Mission
NeuroDevNet is a national multi- and trans-disciplinary network dedicated to bringing hope to children with Autism Spectrum Disorder (ASD), Cerebral Palsy (CP), Fetal Alcohol Spectrum Disorder (FASD) and related neurodevelopmental disorders, as well as to their families and caregivers. NeuroDevNet focuses its funding on integrated, team-based, research initiatives related to cause, early diagnosis, and interventions. Engaging families, clinicians, other stakeholders and partners both nationally and internationally, NeuroDevNet leverages and enhances the talents of new and seasoned researchers to translate research findings into effective therapies and changes in policy and practice.

Vision
To improve the lives of children with neurodevelopmental disorders and their families, by accelerating and integrating the discovery and utilization of knowledge about disorders of the brain, their early diagnosis, prevention and therapy.

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Accreditation
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Prospective Examination of Visual Attention During Play in Infants at High-Risk for Autism Spectrum Disorder.

Lori Sacrey  Postdoctoral Fellow

Mentor: Lonnie Zwaigenbaum
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Institution(s): ¹University of Alberta; ²Dalhousie University; ³IWK Health Centre; ⁴Glenrose Rehabilitation Hospital

Abstract:
Regulation of visual attention is essential to learning about one’s environment. Children with Autism Spectrum Disorder (ASD) exhibit impairments in regulating their visual attention, but little is known about how such impairments develop over time. This prospective longitudinal study is the first to describe the development of components of visual attention, including engaging, sustaining, and disengaging attention, in infants at high-risk of developing ASD (each with an older sibling with ASD). Non-sibling controls and high-risk infant siblings were filmed at 6, 9, 12, 15, 18, 24, and 36 months of age as they engaged in play with small, easily graspable toys. Duration of time spent looking at toy targets before moving the hand towards the target and the duration of time spent looking at the target after grasp were measured. At 36 months of age, an independent, gold standard diagnostic assessment for ASD was conducted for all participants. As predicted, infant siblings subsequently diagnosed with ASD were distinguished by prolonged latency to disengage (‘sticky attention’) by 12 months of age, and continued to show this characteristic at 15, 18, and 24 months of age. The results are discussed in relation to how the development of visual attention may impact later cognitive outcomes of children diagnosed with ASD.

Keywords: Vision, Grasping, Disengagement, visual attention, infants, autism

Funded by: CIHR, Autism Speaks Canada, Stollery Children’s Hospital Foundation, AIHS, ART, Craig Chair in Autism Research
Theme 1 - Clinical Diagnostics  Poster # 2

Presentation of Restless Legs Syndrome in Children with Autism Spectrum Disorders: “Challenging Disruptive Poor Repertoire Daytime Behaviours”.

Osman Ipsiroglu  Associate Investigator

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Abstract:

Introduction: Restless Legs Syndrome (RLS) is a clinical diagnosis based on an urge to move, in particular during rest, and on patient reported sensory discomfort [prevalence in 5-10% of the general population; causing clinically significant sleep problems (SP) in 2-3%]. Clinical RLS has never been investigated in children with ASD. Diagnosis is challenging as children with ASD are frequently unable to express their discomfort and/or rationale for an urge to move. We report familial RLS daytime presentations, which can be considered as challenging and disruptive, and some repetitive motor activities which may be considered as ‘poor repertoire’.

Methods: In our Person Centered Medicine/Life Trajectories research we use an ethnographic approach adapted from medical anthropology to explore parent[s]/caregiver[s]’ perceptions of ‘challenging disruptive’ and ‘poor repertoire’ behaviours, as well as sleep problems (SP). We conduct “Comprehensive Clinical Sleep Assessments”, a clinical practice strategy based on therapeutic emplotment [Ipsiroglu et al. 2012], in which clinical history taking utilizes qualitative interviews and incorporate patients’ and parents’ contributions in recognizing familial SPs and their sequelae.

Results: We are presenting video recorded typical daytime symptoms and behaviours in 15 children and youth (2-17 years) with global developmental delay or intellectual disability with familial RLS and diagnoses of ASD, cerebral paresis, and additional genetic syndromes (e.g. Trisomy-21, cri-du-chat, 22q-deletion, 13x chromosome deletion). The challenging behaviours of these patients were given diagnoses such as ADHD, anxiety, obsessive compulsive, oppositional defiant disorders, emotional lability, and/or depression; however, RLS-related discomfort has been never considered and treated. We identified RLS as one main cause of insomnia, which aggravated “challenging disruptive poor repertoire daytime behaviours,” and have been able to treat most patients successfully with neuropathic pain medication. Initially, all parents/caregivers had described the sleep quality of their child as restless and light, with major problems in sleep maintenance; all children were described as having Sensory Processing Abnormalities.

Conclusion: We believe that at a young age these children develop movement-based adaptive strategies to overcome difficulties in sitting still and falling asleep. Such adaptive strategies range from subtle to extreme, and can result in passing out from exhaustion which hides typical symptoms that may indicate RLS. Therefore history and analysis of behavioural movement patterns, in conjunction with family sleep history, seems to be a key in understanding RLS of patients with ASD. These observations open our understanding for RLS-caused chronic SPs and some novel therapeutic options.

Keywords: Sleep Problems, Sleep Assessments, Restless Legs Syndrome, Therapeutic Emplotment, Person-centered Medicine, Paediatrics

Funded by: Treatable Intellectual Disability-Endeavour-British Columbia
Theme 1 - Clinical Diagnostics  Poster # 3

Differences in Cerebral Palsy Phenotypes and Risk Factors in Term Singleton Born Small for Gestational Age.

Gabrielle Freire  Medical Resident

Mentor: Maryam Oskoui
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Abstract:
Introduction: Cerebral palsy (CP) is the most common cause of motor dysfunction in children. Children born small for gestational age (SGA) are at increased risk to develop CP. The pathophysiology behind this association remains unclear.

Objectives: Compare the phenotypic profile of children with CP born SGA to other children with CP. Explore differences in antenatal and perinatal factors between them.

Methods: We conducted a retrospective cohort study of term singletons with CP, extracting data on 481 children from the Canadian Cerebral Palsy Registry. Small for gestational age was determined as birth weight for gestational age and sex below the tenth percentile. The probable timing of injury was determined based on neuroimaging and clinical characteristics. Chi square and student t-test were used as appropriate, with descriptive statistics.

Results: Mothers of children with CP born SGA were more likely to be of African-American ethnicity (p=0.021), and to have gestational hypertension (p=0.031). Children with CP born SGA had a smaller head circumference at birth (p<0.001) and higher frequencies of being born by emergency caesarean-section (p=0.004). They showed a trend for higher frequency of birth asphyxia (p=0.052), neonatal encephalopathy (p=0.091) and placental abnormalities (p=0.062). Children with CP born SGA had a more severe CP phenotype, having more fine motor (p=0.054) and gross motor (p=0.012) impairment, more communication impairment (p=0.005), and more cognitive impairment (p=0.031), and a trend for a higher frequency of the spastic quadriplegia subtype (p=0.071).

Conclusion: Children with CP born SGA have different antenatal and perinatal clinical factors and phenotypic profiles than other children with CP. These differences support the hypothesis of antenatal causes of CP in children born SGA and will help in the development of animal models for CP. Future case control studies would be desired to further define this causal pathway.

Keywords: Cerebral palsy, small for gestational age, intra-uterine growth restriction

Funded by: NeuroDevNet CP Demonstration Project, the Public Health Agency of Canada. les Fonds de Recherche en Santé du Québec (FRSQ) funded the CP registry
Does the level of obstetrical care influence the ambulatory status of children with Cerebral Palsy?

Corneliu Bolbocean  Doctoral Candidate

Mentor: Krishna Pendakur
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Abstract:
Introduction: Few studies have explored the relation between type of intrapartum care [primary, secondary and tertiary level] and cerebral palsy [CP] incidence. However, the relationship between the type of the intrapartum care and CP phenotype is unknown.

Objective: To estimate the impact of type of intrapartum care on the probability of developing a severe CP phenotype [defined as level IV or V according to Gross Motor Function Classification System].

Methods: We use the Quebec Cerebral Palsy Registry dataset, which contains rich information on the main known CP antepartum and intrapartum risk factors. The availability of these risk factors in the data allows the use of matching-type treatment effect estimators. We use propensity score matching combined with weighted regression [a doubly robust method] to identify the impact of hospital types on the probability of developing a severe CP phenotype.

Results: The estimate of the causal effect of treatment in secondary versus primary care on CP phenotype is zero. Specifically, we find a point estimate of about -0.05, with a standard error of about 0.06, suggesting that the true causal effect is within 10 percentage points of zero. Our preliminary results suggest that birth given within the secondary care versus primary care institution has no effect on the probability of developing a severe CP phenotype [GMFCS levels IV or V], ceteris paribus.

Conclusions: The causes of cerebral palsy are heterogeneous and relate to both antepartum and intrapartum periods. However, our results provide evidence that the major risk factors that determine a severe CP phenotype do not occur in the intrapartum period.

Keywords: Cerebral Palsy, health econometrics, treatment effects

Funded by: NeuroDevNet Doctoral Fellowship [CB] and NeuroDevNet CP Demonstration Project
Theme 2 - Therapeutics  Poster # 5

Movement Characteristics and Energy Expenditure of Virtual Reality Game Play in Children and Youth with Cerebral Palsy.

Danielle Levac  Postdoctoral Fellow

Mentor:  Heidi Sveistrup
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Abstract:

Introduction: The use of virtual reality (VR) systems within pediatric rehabilitation is an active area of clinical practice and research. VR systems utilize hardware and software options to create interactive simulations that embed and engage the user in realistic environments. The use of VR in pediatric rehabilitation to improve motor performance has primarily been evaluated in children living with Cerebral Palsy (CP) classified at Gross Motor Function Classification System (GMFCS) Levels I and II. These children have balance impairments that interfere with functional mobility and participation in physical activities. Growing evidence supports the effectiveness of VR as a treatment modality for this population. As such, clinicians require information as to the relationship between VR game play, energy expenditure and atypical movement patterns. Indeed, clinicians are concerned that may elicit maladaptive movement patterns of hemiplegic limbs or of the full body, including (but not limited to) increased co-contraction across involved joints, lack of graded movement control, and fixing of degrees of freedom into joint hyperextension.

Objectives:
1. To quantify energy expenditure (heart rate, respiratory rate, skin conductance) of VR game play in children with CP.
2. To describe movement characteristics (upper and lower limb acceleration, centre of pressure displacement and other full-body and upper limb movement kinematics) of VR game play in children with CP.
3. To compare energy expenditure and movement characteristics of game play between a rehabilitation-specific (Interactive Rehabilitation Exercise System [IREX]) and a gaming-specific (Kinect for Xbox 360) VR system.

Methods & Results: Children and youth will attend the Virtual Reality laboratory to be instrumented and videotaped while playing 8 different games in a randomized order for three minutes each. This poster will describe preliminary results comparing children and youth with CP in GMFCS levels 1 and II to age-matched typically developing children. Of additional interest will be a description of use of the Kinect sensor and Software Development Kit for Windows for kinematic analysis purposes.

Conclusions: Describing energy expenditure and movement characteristics of VR game play in two common rehabilitation-specific and commercially-available gaming platforms will support decisions about carry-over of VR-based therapy from clinic to home and contribute to client-centered, evidence-based use of VR systems in pediatric rehabilitation. Exciting potential for use of the Kinect sensor as a clinically-feasible movement analysis tool will be highlighted.

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Keywords:  Virtual reality, cerebral palsy, energy expenditure, movement characteristics, Kinect, video games

Funded by:  NeuroDevNet Postdoctoral Fellowship (DL), Canadian Child Health Clinician Scientist Program, CIHR
An Innovative Cycling Exergame to Promote Cardiovascular Fitness and Health-Related Quality of Life in Youth with Cerebral Palsy.

Shannon Knights  Medical Resident

Mentor: Darcy Fehlings
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Institution(s): 1Holland Bloorview Kids Rehabilitation Hospital; 2University of Toronto; 3Queen’s University

Abstract:
Introduction: Youth with Gross Motor Function Classification System (GMFCS) level III cerebral palsy (CP) have lower levels of physical activity, fitness, and social interaction than their typically developing peers. Videogames that require physical activity, known as exergames, are emerging as a novel approach to address these challenges. Exergames offer opportunities for social interaction through multiplayer activity. Exergames have been shown to be enjoyable, to increase energy expenditure, and to improve motor function in children with CP.

Objectives: The objective of this study was to evaluate the effect of a home-based exergame cycling program on the cardiovascular fitness and health-related quality of life of youth with GMFCS level III CP.

Methods: Eight youth (6 males, 2 females; mean age 14y4m, SD 2y6m) with GMFCS level III CP completed a 6-week exergame cycling program. Participants were asked to cycle at least 30 minutes 3 times per week, including 60 minutes per week at target heart rate (HR) (defined as 41% of HR reserve). Outcomes were obtained at baseline and post-intervention. Primary outcome measures were the GMFCS III-specific shuttle run test (SRT-III) (for cardiovascular fitness) and the “Physical Activities and Health” domain of the KIDSCREEN-52 questionnaire (for health-related quality of life). Secondary outcomes included the 6-Minute Walk Test, Wingate Arm Cranking Test, anthropomorphic measurements, and other domains of the KIDSCREEN-52. Descriptive statistics were calculated for HR and playtime. Paired t-tests were performed to assess pre- and post-intervention changes in outcome measures. Bonferroni corrections were applied to secondary outcome measures (p=0.006).

Results: Mean (SD) weekly playtime per participant was 202 (95) minutes, with 79 (48) minutes (39.1% of playtime) above target heart rate (HR). There were significant improvements in the SRT-III (t=-2.5, p=0.04) and the “Physical Activities and Health” domain of the KIDSCREEN-52 (t=-2.8, p=0.03) post-intervention. There were no significant changes in secondary outcome measures, but there was a trend towards decreased waist circumference (p=0.03).

Conclusions: Participants achieved their HR and playtime targets throughout the intervention. Cardiovascular fitness and health-related quality of life in youth with GMFCS level III CP improved following an innovative exergame cycling program.

Keywords: cerebral palsy, exergames, cardiovascular fitness, health-related quality of life

Funded by: NeuroDevNet Opportunities Initiative Award and GRAND
The Role of the Environment in Improving the Participation of Youth with Physical Disabilities in Community Activities: An Evaluation and Review.

Dana Anaby  Associate Investigator

Author(s):  D. Anaby1, M. Law2, C. Imms3, L. Turner2, and R. Teplicky2
Institution(s):  1McGill University; 2McMaster University; 3La Trobe University

Abstract:

Background: Youth with physical disabilities experience restrictions to participation in community-based leisure activities, which can lead to poor health outcomes. There is little evidence; however, about how to promote adolescents’ involvement in community activities. The International Classification of Functioning, Disability and Health (ICF) identifies the environment as a key factor in influencing participation. A synthesis of the current evidence is needed to understand the impact of the environment, followed by evaluation of the effect of environmental-based interventions on youth’s participation.

Objectives: The purpose of this presentation is: 1) to share the results of a scoping review of current evidence regarding the impact of the environment on participation of children and youth living with disabilities; and 2) to examine whether an intervention that aims to remove environmental barriers and provide education for parents, in the form of coaching, can effectively improve youth’s participation in community activities.

Methods: Peer-reviewed studies published from 1990 to 2011 were systematically reviewed using a variety of electronic databases in order to address objective 1; the scoping review. To test the intervention study in objective 2, an Interrupted Time Series design with a multi-baseline approach was employed where a replication of the intervention effect was examined across three individualized participation goals and across participants. Five male adolescents, ages 13 to 20 years with a physical disability due to a neurological condition [e.g., cerebral palsy] and living in Ontario participated in a 12-week environment-focused intervention. An occupational therapist worked with each youth and their family individually to set 3 participation goals, then identified and implemented strategies to remove environmental barriers. The therapist also coached the youth and parents about methods to overcome barriers autonomously.

Results: The scoping review indicated that the majority of studies focus on children with physical disabilities, in particular cerebral palsy, and each domain of the environment as suggested by the ICF influenced participation as a barrier and/or support; the most common barrier was attitudes and the most common facilitator was social support. Results of the intervention study indicated clinically significant improvements in COPM performance scores for all three participation goals and across all participants (overall 15 goals); an average change of 4.5 points in the COPM scale was observed within the first two weeks post-intervention. Statistical analysis using the celeration line indicated a significant treatment effect.

Conclusions: These projects highlight the unique role of the environment in improving youth’s participation. Such findings can inform the design of a larger study that aims to test this environmental-focused intervention among a larger sample of youth with physical disabilities and, consequently, can guide clinical practice.

Keywords: leisure participation, intervention, environment

Funded by: Ontario Federation for Cerebral Palsy
Broccoli Sprouts: Primary Prevention Targeting the Fetal Inflammatory Response.

**Antoinette Nguyen** Doctoral Candidate

**Mentor:** Jerome Yager  
**Author(s):** A. Nguyen, E. Armstrong, A. Bahry, and J. Yager  
**Institution(s):** University of Alberta

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**Abstract:**

**Introduction:** Epidemiological studies have shown that the fetal inflammatory response (FIR) is associated with adverse fetal brain development. It has been demonstrated that FIR is a significant risk factor leading to an increase in the incidence of cerebral palsy (CP) and seizures. Cerebral injury from FIR augments the production of pro-inflammatory cytokines and oxidative stress, leading to white matter and/or gray matter injury. Therapeutic interventions to deter the consequences of FIR are absent. Experimental studies have provided evidence that broccoli sprouts (BrSp), a natural health product, is capable of reducing inflammation and enhancing endogenous antioxidant systems. This has led to our investigation of whether BrSp will be neuroprotective in a model of FIR.

**Objectives:** The objectives of our study are to: (i) develop a model of FIR, resulting in behavioral and/or pathological consequences consistent with CP, (ii) determine whether maternal BrSp dietary supplementation during pregnancy will reduce or prevent the developmental delays typical of CP, and (iii) determine the underlying mechanisms of injury and prevention.

**Methods:** FIR is induced by intraperitoneal injections of 200 μg/kg of the endotoxin lipopolysaccharide (LPS) to pregnant rats. Pregnant rats are fed 200 mg of dried BrSp per day, beginning on gestational day 14 up until weaning on postnatal day 21. The study will consist of four groups: i) saline ii) LPS, iii) saline + BrSp, and iv) LPS + BrSp. Offspring undergo a series of neurodevelopmental reflexes. Following the final day of behavioural testing after which they will be euthanized for neuropathological analyses.

**Results:** Our data show that offspring born to pregnant rats receiving LPS are growth restricted (p < 0.05) compared to controls. Broccoli sprout supplementation along with LPS prevented the observed intrauterine growth restriction (p < 0.05) compared to those who received LPS alone. Rat pups from the LPS group displayed developmental delay in several of the neurological reflex tested such as hindlimb placing, righting, and gait. BrSp supplementation significantly prevented these disabilities (p < 0.05). Interestingly, to date we have not seen alterations in neuropathologic assessment, attesting to the subtleness of the lesion.

**Conclusions:** Our model of FIR produces both growth restriction and developmental disability consistent with “mild to moderate” forms of CP. Supplementation with BrSp during late gestation prevents this injury and may be a safe and effective intervention during late pregnancy. Further study is required to determine the effectiveness of this therapy in more severe forms of FIR as a complicating risk factor in CP.

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**Keywords:** Cerebral palsy, fetal inflammatory response, prevention  
**Funded by:** NeuroDevNet CP Demonstration Project, Heart and Stroke Foundation of Alberta NWT and Nunavut, and Alva Foundation
Effects of Adult Neural Precursor-Derived Myelination on Axonal Function in the Perinatal Congenitally Dysmyelinated Brain.

Crystal Ruff  Postdoctoral Fellow

Mentor: Michael Fehlings
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Institution(s): 1Krembil Neuroscience Centre, Toronto Western Hospital (TWH), University Health Network (UHN); 2Toronto Western Research Institute (TWRI), TWH, UHN; 3Department of Biology, Loyola University; 4Division of Fundamental Neurobiology, Department of Medicine, TWRI, UHN; 5Department of Surgery, Division of Neurosurgery, TWH.
*Authors Contributed Equally to this Manuscript

Abstract:
Introduction: Stem cell repair shows substantial translational potential for neurological injury, but the mechanisms of action remain unclear.

Objectives: This study aimed to investigate whether transplanted stem cells could induce comprehensive functional remyelination.

Methods: Sub-ventricular zone (SVZ)-derived adult neural precursor cells (aNPCs) were injected bilaterally into major cerebral white matter tracts of myelin-deficient shiverer mice on P0, P7 and P21.

Results: Tri-potential NPCs, when transplanted in vivo, integrated anatomically and functionally into local white matter and preferentially became Olig2+, MAG+, MBP+ oligodendrocytes, rather than GFAP+ astrocytes or NF200+ neurons. Processes interacted with axons and TEM showed multilamellar axonal ensheathment. Nodal architecture was restored and by quantifying these anatomical parameters a computer model was generated that accurately predicted action potential velocity, determined by ex vivo slice recordings. Although there was no obvious phenotypic improvement in transplanted shiverers, myelinated axons exhibited faster conduction, lower activation threshold, less refractoriness and improved response to high frequency stimulation than dysmyelinated counterparts. Furthermore, they showed improved resilience to ischemic insult, a promising finding in the context of perinatal brain injury.

Conclusions: This study describes, for the first time mechanistically, the functional characteristics and anatomical integration of non-immortalized donor-SVZ-derived murine aNPCs in the dysmyelinated brain at key developmental timepoints.

Keywords: Neural Stem Cells, Brain injury, Cerebral Palsy, Remyelination, Regeneration, Perinatal Brain Repair

Funded by: NeuroDevNet CP Demonstration Project, Ontario Brain Institute, CIHR & Heart and Stroke Foundation of Canada
A Translational Model of Intrauterine Growth Restriction: Evaluating Abnormalities in Neurobehavioural Gait and White Matter Myelination.

Stuart Faulkner  Postdoctoral Fellow

Mentor: Michael Fehlings
Author(s): *S. Faulkner1, *C. Ruff1, W. Foltz2, E. Armstrong3, A. Basilious1, S. Fan1, J. Yager3, and M. Fehlings1
Institution(s): 1Division of Genetics and Development, Department of Surgery, Toronto Western Research Institute (TWRI), University Health Network (UHN); 2STARR facility, Toronto Medical Discovery Tower; 3Department of Paediatrics, University of Alberta
*Co-authors

Abstract:
Introduction and Objectives: Cerebral Palsy (CP) is the most common pediatric neurodevelopmental physical disability. Survivors of premature birth constitute the largest etiologic subgroup of children with CP and periventricular leukomalacia (PVL) is the most common form of brain injury in this cohort. Translationally relevant models of placental insufficiency and intrauterine growth restriction (IUGR) are vital in elucidating the mechanisms of injury and as a tool to evaluate novel cellular regenerative/reparative solutions for CP.

Methods: Two anaesthetized, pregnant LE rats underwent bilateral surgical ligation of the uterine arteries at E20 (1 SHAM surgery, 1 IUGR surgery) to induce placental insufficiency, IUGR and subsequent diplegia in offspring (n=5 SHAM, n=5 IUGR). Between P21-P84, pups underwent weekly behavioural gait analysis to assess relative paw placement(s) and inter-limb coordination. Coronal magnetisation transfer (MT) imaging was recorded at P21, 42 and 84 to assess sequential MR-based WM myelination.

MT ratios [MTR] were evaluated across white matter regions including, genu [gCC] and splenium [sCC] corpus collosum [CC], internal (Ic) and external capsule (Ec), and optic tract (Opt).

Results: Body weight was lower in IUGR vs SHAM rats at P0 and P21 [P<0.001 each] - body weights normalized thereafter. Relative print positions (mm) [front vs hind] were smaller and stride length (mm) longer (front and hind limbs) between IUGR vs SHAM animals at P21 (all P<0.01). Relative print positions were smaller and swing speed (m/s) faster (front limb) between IUGR vs SHAM animals at P28 (all P<0.01). Thereafter, no behavioral deficits were present between groups.

At P21, MTR was lower in IUGR vs SHAM animals in the Ec at the level of the gCC [P=0.008] and in the CC and Ic at the level of anterior hippocampus [P<0.001]. By P42, MTR was not different between groups.

Conclusions: This model of IUGR demonstrates reproducible deficits in birth weight, early walking gait abnormalities and MRI-based delayed myelination of WM tracts. It is suitable for exploring novel therapeutics for diplegic CP resulting from placental insufficiency and fetal growth restriction.

Keywords: Intrauterine growth restriction, cerebral palsy, MRI, translational model, white matter, myelination

Funded by: NeuroDevNet CP Demonstration Project and Ontario Brain Institute
Theme 2 - Therapeutics  

Poster # 11

The Effect of Intrauterine Growth Restriction on Postnatal Cerebellar Development and Function.

Gloria Mak  
Postdoctoral Fellow

Mentor: Daniel Goldowitz  
Author(s): G. Mak, and D. Goldowitz  
Institution(s): Child and Family Research Institute, Centre for Molecular Medicine and Therapeutics, University of British Columbia.

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Abstract:
Intrauterine growth restriction (IUGR) is a pathological reduction in the expected growth potential of a developing fetus. Approximately 5-12% of preterm infants experience IUGR. The most common etiology leading to IUGR is placental insufficiency, which deprives the developing fetus of oxygen and nutrients. Although it is thought that the IUGR fetal environment leads to adaptive epigenetic programming, which increases the risk onset for specific adult diseases, relatively little is known about how this epigenetic programming affects the developing brain. Longitudinal studies of IUGR infants have revealed a high incidence of neuropsychiatric disorders and neurodevelopmental impairments, which are thought to arise from regional-specific reductions in cortical and cerebellar gray matter volumes in the IUGR brain. Given that the developmental processes of the cerebellum are well known, this brain region is an ideal site to determine the influence IUGR has on neurodevelopment. The neurodevelopmental disorders and impairments associated with IUGR involve cerebellar circuitry. Therefore, we hypothesize that IUGR impairs postnatal cerebellar development and function, which is, in part, a result of altered cerebellar DNA methylation. IUGR is induced in female mice by performing a unilateral ovariectomy, which produces a crowded uterine horn and results in reduced placental blood flow among the developing embryos. In selecting for IUGR and control mice at various postnatal ages, we found that IUGR leads to a reduction in the size of the cerebellum, the postnatal germinal region of the cerebellum, known as the external granular layer, and cerebellar white matter. By administering bromodeoxyuridine (a marker of cell proliferation), we determined that IUGR decreases the survival of newly generated cells in the developing postnatal cerebellum, which subsequently leads to reduced granule and astroglial cells in the cerebellum. In examining cerebellar-associated behaviours of IUGR and control mice, we found that IUGR mice display deficits in motor, social and learning function. By performing genome-wide reduced representation bisulfite sequencing on the perinatal IUGR cerebellum, we found that the IUGR cerebellum is hypomethylated compared to controls. Candidate genes specific to cerebellar development were selected to validate the hypomethylated status of the IUGR cerebellum, as well as the transcriptional expression of the selected genes. Interestingly, in supplementing IUGR mice with methyl donor (MD) diet throughout development, we found a dramatic improvement in cerebellar-associated function. Future studies will determine the effects MD supplementation has on postnatal cerebellar development, DNA methylation and gene expression in IUGR mice. As such, our study establishes critical steps towards building a foundation for effective treatment strategies to improve the health of IUGR infants within an epigenetic-dependent gene regulatory framework.

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Keywords: prematurity, brain development, cerebellum, function, IUGR

Funded by: Alberta Health Innovates and CIFAR
Theme 2 - Therapeutics  Poster # 12

Omega-3 Fatty Acids can Reverse the Long-Term Deficits in Glutathione and Rescue Hippocampal Synaptic Plasticity Caused by Prenatal Ethanol Exposure.

Anna Patten  Postdoctoral Fellow

Mentor:  Brian Christie
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Institution(s):  1Division of Medical Sciences, Island Medical Program, University of Victoria; 2Department of Biology, University of Victoria; 3Brain Research Centre and Program in Neuroscience, University of British Columbia; 4Department of Cellular and Physiological Sciences, University of British Columbia; 5Department of Drug Design and Pharmacology, University of Copenhagen

Abstract:

Introduction: One of the characteristic hallmarks of fetal alcohol spectrum disorders (FASD) is impairment in learning and memory processes. Experimentally we can study long-term potentiation (LTP), a biological model of learning and memory, in the dentate gyrus of the hippocampus. Learning and memory problems may be a result of increased oxidative damage or reduced antioxidant protection, causing changes in the redox state of the neurons in the hippocampus. Therefore the goals of this study were to examine learning and memory and the relationship to antioxidant protection in a rat model of FASD, and to develop specific therapeutics to rescue any deficits that may occur.

Objectives:
• To determine whether there are sex-specific deficits in LTP following prenatal ethanol exposure
• To determine whether the deficits in LTP are due to a reduction in antioxidant protection
• To attempt to ameliorate the deficits in LTP using supplementation to enhance antioxidant protection

Results: In this study we have observed deficits in LTP in adult males who have been exposed to alcohol prenatally, while females are spared. These deficits are accompanied by reductions in the important neuronal antioxidant glutathione in both male and female offspring.

Further to this, we have determined that the deficit in LTP in alcohol exposed animals may be a direct cause of glutathione depletion, as depleting glutathione in control males produces a similar deficit in LTP to that observed in alcohol exposed males, but glutathione depletion in control females does not affect LTP, mirroring the effects of prenatal ethanol exposure. Future studies are aimed at determining the interaction between glutathione and LTP. To try and ameliorate the deficits caused by prenatal alcohol exposure, we have given animals’ access to a diet supplemented with omega-3 fatty acids. Omega-3 fatty acids are important for membrane fluidity, participate in many signaling cascades in the brain and can increase antioxidant protection. We have found that supplementation can increase glutathione in the brain and completely reverse the deficits in LTP observed in male animals.

Conclusions: These results indicate that omega-3 fatty acids may be an important addition to the diet of children suffering from FASD and may be able to “rescue” the deficits in learning and memory common with this disorder.

Keywords:  FASD, omega-3, oxidative stress, glutathione, Long-term potentiation

Funded by:  NeuroDevNet Doctoral Fellowship [AP]
Abstract:

Introduction: Prenatal alcohol exposure (PAE) results in a wide range of cognitive, physiological, and neurobehavioural deficits, including dysregulation of the stress system. Besides these effects, PAE also increases vulnerability to psychopathologies such as depression and anxiety. Clinical and animal studies have shown that pre-existing dysregulation of the stress system may be a major factor underlying the development of later psychopathologies, particularly if the individual is exposed to stressors later in life.

Objectives: As the onset of many psychopathologies often occurs around adolescence, here we explore the short- and long-term effects of chronic mild stress (CMS) during adolescence on the emergence of anxiety- and depressive-like behaviours in PAE rats.

Methods: Pregnant rats were assigned to either Alcohol (PAE) – liquid alcohol diet ad libitum; Pair-fed (PF) – liquid control diet yoked to PAE consumption; or Control – pelleted control diet ad libitum. Offspring were exposed to 10 days of CMS starting at postnatal day 31 (females) or 37 (males), or remained undisturbed (non-CMS). A cohort of animals was tested immediately following CMS, during adolescence (short-term) and another cohort was tested in adulthood (long-term). Rats were tested first in the open-field (OF; anxiety) and then in the forced swim test (FST; depression).

Results: Males from all prenatal treatment groups exposed to CMS traveled greater distances in the center of the OF when tested in adolescence, whereas neither PAE nor CMS differentially altered activity in the OF in adulthood. By contrast, PAE females in both the Non-CMS and CMS conditions spent more time and traveled greater distances in center if tested in adolescence, but spent less time and traveled shorter distances in center if tested in adulthood. In the FST, Non-CMS PAE males tested during adolescence showed an increase in time spent immobile. However, all adolescent males exposed to CMS showed an increased latency to immobility and decreased time immobile, independent of prenatal treatment, whereas neither PAE nor CMS altered the behavior in the FST in adulthood. Adolescent females showed no effects of either PAE or CMS in the FST. However, adult PAE females showed an increased latency to immobility.

Conclusions: Our results indicate that the effects of PAE on depressive- and anxiety-like behaviours change over time in a sexually dimorphic manner. Moreover, adolescent CMS resulted primarily in short-term effects in all prenatal treatment groups.

Keywords: prenatal alcohol exposure, rat, stress, depressive-like behavior, anxiety-like behavior, adolescent

Funded by: NeuroDevNet FASD Demonstration Project, NIH R37 AA007789, and CCSDRF to JW
Theme 3 - Cellular and Molecular  

Poster # 14

The Influence of Maternal Inflammation on Embryonic Hypothalamic Development.

Candace Marsters  Doctoral Candidate

Mentor: Deborah Kurrasch

Author(s): C.M. Marsters1,2, Q.J. Pittman2, and D.M. Kurrasch3

Institution(s): 1Department of Neuroscience, Hotchkiss Brain Institute, University of Calgary; 2Department of Pharmacology and Physiology, Hotchkiss Brain Institute, University of Calgary; 3Department of Medical Genetics, Alberta Children’s Hospital Research Institute, University of Calgary

Abstract:

Maternal infection has been linked to disorders such as autism, anxiety, cerebral palsy, and schizophrenia in the offspring children. Exactly how exposure to maternal infection in utero leads to changes in brain architecture in the fetus remain poorly understood. Recent research suggests that an inflammatory immune response mounted by the mother may alter the fetal environment and disrupt normal developmental processes. It has been previously shown that increased inflammatory cytokine levels in fetal brains, as seen during maternal inflammation, can affect the timing of neuronal differentiation and survival, thereby providing a potential link between maternal inflammation, fetal neurodevelopment, and the onset of disorders during childhood.

Here, we expand upon these studies and explore whether maternal inflammation causes changes in hypothalamic development, a key region known to respond to inflammatory signals and contribute to various disorders. Our overarching goal is to determine whether exposure to maternal inflammation at specific periods in gestation leads to changes in the onset and/or duration of hypothalamic neurogenesis, as an entry point towards linking in utero environment with adverse health outcome in offspring. To start, here we examine the timing of hypothalamic neuronal birth using 5-Bromol-2'-deoxyuridine (BrdU) labeling to determine whether neurogenesis is affected in embryos by onset of maternal inflammation induced by lipopolysaccharide (LPS) during key windows of development. One such window is the time course e11.5-e15.5, when neurogenesis normally occurs in the hypothalamus. We hypothesize that there will be alternations in neuronal birth at the onset of embryonic hypothalamic neurogenesis in pups born of dams treated with LPS.

Due to the early stage of the developing embryo at e11.5, with its newly developing circulatory system and blood brain barrier, the placenta is in position to have direct influence on the inflammatory signaling to the developing embryonic brain. To complement our neurogenesis studies, we have asked if changes affecting the fetus are dependent on the maternal-fetal interface of the placenta. We have quantified levels of inflammatory markers within the placentas of inflamed pregnant dams then compared these to the inflammatory molecules in the maternal serum. As well, because of well known gender differences in offspring outcome in animal models of maternal inflammation, we have compared placental inflammatory response between male and female embryos. This may reveal differences in placental cytokine signaling between embryo sexes but will also identify variability in placental inflammation within the same pregnant dam and between different pregnant dams.

Keywords: maternal inflammation, hypothalamus, placenta

Funded by: Alberta Innovates-Health Solutions, Canadian Institute of Health Research
Decoding Fetal Brain-Gut Communication During Inflammation to Identify Babies at Risk of Necrotizing Enterocolitis.

Hai Lun Liu  BSc Student

Mentor: Martin Frasch
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Abstract:

Objectives: Necrotizing enterocolitis (NEC) of the neonate is an acute inflammatory intestinal disease that can cause necrosis, systemic sepsis and multiorgan failure. It is characterized by high prevalence, morbidity and mortality accounting for up to 8% of all admissions to the neonatal intensive care unit. Chorioamnionitis (CA) is a risk factor of NEC. Higher levels of vagal activity are associated with lower systemic levels of pro-immunflamatory responses and activation of macrophages, mediated by the cholinergic anti-inflammatory pathway (CAP). Fetal heart rate variability (fHRV) serves as a proxy marker of CAP activity. The gut represents the biggest vagus-innervated organ and the primary innate immunologic venue of newborns. Consequently, changes of HRV may reflect changes of inflammatory status in gut. We hypothesized that fHRV can identify fetuses with gut inflammation.

Methods: Six near-term fetal sheep were surgically prepared with arterial and venous catheters, and ECG electrodes. In four fetal sheep, varied degrees of inflammatory responses were induced with lipopolysaccharide (LPS) through intravenous injection to mimic mild CA. Fetal arterial blood samples were drawn and regional blood flow (rBF) was measured at baseline and selected time points. At 54 h post LPS, necropsy was performed. Blood samples were analyzed for cytokines IL-1β, IL-6 and TNF-α. Fetal HRV was quantified continuously by 99 measures using Continuous Individualized Multivariate Variability Analysis (CMIVA). The time-matched fHRV measures were correlated to the levels of IL-1β, IL-6 and TNF-α and to the Iba1 density in terminal ileum to quantify the degree of macrophage activation in relation to CAP activity.

Results: We detected an elevation of IL-6, but not IL-1β and TNF-α, at 3 hours post LPS. 24 hours post LPS, the rBF peaked in terminal ileum and brain and the asymmetry index (AsymI) of fHRV correlated to sum intensity of Iba1+ macrophages (R=-0.83, p=0.042) identifying a cluster of LPS-receiving fetuses versus controls; concomitantly, fetuses with higher TNF-α showed larger areas of Iba1+ cells (R=0.90, p=0.037).

Conclusion: Confirming our hypothesis, we identified the AsymI of fHRV as reflecting the levels of macrophage activation in terminal ileum at the same time when the rBF peaked in this organ. AsymI quantifies the degree of temporal asymmetry of HRV. In adults, AsymI is highest in young subjects and decreases with aging or heart disease. Our pilot study indicates the potential of non-invasively obtaining CAP response signatures via fHRV that would then help identify neonates at risk of developing NEC and sepsis.

Keywords: Necrotizing enterocolitis, cholinergic anti-inflammatory pathway, fetal brain, Fetal heart rate variability, inflammation

Funded by: CIHR, FRSQ and Molly Towell Perinatal Research Foundation
Theme 3 - Cellular and Molecular  

Poster # 16


Emily White  Master's Candidate

Mentor: Brian Christie
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Abstract:
Traumatic brain injury (TBI) is the leading cause of disability in individuals under 45 years of age, with mild TBI encompassing the majority of cases. While motor vehicle accidents and falls account for the majority of mild TBIs, sports injury is the most prevalent cause of mild TBI in youth, age 11-18, with incidents rising 60% over the past decade. Synaptic reorganization as well as myelination is still occurring during childhood, which makes the juvenile brain especially vulnerable to injury. Mild TBI often causes impairment of normal hippocampal function, which results in a variety of cognitive deficits, including perpetual difficulties in learning and memory processing. Adult rodents show persistent and significant deficits in working memory and long-term potentiation (LTP) following mild and severe TBI. Our objective was to determine the short and long-term deficits on hippocampal synaptic plasticity in the juvenile rat brain caused by mild TBI. At postnatal day 25-28, male and female Long-Evans rats were subjected to a mild brain injury by delivering a direct force to the mid-parietal area of the left hemisphere using the weight drop model. At one hour, one day, seven days, and 28 days following TBI, animals were sacrificed and alterations in LTP were observed via extracellular field recordings in the dentate gyrus (DG) and CA1 regions of the hippocampus. In female rats, DG-LTP was impaired one day following TBI, although no deficits were detected seven days following injury. In male rats, a deficit in both DG and CA1-LTP was apparent in the ipsilateral hemisphere seven days following injury, but LTP was no different from Sham animals in either region 28 days post-injury. These data suggest that the juvenile brain is susceptible to TBI-induced impairments of plasticity in the hippocampus, although they also show the potential to fully recover with time.

Keywords: Electrophysiology, synaptic plasticity, learning, memory, mild traumatic brain injury

Funded by: CIHR
Developmental Impact of Prenatal Alcohol Exposure: Evidence for a Unique Early-Life Immune Signature.

Tamara Bodnar  Doctoral Candidate

**Mentor:** Joanne Weinberg  
**Author(s):** T. Bodnar, W. Comeau, and J. Weinberg  
**Institution(s):** Department of Cellular & Physiological Sciences, University of British Columbia

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**Abstract:**

**Introduction:** Prenatal alcohol exposure (PAE) affects development of numerous physiological systems, resulting in a wide array of deficits, many of which may persist into adulthood. One such physiological system affected by alcohol is the immune system. PAE has been shown to affect numerous immunological parameters including thymic development, resulting in decreased T-lymphocyte proliferative responses to mitogens, and giving rise to an increased susceptibility to pathogenic infection. It has also been shown that exposures and experiences that alter levels of key immune and endocrine factors can result in reprogramming of neuronal cells, with long-term effects on their reactivity and response to future challenge. As a result, hypersensitivity to neuroinflammation and/or low-grade neuroinflammation may occur.

**Objectives:** We investigated whether PAE acts as an early-life insult to the developing immune system, and whether this results in a pro-inflammatory biased organism that may display alterations in immune organ development as well as changes in cytokine and hormone expression at key developmental time points.

**Methods:** We assessed the developmental immune profile using a rat model with pregnant dams assigned to: 1) PAE – ad libitum access to a liquid ethanol diet (36% EtOH-derived calories); 2) Pair-fed (PF) - liquid control diet with maltose-dextrin isocalorically substituted for ethanol in the amount consumed by a PAE partner; or 3) Control (C) - ad libitum access to control diet. Female offspring were terminated and blood, brain, and spleens collected at postnatal day 0 (P0), P8, P15, and P22.

**Results:** Initial results indicate that PAE affects the developmental trajectory of the spleen, with PAE animals showing increased spleen weight on P8, 15, and 22. PAE animals also show a unique cytokine expression profile with increased plasma levels of pro-inflammatory cytokines (IL-6, TNF-α, IFN-γ, and KC/GRO) and decreased levels of both pro- and anti-inflammatory cytokines (TNF-α, IL-1β, IL-6, IL-4, and IL-10) in the spleen, at various time points during the preweaning period.

**Conclusions:** Overall, our results indicate that in utero alcohol exposure affects the developmental trajectory of the spleen, a critical immune organ. The resulting alterations in cytokine expression levels may have long-term consequences for development of immune function. Moreover, increased levels of circulating pro-inflammatory cytokines in PAE animals is suggestive of early-life inflammation, which may have negative consequences for brain development.

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**Keywords:** Immune, development, alcohol, cytokines, inflammation, spleen

**Funded by:** NeuroDevNet FASD Demonstration Project, NIH/NIAAA R37 AA007789, and R01 AA022460 to JW and NSERC CGS-D to TB.
Disruption of the ASTN2 and TRIM32 Genes in Gender Modulated Risk for Autism, ADHD and other Neurodevelopmental Disorders.

Anath Lionel  Doctoral Candidate

Mentor: Stephen Scherer

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Abstract:
Introduction: Genomic studies have begun to uncover the architecture of genetic risk for different neurodevelopmental disorders (NDDs) including Autism Spectrum Disorder (ASD), schizophrenia, Attention Deficit Hyperactivity Disorder (ADHD) and others. Data from these studies have highlighted rare copy number variants (CNVs) and single nucleotide variants impacting several genes encoding cell-adhesion and scaffolding proteins at the neuronal synapse. Rare CNVs disrupting ASTN2 and/or TRIM32, a small gene intronic to ASTN2, have been reported by genome-wide studies in a few individuals with NDDs. The vertebrate-specific astrotactin proteins, ASTN2 and its closely related paralog ASTN1, have key roles in glial-guided neuronal migration during brain development. The intriguing preliminary human genetic findings and the well-established functions of the astrotactins in mammalian brain development highlight ASTN1 and ASTN2 as promising NDD candidate risk genes.

Objectives: To better understand the prevalence of astrotactin mutations and delineate their associated phenotype spectrum, we screened ASTN2/TRIM32 (at chromosome 9q33.1) and ASTN1 (at chromosome 1q25.2) for exonic CNVs in clinical microarray data from 89,320 patients tested across 10 molecular diagnostic laboratories including 63,903 subjects with NDDs.

Results: In this large clinical dataset, we identified 45 deletions and 11 duplications affecting ASTN2. Deletions near the 3’ end of ASTN2, which disrupted all its transcript isoforms and/or included TRIM32 were significantly enriched in the NDD subjects (p=0.006) compared to 41,536 population-based controls. Common traits observed in individuals with such deletions included ASD, ADHD, anxiety, OCD and speech delay. Gender-biased penetrance of the deletions was observed, with enrichment compared to controls in males but not in females. Quantification of ASTN2 human brain RNA revealed smaller isoforms expressed from an alternative transcription start site of recent evolutionary origin near the 3’ end. Deletions affecting ASTN1 were far rarer than those at ASTN2 and were predominantly of de novo origin. Spatiotemporal expression profiling in the human brain revealed consistently high ASTN1 expression while ASTN2 expression peaked in the early embryonic neocortex and postnatal cerebellar cortex.

Conclusions: Our findings shed new light on the role of the astrotactins in psychopathology and their complex interplay in human brain development. Future studies are required to investigate the molecular basis of the findings presented here including the gender-biased penetrance and phenotypic heterogeneity of the ASTN2/TRIM32 deletions and the functional relevance of the ASTN2 shorter isoforms.

Keywords: Genomics, Autism, ADHD, Microarrays, CNVs, Neuronal migration

Funded by: NeuroDevNet Doctoral Fellowship [AL], NeuroDevNet ASD Demonstration Project, Genome Canada and CIHR
Theme 4 - Clinical Genomics  Poster # 19

International Classification of Functioning, Disability and Health Core Set for 15q11.2 Duplication Syndrome Associated with Autism Spectrum Disorders.

Kama Guezalova  BSc Student

Mentor: M.E. Suzanne Lewis
Author(s): K. Guezalova1,2, K. Calli1,2, J. Hildebrand1,2, M.E.S. Lewis1,2
Institution(s): 1Department of Medical Genetics, University of British Columbia; 2The Autism Spectrum Interdisciplinary Research (ASPIRE) Programme

Abstract:

Introduction: Diagnosis of genetic syndromes has focused primarily on providing patients with an explanation for their physical and behavioural phenotype, with little direction in regards to personalized treatment and management of their syndrome. The impact of a genetic syndrome on an individual’s ability to function varies from one person to another depending on many different factors. The International Classification of Functioning and Disability (ICF) developed by the World Health Organization (2001) provides a universal language that is based on a comprehensive set of criteria that assesses disabilities related to body structures, body functions, ability to engage in activities and environmental factors. The development of ICF core sets in the diagnosis and treatment of genetic syndromes offers a standardized approach to resolve the need for individualized treatment plans that can be developed through a multidisciplinary team of medical and community professionals.

Objectives: To develop an ICF core set criteria for assisting adaptation and optimal functioning of individuals living with autism/intellectual disability due to a copy number variation at 15q11 (duplication) for use in a clinical setting.

Methods: The ICF Core Sets Development Process was followed as per the ICF research branch. A systematic review of the literature, and cases within our autism cohort (n=583; selected from the ASD-CARC Research Registry; autismresearch.com) was conducted to identify diagnostic and outcome measures for individuals with 15q11 duplication syndromes. Measures included information from medical records including physical examination reports by geneticists, parent interview during clinical appointments, EEG reports, psychological testing, occupational and physical therapy reports. Each measure is linked to the ICF criteria following ICF linking rules and all identified criteria are then extracted to establish a proposed ICF Core Set as a health and function guide for persons living with 15q11 duplication conditions.

Results: The proposed ICF Core Set values for 15q11 duplication syndromes allow for identification of specific disabilities and subsequent personalized treatment plans to optimize functions and quality of life, as there is great variability in the functional outcomes of individuals with 15q11 duplication disorders.

Conclusions: The continued development and translation of ICF Core Sets for the growing number of genomic disorders associated with neurodevelopmental disabilities and their increased implementation in clinical practice will heighten the standard of personalized care and treatments for optimizing function across the lifespan for persons and families living with these conditions impacting autism and intellectual disability.

Keywords:  autism spectrum disorder, ICF, 15q11, copy number variant, core set

Funded by: The Canadian Foundation for Innovation Leading Edge, BC Knowledge Development Fund, Canadian Institutes for Health Research
Theme 4 - Clinical Genomics  Poster # 20

Uncovering Obsessive-Compulsive Disorder Risk Genes using a High-Resolution Genome-Wide CNV Approach.

Matthew Gazzellone  Master’s Candidate

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Abstract:

Background: Obsessive-Compulsive Disorder (OCD) is a neuropsychiatric condition characterized by persistent unwanted thoughts (obsessions), ritualized actions and repetitive behaviors (compulsions), and excessive anxiety. It is common (2% lifetime prevalence) and often presents during childhood. Family and twin studies suggest that genetic factors underlie the pathology of OCD, particularly when the symptoms begin in childhood. To date, genetic investigations have focused primarily on candidate gene, genetic linkage, and genome-wide association approaches, but there have been no published copy number variation (CNV) studies. Findings reported to date explain only a fraction of the genetic architecture of OCD. Our approach seeks to build upon the foundation established in studies of other neuropsychiatric conditions which posit that rare inherited and de novo CNVs may elevate disorder risk. We aimed to establish whether this type of variation contributes to the pathogenesis of OCD.

Methods: We undertook a genome-wide CNV scan using two high-resolution microarrays: the Affymetrix CytoScan HD array and the Illumina OMNI 2.5M Quad array (both featuring around 2.5 million probes). In stage one of the project, DNA was obtained from 140 affected children and their parents and run on the CytoScan HD array. We then conducted a second scan of unrelated probands on either the CytoScan HD array (57 probands) or the OMNI 2.5M Quad array (111 probands). We identified high-confidence CNVs by requiring their identification by two or more CNV detection algorithms. Rare variants were identified by comparing the stringent CNV calls from our case cohorts to stringent calls obtained from population-based controls genotyped on the same array (873 CytoScan HD controls and 2,988 OMNI 2.5M Quad controls).

Results: Rare CNVs overlapping genes previously implicated in neuropsychiatric disorders, and absent in the controls, were uncovered in the OCD probands. These include exonic deletions or duplications of genes involved in neuronal migration (i.e. ASTN2), synaptic function and signal transmission (i.e. NLGN1 and NLGN4X), and postsynaptic scaffolding in glutamatergic synapses (i.e. DLGAP1 and DLGAP2). In addition, we identified new candidate OCD genes involved in synaptic function or plasticity (i.e. BTBD9).

Conclusions: Our findings suggest that rare copy number changes contribute to OCD risk and that genes expressed at the synapse may play a role in the onset of OCD when perturbed.

Keywords: psychiatric genetics, microarray, copy number variation, rare variants

Funded by: Canadian Institutes of Health Research Masters Award and Ontario Graduate Scholarship

Taimoor Sheikh  Master’s Candidate

Mentor: John Vincent
Author(s): T.I. Sheikh1,2, K. Mittal1, M.J. Willis3, and J.B. Vincent1,2,4
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Abstract:

Background: Mutations in MECP2 are the main cause of Rett Syndrome. To date, no pathogenic synonymous MECP2 mutation has yet been identified. Here, we investigated a de novo synonymous variant c.48C>T (p.Gly16Gly) identified in a girl presenting with a typical RTT phenotype.


Methods: In silico analyses to predict the effects of sequence variation on mRNA splicing were employed, followed by sequencing and quantification of lymphocyte mRNAs from the subject for splice variants MECP2_E1 and MECP2_E2.

Results: Analysis of mRNA confirmed predictions that this synonymous mutation activates a splice-donor site at an early position in exon 1, leading to a deletion [r.63_48del], codon frameshift and premature stop codon [p.Glu17Lysfs*16] for MECP2_E1. For MECP2_E2, the same premature splice site is used, but as this is located in the 5’untranslated region, no effect on the amino acid sequence is predicted. Quantitative analysis that specifically measured this cryptic splice variant also revealed a significant decrease in the quantity of the correct MECP2_E1 transcript, which indicates that this is the etiologically significant mutation in this patient.

Conclusions: These findings suggest that synonymous variants of MECP2 as well as other known disease genes—and de novo variants in particular—should be re-evaluated for potential effects on splicing.

Keywords: Cryptic splice site; synonymous mutation; MECP2, exon 1; Rett Syndrome; silent mutation; frame-shift mutation

Funded by: Canadian Institutes for Health Research
Genotype-Phenotype Analyses of Maternal versus Paternal Inherited 15q11.2 Duplication in Autism, Intellectual Disability and Epilepsy.

Peter Wang  BSc Student

Mentor:  Suzanne Lewis

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Abstract:

Introduction: The proximal long arm of chromosome 15 is prone to recombination events and DNA copy number variants (CNV) due to flanking segmental duplications. The most common 15q copy number gains are inverted duplications [idic(15)] and interstitial duplications [dup(15q11-q13)] resulting in tetrasomy and trisomy of the region, respectively. Most reported cases of interstitial proximal 15q duplications are maternal in origin and frequently associated with autism and variable comorbidities such as physical anomalies, epilepsy and intellectual disability. Recently, smaller duplications 15q11.2 integral to dup(15q11-q13) have been reported. However, the clinical phenotype and molecular pathogenicity of paternal 15q11.2 duplications has yet to be established.

Objectives: We aim to characterize and compare the phenomic and genomic underpinnings of 15q11.2 duplications contributing to the pathogenesis of autism spectrum and related cognitive and electroclinical disorders.

Methods: Chromosome microarray analysis (CMA) was used to detect CNV changes in the proband. Findings were confirmed by fluorescent in situ hybridization (FISH) in the proband and parents. Review of the literature and in silico analyses allowed for comparison of phenotype and genotype and within the 15q11.2 autism susceptibility locus for differentiating key candidate genes.

Results: We describe a nondysmorphic 8-year-old girl who harbors a 849.7 kb duplication of chromosome 15q11.2 inherited paternally. The patient has autism spectrum disorder (ASD), neuromotor delay (hypotonia), mild intellectual disability (ID), and attention deficit hyperactivity disorder (ADHD). The proband also has a complex seizure disorder concordant with abnormal EEG, revealing focal seizures and clusters of spasms in the mid-frontal parietal region. This region contains 12 RefSeq genes (including 1 OMIM gene, NIPA1). Several studies have found CNVs in this region in healthy individuals according to the Database of Genomic Variants (DGV). Nevertheless, a review of the literature for cases which overlap with the present CNV has identified recurrent phenotypes, including ASD, ADHD, ID, developmental delay, hypotonia and epilepsy, albeit with low penetrance and/or variable expressivity. Four of the integral genes are highly conserved and have roles in neuronal development (NIPA1 and CYFIP1), magnesium transport (NIPA2) and tubulin structure (TUBGCP5).

Conclusions: We present evidence of the complex interactions between genetic and epigenetic factors that explain the observed phenotype and parent-of-origin differences. Further, we provide evidence of a novel critical region integral to the 15q11.2 ASD susceptibility locus that focuses involvement of NIPA1 and CYFIP1 as non-imprinted genes independent of parental origin effects typically associated with autism spectrum conditions and duplications at the 15q11.2 locus.

Keywords:  Autism Spectrum Disorder, 15q11.2 duplication, copy number variants, imprinting, epilepsy, intellectual disability

Funded by:  The Canadian Foundation of Innovation Leading Edge, BC Knowledge Development Fund, Canadian Institutes for Health Research
Theme 4 - Clinical Genomics  

**Poster # 23**

**The Intersection of Rare and Common Genomic Variation in Autism Spectrum Disorders – the Paradigm of 2q37 Deletion Syndrome and 2q37.3 Polymorphism.**

**Kristina Calli**  
Research Coordinator

**Mentor:** M.E. Suzanne Lewis  

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**Institution(s):**  
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**Abstract:**

**Introduction:** 2q37 Deletion Syndrome (DS), causing autism and intellectual disability (ID), is a rare genomic disorder reported in ~100 cases world-wide. The variability and severity of features associate with deletion size, underscoring the importance of identifying the critical region and genes involved. Ambiguity arises from how a distal polymorphic deletion (PD) at 2q37.3 (PD2q37.3; ~155kb) associates with 2q37DS, since it is also found in unaffected controls and is thereby designated as a benign copy number variant (bCNV). However, a so called bCNV may be reclassified as capable of causing disease if identified at a higher incidence within affected populations.

**Objectives:** To identify clinical and genomic biomarkers that may be indicative of ASD susceptibility involving genomic rearrangements of the 2q37.3 subtelomeric region.

**Methods:** Participating subjects were recruited from the Research Registry of ASD-CARC [www.autismresearch.com]. The following sub-studies were performed:

1. Investigation of the incidence of PD2q37.3 within our autism cohort based on overlapping CNVs in the Database of Genomic Variants. Subjects with PD2q37.3 had fluorescence in situ hybridization evidence for the presence of one polymorphic probe (D2S2986) and two proximal non-polymorphic probes (D2S447), one on each chromosome 2, providing evidence that this region (2q37DS) was not deleted.

2. Phenotype comparison of features found in subjects with the 2q37DS and the PD2q37.3.

3. Comparison of size and gene content of the cytogenetically identified CNVs at 2q37 within subjects with 2q37DS using Affymetrix® Whole Genome 2.7M array.

**Results:** [1] We identified 37 cases with PD2q37.3 in 630 autism subjects (5.9%); and a conservatively calculated population incidence of 4.4%. [2] Comparison of 37 subjects harbouring PD2q37.3 revealed strikingly similar phenotypes to 3 subjects having full 2q37DS, including ID. [3] 3 subjects with 2q37DS were monosomic for 7, 6, and 4 integral genes respectively, five of which expression has previously been studied in association with 2q37DS: AGAP, HDAC4, PASK, HDLBP, FARP, plus 2 novel genes yet to be explored: GPR35, a possible ligand of the GNAS1 protein, and STK25, closest to PD2q37.3, a serine/threonine kinase effecting response to environmental stress, expressed largely in brain, and known to be involved in human neuropathogenesis.

**Conclusions:** The increased incidence of PD2q37.3 within our autism cohort (35% as compared to unaffected population controls), in addition to the strikingly similar phenotypes to subjects having the full 2q37DS, including autism and ID, further heightens the need to study the etiologic and functional impact of this polymorphism in autism.

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**Keywords:** 2q37 Deletion Syndrome, Autism Spectrum Disorder, Intellectual Disability, Copy Number Variants, Polymorphism

**Funded by:** Rare Disease Foundation, BC Children’s Hospital Foundation, the CFI Leading Edge, and BC Knowledge Development Fund
Exome Sequencing in Autism Spectrum Disorder.

Susan Walker  
Postdoctoral Fellow

**Mentor:** Stephen Scherer

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**Abstract:**
Autism Spectrum Disorder (ASD) is neurological condition characterised by limited communication skills, impaired social interaction and repetitive behaviours. There is a strong but complex genetic etiology with perhaps hundreds of contributing risk loci, some of which are now known (e.g. SHANK1, SHANK2, SHANK3, NRXN1, NRXN3, PTCHD1 and 16p11.2). Recently, Next Generation Sequencing (NGS) technologies have proven to be powerful tools for identifying mutations underlying Mendelian diseases and contributing to multigenic disorders. To discover rare genetic variants and new genes associated with ASD, we are carrying out detailed genomic analysis combining exome and whole-genome sequence data with high resolution micro-arrays in a cohort of 1000 Canadian families.

From the first 700 individuals analysed by exome sequencing with SOLiD 5500xl, we find in the order of 24,000 single nucleotide variants per individual, of which approximately 350 are novel and in coding regions. We have uncovered numerous rare and novel inherited variants that appear to segregate with the phenotype in genes previously associated with ASD such as NRXN1, NLGN4X, ARID1B and CHD8, including mutations resulting in likely haploinsufficiency. De novo mutations have also been discovered implicating new genes such as RIMS2, TAOK2, and LYPD6B in the disorders. We have found multiple individuals carrying potentially pathogenic both CNVs and SNVs and in some cases more than one arising de novo. Additional incidental findings from our study have also instigated clinical follow-up such as early cancer screening in families with cancer syndromes.

Now, we are pursuing sequencing using semiconductor sequencing on the Ion Proton System. In the first trio family analysed we detected approximately 19,800 coding single nucleotide variants per person. In comparison with whole genome sequencing data from the same individuals, we identified 91% of the known exonic variants with an estimated false positive rate of 9%. Moreover, analyses of these data correctly recognised four known de novo mutations including three substitution variants in genes KIAA1217, FAT3, STXBPS5L and a single base insertion in USP54.

Our data support a multigenic, multifactorial model for Autism susceptibility and highlight the necessity for extensive information of both genotypes and phenotypes to further our understanding of complex disorders.

**Keywords:** Autism, Gene, Variant, Exome, Micro-array

**Funded by:** NeuroDevNet Postdoctoral Fellowship (SW), NeuroDevNet ASD Demonstration Project, Ontario Research Fund
Theme 5 - Genes and Epigenetics  Poster # 25

Meta-Analysis of Gene Expression Profiles in the Blood and Brain Tissues of Individuals with Autism Spectrum Disorders.

Carolyn Ch’ng  Master’s Candidate

Mentor:          Paul Pavlidis
Author(s):       C. Ch’ng, W. Kwok, S. Rogic, and P. Pavlidis
Institution(s):  Centre for High-Throughput Biology, University of British Columbia

Abstract:
Autism spectrum disorder (ASD) is clinically heterogeneous and biologically complex. In general it remains unclear, what biological factors lead to changes in the brains of autistic individuals. A considerable number of transcriptome analyses have been performed in attempts to address this question, but have not yielded a clear consensus. Individually, they have not led to any significant advance in understanding the autistic phenotype as a whole. We hypothesized that there might be molecular commonalities in the transcriptome that would emerge in a combined or meta-analysis. Here, we report a meta-analysis of over 1000 microarrays across 12 independent studies on expression changes in ASD compared to unaffected individuals, in blood and brain. We identified a number of genes that are consistently differentially expressed across studies of the brain, suggestive of effects on mitochondrial function. Consistent changes were more difficult to identify in blood, despite individual studies tending to exhibit larger effects than the brain studies. In conclusion, our meta-analysis reveals subtle but consistent expression changes in the brains of individuals with ASD. Our results are the strongest evidence to date of a common transcriptome signature in the brains of individuals with ASD.

Keywords:         autism spectrum disorders, gene expression, blood, post-mortem brain, meta-analysis
Funded by:         NeuroDevNet Opportunities Initiative Award, Canadian Institutes of Health Research
Theme 5 - Genes and Epigenetics  Poster # 26

Meta-Analysis of Gene Expression in Animal Models of FASD.

Sanja Rogic  Research Associate

Mentor:  Paul Pavlidis
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Institution(s):  Centre for Highthroughput Biology, University of British Columbia

Abstract:
Introduction: While significant progress has been made in understanding the spectrum of possible malformations and neurobehavioral abnormalities in FASD and number of maternal risk factors has been identified, the molecular mechanisms of alcohol responses still remain unclear.

Objectives: The objective of our study is to use meta-analysis of publicly available gene expression datasets of prenatal alcohol exposure (PAE) to identify genes with consistent expression changes.

Methods: We searched public data repositories as well as publish literature for PAE gene expression datasets. After retaining only datasets with appropriate experimental design, we obtained 10 rodent datasets, comprised of 63 alcohol-exposed and 83 control samples. The collected datasets were heterogeneous in a number of ways; they differed with respect to the array platform employed, organism part used for RNA extraction, developmental stage at the time of the treatment and at the time of RNA extraction, and alcohol exposure method and duration. While this posed some challenges in data integration, it also allowed us to look for similarity and differences in terms of gene expression changes between different models of PAE.

The datasets were first processed and analyzed independently: after excluding low-quality samples and performing batch correction where needed, the datasets were uniformly normalized and differential gene expression analysis was done using a linear modeling approach. The resulting data was integrated at the gene level using Fisher’s combined probability method and meta-ranking method.

Results: When all 10 dataset were included in the meta-analysis, we obtained 5 up-regulated and 531 down-regulated genes at FDR<0.05. To test the robustness of these findings, we performed jackknife analysis, by removing one dataset at the time and performing the meta-analysis on the remaining ones, for each study in turn. There were 112 down-regulated genes that had FDR<0.1 in each of the jackknife runs and they were selected as the core signature genes. Further analysis of identified signature genes is underway.

Conclusions: Using meta-analytical approaches we were able to identify a number of genes that are consistently differentially expressed in PAE animals across multiple studies, which otherwise seemed to be discordant. Our results may give new insights into the effects of PAE. The genes we identified are also being used as candidates in the NeuroDevNet FASD genetics study.

Keywords: FASD, PAE, alcohol, gene expression, meta-analysis

Funded by: NeuroDevNet Opportunities Initiative Award, NIH R01GM076990
Epidemiological Findings and Epigenetic Changes in Human Brain Tissue Exposed to Alcohol In Utero.

Jessica Jarmasz  Master’s Candidate

Mentor: Marc R. Del Bigio
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Institution(s): 1University of Manitoba, Department of Pathology; 2Manitoba Institute of Child Health (MICH); 3University of Manitoba, Department of Biochemistry & Medical Genetics

Abstract:
Introduction: Alcohol consumption during pregnancy continues to occur despite the known negative effects on the developing fetus such as birth defects, brain underdevelopment and facial abnormalities. Fetal Alcohol Spectrum Disorder (FASD) costs Canada billions of dollars each year. Considerable research has been conducted to investigate how alcohol affects development, with the majority being animal studies and <25 human autopsy cases.

Objectives & Methods: With appropriate ethics approval, autopsy records at Health Sciences Centre (Winnipeg, Manitoba) were retrospectively reviewed. Maternal alcohol consumption during pregnancy and/or an FASD diagnosis was identified in 154 human autopsy reports. An epidemiological review of the cases will be established. A qualitative rating of estimated alcohol exposure among the younger cases will be established (e.g. low, early on, heavy throughout). Congenital anomalies and developmental malformations will be identified, along with facial dysmorphisms and certain cardiac and brain malformations that are associated with FASD (e.g. ventricular and atrial septal defects, microcephaly etc.). Neuropathological findings are the focus of an accompanying poster (Basalah et al.). One of the major hypotheses addressing the adverse effect of alcohol on the developing brain relates to the ability of alcohol to cause epigenetic changes. Epigenetics is the study of heritable changes in gene expression that do not result in DNA sequence changes. Of the 154 cases, 27 human hippocampal/medial temporal brain samples will be examined at a molecular level as an age progression series. Samples are split up into 5 age groups: fetuses (6), infants (6), children (6), teens (7) and adults (2).

Results: Using immunohistochemistry, age groups are stained with 12 epigenetic markers and microscopically examined for differences. Preliminary data shows obvious differences in the germinal matrix and temporal cortex among the younger age groups [fetuses (6), infants (6), children (6), teens (7) and adults (2)].

Conclusions: The epigenetic focus of this study is important because it can confirm the findings found among the animal experiments. This is part of a larger CIHR-funded group project designed to explore epigenetic changes, especially DNA methylation, in a range of FASD models. A potential future application of the knowledge might be in the earlier diagnosis of FASD, which will allow provision of better care to affected children.

Keywords: FASD, Epigenetics, hippocampus, human development, epidemiology, alcohol

Funded by: Canada Research Chair funding to MRD
Ethanol Alters DNA Methylation and Methylation-Related Genes in Differentiating Neural Stem Cells: Implications for Fetal Alcohol Spectrum Disorders.

Vichithra Rasangi Batuwita Liyanage  Doctoral Candidate

Mentor:  Mojgan Rastegar
Author(s):  V.R.B. Liyanage, R.M. Zachariah, and M. Rastegar
Institution(s):  Regenerative Medicine Program, Faculty of Medicine, University of Manitoba, Department of Biochemistry and Medical Genetics, University of Manitoba

Abstract:
Introduction: Prenatal exposure to ethanol leads to range of neurodevelopmental disorders known as Fetal Alcohol Spectrum Disorders (FASD). Apart from the genetic factors, recent studies show the role of epigenetic reprogramming as a mechanism of ethanol teratogenesis. There is evidence for the role of DNA methylation and methylation related genes in FASD pathogenesis. MeCP2 and DNMT proteins are key epigenetic regulators in brain. Previous studies have shown the misregulation of these methylation-related genes in response to ethanol exposure.

Objectives: In this study, we aimed to assess the effects of ethanol on the global DNA methylation program, expression of methylation-related genes and role of epigenetic mechanisms in regulating selected methylation-related genes.

Methods: We utilized differentiating neural stem cells as an in vitro system to model binge ethanol exposure during neural development.

Results: Our results show differential effects of ethanol on global DNA methylation and the expression of methylation-related genes. We also provide novel epigenetic mechanisms for ethanol-mediated misregulation of methylation-related genes expression during neural stem cell differentiation.

Conclusions: Our studies provide insights on understanding the role of epigenetic mechanisms, specifically DNA methylation in FASD pathogenesis.

Keywords: DNA methylation; Epigenetics; Fetal Alcohol Spectrum Disorders (FASD)

Funded by: Scottish Rite Charitable Foundation of Canada (SRCFC, Grant 10110) and Natural Sciences and Engineering Research Council of Canada
DNA Methylation Changes in Fetal Alcohol Spectrum Disorder.

Elodie Portales-Casamar  
Research Associate

Mentor: Paul Pavlidis
Author(s): E. Portales-Casamar¹, S. Mah², J. MacIsaac², M. Jones², S. Provost³, M-P. Dubé³, J. Reynolds⁴, P. Pavlidis¹, and M. Kobor²
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Abstract: Prenatal alcohol exposure is a major, preventable cause of behavioural and cognitive deficits in children. Despite extensive research, a unique neurobehavioural profile for children affected by prenatal alcohol exposure remains elusive. The NeuroDevNet Fetal Alcohol Spectrum Disorder (FASD) project is investigating how genetic and environmental factors interact with gestational alcohol exposure to produce neurobehavioural and neurobiological deficits in children.

Objectives: To investigate differences in DNA methylation between FASD cases and controls and gain understanding in the molecular mechanisms underlying brain function.

Methods: The epigenetics cohort included 214 children from 5 to 18 years of age (112 FASD:102 Control). DNA methylation was assessed using the Illumina HumanMethylation450 array on DNA extracted from buccal swabs. Each child also completed an extensive battery of psychometric tests, neuroimaging, and novel eye tracking assessments.

Results and Conclusions: After performing quality control assessments of the raw data and filtering out problematic samples and probes, we obtained a dataset of 206 samples (110 FASD:96 Control) and 404030 probes. After normalization, we performed a Surrogate Variable Analysis (SVA) to identify batch effects as well as any other unwanted variation in the data. The surrogate variables identified were included in our linear model to assess differential methylation between cases and controls. We identified 1661 differentially methylated probes (FDR-corrected Pvalue < 0.05). After correcting for confounding effects of genetic background we were left with 658 significantly differentially methylated probes that were further investigated for biological significance. Preliminary analyses point to several genes of interest that contain multiple probes up- or down-methylated in FASD samples. Enrichment analyses using the genes up-methylated in FASD and disease annotations from Neurocarta show a significant enrichment in genes associated with epilepsy and autism. This finding could reflect the fact that these genes are generally involved in brain development and affected in FASD cases.

Keywords: Epigenetics, FASD, Differential Methylation

Funded by: NeuroDevNet Neuroinformatics Core and NeuroDevNet FASD Demonstration Project
Theme 5 - Genes and Epigenetics  Poster # 30


Kaia Hookenson  Master’s Candidate

Mentor:  Tim Oberlander
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Institution(s):  University of British Columbia

Abstract:

Introduction: Methyl nutrient status (folate and vitamin B12) imbalances disrupts one-carbon metabolism, influences DNA methylation and may increase risk for mood disorders. Folate and vitamin B12 (B12) are required as enzymatic cofactors to produce S-Adenosylmethionine, the key methyl donor. The neurotransmitter serotonin (5-HT) plays a critical role in fetal neurodevelopment and function. DNA methylation has been shown to influence SLC6A4 expression (encodes 5-HTT), the transmembrane serotonin transporter (5-HTT) that governs 5-HT reuptake. The role of folate and B12 in depression remains unclear, particularly the influence of methyl nutrient status on SLC6A4 methylation in mothers and newborns.

Objectives: To study the associations between maternal mood, serum folate and B12 concentrations during pregnancy, and SLC6A4 methylation in mothers and their newborns.

Methods: In a prospective cohort of pregnant women (treated (n=58) and not treated (n=34) with SSRI antidepressant), folate and B12 concentrations were determined in 3rd trimester maternal serum samples (n=83) [Abbott AxSYM microparticle enzyme immunoassay]. Maternal mood was assessed using the Hamilton Rating Scale for Depression (HAM-D) and Anxiety (HAM-A) during the 2nd (n=91) and 3rd (n=85) trimester of pregnancy. The methylation status at 10 CpG sites of the SLC6A4 promoter region in 3rd trimester maternal peripheral blood leukocytes (n=85), and cord blood leukocytes collected from infants at birth (n=66), was quantified (bisulfite pyrosequencing). Data were analyzed by linear models and adjusted for reported influences of maternal mood scores and SLC6A4 methylation.

Results: Lower maternal folate concentrations were associated with higher 2nd trimester anxiety symptoms (HAM-A) (p<0.05). Maternal folate concentrations were positively associated with maternal SLC6A4 methylation at CpGs 1,3,9, and mean methylation across all 10 CpG sites (p<0.05). There was no association between maternal serum B12 concentrations and maternal SLC6A4 methylation. An interaction was observed between maternal serum folate and B12 concentrations, whereby women with lower serum folate and B12 concentrations had higher SLC6A4 Cp9 methylation compared to those with lower serum folate concentrations and higher serum B12 concentrations (p<0.05). Higher maternal serum B12 concentrations were associated with higher infant SLC6A4 methylation at CpG5 (p<0.05). Lower SLC6A4 CpG1 methylation was observed in infants from women with lower serum folate and B12 concentrations compared to infants from women with lower serum folate concentrations but higher serum B12 concentrations (p<0.05).

Conclusions: These findings suggest maternal methyl nutrient status affects maternal mood during pregnancy and SLC6A4 methylation in mothers and their newborns. The clinical implications of maternal B12/folate imbalance remains to be studied.

Keywords: Folate, Vitamin B12, DNA Methylation, SLC6A4, Pregnancy, Mood Disorders

Funded by: NeuroDevNet-CFRI Graduate Studentship [JW], Canadian Institutes of Health Research, Child and Family Research Institute
Epigenetics and Early Intervention: A Study of DNA Methylation in the Nurse Family Partnership.

Kieran O’Donnell  Postdoctoral Fellow

Mentor: Michael Meaney
Author(s): K. O’Donnell, K. Beckmann, C. Li, D. Olds, E. Grigorenko, J. Holbrook, M. Kobor, J. Leckman and M. Meaney
Institution(s): McGill University

Abstract:
Maternal perinatal anxiety/depression, lower socioeconomic status (SES) and child abuse all associate with poor child and adolescent mental health. These effects are, in part at least, mediated by parent – child interactions. Parenting interventions such as the Nurse Family Partnership (NFP) are effective at reducing some of the sequelae associated with early adversity. This perinatal nurse visitation program targets high risk (teenage, unmarried and low SES) mothers and reduces cases of child neglect and child behavioral problems. The biological mechanisms which mediate these treatment effects are unknown, although recent work highlights genetic influences reflecting the potential importance of gene x environment (G x E) interactions. The possibility that this intervention may influence epigenetic processes is unexplored.

We used a genome-wide approach (Illumina humanmethylation 450 Beadchip array) to assess DNA methylation in whole blood samples from adult offspring [age 27 years] of women from treatment and control groups [n=89]. Methylation data were analysed using principal component analysis and Bartlett’s test for variance analyses. We found a significant effect of perinatal intervention on DNA methylation at age 27. Strikingly, intervention was associated with significantly increased variance in DNA methylation profiles in the treatment group. Enrichment analyses of differentially and variably methylated probes point to neurodevelopmental pathways of relevance to psychiatric disorders. We provide some of the first clinical evidence that early intervention is associated with persistent alterations in DNA methylation. Future research will determine the importance of these altered DNA methylation profiles for psychiatric outcomes at age 27 and potential G x E effects. These preliminary data provide a potential epigenetic mechanism to explain some of the treatment effects associated with early intervention programmes such as the NFP.

Keywords: Epigenetics, intervention, DNA methylation

Funded by: NeuroDevNet-CIFAR Postdoctoral Fellowship (KO’D), CIHR, Sackler program for epigenetics and psychobiology
Theme 5 - Genes and Epigenetics  Poster # 32

Acute Ethanol Exposure Alters Histone Modifications and Apoptotic Gene Expression in the Mouse Brain.

Alexandre Lussier  Master’s Candidate

Mentor: Michael Kobor
Author(s): A. Lussier¹, K. Hamre², D. Goldowitz¹, and M. S. Kobor¹
Institution(s): ¹Centre for Molecular Medicine and Therapeutics, Child and Family Research Institute, University of British Columbia; ²University of Tennessee Health Science Center

Abstract:
Introduction: Exposure to alcohol during the early stages of life disrupts a number of key molecular pathways, often resulting in abnormal brain development. Binge-like ethanol exposure during development induces widespread apoptosis in the developing brain, and while the exact mechanisms through which this occurs remain unknown, it could be mediated by alterations in epigenetic programming. Various histone modifications, such as H2AX phosphorylation (γH2AX), respond to DNA damage and apoptosis. Combined with subtle changes in the pattern of repressive or active histone marks, these modifications may lead to the activation of apoptotic programs and subsequent neurodegeneration.

Objectives: To determine the role of histone modifications in ethanol-induced neurodegeneration.
Aim 1: Identify histone modifications patterns altered by acute ethanol exposure
Aim 2: Identify changes in gene expression associated with apoptosis and correlating with changes in various histone marks.

Methods: C57BL/6J mice were exposed to alcohol on postnatal day 7 via 2 subcutaneous injections of 2.5 g/kg of ethanol 2 hours apart with controls given isovolumetric saline. Brain tissue (cerebellum, hippocampus and cerebral cortex) was collected and flash frozen 7 hours after the initial injection. Histones were extracted from the tissue and the changes in various chromatin marks were assayed by western blot analysis. Changes in gene expression were assayed by quantitative PCR.

Results: The observed shifts in histone modifications favor changes in transcriptional activity, with the ethanol treated samples showing altered levels of H3K4 and H3K9 methylation, as well as H4 acetylation. These differences were region specific, with the hippocampus showing little change, and were also marked by differences between male and female mice. A shift in the expression of apoptotic genes was also observed, along with an increase in H2AX phosphorylation across brain regions.

Conclusions: These results provide evidence that changes in histone acetylation and methylation may be an important means through which ethanol alters apoptotic gene expression and induces neurodegeneration. The increase in γH2AX is indicative of double-stranded breaks, which may act to potentiate apoptosis after alcohol exposure. These results also offer a potential therapeutic avenue for treating and preventing the defects caused by developmental exposure to alcohol.

Keywords: Alcohol, histone modifications, apoptosis, gene expression

Funded by: NeuroDevNet FASD Demonstration Project, Canadian Institute For Advanced Research (CIFAR), Dept. of Anat. & Neurobiol., Univ. of Tenn. Health Sci. Center
Theme 5 - Genes and Epigenetics  **Poster # 33**

**Disruption of TrkB Isoform Balance and Signaling via mTOR/p70S6K is Associated with Decreased Excitatory Synapses in a Valproic Acid-Induced Mouse Model of Autism.**

**Chiara Nicolini**  Doctoral Candidate

**Mentor:** Margaret Fahnestock  
**Author(s):** C. Nicolini¹, V. Aksenov², E. Rosa¹, and M. Fahnestock¹²  
**Institution(s):** ¹Department of Psychiatry and Behavioural Neurosciences, McMaster University; ²Department of Biology, McMaster University

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**Abstract:**

**Background:** Maternal exposure to the anticonvulsant valproic acid (VPA) during pregnancy has been reported to induce autism-like phenotypes in both humans and rodents. Nonetheless, the molecular mechanisms underlying autism-like behaviours are yet to be elucidated. Genetic studies point to a major role for synapse abnormalities in Autism Spectrum Disorder (ASD). ASD-linked mutations have been identified in specific synaptic genes including those involved in the Akt/mTOR pathway which regulates spine protein synthesis and the Neurexin-Neuroligin-Shank pathway associated with excitation-inhibition imbalance. We previously demonstrated disruptions of the BDNF/TrkB/mTOR signaling pathway in human post mortem autism versus control fusiform gyrus, an area of the brain implicated in social interaction and face recognition deficits characteristic of ASD.

**Objectives:** We aimed to investigate whether alterations in TrkB and its downstream signaling cascade were present and associated with changes in excitatory/inhibitory synapse balance and autism-like behaviour in the offspring of VPA-injected mice.

**Methods:** Pregnant CD1 females received a single intraperitoneal injection of 500mg/kg VPA on gestational day 12, while controls were injected with only saline. Dams were weaned on postnatal day (PND) 21 and offspring’s behaviour and somatosensory function were evaluated on PND29. Litters were then sacrificed and brain tissue harvested on PND30. Protein expression of TrkB isoforms, mTOR, p70S6K and the excitatory postsynaptic marker PSD-95 were measured by Western blotting in the temporal/parietal neocortices of 14 VPA-induced ASD mice and 11 saline-injected controls.

**Results:** Offspring of VPA-injected mothers exhibited autism-like behaviour in tests of nest-seeking, negative geotaxis and social interaction preference. Furthermore, we found a significant increase in truncated TrkB isoforms and a significant decrease in full-length TrkB (TrkB-FL), mTOR, p70S6K and PSD-95 protein in VPA-exposed mice versus controls.

**Conclusions:** Behavioural and molecular results indicate that imbalances in TrkB isoforms leading to decreased downstream signaling and ultimately reduced excitatory synapses may play a key role in the etiology of autistic traits in VPA-exposed CD1 mice. Increased truncated TrkB isoforms and decreased TrkB-FL, mTOR, p70S6K and PSD-95 suggest that a dysfunctional BDNF/TrkB signaling pathway through mTOR/p70S6K may result in decreased protein translation at spines. This may affect excitatory synapses and consequently development and maintenance of functional neuronal circuits causing the autism-like behaviours exhibited by the offspring of VPA-injected mice. VPA-exposed mice will aid in determining the contribution of abnormalities in BDNF/TrkB signaling to ASD deficits and thus improve our understanding of ASD etiology.

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**Keywords:** BDNF, protein, Western blot, behavioural tests, PSD-95, VPA-induced ASD mouse model

**Funded by:** A scholarship from the Autism Research Training [ART] program to C.N.
Corticotropin-Releasing Hormone mRNA Expression in the PVN and the Amygdala and Anxiety-Like Behaviour Profile Following Prenatal Alcohol Exposure and Chronic Mild Stress in Adulthood.

Ni Lan  Research Associate

Mentor: Joanne Weinberg  
Author(s): N. Lan¹², K.G.C. Hellemans¹³, L. Ellis¹, and J. Weinberg¹  
Institution(s): ¹Department of Cellular and Physiological Sciences, University of British Columbia; ²Department of Anatomy, China Medical University; ³Department of Psychology, Carleton University Ottawa

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Abstract:

Introduction: The predisposition toward neurodevelopmental disorders, including affective disorders and autism, has been associated with stress-related early life adverse events, such as prenatal stress. Similarly, prenatal alcohol exposure (PAE) may increase the risk for mental health problems across the lifespan. Pre-existing hypothalamic-pituitary-adrenal (HPA) abnormalities and therefore a sensitized stress response system may be a major contributory factor in the pathogenesis of some forms of depression and anxiety disorders. Both clinical and animal studies have shown that PAE reprograms the fetal HPA axis such that HPA tone is increased throughout life.

Objectives: Utilizing an animal model, we investigated whether PAE combined with exposure to unpredictable chronic mild stress (CMS) in adulthood leads to neurobehavioural changes that increase susceptibility to the development of anxiety/depressive-like behaviours. Specifically, we examined the central corticotropin-releasing hormone (CRH) pathway that plays a key role in physiological responses to stress and pathophysiology of anxiety and depression.

Methods: Adult male and female offspring from PAE, pair-fed (PF), and ad libitum-fed control (C) groups were exposed to 10 days of CMS or remained undisturbed (non-CMS). Animals were then tested on the elevated plus maze, a task commonly used to assess anxiety-like behaviors in rodents. Brains were collected to analyze CRH mRNA in the PVN and amygdala, areas that regulate HPA activity and are important in depression/anxiety-like behavior. We have previously reported that CMS exposure leads to a significant increase in anxiety-like behaviours overall in a sexually dimorphic manner: following CMS, PAE males showed a decrease in percent time in the open arms, and PAE females showed reduced total open arm entries.

Results: We found that for PAE but not control males, CMS increased CRH mRNA levels in the PVN compared to those in the non-CMS condition, and levels were higher in PAE compared to PF and C males. Preliminary analysis of CRH mRNA levels in the central nucleus of the amygdala suggest a similar change toward higher CRH mRNA levels following CMS compared to those in the non-CMS condition in PAE but not control males.

Conclusions: The present data suggest that PAE may sensitize HPA activity through changes in central HPA regulation in the hypothalamus and amygdala, and thus may be a predisposing factor for the prevalence of mood disorders in FASD populations. Further investigation of the interplay between the stress and sex hormones will help to elucidate mechanisms underlying the anxiety-like behavioural profile found in this study.

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Keywords: prenatal alcohol exposure; chronic mild stress; hypothalamic-pituitary-adrenal; anxiety; CRH; amygdala

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Theme 5 - Genes and Epigenetics  

Poster # 35

DLX Transcriptional Regulation of Neural Progenitor Cell Fate in the Developing Forebrain.

David Eisenstat  Associate Investigator

Author(s):  S. Japoni1, M. Casey1, D.D. Eisenstat1,2  
Institution(s):  1Department of Medical Genetics, University of Alberta; 2Department of Pediatrics, University of Alberta

Abstract:

Introduction: Dlx homeobox genes are required for central nervous system development. Of the six Dlx genes in mice, Dlx1, Dlx2, Dlx5 and Dlx6 are expressed in the developing forebrain. Dlx genes encode transcription factors that bind to TAAT/ATTA motifs of regulatory regions and activate or repress target gene expression. The ventral forebrain gives rise to both glial and neuronal progenitors, the latter of which express Dlx. DLX1/DLX2 regulate the expression of Gad genes required for GABA synthesis. In the Dlx1/Dlx2 double knockout (DKO) mouse, tangential migration of inhibitory interneurons to the neocortex from the ganglionic eminences is disrupted. Additionally, Dlx1/Dlx2 DKO progenitors differentiate into oligodendrocytes when transplanted into a wild-type background. We hypothesize that Dlx1/Dlx2 actively repress oligodendrocyte differentiation while promoting interneuron differentiation and migration.

Objectives: Our goal is to identify DLX2 transcriptional targets required for interneuron migration and/or differentiation. Candidate homeodomain binding sites in several gene promoters required for oligodendrocyte and interneuron differentiation and migration have been identified. Nkx2.2 is required for proper oligodendrocyte differentiation. Myelin transcription factor 1 (Myt1) is proposed to regulate oligodendrocyte proliferation and differentiation. Disruption of signaling by the CXCR4 chemokine receptor and/or its ligand CXCL12 results in improper migration of interneurons in the forebrain.

Methods: We have used chromatin immunoprecipitation (ChIP) of embryonic mouse forebrain (E13.5) using a specific polyclonal antibody to DLX2 followed by PCR using oligonucleotide primers flanking candidate homeodomain binding motifs. Targets are characterized using gel shift and reporter gene assays in vitro and validated by gene expression studies in vivo comparing wild-type and DKO forebrain tissues.

Results: ChIP-based PCR of embryonic mouse forebrain demonstrated that DLX2 binds to regions containing putative DLX2 binding sites upstream of the transcriptional start sites of Nkx2.2, Myt1, and Cxcr4. DLX2 significantly affected luciferase reporter gene expression in vitro when co-expressed with the regulatory regions of Cxcr4 and Nkx2.2 occupied by DLX2 in vivo.

Conclusions: Our results support the hypothesis that DLX2 regulates expression of Cxcr4, Nkx2.2, and Myt1 in order to maintain proper differentiation and migration of interneurons and concurrently repress oligodendrocyte cell fate in the developing forebrain. Experiments are ongoing to assess specificity of DLX2 binding to these regulatory regions and to assess the expression of these genes in the Dlx1/Dlx2 DKO mouse forebrain.

Keywords:  Forebrain Development, Neuronal Cell Fate, Homeobox Gene, Chromatin Immunoprecipitation, Interneuron differentiation/migration

Funded by:  University of Alberta, Women and Children’s Health Research Institute (WCHRI) and the Kids with Cancer Society (AB)
Theme 5 - Genes and Epigenetics  Poster # 36

Functional Analysis of PTCHD1 Reveals Interactions with Synaptic Machinery and Involvement in the Hedgehog Pathway.

Kirti Mittal  Postdoctoral Fellow

Mentor: John Vincent
Author(s): K. Mittal, K. Sritharan, B. Degagne, and J. Vincent
Institution(s): Centre for Addiction and Mental Health, Toronto

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Abstract:
Introduction: Autism Spectrum Disorder (ASD) includes a range of complex neurodevelopment disorders. Approximately 75% have lifelong disability requiring substantial social and educational support.

Objectives: This study is focused on investigating the complex functional aspects of a recently identified gene -- PTCHD1, and how its disruption leads to Autism Spectrum Disorder and/or Intellectual Disability.

Methods: Firstly, we sought to identify PTCHD1 splice variants that might have higher or more specific expression in brain, and may thus be more relevant to the neurobiology in individuals with autism and/or intellectual disability who have PTCHD1 mutations. We performed mRNA expression analysis using mRNA from multiple tissues, including brain regions. Western blots were performed to confirm these findings.

To establish the involvement of PTCHD1 in the Hedgehog (Hh) signaling pathway, expression analysis was carried out with Hh pathway genes. We also probed for sub-cellular localization of PTCHD1 in cilia. Immunoprecipitation studies and expression studies were also performed to identify potential synaptic interacting partners or downstream targets.

Results: We identified a new transcript skipping exon 2 which is predicted to encode a 542 amino acid protein in comparison to the 888 amino acid protein encoded by the PTCHD1 long isoform. We also found the presence of an additional exon upstream of exon 1. The expression of these PTCHD1 transcripts is highest in human cerebellum.

The quantitative expression analysis with over expression of PTCHD1 revealed increased levels of neuroligin and neurexin mRNAs. Immunoprecipitation studies indicate interactions between PTCHD1 and Postsynaptic Density protein 95 (PSD-95) proteins. We also confirmed localization of PTCHD1 in cilia- which is where Hh receptors PTCH1 and 2 function, as well as evidence of PTCHD1 dimerization.

Conclusions: The new PTCHD1 transcripts are expressed chiefly in the brain, thus, these transcripts and encoded isoforms may be more relevant to autism and ID.

The quantitative expression analysis suggests a possible regulatory effect of PTCHD1 on genes that encode synaptic proteins. PSD-95 determines the size and strength of synapses in the postsynaptic density of neuronal excitatory synapses, and this putative interaction with the PTCHD1 protein could be important to elucidate disease etiology.

The Hh pathway plays an important role in embryonic development and adult stem cell functioning. Protein components of primary cilia are required for Hh signaling. We hypothesize that PTCHD1 localization to primary cilia could inhibit the Hh pathway in the developing brain, also that PTCHD1, as a chemosensor for extracellular SHh, may influence generation or functioning of synapses.

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Keywords: PTCHD1, Autism, Isoform, Hedgehog, Neuronal
Funded by: CIHR operating grant to J.B.V.
Theme 5 - Genes and Epigenetics  Poster # 37

**Behaviour and Neuroanatomy in Fragile X Mice.**

**Jonathan Lai**  Doctoral Candidate

**Mentor:** Jane Foster  
**Institution(s):** 1MiNDS Graduate Neuroscience Program; 2Psychiatry and Behavioural Neuroscience, McMaster University; 3Mouse Imaging Centre, SickKids

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**Abstract:**
Fragile X Syndrome (FXS) is the most common single gene cause of autism. Studies of children with FXS have identified different developmental trajectories of behaviour and neuroanatomical changes. Fmr1-/- mice mimic the etiology and phenotypic manifestations of FXS. These mice have been generated in 2 strains, C57Bl/6 and FVB. Fmr1-/- mice on a C57Bl/6 background have decreased cerebellar nuclei volume compared to wild type (WT) mice. The objective of this study is to associate early-life behaviours with neuroanatomical differences in fmr1-/- mice. Tests includes measures of growth and development – weight, righting reflex, eye opening, stress responsiveness – ultrasonic vocalizations in response to maternal separation at P7, open field behaviour at P17, sociability on P24, self-grooming at P25, social interaction at P27. Brains are perfused and fixed at P28, and imaged using a 7.0 Tesla MRI scanner. A separate cohort of 10 WT males and fmr1-/- mice are perfused and imaged at P60. Preliminary results show genotype and sex differences in behavioural outcomes. Male fmr1-/- mice showed accelerated development of righting reflex, whereas female fmr1-/- mice were not different than WT. Male FVB mice showed normal sociability while female FVB mice did not. Similarly, male and female fmr1-/- mice did not show social preference. Social interaction was increased in female fmr1-/- mice but not in males. In addition, the frequency of repetitive self-grooming bouts was increased in male but decreased in female fmr1-/- mice compared to WT mice. At P60, in contrast to fmr1-/-y mice on a C57Bl/6 background where a subtle neuroanatomical phenotype was observed, our MRI analysis revealed multiple changes in brain volume in the fmr1-/-y mice on a FVB background. Significant increases in relative volume (% total brain volume) were found in major white matter structures throughout the brain. Decreases were found in the globus pallidus (-2.5%, q=0.02) and a trend towards a decrease in the striatum (-1.9%,q=0.16) may be indicative of the increase in repetitive grooming bouts as this has been reported to correlate with self-groom time in BTBR mice. These results highlight the importance of genetic strain contribution on brain structure. In addition, combined results of behavioural analysis and imaging will shed light on biological mechanisms that may contribute to early life brain dysfunction and to neurodevelopmental disorders.

**Keywords:** autism, genetic mouse models, imaging, individual differences, developmental trajectory

**Funded by:** CFI, NSERC, OBI, Vanier-CIHR
Chronic Prenatal Ethanol Exposure Alters Insulin-Like Growth Factor Signaling in the Adult Guinea Pig.

Christine Dobson  Doctoral Candidate

Mentor:  James Reynolds
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Institution(s):  1Pharmacology and Toxicology Graduate Program, Department of Biomedical and Molecular Sciences, Queen’s University; 2Centre for Neuroscience Studies, Queen’s University; 3Office of the University Veterinarian, Queen’s University; 4Department of Obstetrics and Gynecology, McMaster University

Abstract:
Introduction: Maternal ethanol consumption during pregnancy can lead to a range of adverse developmental outcomes in offspring. Studies in children and animal models suggest that prenatal ethanol exposure causes metabolic dysregulation, including impaired glucose metabolism and insulin resistance. The mechanisms underlying ethanol-induced metabolic teratogenicity remain poorly understood, but may involve alterations in insulin and insulin-like growth factor (IGF) signaling pathways.

Objectives: The objective of this study was to test the hypothesis that chronic prenatal ethanol exposure (CPEE) causes altered IGF-1 and IGF-2 mRNA expression in the brain and liver of the adult guinea pig.

Methods: Pregnant Dunkin-Hartley-strain guinea pigs received ethanol (4 g/kg maternal body weight/day) or isocaloric-sucrose/pair-feeding (nutritional control) throughout gestation. Brain and liver were excised from both male and female offspring at postnatal day 150-200, followed by RNA extraction from tissue. IGF-1 and IGF-2 mRNA expression levels were measured in brain and liver using quantitative real-time PCR.

Results: In the liver, IGF-1 and IGF-2 mRNA levels were both decreased in CPEE offspring compared with nutritional control offspring. In the brain, there was a statistical interaction between maternal treatment and sex, such that IGF-2 mRNA expression was increased only in male CPEE offspring. There was no effect of CPEE on IGF-1 mRNA expression in brain. Ongoing analyses will assess IGF-1 receptor, IGF-2 receptor, insulin receptor, and insulin receptor substrate mRNA expression in offspring.

Conclusions: The data demonstrate that CPEE alters central and peripheral IGF-1 and IGF-2 signaling in adult guinea pig offspring, which may result in functional metabolic dysregulation.

Keywords: FASD, animal model, metabolism

Funded by:  CIHR grants MOP84553 and ELA80227.
Recombinant Inbred Strain Differences in Cell Death in a Mouse Model of FASD.

Julia Boyle  Research Assistant

Mentor: Daniel Goldowitz
Author(s): J. Boyle¹, K. Hamre², K. Wong¹, M. Kwon¹, S. Lattimer², A. Lussier¹, M. Korb¹, and D. Goldowitz¹
Institution(s): ¹Centre for Molecular Medicine and Therapeutics, University of British Columbia;
²University of Tennessee Health Science Center

Abstract:
FASD, recombinant inbred, QTL

Funded by: NeuroDevNet FASD Demonstration Project
Theme 6 – Neurocognitive  Poster # 40

The Association Between Reading Abilities and ADHD Dimensions: Evidence from a Twin Study.

Vickie Plourde  Doctoral Candidate

Mentor:  Ginette Dionne
Author(s):  V. Plourde1,2, N. Forget-Dubois1,2, M. Boivin1,2, M. Brendgen1,3, F. Vitaro1,4, G. Dionne1,2
Institution(s):  1Research unit on children’s psychosocial maladjustment; 2Université Laval;
3Université du Québec à Montréal; 4Université de Montréal

Abstract:
The association between reading difficulties and ADHD symptoms is well established in the scientific literature, although the underlying mechanisms are still little known. The objectives of the present study are 1) to study the associations between two reading abilities, decoding and comprehension and both ADHD dimensions, inattention and hyperactivity/impulsivity, 2) to estimate the genetic and environmental contributions to individual differences in reading abilities and ADHD, and 3) to decompose the associations between reading abilities and ADHD in their genetic and environmental components. Data were collected in a large population-based sample of twins (Québec Newborn Twin Study – QNTS). A total of 962 children were assessed for ADHD. A subgroup of 521 French-speaking children was assessed on reading. Reading abilities were assessed with normed computerized measures (THAL: Pépin & Loranger, 1999) in second grade. Teachers assessed ADHD symptoms with a questionnaire (QECS: Tremblay et al., 1987) in kindergarten and first grade. Results showed that the listwise correlations were stronger ($p < .01$) between reading abilities and inattention ($r = -.27$ to -.337) than between reading abilities and hyperactivity/impulsivity ($r = -.09$ to -.170). Moreover, the associations between reading abilities and inattention remained significant when control variables were considered (non-verbal intellectual quotient – Block Design test, behavior disorder symptoms) but the small correlations between reading and hyperactivity/impulsivity were no longer significant. In addition, the reading and the ADHD measures were all substantially heritable (range: 53% – 72%), and the associations between reading and inattention were mostly explained by genetic factors ($r_g = -.40$ to -.85). These results indicate that inattention is the principal ADHD component associated with reading abilities and that these associations are mainly explained by shared genetic factors.

Keywords:  Reading [decoding, comprehension], ADHD, Twin study

Funded by:  Canadian Institutes of Health Research (CIHR)
Comparison of Infant/Toddler Sensory Profile Scores in Autism Spectrum Disorder Sibling Groups.

Tamara Germani  Doctoral Candidate

Mentor: Lonnie Zwaigenbaum
Author(s): T. Germani1, L. Zwaigenbaum1, S. Bryson2, J. Brian3, I. Smith2, W. Roberts1, 5, P. Szatmari6, C. Roncadin7, N. Garon6, and T. Vaillancourt7
Institution(s): 1Autism Research Centre, Glenrose Rehab Hospital and University of Alberta; 2IWK Health Centre and Dalhousie University; 3Bloorview Research Institute; 4University of Toronto; 5The Hospital for Sick Children; 6Offord Centre for Child Studies and McMaster University; 7Peel’s Children Centre; 8Mount Allison University; 9University of Ottawa

Abstract:
Introduction: Sensory processing is the ability to receive, organize, and interpret sensory stimuli including, but not limited to, tactile, vestibular, and auditory experiences. Difficulties with sensory processing have been widely reported in children with autism spectrum disorder (ASD). The Infant/Toddler Sensory Profile (ITSP) is a parent report measure designed to detect potential sensory processing difficulties from birth to age 36 months. The ITSP assesses sensory processing within four quadrants: low registration, sensory seeking, sensory sensitivity, and sensation avoiding. In addition, the ITSP assesses six subscales (general, auditory, visual, tactile, vestibular, and oral sensory) of sensory processes. To date, no published study has prospectively investigated whether sensory processing in the first 2 years of life is predictive of subsequent ASD diagnoses.

Objectives: To compare ITSP Scores at 24 months between 3 groups, defined based on outcomes at age 3 years: a) high-risk infants (HR; with an older sibling with ASD) subsequently diagnosed with ASD (HR-ASD); b) high-risk infants not diagnosed with ASD (HR-N); and c) low risk infants with no family history of ASD (LR).

Methods: Data was collected as part of a multi-site longitudinal study aimed at prospectively monitoring the development of HR infants and for comparison, LR infants. Ethical approval was received at each participating site. The ITSP was administered at 24 months. Assessments at 3 years included the Autism Diagnostic Observation Scale, Autism Diagnostic Interview – Revised, standardized developmental measures and expert clinical judgment, blind to risk status and prior study assessments. A one-way MANOVA was performed to compare groups on overall sensory processing. Groups were also compared on the six sensory processing subscales with subsequently pair wise comparisons, applying a Bonferroni correction for multiple comparisons.

Results: There were 34 LR and 63 HR infants (including 15 HR-ASD) who completed the ITSP at a mean age of 24.7±1.1 months. The mean age at the 3-year assessment was 37.6±1.8 months. There were no differences in quadrant classifications of the ITSP between HR-ASD, HR-N, and LR groups at 3 years. However, there was a significant group difference in auditory processing (e.g., startles more easily than other infants) [F(2,92)=6.87, p=0.0016], with HR-ASD showing more difficulties than HR-N and LR groups. No other subscale group differences were detected.

Conclusions: Early auditory processing differences at 24 months were associated with subsequent ASD diagnoses among HR infants and thus may represent an early risk marker of ASD.

Keywords: autism, sensory, audition, infants, siblings

Funded by: NeuroDevNet ASD Demonstration Project, CIHR, Autism Speaks, AIHS, Stollery Children’s Hospital
Theme 6 – Neurocognitive  Poster # 42

Visual Scanning Patterns During Facial Identity and Emotion Processing in Typically Developing Individuals and those along the Autism Spectrum.

Heath Matheson  Postdoctoral Fellow

Mentor: Shannon Johnson
Author(s): H.E. Matheson, J.H. Filliter, P.A. McMullen, and S.A. Johnson
Institution(s): Department of Psychology and Neuroscience, Dalhousie University, Halifax Nova Scotia

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Abstract:
Introduction: Eye movement patterns are influenced by task demands. Malcolm et al. (2008) reported preferential scanning of the upper and lower face for information about identity and emotion, respectively. However, their data were based on scanning of faces displaying only two emotions: happiness and disgust. The use of two emotions limits the generalizability of their findings because both of these emotions are expressed using the lower half of the face.

Objectives: We sought to determine whether Malcolm et al.’s conclusions would extend to the perception of other emotions. Additionally, we investigated whether adults with autism spectrum disorder (ASD), a clinical population with known face processing difficulties, showed similar eye movement preferences to those of matched controls.

Methods: We used faces that expressed anger, disgust, fear, happiness, neutrality, sadness, and surprise. Participants made judgments of face identity or face emotion. Eye-tracking, reaction time, and accuracy data were collected.

Results: Participants made more upper- than lower-face fixations for both the emotion and identity tasks. The proportion of upper- to lower-face fixations was greater for the identity than the emotion task, regardless of face-emotions. However, relative reliance on the upper and lower regions of the face varied with emotion. Though participants with ASD fixated the upper face regions less than control participants, they still showed a general trend to fixate the upper more than the lower face.

Conclusions: Results of this experiment confirm the presence of top-down, task-driven effects on the visual scanning of faces. These effects depend on facial emotion and task though they are not as dramatic when considering all of the basic emotions. Additionally, there are qualitative similarities of visual scanning in individuals with and without ASD.

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Keywords: emotion processing, face processing, ASD, eye-movements
Funded by: Autism Research Training Program
Sex Differences in Visual Attention to Faces and Processing of Faces in Infancy.

Nurit Gazit Gurel  Doctoral Candidate

Mentor: Janet Werker
Author(s): N.G. Gurel, and J.F. Werker
Institution(s): University of British Columbia

Abstract:

Introduction: Research has shown that individuals with Autism observe and process faces differently than controls. Autism is not diagnosed in early infancy, so it is difficult to test when this abnormal pattern begins, and how it affects later developmental trajectories. However, Autism has been proposed to be an extreme form of maleness, and is more prevalent in males. Thus, observing the development of attention to faces and face processing in the two sexes may shed light on what may be missing or delayed in Autistic development, and perhaps on the mechanisms by which any differences come about.

Objectives: The aim of the study was to test whether male and female infants emerge from the early period of limited locomotion and manual control, at 4-5 months, with differences in attention to faces and eyes and in processing of faces, and whether any observed differences change with development. It was hypothesized that females would be better in detecting changes in the eye area and changes in face identity.

Methods: Two groups of infants – 4-5 month olds and 7-8 month olds, were tested. Infants were habituated to a colored static image of a single face, using the method of infant controlled habituation. At test, infants were presented with 6 test trials – 2 trials with the original stimulus, 2 trials with the same image except for a change in the eye area, and 2 trials with a different face in a similar pose to the habituation stimulus. Looking time to the images was recorded. In habituation it is predicted that if infants discriminate a change, they will show longer looking to the new image in comparison to the previously seen image, i.e. show a “novelty preference”.

Results: At 4-5 months, females showed a novelty preference for the stimulus with the change in eyes (p < 0.05), and for the change in face identity (p < 0.001), while the males did not. At 7-8 months, both sexes showed a novelty preference for the change in face identity.

Conclusions: The study reveals sex differences in attention to and/or processing of, faces and eyes in early infancy. This difference may be related to the sex difference in autism prevalence. Finding the underlying causes for these early differences, and looking at the developmental trajectories of these skills in infants at risk for autism, may help illuminate the development of autism and lead to better diagnosis and treatment.

Keywords: Autism, sex differences, face processing, development

Funded by: NSERC Vanier CGS funding to N. Gazit Gurel. NSERC and CIFAR funding to J. Werker.
Relationship Between Performance in High-Level Visual Recognition and Low-Level Visual Abilities in Individuals with Autism.

Fakhri Shafai
Doctoral Candidate

Mentor: Ipek Oruç
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Abstract:
Introduction: Individuals with autism spectrum disorder (ASD) are often found to be impaired in high-level visual recognition tasks, such as identification of faces or facial expressions. The relatively few studies of lower-level visual tasks have shown comparable visual perceptual abilities in ASD related to neurotypical controls. In fact, individuals with autism may even outperform controls with detail-oriented tasks (Dakin & Frith, 2005; Behrmann et. al., 2006). These results suggest that low-level tasks are less impacted in ASD compared to the high-level visual tasks such as face identification.

Objectives: Our goal was to determine whether high-level visual impairments in ASD, e.g., in the processing of faces, can be accounted for by problems in early stages of vision involving processing of spatial frequency and orientation.

Methods: Our ongoing study has examined 32 adult participants (16 adults with ASD and 16 controls) in a visual test battery that included two low-level and three high-level tasks. The low-level protocols measured (1) orientation discrimination performance across a range of base orientations, and (2) contrast sensitivity across a range of spatial frequencies. The high-level protocols measured performance in (1) face identification, (2) house recognition, and (3) facial expression discrimination.

Results: Performance patterns in both low-level tasks revealed two distinct clusters within the ASD group. One group of ASD participants were minimally impaired and their response patterns were indistinguishable from neurotypical controls. The other group, however, were significantly impaired compared to controls and yielded atypical patterns of performance for each low-level task. Performance in all three high-level tasks were significantly impaired in both ASD groups compared to controls. However, the high-level impairments seen in the “atypical” ASD group were significantly more severe than the “typical” ASD group.

Conclusions: ASD participant response patterns fell into one of two clusters in the tasks designed to test the most basic levels of vision. Following these clusters into the high-level tasks revealed that those with greater abnormalities in response patterns on low-level tasks also had greater impairments in high-level stimuli. On the other hand, both clusters in the ASD group showed significant high-level impairments compared to controls, despite the fact that one cluster within the ASD group showed minimal low-level impairment. Our results indicate that impairments in high-level visual recognition e.g. of faces, seen in autism partly stem from, but cannot be fully accounted for by problems in processing of lower-level visual properties.

Keywords: visual perception; autism; face recognition; contrast sensitivity; psychophysics

Funded by: NSERC Discovery grant RGPIN 402654-11

Jacalyn Guy  Doctoral Candidate

Mentor:  Armando Bertone
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Abstract:
Background: Individuals with Autism Spectrum Disorder (ASD) present both an atypical and distinctive visuo-perceptual profile (Mottron et al., 2006). Despite marked social and behavioural impairments, individuals with ASD often excel at tasks requiring the local analysis of detailed information and preferentially attend to the constituent parts of a stimulus rather than its whole form. It remains unknown, however, whether a bias for such local analysis is at the origin of other aspects of the social cognitive phenotype in ASD, such as facial information processing (Behrmann et al., 2006; Bertone et al., 2010).

Objectives: To assess local and global visual processing strategies used during social and non-social visuo-perceptual tasks in the same group of autistic and non-autistic children and adolescents.

Methods: A total of 70 children and adolescents (6–15 years) with and without ASD performed both a face identity discrimination (Exp 1) and Navon task (Exp 2) under conditions favouring either a local or global analysis. In Exp 1, performance was measured using face identity discrimination thresholds for conditions where the target and choice faces were presented in the same view, biasing a local analysis (front-front or same-view condition), and in different views, biasing a global analysis (front-side or view-change condition) (Morin et al., 2012). Local and global visual processing for nonsocial information was assessed for the same participants in Exp 2 using the Navon task (Navon 1977): a local and global hierarchical, compound letter task. Participants responded to either local or global features of the stimuli in two separate conditions. Performance was measured in terms of accuracy and reaction time.

Results: Performance across groups was comparable for the social, face identity discrimination task in both local and global conditions (Exp 1). For the non-social, Navon task, the ASD group performed significantly worse in the global condition, reflected by a higher error rate and slower average reaction time. When performance was assessed for the same participants across social and nonsocial tasks, decreased performance in the view-change condition of the face identity discrimination task was significantly correlated with slower reaction time in the global condition of the non-social, Navon task.

Conclusions: While the findings reveal a pattern of local interference for non-social information processing only, correlations across social and nonsocial tasks suggest that individuals with ASD may use a similar strategy for the processing of both social and nonsocial information in childhood and adolescence. We aim to further assess the role that development plays in this relationship.

Keywords: Autism spectrum disorder, vision, perception, cognition, global/local processing

Funded by: NeuroDevNet-ART Doctoral Fellowship (JG), fonds de la recherche en santé du québec
Theme 6 – Neurocognitive  Poster # 46

Adolescent Adversity and Prenatal Alcohol Exposure: Keep it Simple Please.

Wendy Comeau  Research Associate

Mentor: Joanne Weinberg
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Institution(s): Department of Cellular & Physiological Sciences, University of British Columbia, Vancouver

Abstract:

Introduction: Prenatal alcohol exposure (PAE)-related cognitive deficits are some of the more persistent negative outcomes found at all levels of alcohol exposure, although often more severe with increased exposure. Nonetheless, individuals with even moderate levels of exposure may show life-long cognitive impairments, although these may become apparent only under conditions of increased task complexity, attention, and working memory demands. Impairments in executive function (EF) with varying levels of PAE are well documented; suggesting that the regions that sub serve EF may be especially vulnerable to the deleterious effects of PAE. One important region is the prefrontal cortex (PFC), which facilitates components of EF including goal setting, planning, appropriate inhibitory responses, and attention. The extent of EF impairment varies considerably with PAE, however. Genetic makeup may account for some of the variability, but individual variability presents in preclinical studies as well where dose and genetics are tightly controlled. This suggests other factors must influence outcome. Indeed, early life adversity is known to impact brain development and is often linked to PAE. Furthermore, the impact of adversity is more harmful during sensitive periods of brain growth, such as adolescence, which is also a period of extensive change and maturation in the PFC, thus potentially increasing the impact on cognitive outcome.

Objectives: We investigated the impact of PAE and the interaction of PAE and adolescent adversity on EF in male rats.

Methods: Subjects were offspring of dams from one of three treatments 1) PAE (liquid diet with 36% of caloric intake from Etoh); 2) Pairfed (PF) yoked to PAE with the same liquid diet but with maltose-dextrin isocalorically substituted for Etoh; and 3) control (pellet control diet). During adolescence, half of the rats were exposed to 5 days of variable chronic mild stress twice daily [postnatal day 40 -45]. In adulthood, cognitive performance and executive function were assessed via initial training in a T-maze task, followed by training in the more complex 5-choice serial reaction time task. The strength of the latter task is that it allows for assessment of various components of EF as task difficulty increases.

Results: PAE animals displayed decreases in performance, visual attention deficits, lack of flexibility and hyperactivity as indicated by an altered learning curve, a decrease in accuracy, increased omissions, perseverations, and tray pokes.

Conclusions: The results show that five days of CMS is sufficient to pull out general PAE-related learning impairments under conditions of increased task difficulty.

Keywords: executive function, development, prenatal alcohol exposure, prefrontal cortex, attention

Funded by: NeuroDevNet FASD Demonstration Project, NIH/NIAAA AA007789, NCE of Canada to JW and NSERC to CAW
Effects of Prenatal Alcohol Exposure and Stress on Social Behaviour and Cognitive Function in Periadolescent and Adult Rats.

Parker Holman  
Doctoral Candidate

Mentor: Joanne Weinberg  
Author(s): P.J. Holman, W. Comeau, and J. Weinberg  
Institution(s): Department of Cellular & Physiological Sciences, University of British Columbia, Vancouver

Abstract:

Introduction: Prenatal alcohol exposure (PAE) is characterized by a range of life-long deficits, including impaired executive function and social behaviour. Importantly, stress has the capacity to exacerbate PAE-related cognitive and social deficits, particularly during vulnerable periods of development such as adolescence.

Objectives: We investigated social behaviour and cognitive function in periadolescent male rats using a social learning task. As adolescence (P30-45) has been identified as a unique time of susceptibility to stress, we also assessed the role of adolescent stress in modulating the effects of social distraction on executive function in adult PAE and control animals.

Methods: Pregnant rats were assigned to: 1) PAE: access to liquid ethanol diet ad libitum; 2) Pair-Fed: access to liquid control diet yoked to PAE consumption; or 3) Control: access to pelleted control diet ad libitum. Experiment 1: Periadolescent (P30) male offspring were tested on a social learning task consisting of four, 2-min sessions with the same social stimulus rat. On a fifth session, a novel social stimulus was introduced and social behaviours were observed. Experiment 2: During adolescence, offspring were subjected to 10 days of chronic mild stress (CMS) or remained undisturbed. In adulthood, executive function was assessed in a delayed Win-Shift task using an 8-arm radial maze (RAM), with a 20 min delay between training and testing. Next, animals repeated the task with the introduction of an unfamiliar conspecific (social distractor) during the 20 min delay, and time spent in social investigation was recorded.

Results: Periadolescent PAE males showed a reduced latency to initiate play in response to a novel social stimulus as compared to control males. In adulthood, CMS increased errors in control but not PAE males after 20 min delay on the RAM. Following social distraction, all animals showed an increase in RAM errors; however, non-CMS PAE females made significantly more errors than non-CMS control females following social distraction. Additionally, PAE animals showed sexually dimorphic alterations in social behaviour with the social distractor: males showed enhanced social investigation and females showed increased non-affiliative behaviour.

Conclusions: The present results indicate that PAE alters social learning, as periadolescent males appeared unable to differentiate between familiar and novel social stimuli. PAE effects on social behaviour are long lasting, as demonstrated by altered social behaviour in adult animals interacting with the social distractor. Furthermore, we found sexually dimorphic effects of prenatal group and adolescent stress on adult executive function both with and without social distraction.

Keywords: Prenatal Alcohol Exposure, Social Behavior, Executive Function

Funded by: NeuroDevNet FASD Demonstration Project, and NIH/NIAAA R37 AA007789 to JW
Theme 6 – Neurocognitive  Poster # 48

Working Memory and Visuospatial Deficits Correlate with Oculomotor Control in Children with Fetal Alcohol Spectrum Disorder.

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³Manitoba FASD Centre; ⁴Department of Genetics, Children’s Hospital of Eastern Ontario; ⁵Glenrose Rehabilitation Hospital; ⁶Lakeland Centre for FASD

Abstract:
Children with Fetal Alcohol Spectrum Disorder (FASD) or Prenatal Alcohol Exposure (PAE) frequently exhibit impairments on working memory and visuospatial tasks. The objective of this study was to determine if a performance-based relationship exists between psychometric tests and eye tracking tasks in children with FASD. Participants for this dataset were aged 5-17 years and included those diagnosed with an FASD (n=71), those with PAE but no clinical FASD diagnosis (n=20), and typically developing controls (n=111). Participants completed a neurobehavioral test battery, which included the NEPSY-II subtests of animal sorting, memory for names and arrows as well as the Working Memory Test Battery subtest of block recall. Each participant completed a series of saccadic eye movement tasks, which included the prosaccade, antisaccade, and memory-guided task. The FASD group performed worse than controls on the psychometric subtest measures of working memory which included animal sorting, memory for names and block recall. The FASD group also performed more poorly on arrows which is a visuospatial subtest. Compared with controls, the FASD group made more sequence errors on the memory-guided task and greater endpoint errors on the antisaccade and prosaccade tasks. Among the combined FASD/PAE group, block recall and animal sorting were highly correlated with sequence errors on the memory-guided task and arrows were highly correlated with prosaccade endpoint error. There were no significant correlations in the control group. This data suggests that working memory and visuospatial deficits in children with FASD/PAE are associated with difficulty controlling saccadic eye movements, and these assessment tools may be measuring overlapping brain regions damaged due to prenatal alcohol exposure. The results of this study demonstrate that eye movement control tasks directly relate to outcome measures obtained with psychometric tests that are used during FASD diagnosis, and may therefore help with early identification of children who would benefit from a multidisciplinary diagnostic assessment.

Keywords: FASD, eye tracking, psychometric testing, working memory, visuospatial skills
Funded by: NeuroDevNet FASD Demonstration Project
Semantic Memory Structure in Children and Adolescents with Autism Spectrum Disorder.

Shannon Johnson  Associate Investigator

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Institution(s): ¹Department of Psychology and Neuroscience, Dalhousie University; ²Departments of Pediatrics and Psychiatry, Dalhousie University; ³IWK Health Centre

Abstract:

Background: Learning and memory are fundamental cognitive processes and are critical for many aspects of skill development. Yet, we currently know little about how people with Autism Spectrum Disorder (ASD) learn and organize new information. One important aspect of learning and memory is semantic categorization, whereby related concepts are grouped and linked to form an organized semantic memory system. Categorization occurs hierarchically across three different levels: superordinate (‘Animal’), basic (‘Dog’), and subordinate (‘Beagle’; Rosch & Lloyed 1978). Typically developing individuals (TD) identify objects fastest at the basic level (Jolicoeur et al., 1984). Furthermore, there are differences in the ways TD categorize living versus non-living objects (McMullen & Purdy, 2006). In ASD, categorization appears to be based on concrete, rather than abstract, features (Shulman et al., 1995), and some studies suggest difficulty forming category prototypes (Klinger & Dawson, 2001).

Objectives: 1) To determine if and how categorization differs in ASD compared to TD using two semantic categorization tasks. 2) To examine group differences in living versus non-living categorization.

Methods: The current sample includes 21 high-functioning youths (8 to 18 years) with ASD and 34 age- and IQ-matched TD. For the Picture-Word Matching Task, participants were shown word and line drawing pairs of living and non-living objects to match at the three levels of categorization. For the Triadic Comparison Task, participants were shown three living or three nonliving words and indicated which two stimuli were most similar.

Results: Picture-Word Matching Task: We conducted three Level (basic, subordinate, superordinate) x Group (TD, ASD) mixed ANOVAs on overall, living, and nonliving reaction times (RTs). Analyses revealed effects of level only (p < .001). Independent samples t-tests on basic and subordinate RTs revealed ASD performed faster than controls at the basic (living: d = .38, nonliving: d = .32) and subordinate (living: d = .24) levels. Triadic Comparison Task: Examination of semantic conceptual maps revealed that maps across groups were highly similar. ASD differentiated animals more than TD (F[1,53] = 6.08, p = .02), primarily along the domesticity dimension (p < .001).

Conclusions: Youths with ASD demonstrated intact semantic organization and structure. ASD were faster at basic and subordinate level (living only) categorization than controls, and semantically differentiated animals to a greater extent than controls. Results indicate several similarities, and interesting differences, in semantic memory in ASD, and highlight the living/non-living distinction as an important direction for future studies.

Keywords: Autism Spectrum, Learning, Categorization

Funded by: NeuroDevNet-ART Doctoral Fellowship [KMR]; Nova Scotia Health Research Foundation
Theme 6 – Neurocognitive  Poster # 50

The Neurobehavioural Profile of Children and Adolescents with FASD: Findings from the NeuroDevNet FASD Project Study.

Kaitlyn McLachlan  Postdoctoral Fellow

Mentor: Carmen Rasmussen


Institutions: 1Department of Pediatrics, University of Alberta; 2Department of Pediatrics, University of British Columbia; 3Centre for Neuroscience Studies, Queens University; 4Department of Educational Psychology, University of Alberta; 5Glenrose Rehabilitation Hospital; 6Manitoba FASD Centre; 7Lakeland Centre for FASD; 8Department of Genetics, Children’s Hospital of Eastern Ontario.

Abstract:

Introduction: Evaluation of neurobehavioral functioning forms a critical element in diagnosing fetal alcohol spectrum disorder (FASD), particularly in the absence of physical features. Researchers continue to work towards identifying a neurobehavioral profile of FASD to better inform differential diagnosis and treatment recommendations, however, there is limited multi-site data in Canada.

Objectives: We sought to assess the neurobehavioral profile of a large multisite sample of Canadian children with FASD and prenatal alcohol exposure (PAE). Differences in neurobehavioral functioning across age and gender were also assessed.

Methods: 224 children and adolescents ages 5 to 18 (M = 11.23, SD = 3.37, 53.1% female) participated from the NeuroDevNet FASD project study cohort. Three groups were recruited across six Canadian clinical sites: FASD (n = 87), PAE but not FASD (n = 27), and typically developing controls (n = 110). Participants completed a neurocognitive battery assessing executive functioning, attention, verbal memory, working memory, visual perception, and academics.

Results: Children with FASD earned significantly lower scores across all measures relative to controls (p < .001), while the PAE group earned scores typically falling between the FASD and control groups. Results from a discriminant function analysis indicated all but one subtest (assessing attention and inhibition) significantly discriminated among groups, though complex tasks of inhibition, verbal memory, and working memory had the greatest discriminatory impact. Overall classification accuracy across the three groups using a cross-validated approach was 64.3%, with better accuracy in the FASD (71.9%) and control (71.8%) groups than the PAE group (13.6%). Gender effects were found on tests of verbal memory (girls outperforming boys) and visual perception (boys outperforming girls). Interactions between gender and diagnosis were not significant. Age was correlated with math ability (r = -.36, p = .001) and word reading scores (r = -.38, p < .001) in the FASD group, and with a measure of inhibition (r = -.43, p = .03) in the PAE group, indicating older participants performed worse (relative to normative levels) than younger participants. No significant associations were evident among controls, suggesting possible differences in the development of these cognitive abilities among children with PAE.

Discussion: Findings compliment a growing body of neurobehavioral profile studies among children with FASD showing deficits across multiple cognitive domains. Tests of executive functioning, verbal, and working memory were particularly sensitive in their ability to discriminate between groups, suggesting the importance of evaluating these domains in clinical assessments. Gender and age specific findings may serve to inform future clinical recommendations regarding intervention.

Keywords: FASD, prenatal alcohol exposure, cognitive functioning, neurobehavioral profile

Funded by: NeuroDevNet Postdoctoral Fellowship (KM), NeuroDevNet FASD Demonstration Project, Women and Children’s Health Research Institute
Does WISC-IV Underestimate the Intelligence of Autistic Children?

Anne-Marie Nader  
Doctoral Candidate

Mentor: Isabelle Soulières  
Author(s): A-M. Nader¹, V. Courchesne², I. Soulières¹,², and M. Dawson³  
Institution(s): ¹University of Quebec in Montreal; ²University of Montreal; ³Service de Recherche, Centre d’excellence en Troubles envahissants du développement de l’Université de Montréal (CETEDUM)

Abstract:
Introduction: Previous findings comparing autistic performance on WISC-III versus Raven’s Progressive Matrices (RPM) suggest that while both tests provide similar estimates of nonautistic intelligence, autistics perform significantly, and sometimes dramatically, better on RPM. These results suggest that RPM, a durable and important marker of fluid intelligence, better represents autistic intelligence than does Wechsler FSIQ. WISC-IV, released in 2004, introduced significant changes in Wechsler subtests and in the structure of different index scores. Indeed, the new perceptual reasoning index (PRI) has only one timed visuo-motor subtest and includes the new Matrix Reasoning subtest, which is similar to some aspects of RPM.

Objectives: We aimed to determine whether the latest WISC version continues to underestimate autistic intelligence.

Methods: 26 autistic and 22 typically developing (TD) children (age 6-16 years) completed WISC-IV and RPM at two different times. Levels of performance were compared through inspecting percentiles derived from mean standard scores (WISC-IV) and from mean raw scores and ages (RPM) for each group.

Results: While TD children achieved similar percentile values on RPM (73rd) and WISC-IV FSIQ (75th), this was not the case for autistic children. A significant difference between RPM (61th) and WISC-IV (21st) scores, with for some cases more than 50 percentile point difference, was found. While three autistic children had standard scores below 70 on WISC-IV, the lowest autistic RPM score was at the 10th percentile (IQ-equivalent estimate 81). The rest of the autistic children achieved RPM percentile scores of 18 or higher, with estimated RPM IQ-equivalents over 85. With respect to WISC-IV index scores, autistic children attained a mean Verbal Comprehension Index standard score of 84.6, compared to a mean PRI score of 104, which in turn was similar to their estimated RPM IQ-equivalent score.

Conclusions: Our results are consistent with and add to existing findings that Wechsler FSIQ significantly underestimates autistic intelligence. Given what is known about RPM as a complex test of fluid and general intelligence, our results also challenge the notion that autistic strengths are at best a collection of simple, isolated, and low-level perceptual abilities. Finally, our results provide preliminary evidence that the WISC-IV PRI index score may better estimate autistic intelligence than WISC-IV FSIQ. These findings merit attention in both research and clinical practice.

Keywords: autism, cognition, intelligence  
Funded by: NeuroDevNet-ART Doctoral Fellowship (A-MN), UQAM, FRSQ
Theme 6 – Neurocognitive  Poster # 52

Self-Perception of Competencies in Adolescents with Autism Spectrum Disorders.

Rosaria Furlano  Master’s Candidate

Mentor: Beth Kelley
Author(s): R. Furlano, E. Kelley, D.E. Wilson, and L. Hall
Institution(s): Queen’s University

Abstract:

Introduction: The positive illusory bias is the disparity between self-report of competence and actual competence, such that self-reported competence is substantially higher than actual competence. In the general population, a better than average effect is common, where individuals self-evaluate themselves more positively when asked to compare themselves to a hypothetical average target. A similar bias is prevalent in children with Autism Spectrum Disorders (ASD). Individuals with ASD self-report greater levels of social competence compared to parental-reports. They also rate themselves as more similar to typically-developing (TD) individuals compared to their parents’ ratings.

Objectives: To extend research on self-perceptions held by adolescents with ASD. The study examines how IQ and executive functioning relate to self-perceptions.

Methods: Forty-six participants, 23 in each group, (age range=12-18 years), participated. ASD and TD groups were matched on mental age. Many studies have examined the positive illusory bias using the Self-Perception Profile for Children [Harter, 1985]. However, individuals with ASD have difficulty describing their own mental states; therefore, we used self-report questions after participants completed both verbal and mathematic tasks. Participants were asked how well they thought they did prior to completing the tasks (pre-prediction). After they completed each task they were asked how well they thought they did (current post-prediction) and how well they thought they would do in the future (future post-prediction). Difference scores between actual performance and predicted performance were analyzed.

Results: A one-way MANOVA was conducted to determine the effect of group diagnosis on the three dependent variables: pre-predictions, current post-performance, and future post-performance. Significant differences were found between groups on the dependent measures, Wilks’s $\Lambda = .63$, $F(3,44) = 8.43$, $p < .001$, $\eta^2 = .55$. Pairwise comparisons indicated that the ASD group had higher difference scores in pre-prediction, current post-performance, and future post-performance questions. Correlation coefficients among difference scores suggest that participants with higher IQ have more accurate post-performance self-perceptions. Correlation coefficients among difference scores and the Delis-Kaplan Executive Function System suggest that participants with greater abilities in inhibition, working memory, and shifting/planning have more accurate post-performance self-perceptions.

Conclusions: Examining self-perceptions in ASD using pre/post task self-competence questions furthers our understanding of the causal mechanisms underlying this phenomenon. By giving adolescents something concrete to predict and reflect upon, we were able to eliminate bias on the part of the parent. This may help future research to develop strategies to deal with the potential negative implications associated with overly positive biases.

Keywords: Self-perceptions, Autism, Cognitive Abilities, Executive Functioning, IQ

Funded by: NeuroDevNet Opportunities Initiative Award [BK and DW]
Theme 6 – Neurocognitive  Poster # 53

**Academic Achievement is Predicted by Attention and Executive Function in Adolescents with ASD.**

**Layla Hall**  Master’s Candidate

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<th>Beth Kelley</th>
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<tr>
<td>Author(s):</td>
<td>L. Hall, E. Kelley, D.E. Wilson, R. Furlano, and J. Rajsic</td>
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<td>Institution(s):</td>
<td>Queen’s University</td>
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**Abstract:**

**Background:** Attention and executive function (EF) are two cognitive abilities that consist of the fundamental skills necessary for directing and maintaining focus, as well as goal-directed behaviour and problem solving. A connection between these cognitive abilities and academic achievement has been identified in typically developing (TD) adolescents. The relationship of attention and EF with academic achievement is relevant to clinical populations that have difficulties in these areas, such as individuals diagnosed with an autism spectrum disorder (ASD).

**Objectives:** The current study aims to extend our understanding of cognitive and academic difficulties among adolescents with ASD. This study examines the predictive relationship of EF and attention on academic achievement in adolescents with ASD. Findings will help clarify the nature of the relationship between cognitive and functional difficulties in adolescents with ASD.

**Methods:** Data collection was conducted on 40 adolescents (20 ASD and 20 TD), 11-18 years of age. Attention was assessed using three custom attention tasks administered on the computer. EF was assessed using five subtests from the Delis-Kaplan Executive Function System (DKEFS). Eye tracking also assessed both attention and EF. Academic ability was assessed using five subtests from the Woodcock-Johnson III Tests of Academic Achievement (WJ-III).

**Results:** Controlling for full-scale IQ and diagnosis, hierarchical multiple regression analysis was conducted with attention as the first set of predictors and EF as the second set or predictors. Attention explained a significant amount of variance for three language based academic scores and one math based academic score (ps < .03, adj R² > .50). EF added a significant amount of explained variance to the remaining math score (p < .05, ΔR² = .15). When the order of predictors was reversed, EF explained a significant amount of variance in both math based academic scores and one language based score (ps < .03, adj R² > .49). Attention did not explain additional variance above and beyond EF.

**Conclusions:** Both attention and EF contribute to explaining a significant amount of variance in academic ability above and beyond the effects of FSIQ for adolescents with ASD, as well as for TD adolescents. Specifically, attention tends to predict language based academic ability while EF tends to predict math abilities. These findings help to clarify the nature of academic difficulties in ASD and provide insight for planning intervention and support as these individuals navigate high school.

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**Keywords:** Autism, Executive Function, Attention, Academic Achievement

**Funded by:** NeuroDevNet Opportunities Initiative Award
Theme 6 – Neurocognitive  Poster # 54


Jason Rajsic  Doctoral Candidate

Mentor: Daryl Wilson
Author[s]: J. Rajsic, D.E. Wilson, E. Kelley, L. Hall, and R. Furlano
Institution[s]: Queen’s University

Abstract:
We present preliminary results for the development of a cognitive training program designed to target attentional difficulties for adolescents with autism spectrum disorder and attention deficit-hyperactivity disorder. The training program involves an internet-based videogame which participants can play from home via a web browser that is engaging and is designed to improve specific components of visual attention. In order to assess the impact of training, attentional performance was measured before and after a 30-day period during which one group of participants played the videogame for a half-hour per day (treatment condition), and another group was placed on a wait-list (control condition). Four experimental tests were used to measure components of visual attention pre-training and post-training: (1) temporal attention: attentional blink task, (2) attentional breadth: useful field of view task, (3) selective attention: flanker task, and (4), attentional capacity: multiple object tracking task. Effects of training on attentional performance indices as a function of treatment condition (trained or wait-listed) and population (typically developing or autism spectrum disorder) are discussed. Performance changes occurred for the flanker and attentional blink task, but not for the multiple object tracking or useful field of view.

Keywords: Training, Autism, Attention, Video Game

Funded by: NeuroDevNet Opportunities Initiative Award
The Presence of Comorbidities is Associated with Impaired Neurobehavioral Functioning in Children with Neurodevelopmental Disorders.

Deborah Dewey  Associate Investigator

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Abstract:

Introduction: Developmental Coordination Disorder (DCD), Attention-Deficit/Hyperactivity Disorder (ADHD), and Reading Disorder (RD) are highly comorbid neurodevelopmental disorders. It is uncertain, however, what influence comorbidity has on neurobehavioural functioning.

Objectives: To investigate the influence of comorbidity on neurobehavioral functioning in children with DCD, ADHD and RD compared to typically developing children.

Methods: For this cross-sectional study, 412 children, 6-16 years of age were recruited through family physicians, community and developmental pediatricians, schools and community organizations and assessed at Alberta Children’s Hospital, Calgary, Canada from 2009 to 2012. Children were assessed on standardized psychometric measures and classified as DCD, ADHD, RD, a comorbid condition (i.e., DCD+ADHD, ADHD+RD, DCD+RD, DCD+ADHD+RD) or typically developing. The main outcomes were intellectual ability, neuropsychological functioning, educational progress, and executive function.

Results: Children with RD, DCD+RD, ADHD+RD, and DCD+ADHD+RD scored significantly below typically developing controls on full-scale IQ (mean differences, -23.6 to -15.9). On measures of attention and executive function, children with DCD, ADHD, DCD+ADHD, ADHD+RD and DCD+ADHD+RD performed significantly worse than controls (mean differences, -4.0 to -1.8). Children with the RD and RD plus co-occurring disorders performed significantly worse than controls on tests of language (mean difference, -3.8 to -2.3). On tests of memory, poorer performance was displayed by children in the DCD+ADHD, DCD+RD, ADHD+RD, and DCD+ADHD+RD groups (mean difference, -3.5- to -1.3). Children with DCD and DCD plus co-occurring disorders scored significantly lower than controls on measures of visual motor processing (mean difference, -3.1 to -0.9). On a measure of mathematics, children with RD and DCD+ADHD+RD performed significantly poorer than controls. (mean difference, -29.4 to -25.6). Children with ADHD and ADHD plus co-occurring disorders, were reported as displaying more problems in executive function behaviors (mean difference, 19. 3 to 23.0).

Conclusions: Compared to children with DCD and ADHD, children with comorbid conditions were more likely to display impairments across a broader range of neurobehavioural functions. To direct more efficacious treatment, children with DCD, ADHD and RD need to be investigated for comorbid disorders.

Keywords: developmental coordination disorder, attention deficit/hyperactivity disorder, reading disorder, comorbidity, outcomes

Funded by: Canadian Institutes of Health Research
Theme 7 - Neuroimaging  Poster # 56

Within-Subject Reliability of MRI Parameters Across Scanners in the NeuroDevNet FASD Project.

Sarah Treit  Doctoral Candidate

Mentor: Christian Beaulieu  
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Institution(s): 1Centre for Neuroscience; 2Department of Biomedical Engineering, University of Alberta

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Abstract:

Background: Multi-site imaging consortia have clear advantages including increased power through large subject numbers and improved generalizability of patient populations. However, combining MRI data from multiple scanners introduces variability from hardware and sequence variations that may impact results. This study aims to quantify within-subject variability in DTI tractography parameters, cortical thickness and brain volumes between 4 NeuroDevNet sites: University of British Columbia (UBC), University of Manitoba (UofM), University of Alberta (UofA), and Queens University (Queens).

Methods: Eight subjects [28 ± 6 years, 2 males/6 females] underwent 2 consecutive MRI scans at 4 sites (64 scans total). 30-direction DTI (2.2 mm isotropic) and high resolution (1x1x1 mm3) MPRAGE were acquired at: UBC (3T Philips Intera) UofA (1.5T Siemens Sonata), UofM and Queens (both 3T Siemens Trio). Total brain, white matter, grey matter volumes and cortical thickness were calculated in CIVET 1.1.11. Automated tractography was performed in ExploreDTI and fractional anisotropy (FA) was calculated for the genu, body and splenium of the corpus callosum, cingulum, cortico-spinal tracts, superior longitudinal, inferior fronto-occipital, and uncinate fasciculi. Intra-class correlation coefficients (ICCs) and relative standard deviations (SD/Mean*100) within and between-subjects were used to measure agreement between scanners for brain volumes, mean cortical thickness, and FA of all tracts.

Results: ICCs indicate excellent absolute agreement between scanners for total brain (0.994), white matter (0.821) and grey matter (0.991) volumes, as well as total mean thickness (0.971). Within-subject relative SDs ranged from ~1-4% for volumes and thickness, and were lower than between-subject relative SDs (5-11%) in all cases. No trends were observed between sites. Low to moderate ICCs were observed for tractography (0.295-0.754). Within-subject relative SDs ranged from 3-7% and were comparable to or greater than between-subject SDs (2-7%) for some association fibres. Consistently lower FA was observed at UBC relative to the other 3 sites; magnitude of difference varied by tract and was greatest for association fibres.

Discussion: These results indicate minimal within-subject variability for volumetric and cortical thickness data across 4 scanners with different field strengths and vendor; however, site is shown to introduce within-subject systematic variability for tractography. UBC consistently yielded lower FA, particularly for association tracts. Lower absolute agreement and greater within-subject variability of DTI data may reflect sensitivity to distortions, which varies by scanner and anatomical location in the brain. Combining imaging data from multiple sites appears feasible; however, DTI data from multiple scanners may require adjustments that differ by tract.

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Keywords: multi-site imaging, DTI, cortical thickness, brain volume, within-subject, reliability

Funded by: NeuroDevNet FASD Demonstration Project
Preserved Cortical Asymmetry Despite Thinner Cortex in Fetal Alcohol Spectrum Disorders.

Dongming Zhou  Research Associate

Mentor: Christian Beaulieu
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Abstract:

Introduction: Cortical thinning has been observed in individuals with fetal alcohol spectrum disorders (FASD) that have cognitive deficits associated with prenatal alcohol exposure. In healthy individuals, the thickness of the cortex is left-right asymmetric in childhood and adolescence, insinuating a role for functional specialization. No studies have yet investigated whether there are cortical thickness asymmetry changes in FASD.

Methods: 239 participants were recruited into the NeuroDevNet FASD subproject and 215 3D T1-weighted MPRAGEs (1×1×1 mm³ in ~ 5-6 min) were acquired at 4 sites. 153 images (FASD: N=75 5.5-18.9 years, 40 females, 60 right and 7 unspecified handedness; controls: N=78, 5.8-18.5 years, 44 females, 68 right and 4 unspecified handedness) were processed (University of British Columbia, 14 FASD, 17 controls, 3T Philips Intera; University of Alberta, 32 FASD, 39 controls, 1.5T Siemens Sonata; University of Manitoba, 9 FASD, 8 controls, 3T Siemens Trio; and Queen’s University, 20 FASD, 14 controls, 3T Siemens Trio). FASD umbrella included: fetal alcohol syndrome (FAS, N=5), partial FAS (N=12), alcohol related neurodevelopmental disorder (N=37), and prenatal alcohol exposure (N=21). Cortical thickness was calculated with the CIVET 1.1.11 pipeline in CBrain.

Group comparison of cortical thickness differences were performed in the SurfStat toolbox for Matlab with a linear model fit at each vertex, controlling for age, gender, handedness and site. An asymmetry index (AI) was calculated at each vertex: AI = (Left – Right)/0.5*(Left + Right). One sample t-tests of AI were performed for each vertex pair (comparing to 0). Group comparisons of AI between FASD and controls were performed with a linear model controlling for age, gender, handedness and site. Significance values were corrected by false discovery rate with a level of 0.05.

Results: Significantly thinner cortex was observed in the FASD group in bilateral pre and post central gyrus, medial occipital gyrus, left inferior frontal, left middle temporal, right middle frontal and right supramarginal gyrus.

Cortical asymmetry was similar for both groups, specifically the lateral inferior frontal and the medial occipital regions were significantly thicker in the right hemisphere and conversely, the lateral parietal region was significantly thicker in the left. No group differences of AI were found in any vertices between FASD and controls.

Conclusions: Participants with FASD showed thinner cortex than controls in childhood/adolescence. Left/right asymmetry was not different between FASD versus control groups suggesting that cortical asymmetry is a developmental process that is preserved in FASD.

Keywords: Fetal alcohol spectrum disorder (FASD), cortical thickness, cortical asymmetry, structural MRI, neurodevelopment.

Funded by: NeuroDevNet FASD Demonstration Project; Alberta Innovates-Health Solutions (CB). CBrain/CIVET
Prognostication and the Contribution of MRI in Hypoxic-Ischemic Injury in Infants.

Emily Bell  Network Investigator

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Abstract:
Introduction: Magnetic resonance imaging (MRI) has the potential to improve prognostication in the context of neonatal brain injury but without consensus about the value of MRI biomarkers, practice may remain inconsistent.
Objectives: Investigate the perspectives of Canadian neonatologists and pediatric neurologists regarding the contribution and role of MRI for prognostication.

Methods: A mixed methods study was carried out with Canadian neonatologists and pediatric neurologists employing a vignette-based survey and qualitative semi-structured interviews. We surveyed physicians about the impact of MRI biomarkers on prognostication in general practice and in response to MRI findings presented in clinical vignettes of neonates with hypoxic-ischemic injury. The semi-structured interviews further explored physician perspectives about the clinical and ethical impacts of utilizing MRI for prognostication, including its contribution to decision making, communication with families, and resolving uncertainty about prognosis.

Results: Fifty eight physicians completed the survey (21% response rate). In general practice, more than two thirds of physicians (N=40, 74%) used MRI in the determination of prognosis, and gave MRI findings a high weight (50%-75%) in making these determinations. Most physicians (N=45, 83%) also indicated that they commonly incorporate MRI findings in their discussions with parents. However, physicians displayed a lack of confidence in the consistency of the interpretation of MRI findings for prognostication across colleagues and this was especially pronounced in neonatologists. Most physicians (N=45, 83%) thought that this inconsistency affected prognostication either on occasion or frequently. Measures of certainty and predicted outcome were correlated in the vignettes, such that as physicians ranked the predicted outcome of a case to be more severe, their certainty increased. Preliminary analysis of the qualitative interviews revealed a range of perspectives related to the usefulness of MRI findings for prognostication as well as the relative weight placed on MRI results compared to other tests and exams. Physician perspectives about prognostication and the incorporation of MRI findings are framed by a context of uncertainty which creates additional challenges for decision making and communicating with parents.

Conclusions: MRI findings generate clinical variability and interact with challenging ethical dilemmas. There is a tendency to acknowledge uncertainty and variability which co-exists paradoxically with practices that imply some level of certainty and confidence. Potential biases in prognostication merit further research and attention.

Keywords: Magnetic resonance imaging, prognostication, ethics, hypoxia-ischemia
Funded by: NeuroDevNet Neuroethics Core
Theme 7 - Neuroimaging  Poster # 59

Crossed Cerebellar Diaschisis in Perinatal Stroke.

Cheyanne Olsen  BSc Student

Mentor: Adam Kirton
Author(s): C. Olsen, S. Mah, X. Wei, and A. Kirton
Institution(s): Calgary Pediatric Stroke Program, Alberta Children’s Hospital Research Institute, University of Calgary

Abstract:

Introduction and Objectives: Perinatal stroke is the leading cause of hemiparetic cerebral palsy and an ideal human model of developmental neuroplasticity. Crossed cerebellar atrophy or “diaschisis” (CCD) refers to chronic cerebellar volume loss following contralateral, supratentorial motor pathway injury. CCD is well described in adult stroke and we recently demonstrated similar processes in childhood stroke. CCD has not been studied in perinatal stroke. We hypothesized that CCD could be quantified in perinatal stroke and would be associated with poor motor outcome.

Methods: Subjects from the population-based Alberta Perinatal Stroke Project registry were included with: (1) unilateral arterial perinatal stroke, (2) axial T1 or T2 MRI > 6 months of age, (3) Pediatric Stroke Outcome Measure (PSOM) score > 12 months, and (4) no other neurological disorders. Blinded scorers used Osirix software and a previously validated method to measure bilateral cerebellar hemisphere and vermis volumes. Cerebellar hemispheric volumes were expressed as ratios of contralesional/ipsilesional hemispheres, whereby ratios < 1 would be suggestive of CCD. Motor function PSOM scores were dichotomized as good (< 2) or poor and compared to cerebellar volume ratios (t-test). More detailed motor outcomes (Assisting Hand Assessment [AHA] and Melbourne Assessment [MA]) were compared to cerebellar asymmetry when available (Pearson).

Results: Of 84 eligible cases, preliminary data from the initial 24 subjects are presented (median age: 7.1 +/- 3.8 years at PSOM, 67% male). Across the sample, mean cerebellar ratios were less than 1.0 (0.971 +/- 0.013, range 0.841–1.071). Three subjects had ratios less than 0.9. Mean cerebellar ratios between good and poor PSOM motor outcome groups were not significantly different. AHA and MA motor scores were available for 11 children and neither was significantly associated with cerebellar ratios. Based on this preliminary data, a sample size of 44 subjects is projected to address the primary hypothesis with 80% power.

Conclusions: Cerebellar volumetrics are feasible in perinatal stroke. CCD may occur in some children with perinatal stroke but prevalence and relationship to motor outcome remain unknown. Further analysis of the larger sample should be able to answer these questions and determine potential clinical significance.

Keywords: perinatal stroke, diaschisis, motor outcome, cerebral palsy

Funded by: Calgary Pediatric Stroke Program
Theme 7 - Neuroimaging  Poster # 60

Spontaneous Cortical Activity Synchronizes Barrel and Hindlimb Sensorimotor Circuits Prior to Their Functional Maturation.

David McVea  Doctoral Candidate

Mentor:  Timothy Murphy
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Abstract:

Introduction and Objectives: Remarkably, the brain and nervous system are active before they are functional. One role of this activity is promoting neural circuit development. While this process is relatively well understood in localized sensory or motor systems, how it contributes to forming large cortical networks remains unclear. One hypothesis is that cortical activity in early life synchronizes neural systems that will be functionally connected in adulthood. Testing this hypothesis requires high-resolution recordings of activity from large regions of the intact brain and examining interactions between spatially remote regions.

Methods: We obtained such recordings using voltage-sensitive dye imaging in the developing rodent cortex in vivo. After craniotomy, we applied dyes directly to the cortex. Under light anesthesia, we collected sequences of spontaneous cortical activity from large portions of the sensorimotor cortex, as well as activity evoked by stimulation of the limbs or whisker.

Results: In one set of experiments, we stimulated the skin of the hindlimbs of 4-6 day old rat pups (n=10). We found that, unlike in adult rats, there was activity only on the contralateral somatosensory cortex following this stimulation. However, when we examined brain activity without stimulation, we found that somatosensory cortices on opposite hemispheres of the brain were active together. This correlated activity arose from small spontaneous movements of the limbs and tail; this simultaneous external stimulation gave rise to simultaneous activation of the sensory cortices. In a second set of experiments, we deflected the whisker of rat pups ranging in age from 5-12 days old (n=25). In the adult rodent, the deflection of the whisker causes an activation of the sensory cortex followed by the motor cortex. The delayed activation of the motor cortex was not present in the five or six day old pups, but was clearly established in twelve day old pups. However, the motor and sensory cortices were spontaneously active together, even in young animals in which whisker deflection only activated the sensory cortex.

Conclusions: In summary, these results show two examples of neural circuits in which the spontaneous brain activity reflects a level of maturity not yet present in their functional connectivity. Together, they suggest an important role for spontaneous cortical activity in forming and shaping long-range neural connections during development.

Keywords:  cortical activity, spontaneous, development, rodent

Funded by:  CIHR, MSFHR
The Effect of Hydrocephalus on Periventricular Venous Infarct Size.

Zeanna Jadavji  BSc. Student

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Abstract:
Introduction: Perinatal stroke causes most term-born hemiparetic cerebral palsy and many are periventricular venous infarctions (PVI). PVI results from in-utero germinal matrix hemorrhage which may also cause post-hemorrhagic hydrocephalus (PHH). Large variations in PVI volumes are unexplained. We hypothesized that arrested PHH contributes to PVI volumes and poor neurological outcome.

Objectives: To determine the relationship between arrested hydrocephalus and PVI volume.

Methods: Children from the Alberta Perinatal Stroke Project (APSP) with unilateral MRI-confirmed PVI, axial T2 MRI >12 months of age, and neurological follow up with the Pediatric Stroke Outcome Measure (PSOM) were included. PVI volumes were determined by previously validated methods and corrected to whole brain volumes. Both intra- and extra-axial CSF volumes were quantified using a novel analysis method (ImageJ software). Extra-axial CSF volume surrounding the contralesional hemisphere was used as an imaging biomarker of relative PHH. Correlations between PVI and contralesional extra-axial CSF volumes (Pearson) were examined. Associations to motor outcome (PSOM dichotomized as good/poor) and more specific functional measures when available (Melbourne Assessment (MA) and Assisting Hand Assessment (AHA)) were examined. Intra-rater method reliability was assessed.

Results: Data for 24 children are presented (67% male). Median age at MRI was 9 years. Median PSOM age was 10.5 years. Method reliability was excellent with intra-rater correlations of 0.94-0.99. PVI volumes varied widely (range: 0.00698%-3.238% brain volume) and did not correlate with dichotomized good versus poor PSOM motor outcome (r=0.672, p=0.837) but were highly correlated with MA (r=0.923, p=0.001) and AHA (r=0.862, p=0.006) scores. Overall, non-lesioned extra-axial CSF volumes were not correlated with PVI volumes (r=0.022, p=0.493). Three outliers with large PVI volumes but small extra-axial CSF volumes were observed, suggesting multiple mechanisms may contribute to PVI volume.

Conclusions: CSF volumetric analysis is feasible in children with PVI. Our preliminary results suggest a possible association between PVI volume and PHH. An improved understanding of PVI pathogenesis might inform better management strategies.

Keywords: PVI, Hydrocephalus, Germinal Matrix Hemorrhage

Funded by: Calgary Pediatric Stroke Program
Neonatal Pain-Related Stress is Associated with Altered Corticospinal Tract Development in Premature Newborns and Gross Motor Outcomes at 18 months.

Jill Zwicker  Postdoctoral Fellow

Abstract: Objectives: Neonatal procedural pain has been associated with reduced white and gray matter brain maturation in premature newborns (Brummelte S, Grunau RE, Chau V, Poskitt KJ, Brant R, Vinall J, Gover A, Synnes A & Miller SP. Ann Neurol 2012;71:385-396), as well as motor outcomes at 8 and 18 months corrected age (CA) (Grunau RE et al. Pain 2009;143:138-146); however, the association of pain and motor pathway development is largely unknown. The purpose of this study was to examine in premature newborns the association of neonatal pain with (i) corticospinal tract (CST) development and (ii) motor outcomes at 18 months CA.

Methods: 100 premature neonates born at 24-32 weeks gestation age (GA) (median:27.3 weeks; IQR:25.6-29.9) were serially scanned with MRI near birth and at term-equivalent age. Diffusion tensor tractography determined CST fractional anisotropy (FA), a measure of microstructural development. Peabody motor outcomes at 18 months CA were categorized into three impairment groups: none (≥90), mild-moderate (80-89.99), and severe (<80). Generalized estimating equations examined the relationship between neonatal pain (# of skin breaking procedures, adjusted for early illness severity and morphine exposure) with (i) CST FA and (ii) motor outcome, adjusting for GA and age at MRI; analyses were further adjusted for other confounders (postnatal infection, white matter injury, and ventilation days).

Results: Higher neonatal pain was associated with slower increase in CST FA from early in life to term-equivalent age [interaction: p=.002]; after adjustment for confounders [p=.003]. Infants with poor gross motor outcome had a slower rise in CST FA in the neonatal period [p=.003]; this association was not seen for fine motor outcome [p=.72]. Poorer gross motor outcome was also predicted by higher neonatal pain [interaction: p=.04], with infants ≤ 28 weeks gestation at greater risk of poorer motor outcomes with increased exposure to pain-related stress. Greater number of ventilation days was also associated with poorer motor outcomes [p=.002].

Conclusions: Greater neonatal procedural pain is associated with slower maturation of the CST from early in life to term-equivalent age. The association of neonatal pain with poor gross motor outcomes is mediated, at least in part, by abnormal early CST development.

Keywords: premature infant, brain development, diffusion tensor tractography, corticospinal tract, pain-related stress, motor outcomes

Funded by: MSFHR-NeuroDevNet Postdoctoral Fellowship (JGZ), Canadian Child Health Clinician Scientist Program (JGZ), Canadian Institutes of Health Research, National Institutes of Health
Brain Changes Detected During Language Therapy: A Down Syndrome Case Study.

Teresa Cheung  Research Associate

Mentor:  Ryan D’Arcy
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Abstract:

Introduction and Objectives: Current assessment methods for therapeutic treatment rely on behavioural testing using standardized tests. With the rapid growth of non-invasive brain imaging technologies, there is an increasing need to integrate behavioural-based measures with physiological assessment tools that identify biomarkers sensitive to individual treatment effects. We present case study functional imaging results for monitoring language therapy in Down syndrome (DS).

Methods: The DS case study used magnetoencephalography (MEG) to monitor changes in semantic processing over an 11-week intensive language therapy session. Behavioural data were obtained using both forms of the Peabody Picture Vocabulary Test 4th edition (PPVT 4) before and after therapy. MEG data were collected at 3 time points: beginning, middle and end. The participant was a 9-year-old female with Down syndrome and normal hearing.

MEG was collected using an established semantic violation paradigm that elicits the neuromagnetic N400 response, a response linked to PPVT 4. The so-called N400 is a change in signal amplitude at around 400 ms that occurs during condition of semantic violation (incongruent) compared to semantically correct sentences (congruent). The stimulus consisted of 252 spoken sentences presented during time-locked MEG recording. MEG data were collected using a 151-channel MEG system at the Down Syndrome Research Foundation laboratory.

Results: PPVT 4 performance showed a significant 21-point improvement between the pre- and post- treatment evaluations. MEG results revealed a neuromagnetic N400 response characterized using an independent component analysis approach. As expected, the N400 showed a clear left lateralized distribution with significantly larger response amplitudes to the incongruent condition (p=0.027). Comparisons across the 3 time points during therapy, there were no significant differences in the congruent condition. However, there was a significant increase in N400 response magnitude for the incongruent condition (p=0.032).

Conclusions: The findings demonstrated strong sensitivity of the neuromagnetic N400 to changes in semantic processing over the 11-week language therapy period. These results were closely consistent with the behavioural performance data and provide the initial demonstration for MEG monitoring in DS language therapy — at the individual level. Future studies plan to further develop individualized MEG biomarkers to better inform language therapy in DS and other developmental applications.

Keywords:  Down syndrome, Magnetoencephalography, Language Therapy, N400, Biomarker, Functional Imaging

Funded by:  PHSA and The Down Syndrome Research Foundation
Theme 7 - Neuroimaging  Poster # 64

Atypical Fronto-Parietal Reading Networks in Adults with Dyslexia.

Sanjay Achal  BSc Student

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Abstract:
Introduction: Developmental dyslexia (also known as reading disability) is a disorder that affects about 5% of children and adults. Reading and language functions depend on a network of brain regions, including left dominant ventral frontal (including inferior frontal gyrus, IFG), temporo-parietal (including inferior parietal lobule, IPL) and occipito-temporal regions. Individuals with dyslexia exhibit reduced activation of these important left hemisphere structures during reading-related tasks, and may compensate with bilateral inferior frontal systems. It has been suggested that in dyslexia the primary dysfunction is a phonological deficit, dependent on the left dorsal pathway, and that this deficit may persist into adulthood. In parallel, compensatory mechanisms in bilateral IFG may develop with age. Resting-state functional magnetic resonance imaging (rs-fMRI) allows task and performance independent assessment of brain networks, and is therefore useful in developmental studies. However, it remains unknown whether reading network abnormalities can be detected from connectivity patterns in dyslexic adults.

Objectives: The goal of this study was to examine whether intrinsic networks supporting reading and language are abnormal in dyslexic adults, using rs-fMRI. Specifically, we investigated whether hypoconnectivity in the left dorsal pathway and bilateral inferior frontal hyperconnectivity could be observed in dyslexic adults, concordant with previous task-based fMRI studies.

Methods: The current study used rs-fMRI to investigate differences in reading networks in adults with dyslexia. Participants were 45 adults aged 30-54, with 30 controls (15 males, 15 females) and 15 dyslexics (8 males, 7 females). Participants were classified as dyslexic if they scored within the lower 25th percentile of the standardized TOWRE Phonemic Decoding Efficiency (PDE[ss]) test (with a score equal to or less than 90). Resting-state networks were identified using whole brain correlations with seed regions of interest, including left IFG and IPL. Correlation patterns were then compared between the dyslexic and typical reading groups.

Results: We observed significant group differences in connectivity with the left IFG, wherein the dyslexic group showed stronger connectivity to the right IFG. The dyslexic group also showed reduced intra-hemispheric connectivity from the left IPL to left IFG, relative to controls.

Conclusions: The weaker connectivity in dyslexic adults compared to typical reading adults in the left fronto-parietal network, as well as enhanced connectivity between bilateral inferior frontal regions, suggest that both dysfunction as well as the putative compensatory mechanisms can be detected in adults using rs-fMRI. Further work is required to clarify the development of connectivity patterns, and relationship to functional compensation.

Keywords: dyslexia, functional connectivity, resting state fMRI, language

Funded by: National Science and Engineering Research Council, US National Institute of Child Health and Human Development
Abstract:

Introduction: The ICF recognizes the importance of characteristics of the environment such as family context and presence of supports and barriers to the quality of life of individuals with disabilities. Adolescents with CP face challenges in accessing spaces and engaging in different activities due to restrictions in the physical, social, and attitudinal environment. However, little is known about specific environmental context of adolescents with CP.

Objectives: The objective of this study was to describe specific characteristics of the environment of adolescents with CP and their relationship with demographic variables and activity limitations.

Methods: Cross-sectional study design. Adolescents 12-19 years of age (15.3±2.2 years, N=168) with CP were recruited from primary care centres, rehabilitation centres and community programs in the province of Quebec. Environmental context was evaluated using the Social Supports Scale (self-report), the Family Environment Scale, the European Child Environment Questionnaire and a demographic questionnaire (proxy-report). An OT or PT performed the GMFM-66 and the Vineland Adaptive Behavior-II (VABS-II) to assess activity limitations. Pearson product-moment correlations, simple linear regressions and t-test were performed to estimate the relation between environmental characteristics and sociodemographic and functional variables.

Results: Of 168 participants recruited, 59% were male. GMFCS: 56% level I and II/ 43% level III-V. Forty-three percent of participants were in special schools. One third of adolescents received no rehabilitation services in the 6 months prior to participation in the study. Families perceived a lack of access to needed physical, social and attitudinal environmental features in the home, in the school and in the community. Adolescents with greater mobility restrictions faced more limitations in the physical environment and social supports (p<.001), but did not perceive greater attitudinal barriers (p=.55). Parents reported high levels of parent support (3.68±40) and friend support (3.44±72). A positive regard of friends was associated with higher communication abilities (r=.21, p<.05), but was not associated with higher gross motor ability. Adolescents in regular schools reported a higher perception of parent support (p=.004), but perceived no difference in the levels of teacher and friend supports.

Conclusions: Several environmental factors related to functional abilities, school setting and family environment are related to access to environmental features for adolescents with CP. Identification of social supports available for the adolescent and his/her family, as well as identification of barriers in the physical, social and attitudinal environment may help prioritize service needs and intervention strategies.

Keywords: Cerebral Palsy, Adolescents, Contextual factors

Funded by: NeuroDevNet CP Demonstration Project, CCHCSP-NeuroDevNet Doctoral Fellowship (KS-T), CIHR
The Predictive Power and Perils of Brain Imaging and Genetic Testing for Mental Illness in At-Risk Youth.

Grace Lee  Postdoctoral Fellow

Mentor: Judy Illes
Author(s): G. Lee¹, A. Mizgalewicz¹, E. Borgelt², and J. Illes¹
Institution(s): ¹National Core for Neuroethics, University of British Columbia; ²Center for Biomedical Ethics, Stanford University

Abstract:
Approximately 20% of Canadians will experience a mental disorder in their lifetime, with the first onset of mental illness usually occurring during childhood or adolescence. Each year, the prevalence of mental illness among Canadian adults is nearly 2 million for mood disorders and 5 million for anxiety disorders. However, for clinical care of mental health disorders in youth, diagnostic criteria remain contentious and treatments under-researched. Advancements in neuroimaging and genetic testing promise to improve diagnostic and predictive capabilities in mental health care and, to some extent, alleviate the associated burden of disease. As these technologies become clinically viable, it is important to anticipate their impact on clinical practice and physician-patient relationships especially related to the care and classification of youth with mental disorders. We present findings from a semi-structured qualitative interview study that sought mental health care providers’ perspectives on the predictive power and risks of neuroimaging and genetic testing for youth. We interviewed 38 psychiatrists, psychologists, and allied mental health professionals who work primarily with children and adolescents about their receptivity towards either the use of neuroimaging or genetic testing in clinical practice and the roles they foresee for these modalities. Practitioners anticipated three major benefits associated with clinical introduction of imaging and genetic testing in the mental health care: (1) improved understanding of illness, (2) more accurate diagnosis, and (3) validation of treatment plans. They also anticipated three major risks: (1) potential impact on employment and insurance as adolescents transition to and reach adulthood, (2) misuse or misinterpretation of the imaging or genetic data, and (3) infringements on self-esteem or self-motivation. As susceptibility testing for mental illness and functional brain imaging broaden in appeal to patients and their families, these findings are essential for informing careful assessments of risks and benefits associating with emerging neurotechnologies, and consideration of both access to and standards regulating their use in clinical care is essential.

Keywords: mental health, neuroethics, genetic testing, neuroimaging, provider attitudes, children, adolescents

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Theme 8 - Social Impacts  Poster # 67

Addressing the Complexities of Sharing and Mining of Data from Children and Adolescents: A Call for Standards and Transparency.

Vera Khramova  Research Associate

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Abstract:
Introduction: Structured data sharing organizations stand to maximize the efficiency of invested research dollars, expedite research findings, minimize the burden on the patient community, and increase citation rates of publications associated with the data. Data sharing initiatives however, hinge on research participation, for which the participant protection and trust are imperatives. The heterogeneity of the three most common neurodevelopmental disorders (NDDs) in North America – Autism spectrum disorder (ASD), cerebral palsy (CP), and fetal alcohol spectrum disorder (FASD) underlies the need for large sample sizes for related studies, and make NDD research an arena that stands to benefit strongly from data sharing initiatives. Indeed, there has been a groundswell of organizations devoted to such efforts.

Objective: This study examined existing ethics and governance information on websites of databases involving NDDs to determine the public availability of information on key factors crucial for their comprehension, trust, and participation in such initiatives.

Methods: Relevant databases were identified through online keyword searches. We retrieved a total of 15 that met our inclusion criteria. We chose themes for content analysis based on the relevant academic literature and supplemented them by consultations with experts in the field. We analyzed the website of each organization using the method of gap analysis.

Results: Results show that 33% of organizations mention special considerations for minors. Discussion of the requirements for storing data is present on 20% of the websites. Disaster recovery protocols are similarly available for 20%. Discussion of incidental findings appear on 7% of websites, as do mentions of quality and procedural controls for submitting data and tissue. Another 20% had separate governance and policy pages, or FAQs that provide information on central ethical and governance matters. When present, special considerations for youth, along with other ethics guidelines and requirements, are scattered throughout the websites, or are available only from associated documents found through live links.

Conclusions: The complexities of sharing data acquired from children and adolescents will only increase with advances in genomic and neuro science. Our findings suggest that governance policies and standards on which these collaborations can lean specifically for vulnerable young populations are lacking, and there is a clear need to improve their consistency, depth and accessibility.

Keywords: Neuroethics, Data Sharing, Databases, Biobanks, Governance, Policy

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Vancouver Virtual Summer Sleep School – Research Seminars: Qualitative Analysis of FASD Caregiver Interviews.

Mai Berger  Clinical Research Assistant

Mentor: Osman Ipsiroglu
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Abstract:
Introduction: Medical understanding of health and disease is affected by social, environmental and cultural factors. Consequently, the clinical management framework is confounded by various background factors of professionals influencing caregivers’ perceptions and understandings. FASDs are a major public health problem representing one of the most vulnerable populations in the neurodevelopmental disabilities (NDDs) spectrum. Individuals diagnosed with a FASD, and their birth mothers and adoptive/foster parents, face social stigma associated with the condition as FASDs are recognized as the result of preventable toxic alcohol exposure during pregnancy. Although children’s functioning and behaviours resemble ADHD, pharmacologic treatment is only partially effective. As a result, these children’s behaviours are considered more challenging to treat than other children with NDDs or ADHD.

Objectives: FASDs are a paradigmatic case for the study of the clinical management questions: 1) What is a challenging situation? 2) What makes a situation challenging?

Methods: 59 caregivers (birth, adoptive/foster parents) of children with FASDs, who participated in a NeuroDevNet research endeavour, were asked questions 1) and 2) in one-to-one and/or telephone interviews (Team Reynolds). Their responses were transcribed and anonymized. Interviews were provided to the VVSSS qualitative research seminars for further analysis. 5 participants (MB, HS, ZT, CY, DW) assessed the interviews and identified several key themes: transitions, ADHD-like-behaviours, medications and routines. Kleinmans’ arenas of health model was applied to analyze from where preconceptions and explanatory models arose that lead to the caregiver’s identification of a challenging situation. For training purposes, five transcripts were collaboratively coded and analyzed with a qualitative analyst (KS); 6 core domains were identified: cognitive, emotional, behavioural, sensorimotor and adaptive skills, and health (including sleep and sleep sequelae). A three-dimensional “Imploded Cube” model was created to visualize the results.

Results: Many caregivers recognize challenging situations through the ‘popular’ arena of health and their explanatory models stem from ‘folk’ or ‘undetermined’ arenas, thus questioning the efficiency of current Knowledge Dissemination activities. Sleep problems are an issue, which have never been addressed in a structured way. The analysis of the caregiver interviews is still ongoing.

Conclusions: Existing explanatory models seem to reflect current research mainstream understanding, mixed with many ‘folk’ or ‘undetermined’ concepts, and may miss significant new developments such as addressing sleep problems and their sequelae and psychiatric co-morbidities. Analyzing all interviews from a ‘sleep sequelae viewpoint’ is the next step of the ongoing research endeavour.

Keywords: Sleep, FASD, Qualitative Analysis, Caregivers, Arenas of Health, Knowledge Dissemination

Funded by: Treatable Intellectual Disability-Endeavour-British Columbia (TIDE-BC)
Self and Proxy Assessment of the Long Term Health Related Quality of Life after Pediatric Stroke.

Satvinder Ghotra  Master’s Candidate

Mentor: Jerome Yager  
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Institution(s): University of Alberta

Abstract:

Introduction: The incidence of pediatric stroke has risen to >3.0/100,000; equal to childhood cancer. Neurological deficits ranging from mild to severe, in both motor and cognitive spheres are witnessed in 70-75% of survivors of pediatric stroke and clearly may influence their health related quality of life (HRQL).

Methods: A cross sectional study at the Stollery Children’s Hospital, Edmonton, Canada. Parents of children diagnosed with pediatric arterial ischemic stroke since January 2003 were approached for participation. Inclusion criteria: (1) age >2years at the time of follow up, (2) at least 1 year follow up after childhood stroke, and (3) 2 years follow up after perinatal stroke. Exclusion criteria: underlying genetic syndromes. Neurological outcome was assessed using the Pediatric Stroke Recurrence and Recovery questionnaire. HRQL was evaluated using self-report [5-18 years] and proxy report [2-18 years] versions of the Pediatric Quality of Life Inventory [PedsQL 4.0] and compared to reference population norms.

Results: Fifty-two children were enrolled. Median age at the onset of stroke was 0 days (IQ range: 0-48.5 days). Mean age at assessment and time elapsed since stroke was 6.3 (SD: 4.3) and 4.9 (SD: 3.0) years respectively. Neonatal onset stroke was documented in the majority (n=23, 44%) of patients, followed by presumed perinatal stroke (n = 16) and childhood onset stroke (n=13). Forty-two (81%) kids had neurological deficits, with 22 (42%) of children reporting severe deficits. Lower overall HRQL scores were reported in both parent-proxy (p=0.001) and self-report (p=0.002) forms compared to the reference normal population. Parents expressed concerns in both physical (p=0.001) and psychosocial (=0.001) domains of HRQL. Although children didn’t express significant concerns in the emotional and social functioning domains, physical (0.038) and school functioning (p=0.001) was reported to be significantly impaired. Moderate to large effect sizes were expressed across multiple domains indicating the clinical significance of the observations drawn.

Conclusions: Both parents and children identify HRQL of their children to be lower than controls. However, parents differ in their assessment of HRQL deficiencies compared to their children’s self-report. The findings have direct implications regarding our approach to the well-being of the children with stroke.

Keywords: Stroke, pediatric, health related quality of life

Funded by: WCHRI and AIHS
Predictors of Victimization in Adolescents with Autism Spectrum Disorders.

Chloe Hudson  Master’s Candidate

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Institution(s): Queen’s University

Abstract:
Children and adolescents diagnosed with autism spectrum disorders (ASD) are more likely than their typically developing peers to experience victimization, with some studies reporting that up to 94% of children with ASD are the victims of bullying (Little, 2002). Bullying has been found to be associated with a number of negative outcomes for typically developing children, including poor social and emotional adjustment, delinquent behaviours, decreased academic achievement and psychiatric illnesses such as depression and anxiety (Rigby, 2003). These outcomes are persistent and often extend into adulthood (Duncan, 1999). Despite these damaging consequences, few studies have investigated the factors that may predict bullying and victimization in children with ASD.

The current study is a part of a larger study titled: Training Attention Using Adaptive Video Games in Children with Autism Spectrum Disorders and Attention Deficit/Hyperactivity Disorders. This study is investigating the effects of training executive functioning and attention in adolescents who are typically developing as well as those diagnosed with ASD and ADHD. The current study has added the World Health Organization (WHO) Bullying/Victimization Questionnaire to the data being collected in this study in order to examine the relationship between bullying behaviours and cognitive factors in children with ASD.

Data collection is still in progress, but initial analyses indicate that, similarly to typically developing children, problems with cognitive flexibility, academics and emotional functioning are related to victimization and bullying in children with ASD.

The results of this study may have implications for bullying interventions targeted at children with ASD. By helping these children with some of their cognitive difficulties, we may be able to minimize their exposure to these hostile social situations and the associated negative long-term consequences.

Keywords: autism, victimization

Funded by: NeuroDevNet Opportunities Initiative Award
Transition to Vocation in ASD: An Examination of Vocational Service Delivery and Consumer Experiences in Alberta.

David Nicholas Network Investigator

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Abstract:
Background: The unemployment rate for Canadians with neurodevelopmental disabilities including ASD, is unacceptably low. This reflects multiple transitional and vocational issues.

Objectives: We analyzed a provincially-administered survey of ASD vocational services in Alberta. Perceptions of individuals with ASD, their caregivers and support service personnel, were also gathered regarding risk and protective factors relating to transitional and vocational access in ASD.

Methods: As part of a larger national study, this mixed method design incorporated the following: (i) a web-based environmental scan based on a website review of international ASD vocational resources, (ii) a telephone survey eliciting transitional and vocational models in ASD, and (iii) interviews with persons with ASD and family members examining transition- and vocation-related experiences and needs.

Results: Administrators from 75 agencies in Alberta that offer vocation-focused services to persons with ASD, participated in a survey examining organizational and regional practices. Interviews were subsequently conducted with 55 service users as well as family members, other formal or informal caregivers, employers, and service providers. Findings identified a range of models comprising community programs, pre-employment (job findings) training, job skills training, life skills facilitation, job coaching, and on site training, using various methodologies including technology-based applications. Benefits and limitations of these various approaches were identified; however overall, services were described to be insufficient to meet current need. Participants identified inconsistencies between the aims of support resources versus the actual experiences and needs of individuals with ASD and their families. To address identified gaps, community-based and targeted models of engagement and learning ‘in environment’ were recommended in both building vocational opportunity and fostering desired community change. Proactive contingency planning and ‘in the moment’ augmentative support were sought in redressing possible crises or challenges that may arise within the workplace. Participants called for more community-based, person-centred and seamless approaches to vocational support than are currently being offered by most agencies. They recommended core services in job skills and social/relational elements needed in the workplace via core curriculum and on-the-job ‘naturalized’ learning opportunities, peer mediation, and a corresponding individualized, tailored menu of support that complements individual needs and job ‘fit’; hence an approach that is intentionally generalizable to the vocational context and community.

Conclusions: Evidence-informed person, family and community-centred approaches are strongly recommended. Community advocacy, support and action-based models that offer periodic assessments of an individual’s needs and generate a range of transitional/vocational pathways, with resources to support such customized needs, are recommended.

Keywords: Autism Spectrum Disorder, Transition, Vocation, Services

Funded by: Sinneave Family Foundation and Autism Speaks
A Retrospective Study of Interests in Adults with ASD: Preliminary Findings.

Kimberly Armstrong  Doctoral Candidate

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Abstract:

Introduction: Restricted interests is one of the diagnostic criteria for Autism Spectrum Disorder (ASD) but little is known about them, or what makes them similar or different from interests people without ASD pursue. Restricted interests are the least researched and understood symptom of the disorder (Attwood, 2003).

Objectives: The goal of this study was to investigate the nature of interests in adults with ASD. Adults were used to obtain information about the development of interests over time.

Methods: Thirteen adults aged 16-50 (7 male, 6 female) with ASD have participated in this study (data collection is ongoing). All participants had average to above-average intelligence and were given a questionnaire developed for this study about their interests. Participants self-reported on the interest they felt was most important, and how it manifested at each developmental period (school age, adolescence, adulthood) if it was present during that time.

Results: Participants reported that their interest started anywhere from 1-36 years old (x = 12 years). For all participants their most important interest was currently ongoing so none reported an end date. Six participants did not have a time where their interest was the strongest, but seven participants reported their interest peaking at an age between 7-18 years old (x = 15 years). The duration of the interests ranged from 1-33 years (x = 12 years). The number of people they shared their interest with ranged from 0-20 across stages, but was the lowest in adolescence (x= 1.7 people) compared to school age (x= 5.2 people) or adulthood (x= 3.2 people). Participants spent around 50% of their spare time on their interest across stages. The percentage of their spare time they would have liked to have spent on their interest decreased across developmental stages (x= 76% of spare time in school age, 64% in adolescence, and 55% in adulthood). The most common interests reported were video/computer games, Japanese culture or animation, and art (including drawing, photography and needlework).

Conclusions: There is a wide range in the content and manifestation of interests in adults with ASD. Intensity measured by the amount of time they would like to spend on their interest diminished over time, while actual time spent remained about the same across development. Individuals were less social and more focused on their interests during adolescence. The duration of interests is quite long in this group (12 years), but a control group is needed for comparison.

Keywords: ASD, restricted interests, adults; diagnostic symptoms

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