurement of oxygen metabolism in the brain and is an important indicator of neonatal brain health. Oxygen metabolism in the brain has historically been difficult to measure in neonates, however recent advances in magnetic resonance imaging (MRI) may prove to be a safe and precise method of measuring CMRO<sub>2</sub>.

**Hypotheses:** CMRO<sub>2</sub> values measured using advanced MRI techniques in preterm neonates at term equivalent age (TEA) will be between 20-45umol/100g/min and in agreement with literature values from studies using more invasive methods. CMRO<sub>2</sub> is also expected to be related to clinical indices of respiratory function in preterm neonates.

**Study Population:** Approximately 20 preterm neonates born <32 weeks gestation receiving standard clinical care in the NICU are being recruited at the Children's and Women's Health Centre of BC.

**Methods:** CMRO<sub>2</sub> is calculated using a standard equation and values obtained from advanced MRI techniques. A partial correlation statistical analysis will be conducted to determine the relationship between CMRO<sub>2</sub> and clinical measure of respiratory health.

**Results:** Currently, CMRO<sub>2</sub> values from 3 subjects have been obtained. These values fall between 25-40umol/100g/min, agreeing with the literature standards of CMRO<sub>2</sub> in preterm neonates at TEA which range from 20-45umol/100g/min.

**Implications for BB&D Theme:** This study will provide preliminary data to establish the feasibility of a non-invasive and precise advanced MRI technique in determining neonatal brain health and oxygen metabolism. This may be clinically relevant in further aiding and optimizing the development of therapies for brain injured neonates.



[Jessica Sevick](#), [Mikaela Correa](#), [Jacob Stubbs](#),  
[Wayne Su](#)

## “Evaluating Neuroimaging Sensitivities to Alterations in Structural Connectivity Following Mild Traumatic Brain Injury”

**SUPERVISOR:** [William Panenka](#)

**Introduction and Hypotheses:** Advanced MRI techniques, including diffusion tensor imaging (DTI) and myelin water imaging (MWI), are commonly used to assess the white matter microstructural architecture in the brain. This study investigated the sensitivity of DTI and MWI to mild traumatic brain injury (mTBI), with the hypothesis that both modalities would be sensitive to mTBI.

**Study Population and Methods:** 51 subjects with mTBI and 30 orthopedic trauma controls (TC) underwent multimodal MRI scanning at 2 weeks and six months post injury. The mTBI groups were separated into two sub-groups: (i) normal day of injury CT scans (CT-) and (ii) abnormal day of injury CT scans (CT+) indicating acute damage. Tract-based spatial statistics was used to compare the DTI measures of fractional anisotropy (FA), axial diffusivity, radial diffusivity (RD), and mean diffusivity, and the MWI measure of myelin water fraction (MWF). Comparisons were made between the groups at the two timepoints, as well as longitudinally within the groups.

**Results:** For the DTI analyses several brain regions demonstrated lower FA and higher RD in the mTBI group relative to the TC, at both timepoints. There were no significant differences between CT+ and CT- groups, although the sample size was small (CT+:N=X; CT-:N=Y) but both CT+ and CT- groups differed from controls. There were no group, or sub-group, differences observed in the change occurring longitudinally between the timepoints for the DTI metrics. There were no statistically significant differences observed between any of the comparisons in the MWF.

**Implications for BB&D Theme:** This suggests that DTI metrics are imaging biomarkers that are sensitive to mTBI, while MWI is not. MWI requires further investigation and validation in order to be used as diagnostic imaging tool for mTBI.



**Jonathan Lim, Ying Qiao, Kristina Calli, Sally Martell, Steven Jones, Stephen Scherer, Suzanne Lewi**

**“Identification of X-Linked Missense Variants in TAF1 in 4 Unrelated Families with Autism Spectrum Disorder (ASD)”**

### **SUPERVISOR: Suzanne Lewis**

TAF1 (TATA-Box Binding Protein Associated Factor 1) is an X-linked gene encoding the largest component and core scaffold of the TFIID basal transcription factor complex. It plays an important role in neurodegenerative diseases and developmental delay. An increasing number of cases have been reported with variants in this gene grouped as a new neurodevelopmental syndrome (TAF1/MRXS33 intellectual disability syndrome). Common clinical features include hypotonia, facial dysmorphism, developmental delay, intellectual disability, and/or autism spectrum disorder (ASD). We hypothesized that TAF1 plays a vital role in the contribution to this phenotype. Using parents-and-affected whole-genome sequencing methods, we identified 4 missense variants of TAF1 in 4 boys among a cohort of 125 patients affected with ASD (p.Asp1496Ala, p.Pro215Leu, p.Leu619Phe, and p.Gly1391Arg). Out of the four probands, one showed a more severe phenotype (Complex-5) while the other three had either Simple-1 or Simple-2 according to our phenotype semi-quantitative evaluation criteria. Interestingly, the genomic location of the variant in the most severely affected patient was in the hot region of the gene. This area is enriched with a higher number of reported pathogenic/likely pathogenic variants. A detailed genotype-phenotype correlation analysis will be summarized among our patients and published cases in the future. Finally, other variants in multiple strong ASD candidate genes were found in each of our cases, inherited from both parents. Our data suggest that different types and locations of the variants in TAF1 genes, as well as variants from different ASD candidate genes might contribute to the diversity of phenotypes in this syndrome.

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**Nima Toussi, Leonardo Arreaza**

## **“Functional Assessment of the fMRI-Derived Extraction of Meaning Network”**

**SUPERVISOR: Todd Woodward**

**Introduction:** The Extraction of Meaning Network (LANG) is one of the twelve fMRI-derived functional brain networks identified through Task-based Functional Magnetic Resonance Imaging (fMRI) and Constrained Principal Component Analysis (CPCA). However, the influence of task demands and conditions on the activity of the network remains ambiguous.

**Hypotheses:** The LANG network is hypothesized to be recruited for the generation of semantic associations.

**Study Population:** The study population is taken from 10 studies which demonstrated recruitment of the LANG network. These studies were completed by several research teams.

**Methods:** Previous works extracted functional brain networks with constrained principal component analysis for fMRI (fMRI-CPCA). LANG networks were identified by characteristic activation and suppression patterns, and a voxelwise region-specific correlation with previously identified FVF networks. Corresponding estimated HDRs were examined for condition effects and interactions.

**Results:** The LANG network demonstrated suppression when responding to non-semantic stimuli. Furthermore, the LANG network was recruited for various modes of semantic stimuli, and its recruitment was not influenced by volitional attention.

**Implications for BB&D Theme:** Next steps for this project includes a behavioral CPCA analysis, which will help determine differences in LANG network recruitment between neurotypical and schizophrenic participants. The long-term goal will be to apply findings from the networks to developing treatments, such as neuromodulation.

**Undergraduate Student**





**Ava Momeni**

**“Functional Assessment of the fMRI-Derived Maintaining Network”**

**SUPERVISOR: Todd Woodward**

The Maintaining network is one of 12 task-based networks that have been recently derived via a novel statistical data-driven approach called fMRI-CPCA. While applying this approach produces an anatomical characterization of the Maintaining network, the function of this network still remains to be fully interpreted. Across multiple studies, the Maintaining network has shown to be differentially recruited over a range of distinct tasks and task conditions. In the following chapter, the neuroimaging results of seven studies analyzed with the fMRI-CPCA, that demonstrated BOLD activity classified as the Maintaining network with sufficient strength were considered. In addition, we identified the task conditions which promoted activity in the Maintaining network, as well as possible underlying commonalities between the various task conditions, in order to arrive at a better understanding of the network's function. We conclude that the Maintaining network is most likely involved in integrating different frontal functions, volitional attention to internal mental representations and conscious inner speech/language processing while being non-specific to the cognitive domain.

**Undergraduate Student**



[Johann Peter Drayne](#), [Mia McLean](#), [Olivia Campbell](#), [Cecil Chau](#), [Steven P Miller](#), [Ruth Grunau](#)

## “Fractal Analysis of Preterm Infants Scanned at Birth and at Term Equivalent Age: Implications for Brain Development and Sucrose Administration”

**SUPERVISOR:** [Alexander Mark Weber](#)

**Introduction:** It has been found that fractal analysis of the BOLD signal in fMRI can be used to measure brain functioning, development, and health. Improved capacity to understand brain health in sick preterm infants is critical to optimise outcomes.

**Hypotheses:** Infants scanned at-term age will have a higher Hurst exponent, reflecting a more structured ordering of the brain signal, than infants scanned at pre-term age.

**Study Population:** After exclusion criteria and preprocessing, 133 scans (mean birth age  $27 \pm 2.5$  weeks) of 3T fMRI data with TR=3s and ~5 minutes was collected from SickKids Toronto (Steven Miller). Infants were scanned shortly after birth and later at term-age.

**Methods:** The Hurst exponent was calculated using Welch's method on the pre-processed data. A Linear Mixed Effects model evaluated how significant the differences of the mean H value in 10 regions of interest was between early and at-term age scans.

**Results:** All regions were found to be statistically different in H values between scan ages (preterm and later term). The largest difference was in the Visual and Motor network whilst the smallest was in the Frontal and Hindbrain.

**Implications for BB&D Theme:** This study provides, 1) a documented pre-processing pipeline (using open-source software and available on GitHub) for infants born pre-term; and 2) fractal-analysis which reveals inherent brain dynamics. With better data, this method may be robust at classifying whether a brain has been impaired and to what degree.



Jenn Huo

## “Functional Assessment of the fMRI-Derived Auditory Attention-For-Response Network”

**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 functional magnetic resonance imaging (fMRI-CPCA). However, the specific cognitive function associated with each network remains undefined. The current study aims to characterize the specific functions of the Auditory Attention-for-Response (AAR) network by comparing hemodynamic response (HDR) patterns across tasks where the AAR configuration emerged. Recruitment of the AAR network involves activation in the bilateral superior temporal gyrus, supplementary motor area, left precentral gyrus, bilateral insula and thalamus. Based on cognitive tasks that revealed engagement of the AAR network in previous studies, 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 the situation where an individual that is visually monitoring their phone is less likely to hear what someone else is saying to them. For the current study, activation of the AAR network was compared across 11 tasks for which its recruitment has already been identified, and evaluation of the AAR network involved comparing anatomical patterns and HDR plots in each of the studies to determine an interpretation that fits all tasks.

Undergraduate Student



**Julia Askew, Jacob Stubbs, Allen Thornton**

**“The Effect of TBI on Symptoms of Depression and Psychosis in Homeless and Precariously Housed Individuals”**

**SUPERVISOR: William Panenka**

Homelessness is a global public health concern, with over 235 000 Canadians experiencing homelessness yearly. Homeless or precariously housed individuals have a high lifetime prevalence of traumatic brain injury (TBI) with 53.1% experiencing any TBI during their lifetime, and 22.5% experiencing a moderate or severe TBI (approx. 4 and 10 times higher than the general population, respectively). Mood and psychotic disorders are also overrepresented in this population, therefore, it is important to investigate symptoms of depression and psychosis following traumatic brain injuries in this population. We hypothesized that individuals who experience a TBI will have higher scores on measures of depression and psychosis compared to their pre-injury scores and change in controls. A total of 170 homeless or precariously housed participants from the Downtown Eastside of Vancouver were enrolled in the study, with 86 TBI and 84 control participants. Participants were monitored for TBI and completed assessments monthly, including the Beck Depression Inventory and the Positive and Negative Syndrome Scale to measure symptoms of depression and psychosis, respectively. At one month post-injury, individuals who experienced TBI had a significant increase in depression scores ( $\beta = 2.3$ ,  $p = 0.018$ ). Additionally, those who experienced TBI and had methamphetamine dependence had a significant increase in psychosis scores compared to those without methamphetamine dependence ( $\beta = 2.4$ ,  $p = 0.020$ ). In conclusion, TBI is associated with increased symptoms of depression and psychosis among individuals who are homeless or precariously housed, and interventions should be targeted at decreasing TBI and symptom management after injury.



**Crystal Han**

**“EXT Network Function”**

**SUPERVISOR: Todd Woodward**

A large majority of previous research done to characterize brain networks focused primarily on the use of resting-state fMRI, which looks at brain activity in the absence of stimuli, however, the specific relationship between regions of brain activity have yet to be identified. The current study utilized task-based fMRI to investigate the relationship between cognition and brain activity through the performance of certain tasks, by both schizophrenic and non-schizophrenic participants. Task-based fMRI allows for the observation of brain activity during performance of selected tasks and can be used to identify brain regions active during various tasks, using the blood-oxygen-level-dependent (BOLD) signals to create a hemodynamic response (HDR) pattern. The current study aimed to analyze HDR patterns in various studies which recruited the Volitional Attention to External Representations (EXT) network to identify a possible function for the EXT network. The EXT network has been hypothesized to be responsible for the maintenance of attention during the performance of tasks over a prolonged period, namely during tasks requiring attention to visual stimuli. With the knowledge of the hypothesized function of the EXT network, the current study analyzed 10 various studies involving the EXT network and compared the HDR patterns to identify an interpretation of the network's function to fit all studies. It was concluded the EXT network showed greater levels of activation in correlation with the cognitive demand of certain tasks, especially during language-based tasks. Schizophrenic patient showed hypoactivation of the EXT network throughout, suggesting decreased levels of sustained attention towards external visual stimuli. By understanding how networks of brain regions function together during tasks, we can understand how the dysfunction of certain brain regions can contribute to the overall dysfunction of the network it's found in.



**Helen Hsiao, Todd Woodward**

**“fMRI Analysis of Functional Brain Networks Involved in Memory Tasks and Visual and Verbal Discrimination Tasks in Healthy Individuals”**

**SUPERVISOR: Todd Woodward**

This project aims to investigate task-based brain networks and patterns in whole-brain activation in the functional MRI (fMRI) Midnight Scanning Club dataset. 10 healthy subjects completed three Incidental Memory tasks and two Coherence Semantic tasks. For the Incidental Memory tasks, subjects completed the Memory faces, Memory scenes, and Memory words tasks where subjects indicated the gender, location, and word type presented to them, respectively. For the Coherence Semantic tasks, subjects completed the visual discrimination and verbal discrimination tasks, where they made binary Concrete/Abstract and Noun/Verb judgements for dot patterns and words, respectively. Constrained Principal Component Analysis for fMRI (fMRI-CPCA) was used to determine functional brain networks and associated hemodynamic responses engaged in each of the tasks. Statistical significance of hemodynamic responses was determined with repeated measures ANOVAs. Brain networks were classified based on differences in estimated HDR, location of anatomical peaks and cluster shapes, and comparison to networks in literature for similar tasks.

Four networks were identified for the Coherence Semantic task: Two-Handed Response, Traditional Default Mode, Focus on Visual Features, and Novel Default Mode. Five networks were identified in the Incidental Memory task: Focus on Visual Features, Two-Handed Response, Traditional Default Mode, Linguistic Processing, and External Attention. The extracted networks match the hypothesized results and are expected based on the tasks involved.

This study will contribute to the future use of neuromodulation to increase or decrease activation of brain networks as an intervention to treat brain disorders.



**Sangeetha Kasturi**

**“Density, Morphology and Distribution of Interlaminar Astrocytes in Prefrontal Cortex in Bipolar Disorder, Schizophrenia and Controls”**

**SUPERVISOR: Clare Beasley**

Schizophrenia and bipolar disorder are severe mental illnesses. Both illnesses present heterogenous symptoms among individuals, making diagnosis and treatment more difficult. Elucidation of common pathophysiological traits among patients could lead to improved treatments. Previous research has shown that disruption of astrocyte-synapse interactions plays a role in schizophrenia and BD.

Density, morphology, and distribution of the interlaminar subtype of astrocytes present in cortical layer I will be significantly different between patients that were diagnosed with BD or schizophrenia in comparison with controls.

Prefrontal cortex from control (n=20), schizophrenia (n=20) and bipolar disorder (n=20) subjects.

Paraffin sections containing the prefrontal cortex were stained for astrocytes using the marker GFAP and imaged via brightfield microscopy. Images were input into FIJI ImageJ to quantify astrocyte cell density and area fraction. Cases were also categorized as having either normal or abnormal astrocyte morphology. Normality tests were performed in Excel, followed by a one-way ANOVA and two-sample t-tests.

In comparing the schizophrenia and control groups, neither cell density nor area fraction values were found to be significantly different. Similarly, area fraction values were not found to be significantly different between BD and controls. However, cell density was significantly lower in BD in comparison to controls.

Though cell density values were not significantly different between schizophrenia and controls, they were found to be significantly lower in the BD group compared to the control group. Future research could focus on elucidating the mechanisms causing lower astrocyte cell density values in BD patients, which may include effects of medications.