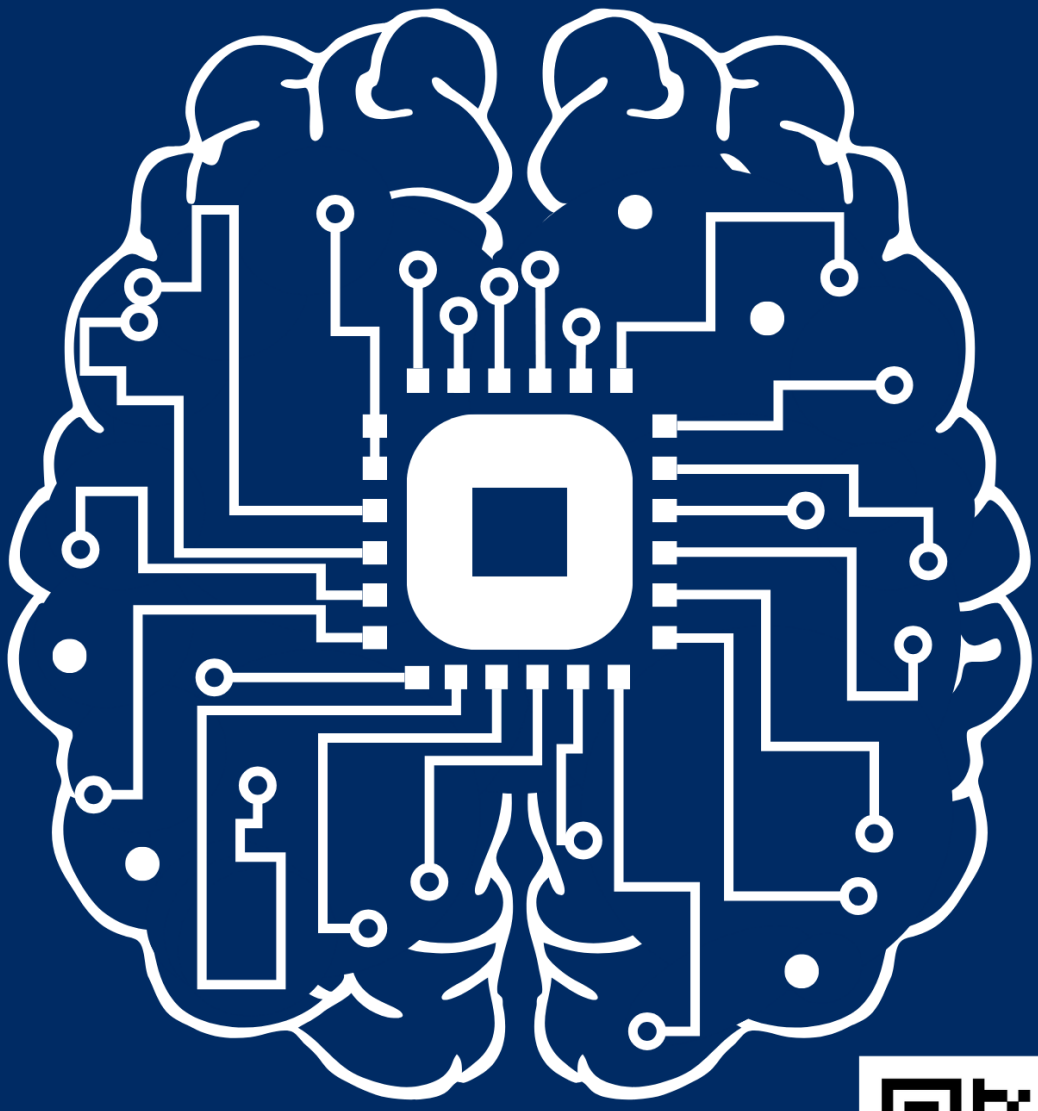
2024
Joint Neuroscience Conference

Collaborative Program in Neuroscience (**CPIN**) Research Day

Max Planck-University of Toronto Centre (**MPUTC**) Research Day

Center for Advancing Neurotechnological Innovation to Applications (**CRANIA**)



Meeting Program

May 2nd, 2024

Medical Sciences Building, 1 King's College Circle,
Toronto, Canada

Cover By Irina Alymova

Table of Contents

Collaborative Program in Neuroscience (CPIN) | Max Planck-University of Toronto Centre (MPUTC) | CenteR for Advancing Neurotechnological Innovation to Applications (CRANIA)

2024 Research Day

JOINT NEUROSCIENCE CONFERENCE

Thursday, May 2nd, 2024

Stone Lobby, Medical Sciences Building, 1 King's College Circle, Toronto, ON

Program Schedule

9:00 – 10:00 AM	**Registration and Poster Setup**	Stone Lobby
10:00 – 10:20 AM	**Welcome and Opening Remarks** **Dr. Zhong-Ping Feng**, Director, Collaborative Program in Neuroscience (CPIN), Professor, Department of Physiology, University of Toronto **Dr. Joyce Poon**, Co-Director, the Max Planck-University of Toronto Centre (MPUTC); Director, Max Planck Institute for Microstructure Physics; Professor, Department of Electrical & Computer Engineering, University of Toronto **Dr. Taufik Valiante**, Co-Director, MPUTC; Co-Director, CenteR for Advancing Neurotechnological Innovation to Applications (CRANIA); Director, Surgical Epilepsy Program; Associate Professor, Department of Surgery, University of Toronto; Senior Scientist, Krembil Research Institute	Room 2158 Macleod Auditorium
10:20 – 11:00 AM	**Keynote Speaker I:** "Stressed? Forget about it!" **Dr. Jaideep Bains**, Professor, Department of Physiology; Director, Krembil Research Institute, University Health Network **Introduction by**: **Dr. Zhong-Ping Feng/Dr. Jeffrey Henderson**, Associate Professor, Leslie Dan Faculty of Pharmacy, University of Toronto	
11:00 AM – 1:00 PM	**CPIN | MPUTC | CRANIA Trainee Poster Presentation/ Evaluation & Lunch** (lunch will be provided to all registrants)	Stone Lobby
1:00 – 2:00 PM	**CPIN | MPUTC | CRANIA Trainee Oral Presentation/Evaluation** Section I. *Behavioral Neuroscience, Cellular & Molecular Neuroscience, Concussion & Brain Injuries* Section II. *Cognitive Neuroscience, Computational Neuroscience, Neuroimaging* Section III. *Neuroanatomy, Neurodegenerative Diseases, Neurodevelopment, Neuroimmunology* Section IV. *Learning and Memory, Pain and Nociception, Synaptic Plasticity, Translational Research* Section V. *Neuropharmacology, Neurophysiology*	Room 2158 Macleod Auditorium Room 2170 Room 2172 Room 4171 Room 4279
2:00 – 2:40 PM	**Keynote Speaker II:** "Using Adversarial Collaboration to Harness Collective Intelligence" **Dr. Lucia Melloni**, W2 Group Leader (Tenure), Max Planck Institute for Empirical Aesthetics, Department of Neuroscience **Introduction by:** **Dr. Taufik Valiante/Dr. Luka Milosevic**, Co-Director, CRANIA; Assistant Professor, Institute of Biomedical Engineering, University of Toronto; Scientist, Krembil Research Institute	Room 2158 Macleod Auditorium
2:40 – 4:00 PM	**Professional Development Workshop:** "Navigating the storm: unmasking collective trauma and embracing resilience in the wake of COVID-19" **Dr. Sakina Rizvi**, Associate Professor, Department of Psychiatry and Institute of Medical Science; Scientist, Li Ka Shing Knowledge Institute and the Arthur Sommer Rotenberg Suicide and Depression Studies Unit, St. Michael's Hospital **Molly Hyde**, PhD Candidate, Institute of Medical Science and ASR Suicide and Depression Studies Unit **Lisa Eunyoung Lee**, PhD candidate, Institute of Medical Science, University of Toronto **Moderators**: **Dr. Zhong-Ping Feng/Dr. Luka Milosevic**	
4:00 PM	**Awards Ceremony & Closing** **Dr. Zhong-Ping Feng/Dr. Jeffrey Henderson** Jonathan Dostrovsky Awards in Neuroscience Trainee Presentation awards Closing	
4:30 – 6:00 PM	**Reception**	Stone Lobby

Keynote Speakers

Jaideep Bains, PhD. Professor, Department of Physiology; Director, Krembil Research Institute, University Health Network.

"Stressed? Forget about it!"

Dr. Jaideep Bains' research uses multiple experimental approaches to reveal key features about neural circuits that regulate internal state and are also purposed to control behavior and store information in response to challenges. Specifically, his lab uses in vitro slice electrophysiology, in vivo imaging, optogenetics, behavioral analysis tools and physiological assays to characterize neural circuits that decode stress, modify internal states and generate specific coping behaviors. One of his goals is to better understand the mechanisms that allow these circuits, or specific cell populations, to store information related to the modality, intensity and temporal features of stress. In addition to his extensive experience in synaptic physiology and electrophysiology he has used circuit mapping approaches to link activity in specific cell populations to different behaviors. His work has linked brief stress exposure and enduring synaptic changes in the hypothalamus (reviewed in Bains et al, Nat Rev Nsci, 2015). His lab has provided clear evidence supporting a role for astrocytes in controlling the strength of excitatory synapses in the hypothalamus (Gordon et al, Nat Nsci, 2005, Neuron, 2009). More recently, his lab has shown new roles for hypothalamic CRH neurons as bottom-up controllers for complex behaviors associated with stress coping (Fuzesi et al, Nat Comm, 2016), the transmission and detection of affective states between mice (Sterley et al, Nat Nsci, 2018) and linking stress controllability and active behaviour strategies (Daviu et al, Nat Nsci, 2020).

Lucia Melloni, PhD. W2 Group Leader (Tenure), Max Planck Institute for Empirical Aesthetics, Department of Neuroscience.

"Using Adversarial Collaboration to Harness Collective Intelligence"

Dr. Lucia Melloni is a W2 Group Leader (Tenure) at the Department of Neuroscience, Max Planck Institute for Empirical Aesthetics, Germany. Her studies investigate how the brain learns to segment continuous speech into relevant units, and where this takes place, by using statistical learning paradigms and intracranial recordings.

Professional Development Workshop Speakers

"Navigating the storm: unmasking collective trauma and embracing resilience in the wake of COVID-19"

This workshop will explore the impacts of COVID-19 on the mental health of students and youth. Engage with expert insight and firsthand perspectives from speakers with lived experience as they discuss unrecognized pandemic trauma, the learning challenges faced by students, and strategies for coping and maintaining hopeful resiliency in a post-pandemic world.

Sakina Rizvi, PhD

Associate Professor, Department of Psychiatry and Institute of Medical Science; Scientist, Li Ka Shing Knowledge Institute and the Arthur Sommer Rotenberg Suicide and Depression Studies Unit, St. Michael's Hospital.

Molly Hyde

PhD Candidate, Institute of Medical Science and ASR Suicide and Depression Studies Unit, St. Michael's Hospital.

Lisa Eunyoung Lee

PhD candidate, Institute of Medical Science, University of Toronto.

Poster Presenter Groups

Group Theme	Abstract No.	Name
Behavioural Neuroscience	1	Jenna Baer
	2	Liv Engel
	3	Melissa Hazen
	4	Yasaman Kambari
	5	Garene Matossian
	6	Diana Peragine
	7	Thomas Prevot
	8	Emily Wong
Cellular and Molecular Neuroscience	9	Mahbod Ebrahimi
	10	Sarah Eide
	11	William McIntyre
	12	Rayan Saghian
	13	Tianze Shi
Cognitive Neuroscience	14	Hassan Abdulrasul
	15	Joel Diaz
	16	Mahnoor Hamid
	17	Daisy Hu
	18	Minarose Ismail
	19	John Kennedy
	20	Felicia Kwan
	21	Cindy Nguyen
	22	Lulia Snan
	23	Hannah Whitehead
Computational Neuroscience	24	Dylan Dingwell
	25	Romesa Khan
	26	Frank Mazza
	27	Faraz Moghbel
	28	Khashayar Namdar
	29	Fatemeh Shomal Zadeh
	30	Bernice Tang
Concussion and Brain Injuries	31	Jing Lin
	32	Andie Ovcjak
	33	Kevin Solar
Depression and Mental Health	34	Noah Chisamore
	35	Katharina Goke
	36	Kateryna Maksyutynska
Learning and Memory	37	Megan Lozzi
Mental Disorders	38	Riddhita De
Neuroanatomy	39	Stefanie Bradley

Group Theme	Abstract No.	Name
Neurodegenerative Diseases	40	Dustin Loren Almanza
	41	Ari Belotserkovsky
	42	Lauren Joe
	43	Bryan Kartono
	44	Laura Kondrataviciute
	45	Sonika Kumari
	46	Jonathan Monteiro
	47	Roseanne Nguyen
	48	Syeda Hania Qamar
	49	Can Sarica
	50	Raghav Sharma
	51	Sandra Shenouda
	52	Ella Bing Xin Song
	53	Claire Verkuyl
Neuroimaging	54	Gloria Tian
Neurological Diseases	55	Natasha Benn
	56	Avery Cameron
	57	Jerry Li
	58	Rafi Matin
	59	Elina Provad
Neurological Rehabilitation	60	Nicole Cesca
Neuropharmacology	61	Tian Kong
	62	Isaac Kuk
	63	Emma Russo
	64	Jianmeng Song
	65	Lola Zovko
Neurophysiology	66	Bojing Gui
	67	Alicia N. Harracksingh
	68	Dallas Leavitt
	69	Suha Sagheer
	70	Shirin Tajali
Pain and Nociception	71	Emili Adhamidhis
	72	Rima El-Sayed
	73	Janet Li
	74	Nikou Kelardashti
	75	Matthew Mockford
Synaptic Plasticity	76	Samuel Fung
Translational Research	77	Sun Eui (Sunny) Choi
	78	Sahara Haylestrom
	79	Kristoffer Panganiban
	80	Katarzyna Pieczonka
	81	Victoria Yuan
Other: Neurophysics	82	Xin Mu

Oral Presenter Groups

Theme	Name	Session	Room
Behavioral Neuroscience	Zeenat Ladak	I	**Room 2158 JJR Macleod Auditorium**
	Linda Marchesano	I	
Cellular and Molecular Neuroscience	Raphael Chan	I	
	Madeleine Falby	I	
Concussion and Brain Injuries	Chloe Buso	I	
	Marc Khoury	I	
Cognitive Neuroscience	Lauren Cole	II	**MSB 2170**
	Hsin-Yun (Angel) Hsieh	II	
	Kai Ian Leung	II	
Computational Neuroscience	Niki Akbarian	II	
	Heng Kang Yao	II	
Neuroimaging	Kevan Clifford	II	
Neuroanatomy	Savina Cammalleri	III	**MSB 2172**
	Babishaa Sauntharrajan	III	
Neurodegenerative Diseases	Anthaea-Grace Patricia Dennis	III	
	Nafia Mirza	III	
Neurodevelopment	Tariq Ahmed	III	
Neuroimmunology	Robert Duba-Kiss	III	
Learning and Memory	Julia Bandura	IV	**MSB 4171**
Pain and Nociception	David Rodriguez	IV	
Synaptic Plasticity	Muchun Han	IV	
	Quinn Pauli	IV	
Translational Research	Ilakkiah Chandran	IV	
	Xinyang Zhang	IV	
Neuropharmacology	Christina Pereira	V	**MSB 4279**
	Nayaab Punjani	V	
	Emily Smith	V	
Neurophysiology	Kayla Baker	V	
	Hanne Bartels	V	
	Darshan Panesar	V	

Event Organizers

Organizing Committee
Zhong-Ping Feng (Chair)
Jeffrey Henderson
Ain Kim (Student Lead)
Luka Milosevic
Joyce Poon
Hong-Shuo Sun
Kaori Takehara
Taufik Valiante

Trainee Volunteers
Irina Alymova
Joel Diaz
Isaac Kuk
Joshua Olorocisimo
Angenelle Rosal
Rayan Saghian
Xianxuan Wang
Micaela Wiseman
Maria Yang
Ryan Yip

Special Acknowledgement
Keynote Lectures
Jaideep Bains
Lucia Melloni

Trainee Workshop
Sakina Rizvi
Molly Hyde
Lisa Eunyoung Lee

Poster Presentation Judges
Gustavo Balbinot
Pushpal Desarkar
Trish Domi
Benjamin Dunkley
Daniel Felsky
Gustavo Grimmer
Eyal Gruntman
Alexandre Guet-McCreight
Jeffrey Henderson
Jenny Lepock
Rodrigo Mansur
Kei Masani
Luka Milosevic
Yuliya Nikolova
Shraddha Pai
Michael Pollanen
Thomas Prevot
Filsy Samuel
Gerold Schmitt-Ulms
Jiannis Taxidis
Tatsuya Tsukahara
Douglas Tweed
Naomi Visanji
Timothy Welsh
Silvia Zampar
Chao Zheng

Oral Presentation Judges
Patricia DiCiano
Cordula Enenkel
Zhong-Ping Feng
Qian Lin
Philip McGoldrick
Joyce Poon
Priyanka Singh
Patcharaporn Srisaikaew
Hong-Shuo Sun
Taufik Valiante

Program Design/Production
Irina Alymova
Joel Diaz
Zhong-Ping Feng
Ain Kim
Kateryna Maksymenko
Angenelle Rosal

Administration
Jenny Fan
Ain Kim
Kateryna Maksymenko
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Institute of Biomedical Engineering | Warren Chan
Cell and Systems Biology | Leslie Buck/John Peever; Nick Provart
Computer Science | Richard Zemel; Ravin Balakrishnan
Dalla Lana School of Public Health | Geoff Anderson; Adalsteinn Brown
Dentistry | Limor Avivi-Arber; Morris Manolson
Laboratory Medicine and Pathobiology | Janice Robertson; Rita Kandel
Immunology | Chao Wang; J.C. Zúñiga-Pflücker
Institute of Medical Science | Albert Wong; Mingyao Liu
Medical Biophysics | Bojana Stefanovic; Thomas Kislinger
Music | Michael Thaut
Pharmaceutical Sciences | Jeffrey Henderson; Lisa Dolovich
Pharmacology and Toxicology | Amy Ramsey/Ruth Ross/Ali Salahpour
Physiology | Zhong-Ping Feng/Doug Tweed; Scott Heximer
Psychology | Kaori Takehara-Nishiuchi; Elizabeth Page-Gould
Rehabilitation Science Institute | Karl Zabjek; Angela Colantonio

POSTER PRESENTATIONS

BEHAVIORAL NEUROSCIENCE

1. Jenna Baer; Institute of Medical Science / Centre for Addiction and Mental Health

Supervisor: Dr. Gwyneth Zai

COGNITIVE INFLEXIBILITY IN OBSESSIVE COMPULSIVE DISORDER (OCD)

Baer J, 1,2; Zai C, 1,2; Solly J, 3; Vaghi M, 3; Robins T, 3; Sahakian B, 3; Richter M, 1,4; Bruhl A, 3; Chamberlain S, 3; Zai G, 1,2

1 Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada; 2 The Centre for Addiction and Mental Health, Toronto, Ontario, Canada; 3 University of Cambridge, Cambridge, United Kingdom; 4 Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada

Introduction: Obsessive compulsive disorder (OCD) is a mental health disorder characterized by obsessions and/or compulsions. Obsessions are unwanted and intrusive thoughts images and urges, and compulsions are mental or physical repetitive behaviours. Individuals with OCD may experience cognitive deficits, specifically regarding cognitive flexibility. The thought patterns associated with OCD are very sticky, and inflexible which is one hypothesis as to why individuals with OCD have trouble being cognitively flexible. **Objective**: The aim of the study is to investigate whether individuals with OCD perform worse on a task of cognitive flexibility compared to healthy controls (HC). **Methods:** An independent sample of 20 participants with OCD and 20 HCs were administered the CANTAB® Intra-extra dimensional set-shifting task (IED), which measures cognitive flexibility. SPSS was used to conduct an analysis of covariance, to compare differences in mean errors between groups. The independent sample was included as part of an update to a meta-analysis (N=622 OCD, N=584 HC) comparing individuals with OCD to HCs on the same cognitive task. The meta-analysis was run on STATA using their random effects model. **Results:** To compare differences in cognitive flexibility, the means of the extra-dimensional (ED) set-shifting stage were compared. When age was included as a covariate, individuals with OCD exhibited higher mean ED errors (p=0.004) and total errors (p=0.002). There was a significant difference in ED mean errors in the meta-analysis, with individuals with OCD having significantly higher mean ED errors (p=0.0001). **Conclusion:** The results from the independent sample and meta-analysis display that individuals with OCD experience cognitive inflexibility compared to HCs. Cognitive inflexibility in OCD, should be further investigated, regarding its role in treatment response, and symptom outcomes.

2. Liv Engel; Department of Psychology

Supervisor: Dr. Robert Rozeske

INVESTIGATION OF PREFRONTAL DOPAMINE DYNAMICS DURING A NOVEL MODEL OF CONTEXT FEAR LEARNING

Engel L, 1; Shahin Far S, 1; Rozeske RR, 1

1 Department of Psychology, University of Toronto, Scarborough, Ontario, Canada

Introduction: Identifying an environment as threatening or safe is essential for survival and depends on integrating past experiences with the present situation to guide context-appropriate behaviour. Individuals experiencing post-traumatic stress disorder (PTSD) often generalize their fear responses to safe environments. The medial prefrontal cortex (mPFC) may be a key structure to investigate during context-guided fear behaviour because a) it's engaged during fear expression b) its neural representation changes when the meaning of a context is altered and c) mesocortical dopamine is associated with guiding adaptive actions. **Objective:** To further characterize the role of the mPFC during context threat uncertainty, we developed an apparatus that "teleports" the mouse between contexts to measure discrimination. **Methods:** We expressed the biosensor GRABDA in the mPFC to monitor dopamine signaling with fiber photometry during context fear learning. **Results:** Our results indicate that mice discriminate between threatening and neutral contexts following "teleportation". Further, we observed transient and prolonged increases in dopamine signalling during context fear conditioning. In addition, "teleportation" between threatening and neutral contexts elicited increased dopamine signaling. **Conclusion:** These results suggest the "teleporter" apparatus can be used to model contextual processing and that prefrontal dopamine dynamics are altered during context fear memory encoding and retrieval. Together our findings indicate prefrontal dopamine signalling may be a useful target for developing therapeutic interventions for those with PTSD.

3. Melissa Hazen; Institute of Medical Science

Supervisor: Dr. Karen Gordon

DEVELOPMENTAL EFFECTS OF CONCURRENT AUDITORY AND VESTIBULAR IMPAIRMENTS ON LANGUAGE, WORKING MEMORY, AND ACADEMIC ABILITIES IN CHILDREN WITH BILATERAL COCHLEAR IMPLANTS

Hazen M, 1,2,4; Cushing SL, 1,2,3; Gordon KA, 1,2,3,4

1 Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada; 2 Department of Otolaryngology-Head & Neck Surgery, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada; 3 Department of Otolaryngology-Head & Neck Surgery, Hospital for Sick Children, Toronto, Ontario, Canada; 4 Department of Communication Disorders, Hospital for Sick Children, Toronto, Ontario, Canada

Introduction: Balance deficits, attributed to vestibular impairments, are prevalent in children with hearing loss. Impaired spatial perception, working memory, academics, and learning have been shown in children with hearing loss (McSweeny et al., 2021) and impaired working memory has been shown in young adults with both hearing and vestibular dysfunction (Benjamin et al., 2023). However, the potential role of the vestibular impairment above and beyond the hearing loss are not clear. **Objective:** This study investigates the developmental consequences of vestibular impairments on working memory, language proficiency, and academic abilities in children with bilateral cochlear implants (BCIs). The hypothesis of the study is that deficits in working memory, language skills, and academic performance in children with bilateral cochlear implants are further exacerbated in the children with concurrent vestibular impairments. **Methods:** The study included 53 children (25 female, 28 male) divided into three groups: 1) typically developing (n=15, average(SD) age = 12.75(2.38), range: 8.11-15.91 years); 2) sensorineural hearing loss (n=13, average(SD) age = 11.42(2.34) years, range: 6.95-15.84 years); and 3) concurrent hearing

loss and vestibular impairment (n=24, average(SD) age = 10.46(3.74), range: 4.65-17.85 years). Working memory was tested by measuring span recalls in the Dot Matrix, Corsi Block, and Digit Span tests. Academic skills were tested using the Weschler Individual Achievement Test 3rd Edition (WIAT) and language was measured with the Clinical Evaluation of Language Fundamentals 5th Edition (CELF). Data analyses utilized mixed model regressions, accounting for group, age, sex as fixed effects. Post-hoc analyses were conducted on significant findings using estimated marginal means. **Results:** Development in all tests increased with age as expected (academics ($F(1)=35.27$, $p<0.01$); working memory ($F(1)=25.57$, $p<0.01$); language ($F(1)=13.33$, $p<0.01$)). Children with bilateral cochlear implants exhibited poorer language skills ($F(2)=7.85$, $p<0.01$) when compared to typically developing peers. Concurrent vestibular impairment may have additional adverse effects on academics ($t(2)=2.21$, $p=0.08$) and language ($t(45)=2.56$, $p<0.04$). **Conclusion**: Early findings of this study suggest developmental effects of hearing loss, which may be further intensified by the presence of concurrent vestibular impairments in academic and language. Non-significant findings will be addressed relative to previous work. Overall, these findings may underscore the importance of early intervention and tailored support to address the unique challenges faced by children with dual sensory impairments.

4. Yasaman Kanbari; Institute of Medical Science

Supervisor: Dr. Philip Gerretsen

EFFICACY OF CATHODAL TRANSCRANIAL DIRECT CURRENT STIMULATION OVER THE LEFT TEMPOROPARIETAL AREA TO IMPROVE INSIGHT INTO ILLNESS IN SCHIZOPHRENIA, A SYSTEMATIC REVIEW AND META-ANALYSIS

Kambari Y, 1,2; Plahouras J, 3; Song J, 1,2; Amaev A, 1,2; Abdolizadeh A, 1,2; Torres-Carmona E, 1,2; Ueno F, 1,2; Koizumi T, 1,2; Graff-Guerrero A, 1,2; Gerretsen P, 1,2*

1 Centre for Addiction and Mental Health (CAMH), Toronto, Ontario; 2 Institute of Medical Science, University of Toronto, Toronto, Ontario; 3 School of Medicine, University of Limerick, Limerick, Ireland

Introduction: Schizophrenia is a chronic psychotic disorder that impacts millions of people worldwide, however only a small percentage receive mental health care. Impaired insight into illness is a common feature of schizophrenia that leads to treatment non-adherence. Poor insight has been linked to an interhemispheric imbalance in the frontoparietal regions. Transcranial direct current stimulation (tDCS) has been explored as a potential treatment for improving insight, with cathodal tDCS over the left temporoparietal area (TPA) showing significant results. **Objective:** The aim of this systematic review and meta-analysis is to investigate the efficacy of cathodal tDCS on the left TPA to improve insight in schizophrenia. **Methods**: The Ovid database was used to conduct a literature search, including databases such as Medline, Embase, and PsycINFO. The most recent search was conducted in January 2024. The following search terms were used: ("transcranial direct current stimulation" OR "tDCS") AND ("PANSS" OR "positive and negative syndrome scale" OR "insight") AND "schizophrenia". **Results**: The search identified 97 unique publications; 13 studies were selected for meta-analysis. We identified 7 studies (n=330) that placed the cathode over the left TPA and 6 studies that placed the cathode over other regions (n=250). The subgroup analyses did not reveal a difference between the studies that located the cathode over the left TPA and those that applied it to other regions. There were not enough studies to explore the effects of other tDCS montages on insight. Meta-regression analysis found an association with mean age and change in insight scores, there wasn't an association between illness duration and insight. **Conclusion:** Results suggest that the improvement of insight associated with cathodal tDCS stimulation over the left TPA is not inferior to other montages. Future sham-controlled studies that use comprehensive insight scales are required to better understand the effects of cathodal tDCS over the left TPA on insight.

5. Garene Matossian; Department of Physiology

Supervisor: Dr. Andrew Dimitrijevic

AUDITORY SPATIAL ATTENTION IN COCHLEAR IMPLANT USERS: RELATION TO NEURAL CORRELATES OF SPEECH PERCEPTION AND QUALITY OF LIFE

Matossian GA, 1,2; Dimitrijevic A, 1,2,4; Alain C, 3,4

1 Department of Physiology, University of Toronto, Toronto, ON, Canada; 2 Evaluative Clinical Sciences Platform, Sunnybrook Research Institute, Toronto, ON, Canada; 3 Rotman Research Institute, Baycrest Health Sciences, Toronto, ON, Canada; 4 Institute of Medical Sciences, University of Toronto, Toronto, ON, Canada

Introduction: Cochlear implants (CIs) have changed the lives of ~700,000 people with profound hearing loss. Though speech perception and quality of life (QoL) have been shown to improve after CI activation, there is a significant amount of individual variability within and between these measures. The environment of speech perception testing may cause variability, as testing occurs in a quiet environment, which does not reflect the abundance of auditory stimuli people experience daily. Attentional differences may also account for some variability, as attention is essential for speech perception, particularly in "cocktail-party" environments with distracting stimuli. Better methods of measuring speech perception that consider attention and a more naturalistic, noisy environment may provide a more accurate measure of speech perception after CI implantation. This research aims to aid in developing these methods by examining auditory spatial attention and speech perception in CI users. We aim to determine if these features can be objectively quantified using electroencephalography (EEG), as measured by speech neural tracking and whether these neural measures are related to subjective measures of QoL and listening effort. **Objectives:** The objectives of this study are to determine the relationship between EEG measures of speech perception and QoL, determine the relationship between behavioural measures of speech perception and QoL, and determine EEG spectral power and neural speech tracking to an audiobook with distractors. **Methods:** Twenty CI users and twenty age- and sex-matched controls with normal hearing (NH) participated in two experiments. The first experiment assessed speech perception and spatial attention through a behavioural test. Participants heard three digits at 0° azimuth while simultaneously being presented with distractor digits at ±45° or ±90° azimuth. The distractor digits were either in the same or different voice as the central speaker. The participants focused on the center speaker and reported the numbers heard. There were 4 runs, 25 trials each. The SNR increased or decreased based on whether the participant got the previous trial correctly or incorrectly. In the second experiment, participants underwent an EEG test while listening to audiobook segments (15 minutes) at 0° azimuth, with distractors at ±45° or ±90° azimuth, presented in the same or different voice as the central speaker. Participants rated their listening effort on a scale of 1 to 10 after each run and answered content questions on the audiobook. Speech neural tracking was measured using temporal response functions (TRF), a

measure that correlates slow fluctuations in speech (e.g., speech envelope) to EEG activity. Time-frequency analysis examined alpha oscillations, as they are known to inhibit the attentional network. Multiple correlational analyses explored relationships between listening effort, speech neural tracking, behavioural speech perception measures, and previously obtained data from AzBio, SSQ, and CIQOL-35 measures. **Results:** Preliminary results show that NH participants have lower SNR during the behavioural test and have higher TRF amplitudes than CI participants. All participants performed better in the behavioural task and had higher TRF amplitudes in conditions with different voice distractors than in the same voice. However, no differences were seen between the locations of the distractors. The behavioural test results and the TRF amplitude were correlated with previously obtained speech perception measures. Finally, the behavioural results and TRF amplitude positively correlate to QoL. **Conclusion:**
The findings suggest that NH participants exhibit superior neural speech tracking compared to CI users. Additionally, behavioural tests show promise in measuring speech perception, correlating with established speech perception measures. Moreover, a positive correlation between QoL and TRF amplitude, along with behavioural results, suggests the predictive accuracy of these tests for QoL. Overall, perception measures incorporating attention in a naturalistic setting may capture listening difficulties not typically observed during standard clinical measures.

6. Diana Peragine; Centre for Addiction and Mental Health

Supervisor: Dr. Doug VanderLaan

WIRED TO DESIRE? WHITE MATTER MICROSTRUCTURE VARIES WITH SEXUAL ATTRACTIONS, NOT SEX OR GENDER, IN A CULTURE BEYOND THE WESTERN GENDER BINARY

Peragine D, 1; Rodkong A, 2; Hu D, 1; Skorska M, 3; Saokieho P, 2; Thurston L, 1; Folkierska-Żukowska M, 3; Supintham T, 2; Kaewthip O, 2; Wantanajittikul K, 2; Chotirosniramit N, 2; Chariyalertsak S, 2; Saekho S, 2; VanderLaan D, 1,3

1 Department of Psychology, University of Toronto Mississauga, Mississauga, Ontario, Canada; 2 Chiang Mai University, Sriphum, Muang Chiang Mai, Thailand; 3 Child and Youth Psychiatry, Centre for Addiction and Mental Health, Toronto, Ontario, Canada

Introduction: The network of nerve fibers that make up the brain's connective architecture, termed white matter microstructure (WMM), underpins neural communication, and is thought to be sex-differentiated in its organization and myelination. Some evidence suggests WMM is further differentiated by sexual orientation and/or gender expression, but studies rarely parse their relative contributions to brain sexual differentiation—or parse attractions to sex versus gender when operationalizing sexual orientation. Thai culture provides a unique opportunity to disentangle these given the high visibility of sexual and gender diversity across sexes, and lay recognition of gender expression as a dimension of sexual orientation. Here, we assessed WMM in a Thai sample of sexual/gender majority individuals (heterosexual women and men), and a range of sexual/gender minorities: feminine females attracted to women (lesbians), and masculine and feminine females attracted to one another (toms and dees). **Objective:** Using whole-brain multivariate analysis of WMM, we sought to disentangle differences owing to the sex and gender of participants, as well as those of their preferred partners—probing whether sex, gender, and sexual attractions have distinct (micro)structural brain signatures. **Methods:** Diffusion-weighted brain images were acquired from 140 Thai adults (n = 26–30/group) at 1.5T. Diffusion tensor modelling was used to generate fractional anisotropy (FA), axial diffusivity (AD), and radial diffusivity (RD) maps reflecting white matter organization and myelination. These diffusion indices were compared across groups with multivariate partial least squares analysis. **Results:** Two latent patterns of FA, AD, and RD were identified at $p < .01$. One indicated less directional diffusion—and less organized/myelinated white matter—in same-sex attracted groups (lesbians, toms, dees) than heterosexual men, with heterosexual women being intermediate. This pattern was apparent across the cingulum, superior longitudinal fasciculus, superior corona radiata, corticospinal tract, anterior thalamic radiation, posterior limb of the internal capsule, and middle cerebellar peduncle. A second latent pattern in the fornix indicated more directional diffusion in groups attracted to masculinity (heterosexual women, dees) relative to heterosexual men, with lesbians and toms being intermediate. **Conclusion:** Results suggest that WMM is not differentiated simply by one's sex or gender expression. Rather, it may be differentiated by attraction to members of the same/other sex, and, to a lesser extent, by attraction to masculine/feminine partners. These findings add important nuance to accounts of brain sexual differentiation, underscore the limits of Western androcentric approaches to its study, and raise the possibility that we are not just wired to want sex, but gender as well.

7. Thomas Prevot; Department of Psychiatry / Department of Pharmacology and Toxicology

TARGETING THE A5-GABAA RECEPTOR ALLEVIATES COGNITIVE DEFICITS AND REVERSES NEURONAL ATROPHY ACROSS ANIMAL MODELS OF BRAIN DISORDERS.

Thomas D. Prevot, 1,2,3; Ashley Bernardo, 1; Michael Marcotte,1; Kayla Wong, 1; Cassandra Marceau-Linhares, 1; Celeste Pina-Leblanc, 1; Prithu Mondal, 4; James M. Cook, 4; & Etienne Sibille, 1,2,3

1 Campbell Family Mental Health Research Institute of CAMH, 250 college street, Toronto, ON, M5T 1R8 Canada; 2 Department of Psychiatry, University of Toronto, 250 college street, Toronto, ON, M5T 1R8 Canada; 3 Department of Pharmacology and Toxicology, University of Toronto, Medical Sciences Building, 1 King's College Cir Room 4207, Toronto, ON, M5S 1A8, Canada; 4 Department of Chemistry and Biochemistry, University of Wisconsin–Milwaukee, 3210 N Cramer Street, 53211, WI, USA

Introduction: Reduced GABA/somatostatin (SST) signaling is reported in psychiatric, stress-related and neurodegenerative disorders. Cortical SST+ interneurons inhibit the dendrites of excitatory neurons, largely through α5-containing GABAA receptors (α5-GABAAR). We showed that an α5-positive allosteric modulator (α5-PAM) alleviates working memory deficits and reverses neuronal atrophy in old mice. **Objective:** We then aimed at investigating the behavioral and neurotrophic effects of this α5-PAM in animal models of aging, chronic stress, β-amyloid load, and tauopathy. **Methods:** Four studies are presented (~6 mice/sex/group): 1) Young C57BL6 subjected to chronic stress. 2) 22-month-old C57BL6 developing an age-related cognitive decline. 3) 5xFAD transgenic mice with progressive amyloid load. 4) PS19 transgenic mice developing tauopathy. Efficacy of 4 weeks of GL-II-73 (30mg/kg, p.o) at rescuing cognitive deficits was assessed for working memory (alternation task), spatial memory (water maze), and cognitive flexibility (set-shifting). Brains were then stained (Golgi-Cox; n=4brain/group; 8cell/brain) for spine density and maturation quantification in the prefrontal cortex and hippocampus. **Results:**

Chronic treatment in all models reversed cognitive deficits (ps<0.01), with a strong effect on working memory. Chronic treatment reversed UCMS-, age-, amyloid- or Tau-protein-induced reduction of spine density at all maturation steps (p<0.001; PFC and CA1). **Conclusions:** Results support that selective α5 targeting of GABAA receptors overcomes chronic stress-, aging-, amyloid- or tau-related cognitive deficits and detriments in neuronal morphology at all maturation steps. For the first time, a GABAergic intervention shows a symptomatic and disease-modifying therapeutic potential and could represent a major avenue for clinical development for patients suffering from cognitive deficits across brain disorders.

8. Emily Hiu Yuet Wong; Department of Cell and Systems Biology

Supervisor: Dr. Robert Rozeske

ENTRAINMENT OF MEDIAL PREFRONTAL CORTEX ACTIVITY USING NON-INVASIVE RHYTHMIC SENSORY STIMULATION

Emily Hiu Yuet Wong, 1; Locas G, 2; Gosselin B, 2; Godin A, 3; Rozeske RR, 1

1 Department of Cell and Systems Biology, University of Toronto, Toronto, Ontario, Canada; 2 Département de Génie Électrique et Informatique, Université Laval, Québec, Québec, Canada; 3 CERVO Brain Research Centre, Québec Mental Health Institute, Québec, Québec, Canada

Introduction: In rodents, repeated exposure to a fear-associated cue reduces fear behavior via fear extinction. Neural circuits involved in fear extinction, particularly connections between the basolateral amygdala and medial prefrontal cortex (mPFC), produce neural oscillations at 6-12 Hz during extinction. Recently, optogenetic entrainment of this amygdala-prefrontal circuitry at these frequencies reduced fear behavior. For translational purposes, an important question is whether extinction-related neural oscillations in the mPFC can be similarly generated using a non-invasive method. **Objectives:** To this end, we developed an apparatus to administer rhythmic sensory stimulation (RSS)—light flickers and auditory pips—to mice. **Methods:** Electrodes were surgically implanted in the mPFC to record in vivo electrophysiological activity while administering RSS at multiple frequencies within the 6-12 Hz range. **Results:** Spectral analysis showed that visual stimulation, but not auditory, significantly increased the local field potential power at the respective RSS frequency delivered. **Conclusion:** These initial findings that indicate RSS entrains mPFC local field potentials warrant further investigation as a potential non-invasive approach to accelerating fear extinction.

CELLULAR AND MOLECUALR NEUROSCIENCE

9. Mahbod Ebrahimi; Institute of Medical Science

Supervisor: Dr. James L. Kennedy

ASSOCIATION STUDY OF C4 GENE VARIANTS AND SUICIDE RISK IN SCHIZOPHRENIA

Ebrahimi M, 1,2; Teymouri K, 1,2; Chen CC, 1,2; Zai CC, 1,2,3; Kennedy LJ, 1,2,4*

1 Tanenbaum Centre for Pharmacogenetics, Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Ontatio, Toronto, Canada; 2 Institute of Medical Science, University of Toronto, Ontario, Toronto, Canada; 3 Laboratory Medicine and Pathobiology, University of Toronto, Ontario, Toronto, Canada; 4 Department of Psychiatry,University of Toronto, Ontario, Toronto, Canada

Introduction: Suicide is a major cause of death among schizophrenia patients, with approximately 50% attempting and 10% dying from suicide1,2. Although genetic components play a significant role in schizophrenia risk, with 79% heritability3, the underlying genetic risk factors for suicide are poorly understood. It is suggested that the immune system plays a key role in suicide vulnerability across psychiatric disorders, including schizophrenia4. The complement component C4 gene, an immune gene involved in the innate immune system, has recently been identified to be strongly associated with schizophrenia risk5,6. In addition, preliminary findings show that the C4 gene has also been associated with suicide risk, making it a potential candidate of interest for studying suicidality in schizophrenia patients7. The C4 gene has a complex genetic structure with two distinct variations, C4A and C4B8. Both C4A and C4B could be further divided into either long (AL, BL) or short (AS, BS) variants, resulting in four possible forms: C4AL, C4BL, C4AS, and C4BS9. It has been reported that the C4AL variant has the highest association with increased schizophrenia risk6. **Objective:** The purpose of this research is to investigate the relationship between the C4 gene variants and suicide risk in patients with schizophrenia, and potentially identify a new genetic marker for suicide risk in this group. With C4AL having the highest association with increased schizophrenia risk6, it is hypothesized that schizophrenia patients with C4AL will have an increased suicide risk than those without. **Methods:** This study will include a sample of N=434 schizophrenia patients (311 males:123 females) from our ongoing study on the genetics of schizophrenia10. All patients have been diagnosed with schizophrenia based on the Structured Clinical Interview for DSM-IV Axis (SCID)11 and have provided blood samples. DNA extractions have been performed from blood samples. The precise C4 gene variant and the number of repeats are determined in three steps: 1- Real-time PCR is used to determine the precise copy number of C4 variants; 2-Long-range PCR is performed in subjects with at least one copy of C4S; 3- The presence of either C4AS and/or C4BS is determined by using a custom genotyping assay. Data on suicide attempts, suicidal ideation, and suicidal plans will be extracted from the mood disorder module of the SCID, referral notes, and summary of medical records. **Results:** Logistic regression analyses showed a significant negative association between the C4AS variant and suicide attempt (p=0.036, OR=0.457)/suicidal ideation (p=0.045, OR=0.565). Further sex-stratified analyses revealed that this association is stronger in males compared to females. **Conclusion**: Despite growing efforts, suicide attempts remain alarmingly high among schizophrenia patients, leading to significant emotional and medical costs for our society12. This study is the first of its kind to analyze the association between the complement component C4 gene and suicide risk. Based on our results, the presence of the C4AS variant in schizophrenia patients may have a protective role against suicide attempt/ideation. Further investigation with a larger sample size may clarify these results.

10. Sarah Eide; Department of Physiology

Supervisor: Dr. Zhong-Ping Feng

THE RISK OF THROMBIN-MEDIATED NEURONAL DEGENERATION WITH INCREASING AGE AND DOWN-STREAM SIGNALLING

Eide S, 1; Sun HS, 1,2; Feng ZP, 1

1 Department of Physiology, University of Toronto, Toronto, Ontario, Canada; 2 Department of Surgery, University of Toronto, Toronto, Ontario, Canada

Introduction: Plasma thrombin, a component of the coagulation cascade, is elevated in neurodegenerative disorders, contributing to disease pathology through cleavage of protease-activated receptors (PAR) in the brain. However, whether age is a risk factor for increased thrombin activity and how age influences thrombin-mediated neurodegeneration is not well understood. **Objective:** We hypothesize active thrombin levels increase with age. We aim to understand how aging influences thrombin's effect on neuronal cells through PAR-1 signalling and identify potential downstream targets that may reduce the risk of neurodegeneration. **Methods:** Meta-analysis of 38 studies reporting on 17,204 healthy adults (18-99 years old) was conducted to compare levels of thrombin markers across age cohorts. Colorimetric viability and neurite outgrowth assays were conducted in vitro in differentiated human SH-SY5Y neuronal cells aged up to 4 weeks in culture treated with thrombin (0.1-1000 nM). The contribution of PAR-1 and identified down-stream signalling protein, Rasal1, was assessed through addition of a small molecule inhibitor (FR171113) and shRNA knockdown, respectively. **Results:** Those over the age of 60 have a greater endogenous thrombin potential associated with elevated plasma levels of activated Factor X, elevated markers of active thrombin (prothrombin fragment 1+2, fibrinopeptide A, and d-dimer), and reduced levels of thrombin inhibitors (antithrombin III and heparin). In vitro, thrombin significantly reduces neuronal viability and neurite outgrowth, which is pronounced in aged neuronal cultures. Thrombin's degenerative effects in aged cultures are associated with an increase in PAR-1 expression. Inhibition of PAR-1 and knockdown of a potential down-stream signalling protein, Rasal1, is found to protect aged neurons in culture from thrombin-mediated degeneration. **Conclusion**: Increasing age is correlated with higher thrombin activity. Thrombin markedly promotes degeneration in aged neuronal culture via PAR-1 signalling, suggesting an increased risk of thrombin-mediated neurodegeneration during physiological aging.

11. Brett Mcintyre; Institute of Medical Science

Supervisor: Dr. Michael Fehlings

HOMEOTIC IDENTITY IN MOUSE AND HUMAN NEURAL STEM CELLS PROMOTES REGENERATIVE SUCCESS WHEN TRANSPLANTED IN SPINAL CORD INJURY

McIntyre WB, 1,2; Lou Z, 1,2; Khazaei M, 2; Fehlings MG, 1,2

1 Institute of Medical Science, University of Toronto, Ontario, Canada; 2 Krembil Research Institute, University Health Network, Toronto, Ontario, Canada;

Introduction: Neural stem cells (NSC) are a viable transplantable therapeutic for sparing and replenishing the cellular niche lost after traumatic spinal cord injury (SCI). Recent experimental evidence suggests that a transplanted NSC with matching "regional" spinal cord identity to the injured cord can yield optimal cell integration and functional outcomes. A potential mechanism for this regenerative success is the expression of homeotic genes (HOX). During Central Nervous System (CNS) development, HOX genes are distinctly expressed in the brain and spinal cord to ensure appropriate neuronal connectivity and promote motor and sensory functions. **Objective:** Evaluate the maintenance of HOX expression in NSCs throughout the cellular transplantation process (primary cell expansion in vitro, transplantation in vivo). We hypothesize NSCs will maintain HOX expression of their native source, thus suggesting a mechanistic explanation of transplant successes in regionally matching cell grafts. **Methods:** (1) NSCs were dissected from the brain (b) and spinal cord (sc) of E12.5 mice, expanded in vitro, and transplanted in vivo. qPCR & immunohistochemistry were used to evaluate gene and protein expression homeotic genes, respectively. (2) Next, potential regenerative effects were evaluated in a clinically translational model using human induced pluripotent stem cell-NSC (hiPSC-NSCs). Prior to transplant, hiPSC-NSCs were exposed to small molecules WNT activator and subsequently Retinoic Acid (RA) in vitro to promote expression of spinal cord HOX genes (caudalization). Caudalization of hiPSC-NSCs is necessary as these cells default to a brain-specific identity following neural induction from pluripotency (iPSC to NSC). **Results:** (1) Notably, both bNSC and scNSC retained region-specific HOX markers (OTX2 & HOXB6, respectively) while in culture, and post-transplantation into naïve & injured spinal cords. (2) Following transplant into an immunodeficient rat model (RNU) of cervical SCI, caudalized NSCs promoted tissue preservation and functional recovery in injured animals. Compared to non-regionalized NSCs, caudalized NSCs uniquely promoted a greater electrically evoked compound action potential (spNSC: 0.6 + 0.5mV; default NSC 0.1 + 0.06mV), suggesting an enhanced electrical conduction with endogenous cells across the injury site. In these animals, caudalized cell grafts also maintained HOX expression post-transplantation. **Conclusions:** Altogether, this work supports that region-specific NSC transplants provide an efficacious therapeutic for SCI, which can be mechanistically described through the maintenance of spinal cord specific HOX genes. This work implicates the importance of regional specificity of NSCs grafted in all contexts of CNS injury and degeneration.

12. Rayan Saghian; Department of Physiology

Supervisor: Dr. Lu-Yang Wang

A MACROMOLECULAR PROTEIN COMPLEX OF PRESYNAPTIC CALCIUM CHANNELS FOR NEUROTRANSMISSION

Saghian R 1,2; Arsenault J 2; Tawfik B 2; Wang LY 1,2*

1 Dept. of Physiology, University of Toronto, Toronto, Ontario, Canada; 2 Neurosciences & Mental Health, Hospital for Sick Children, Toronto, Ontario, Canada

Introduction: Neuronal communication depends highly on integrating the action potentials with calcium dependent neurotransmitter release through physical couplings between voltage-gated calcium channels (VGCCs) and synaptic vesicles (SVs) at nerve terminals. An evolutionarily conserved set of proteins that form active zones at the synaptic terminals bridges the activity of VGCCs to the fusion of vesicles. Whereas significant progress has been made in uncovering fusion machinery, much remain to be discovered about the release and refilling mechanisms of SVs. **Objective:** In this study, we hypothesize that intracellular domains of P/Q type voltage-gated calcium channels (Cav2.1) may serve as the core scaffold for organizing macro-molecular complex for the release sites. **Methods:** We have developed an experimental approach focusing on Cav2.1 in the cerebellum where this channel is most abundantly found. **Results:** By combining Mass Spec, FLIM-FRET and super-resolution microscopy and patch-clamp electrophysiology, we identified a series of new interacting proteins with Cav2.1, among which "Protein R" was found dynamically regulate the loading of glutamate into SVs via novel, direct interactions with Cav2.1 and vesicular glutamate transporter (VGLUT), significantly impacting

synaptic strength and short-term plasticity. **Conclusion:** Our long-term goal of this project is to shed light on the modular composition of the active release machinery with "Protein Y" as a key building block to better understand the molecular organization of neurotransmission in healthy and diseased brain.

13. Tianze Shi; Department of Pharmacology and Toxicology

Supervisor: Dr. Etienne Sibille

BRAIN-DERIVED NEUROTROPHIC FACTOR-INDUCED PROTEOSTASIS DEFICIT

Shi T, 1,2; Sumitomo A, 1; Tripathy S, 1,3; Chikina M, 4; MacDonald M, 4; Tomoda T, 1,3* and Sibille E, 1,2,3*

1 Centre for Addiction and Mental Health (CAMH), Toronto, Ontario M5T 1R8, Canada; 2 Department of Pharmacology and Toxicology, University of Toronto, Toronto, Ontario M5T 1R8, Canada; 3 Department of Psychiatry, University of Toronto, Toronto, Ontario M5T 1R8, Canada; 4 Department of Computational and Systems Biology, University of Pittsburgh School of Medicine, Pennsylvania, 15213, USA; 5 Department of Psychiatry, University of Pittsburgh School of Medicine, Pennsylvania, 15213, USA

Introduction: Neuropeptides are small neuromodulatory proteins that are produced on demand in the endoplasmic reticulum (ER) and secreted either constitutively or in an activity-dependent manner to regulate brain functions (emotion, cognition). Post-mortem transcriptomic analysis on young (N=201) vs. old human brains (N=200) showed that expression of neuropeptides, including brain-derived neurotrophic factor (BDNF), is disproportionately decreased ($p<10^{-5}$) during aging and in neuropsychiatric disorders. However, the molecular and cellular mechanisms underlying reduced neuropeptides remains elusive. We hypothesized that this vulnerability may originate in the ER, where excess demand on neuropeptide synthesis causes ER stress, as in brain disorders. **Objectives:** To determine the contribution of ER stress as a mechanistic origin of cell type-selective vulnerability that may underpin emotional and cognitive deficits universally seen across neuropsychiatric conditions. **Methods:** Using adeno-associated virus encoding BDNF precursor (preproBDNF), we modelled this excess demand on BDNF by inducing various forms of BDNF affecting ER processing in selective neuron subtypes in-vivo and in-vitro and evaluated ER stress levels via immunofluorescence with ER stress markers (GRP78, p-eIF2a) and quantified ER proteomic changes by mass-spectrometry. **Results:** Forced expression of preproBDNF induced ER stress, as evidenced by elevated GRP78 immunofluorescence. Mass-spectrometry analysis showed that preproBDNF overexpression in cortical pyramidal cells led to the upregulation of 73 proteins, most of which were associated with ER stress, chaperones, unfolded protein binding, and post-translational modifications. **Conclusions:** BDNF precursor overexpression can exceed ER processing capacity, leading to ER stress-mediated proteostasis deficit and protein aggregation. Experiments are underway to validate cell-type selectivity and the requirement of ER processing for ER stress induction, by overexpressing the processing-deficient BDNF mutants (e.g. mature BDNF, BDNF without signal peptide) as referenced to other neuropeptides (e.g. SST, NPY) in distinct neuron types.

COGNITIVE NEUROSCIENCE

14. Hassan Abdulrasul; Applied Psychology and Human Development

Supervisor: Dr. Kaja Jasinska

THE IMPACT OF INTERRUPTED SCHOOLING ON THE FUNCTIONAL CONNECTIVITY FOR READING IN RESETTLED REFUGEE

Abdulrasul H, 1; Capani A, 1; Brice H, 1;Jasińska KK, 1,2

1 Department of Applied Psychology and Human Development, University of Toronto, Toronto, Ontario, Canada; 2 Haskins Laboratories, Yale University, New Haven, Connecticut, United States

Introduction: Reading, a complex cognitive ability, emerges from dynamic interactions among multiple brain regions, not supported by innate dedicated neural circuits. A significant gap in our understanding, however, lies in comprehending how the timing of literacy instruction affects the development of reading networks. Current literature predominantly focuses on children who commence reading instruction concurrently with their formal schooling, leaving a gap in understanding about how delayed or interrupted literacy instruction impacts the neural underpinnings of reading. **Objective:** We investigate the impact of educational interruptions on the functional connectivity within the developing reading network, specifically in the context of recently resettled refugee children. This population, often experiencing disrupted schooling and delayed literacy development, presents a unique opportunity to explore the trajectory of reading network development. **Methods:** We examined the resting-state functional connectivity of the reading network using fNIRS in a cohort of 54 resettled Syrian refugee children (age 8-17), who have encountered varying durations of educational interruptions at different ages. The study correlated the observed neural connectivity with standardized reading assessment scores to examine how the age and duration of educational interruptions affect the functional connectivity of the reading network. **Results and Conclusion:** Our preliminary results suggest that the younger the age at which the interruption occurred and its duration, the more variable the changes are on the reading network. Specifically, some connectivity measures were positively associated with the interruptions, while others showed a negative association, particularly within the dorsal and ventral streams of the reading network and additionally these children performed worse on reading assessments.

15. Joel Diaz; Institute of Medical Science

Supervisor: Dr. Jamie Feusner

THETA-BAND CONNECTIVITY RELATED TO BODY SIZE ESTIMATION IN ADOLESCENTS WITH ANOREXIA NERVOSA: A PILOT STUDY

Diaz-Fong JP, 1,2,3; Devine A, 1; Karsan S, 1; Lewis M, 1; Dickinson A, 3; Jeste S, 3; Strober M, 3; Feusner JD, 1,2,3,4

1 Centre for Addiction and Mental Health, Toronto, Ontario, Canada; 2 Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada; 3 Semel Institute for Neuroscience & Human Behavior, Department of Psychiatry & Biobehavioral Science, University of California Los Angeles, California, United States; 4 Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada

Introduction: Disturbance in the experience of one's weight or shape is a core symptom of anorexia nervosa (AN), with high prognostic and therapeutic relevance. Somatomap 3D is a digital avatar tool used to quantify body size estimation accuracy. **Objective:** The purpose of this study was to examine electrophysiological markers of abnormal self-body processing in AN using EEG. Findings from this pilot study can help us better understand abnormalities in self-body processing related to body image disturbance, which can aid in novel treatment strategies such as perceptual retraining and noninvasive brain stimulation. **Methods:** Twenty-two adolescent girls (16 AN, 6 controls) participated. 125-channel EEG was recorded continuously while participants used a 3D avatar to estimate their body size. Standard EEG preprocessing was performed (band-pass filter: 1-30 Hz; downsampling:100 Hz; ICA artifact removal). Source activity was reconstructed using LCMV beamformer. Regions of interests (ROIs) were defined by a reduced Desikan-Killiany atlas and included 23 ROIs related to body processing. Group differences in effective connectivity using time-reversed Granger causality was estimated. Two-sample t-tests were used to compare groups in theta (4-7 Hz), alpha (8-13 Hz), and beta (14-30 Hz) bands. **Results:** Participants with AN showed significantly higher theta-band connectivity from right fusiform to left insula (t=3.04, p=.006), decreases from left insula to left supramarginal gyrus (t=-3.13, p=.005), and decreases from bilateral precuneus to superior frontal gyrus (L-R: t=-2.93, p=.008; R-L: t=-3.14, p=.005). **Conclusion:** This pilot study suggests that body size estimation in AN may be associated with abnormal theta-band connectivity: increased from visual processing to interoceptive regions, decreased connectivity from interoceptive to somatosensory regions, and decreased connectivity from visuospatial/self-referential areas to regions involved in higher cognitive functions. Results recapitulate fMRI studies of body processing in AN and provide insights into distinctive oscillatory patterns.

16. Mahnoor Hamid; Institute of Medical Science

Supervisor: Dr. Andrew Lim

SLEEP FRAGMENTATION, PERICYTE GENE EXPRESSION, AND COGNITIVE DECLINE IN OLDER ADULTS WITH AND WITHOUT ALZHEIMER'S DISEASE

Hamid M, 1,2; Detroja TS, 1,2; Tripathy SJ, 2,3,4,5; Menon V, 6; Xu J, 7,8; Yu L, 7,8; Buchman AS, 7,8; Bennett DA, 7,8; De Jager PL, 6; Lim ASP, 1,2*

1 Division of Neurology, Department of Medicine, Hurvitz Brain Sciences Program, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada; 2 Institute of Medical Sciences, University of Toronto, Toronto, Ontario, Canada; 3 Krembil Centre for Neuroinformatics, Centre for Addiction and Mental Health, Toronto, Ontario, Canada; 4 Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada; 5 Department of Physiology, University of Toronto, Toronto, Ontario, Canada; 6 Center for Translational & Computational Neuroimmunology, Department of Neurology, Columbia University Irving Medical Center and the Taub Institute for Research on Alzheimer's Disease and the Aging Brain, New York, New York, USA.; 7 Rush Alzheimer Disease Center, Rush University Medical Center, Chicago, Illinois, USA; 8 Department of Neurological Sciences, Rush University, Chicago, Illinois, USA;

Introduction: Sleep fragmentation (SF) is common in older adults and is associated with cognitive impairment and dementia, as well as key histopathological correlates of dementia including small vessel disease and cerebral infarcts. Vascular and blood brain barrier (BBB) dysfunction are contributors to cognitive decline and dementia. Pericytes are a key vascular cell type contributing to BBB integrity. In model organisms, sleep disruption is associated with pericyte dysfunction and BBB breakdown. Recent advances in single-nucleus RNA sequencing (snRNAseq) technology have identified two transcriptionally distinct subtypes of pericytes: extracellular matrix maintaining M-pericytes, and solute carrier-expressing T-pericytes. However, the relationship between sleep, pericyte biology, and cognition in humans remains unclear. **Objective:** We tested the hypothesis that differences in the composition of brain pericyte subpopulations, as inferred from marker gene expression, may link SF and cognitive decline. **Methods:** We leveraged two published human brain snRNAseq datasets to identify specific marker genes for M- and T- type pericytes. We then used bulk RNA sequencing data from the dorsolateral prefrontal cortex (DLPFC; n=1071) and lateral orbitofrontal cortex (LOFC, n=472) to quantify expression of these marker genes in older adults in the Religious Orders Study and Rush Memory and Aging Project, 533 of whose participants underwent antemortem multi-day wrist-actigraphy recordings We used multivariate linear regression to relate marker gene expression to SF, measured by actigraphy, and to cognitive decline in the decade preceding death. **Results:** In the DLPFC, greater average SF was associated with greater expression of M-pericyte marker genes (Estimate=9.77e−02; SE=5.09e−02; p=0.055) but not T-pericyte marker genes (Estimate=3.99e−02; SE=5.02e−02; p=0.43). Expression of M-pericyte (Estimate=−8.14e−05; SE=2.51e−05; p=0.0012) but not T-pericyte marker genes was associated with more rapid cognitive decline in the 10 years leading up to death. In the LOFC, SF was associated with greater composite M-pericyte gene expression (Estimate=1.17e−01; SE=5.84e−02; p=0.046), while there was no significant association between the M-pericyte gene expression and cognitive outcomes. **Conclusions:** These findings identify a potential role of M-pericytes in linking SF and cognitive trajectories in older adults.

17. Daisy Hu; Department of Psychology

Supervisor: Dr. Doug VanderLaan

CORTICAL STRUCTURE AND FEMALE SEXUAL/GENDER DIVERSITY: A COMPARISON OF THAI HETEROSEXUAL MEN AND WOMEN, LESBIANS, TOMS, AND DEES

Hu DZ, 1; Rodkong A, 2; Skorska MN, 3; Saokhieo P, 2; Peragine DE, 1; Kaur S, 1; Parent O, 4; Devenyi GA, 4; Thurston LT, 1; Folkierska-Żukowska M, 3; Supintham T, 2; Kaewthip O, 2; Wantanajittikul K, 2; Chotirosniramit N, 2; Chakravarty MM, 4; Chariyalertsak S, 2; Saekho S, 2; VanderLaan DP, 1,3

1 University of Toronto Mississauga, Mississauga, Ontario, Canada; 2 Chiang Mai University, Chiang Mai, Thailand; 3 Centre for Addiction and Mental Health, Toronto, Ontario, Canada; 4 Douglas Mental Health University Institute, Verdun, Quebec, Canada

Introduction: Sex-differentiated brain features, including cortical thickness (CT; thicker in females) and surface area (SA; greater in males), have been hypothesized to vary based on sexual orientation and gender diversity. Past research in sexually and gender-diverse samples is primarily limited to Western populations. Cortical structure in individuals oriented towards the same birth-assigned sex appears similar to that of other-birth-sex heterosexuals, especially in studies of transgender, as compared with cisgender, same-birth-sex-oriented individuals. Thus, gender identity might moderate the relationship between sexual orientation and brain structural variations. **Objective**:

To disentangle sex, sexual orientation, and gender identity in female cortical phenotype and broaden the literature beyond Western populations, we compared CT and SA in Thai cisgender heterosexual men and women, cisgender lesbian women, toms (transmasculine gynephilic birth-assigned females), and dees (birth-assigned females attracted to toms). Cortical structure in same-sex attracted birth-assigned females (lesbian women, toms, and dees) is predicted to be "shifted" towards patterns observed in cisgender heterosexual men (i.e., reduced CT, increased SA). **Methods**: Magnetic Resonance Imaging (MRI) data were acquired using a 1.5T scanner with a 16-channel head coil (N = 152, 30-31/group). T1-weighted images were used to compute CT and SA via CIVET image processing and analysis software, which extracted the cortical ribbon's white matter and pial surfaces at 40,962 vertices per hemisphere. A partial least squares (PLS) analysis controlling for brain size was conducted to identify multivariate latent variables (LVs) of covarying vertex-wise CT and SA that maximally differentiated the groups. **Results:** There was one significant LV (p = .009) explaining 39% of the covariance between group and the brain data. Heterosexual women and dees had thicker cortices in the frontal, parietal, and occipital regions, as well as a mix of greater and lower SA in small areas of the parietal and occipital regions, which significantly differentiated them from heterosexual men. Toms and lesbian women showed a cortical pattern that was intermediate and, thus, "shifted" away from heterosexual women and dees and towards heterosexual men. **Conclusion:** This study investigated cortical structure in sexually and gender-diverse Thai birth-assigned females. Cisgender heterosexual women and dees displayed patterns that differed from heterosexual men, whereas toms and lesbian women showed an intermediate (defeminized, but not masculinized) cortical structure. These findings partially align with predictions. Gender expression and/or attraction towards masculine versus feminine individuals appear to be related to variation in brain phenotypes within the context of female sexual/gender diversity.

18. Minarose Ismail; Department of Physiology

Supervisor: Dr. Darren Kadis

COMPUTATIONAL MODELING OF MEG EVENT-RELATED BETA OSCILLATIONS FOR EXPRESSIVE LANGUAGE IN CHILDHOOD

Ismail MM, 1,2; Momi D, 3; Wang Z, 3; Barr CL, 1,2; McIntosh AR, 5; Griffiths JD, 3,4; Kadis DS, 1,2

1 Department of Physiology, University of Toronto, Toronto, ON, Canada; 2 Neurosciences & Mental Health, The Hospital for Sick Children, Toronto, ON, Canada; 3 Krembil Centre for Neuroinformatics, Centre for Addiction and Mental Health, Toronto, ON, Canada; 4 Department of Psychiatry, University of Toronto, Toronto, ON, Canada; 5 Simon Fraser University, Vancouver, BC, Canada

Introduction: Lateralization of low beta (13-23Hz) event-related desynchrony (ERD) and synchrony (ERS) during verb generation in MEG provides a robust assay of expressive language hemispheric dominance. In young children, low beta ERD and ERS are observed bilaterally, with lateralization emerging in early adolescence. These task-related oscillatory changes could serve as neural signatures of language network maturation, as well as its potential for plasticity. However, the neural mechanisms underlying lateralization remain unclear. Exploring the emergence of macro-scale brain activity from anatomical network structure and micro-scale neuronal dynamics using biologically inspired neurocomputational models holds promise in addressing this gap. **Objective:** In this study, we investigate the neural mechanisms underlying the lateralization of these task-related oscillatory changes in childhood. **Methods:**Utilizing the Whole-Brain Modelling in PyTorch (WhoBPyt) library (github.com/griffithslab/whobpyt), we fit individual connectome-based neural mass models for adolescents (15-18 years old; n=10) and young children (4-7 years old; n=12), constructed from multi-shell diffusion-weighted MRI tractography, with trial-averaged MEG time series representing the early (-100-400ms) auditory evoked response in a verb generation task. Individual models were then used to simulate 1200ms epochs, and power spectral densities (PSDs) were computed using Welch's method for the 700-1200ms time window that, critically, was not used for fitting. **Results:** Brain network models predicted the late (700-1200ms) lateralized beta oscillatory responses in high-order language-related regions, as observed in the empirical data. These models successfully predicted the laterality of beta oscillatory changes in both adolescents and young children. Notably, adolescent models demonstrated a significantly higher strength of interhemispheric inhibitory coupling compared to the young children models ($p<0.05$), suggesting this as a potential mechanism for the lateralization of these oscillatory rhythms. **Conclusion:** Our findings suggest that language hemispheric dominance is encoded in the interaction between the structure and the dynamics of early sensory responses to language stimuli, thereby predicting the lateralization of late event-related beta oscillations. Further research will be conducted to examine the impact of interhemispheric inhibitory coupling on the laterality of beta oscillatory responses.

19. John Kennedy; Department of Psychology

POINTING AND THE MIRROR-IMAGE ILLUSION: 4 CASES

Kennedy JM, 1; Wnuczko M, 1

1 Department of Psychology, University of Toronto, Toronto, Ontario, Canada; 2 Department of Psychology, University of Guelph-Humber, Guelph, Ontario, Canada

Introduction: After pointing ballistically to several real targets, participants are asked to use their right arm to point ballistically to their left shoulder's mirror-image. We consider 4 cases. **Objective:** The goal is to distinguish cases of success and failure of the illusion, including a limiting case. **Materials:** The materials were a mirror and measures of distance and angles of the arm when pointing. **Results:** Two pointing postures suffer the illusion. Two did not. **Conclusion:** The illusion is present and has a maximum if Os point ballistically and aim for a mirror target.

20. Felicia Kwan; Department of Pharmacology and Toxicology

Supervisor: Dr. Walter Swardfager

INTERACTION BETWEEN DEPRESSION AND THE NLRP3 INFLAMMASOME ON COGNITION IN TYPE 2 DIABETES MELLITUS PATIENTS

Kwan F, 1,2,3; Anita NZ, 1,2,3; Ryoo SW, 1,2,3; Major-Orfao C, 2,3; Noor S, 1,2,3; Perfetto S, 1,2,3; Lin WZ, 1,2,3; Andreazza AC, 1,4; Lanctôt KL, 1,2,3,4; Herrmann N, 2,4,5; Gilbert J, 5; Swardfager W, 1,2,3

1 Department of Pharmacology and Toxicology – University of Toronto, Ontario, Canada; 2 Sunnybrook Research Institute, Toronto, Ontario, Canada; 3 KITE Research Institute, Toronto Rehabilitation Institute-

University Health Network, Ontario, Canada; 4 Department of Psychiatry - University of Toronto, Ontario, Canada; 5 Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada

Introduction: Chronic inflammation may contribute to depression and cognitive impairment in type 2 diabetes mellitus (T2DM), through increased activation of the nucleotide binding domain-, leucine-rich repeat-, and pyrin domain-containing protein 3 (NLRP3) inflammasome. The inflammasome (NLRP3 protein, apoptosis-associated speck-like protein containing a CARD (ASC), procaspase-1) activates the pro-inflammatory cytokine, interleukin-1β (IL-1β). **Objective:** To explore in T2DM individuals whether depressive symptoms moderate an association between the inflammasome and cognition. **Methods:** Sunnybrook Type 2 Diabetes Study participants were diagnosed with pre-diabetes or T2DM. Inflammasome activation sensitivity (ΔASC Specks, ΔCaspase-1, ΔIL-1β) was assessed in isolated white blood cells. Executive function was measured through the Trails Making Test Part B, Digit Symbol Substitution Test, Stroop Colour-Word Interference Test, and FAS Verbal Fluency Test. The Beck Depression Inventory 2nd Edition test categorized participants based on depressive symptom severity. **Results:** ΔASC Specks were positively correlated with executive function z-scores in participants with depressive symptoms, but negatively in those without symptoms (n=78; mean age: 63.8+11.7, 50% female, 23.4% with symptoms). In the adjusted analysis of covariance model, depressive symptoms significantly interacted with ΔASC Specks to predict executive function z-scores. **Conclusion:** Depressive symptoms may moderate the relationship between the inflammasome and cognition in T2DM patients.

21. Cindy Nguyen; Rehabilitation Sciences Institute

Supervisor: Dr. Luc De Nil

THE EFFECTS OF ANODAL TDCS ON MOTOR SEQUENCE PRACTICE IN NON-STUTTERING CONTROLS AND PEOPLE WHO STUTTER

Nguyen C, 1; Moein N, 1,3; Cheyne D, 2,3,4; De Nil L,1,2

1 Rehabilitation Sciences Institute, Temerty Faculty of Medicine, University of Toronto; 2 Department of Speech-Language Pathology, Temerty Faculty of Medicine, University of Toronto; 3 Research Institute, Program in Neurosciences and Mental Health, Hospital of Sick Children; 4 Institute of Biomaterials and Biomedical Engineering, University of Toronto

Introduction: Transcranial Direct Current Stimulation (tDCS), whereby electrical current is applied to specific brain areas, has been used to improve speech motor learning in stuttering. However, the effects of tDCS on non-speech motor skill training in stuttering has yet been investigated. As both speech and non-speech motor impairments are interrelated, it is worthwhile to explore how tDCS affects non-speech motor sequence practice. **Objective:** To investigate the extent to which anodal tDCS modulation of the right primary motor cortex influences performance on a non-speech sequential motor practice task. **Methods:** 20 right-handed adults who stutter (stutter group) and 30 adults who do not stutter (control group) between 18-50 years old were recruited.The motor task involves participants typing a 10-numbered sequence repetitively with their left hand. The participants are divided into two conditions: a sham and active. The active condition types the sequences while the right primary motor region is stimulated at 2mA for 20 minutes. The sham types the sequences with the tDCS set-up and no stimulation applied. We evaluated reaction time and sequence duration between active and sham conditions of both groups. **Results:** The active condition in the stutter group unexpectedly performed slower than all other cohorts while the sham in stutter group performed similarly to control group. No differences were observed between conditions in the control. **Conclusion:** This study contributes insights into the potential of tDCS for neurorehabilitation in fluency disorders. This research is funded through an NSERC grant held by Dr. Luc De Nil.

22. Lulia Snan; Institute of Medical Science

Supervisor: Dr. Karen Gordon

ATTENTION TO INTERAURAL LEVEL CUES MEASURED BY CORTICAL AND BEHAVIORAL RESPONSES IN CHILDREN WITH BILATERAL COCHLEAR IMPLANTS

Snan L, 1,2; Negandhi J, 1; Lim R, 1; Papsin B, 1,3; Cushing S, 3; Gordon KA, 1,3

1 Archie's Cochlear Implant Laboratory, The Hospital for Sick Children, Toronto, ON, Canada; 2 Institute of Medical Sciences, Faculty of Medicine, University of Toronto, Toronto, ON, Canada; 3 Department of Otolaryngology – Head and Neck Surgery and Institute of Medical Sciences, Faculty of Medicine, University of Toronto, Toronto, ON, Canada

Introduction: Bilateral cochlear implants (BCIs) have been provided to children to provide access to the interaural cues that are the foundation of spatial hearing. However, prior work has shown that these children do not gain normal spatial hearing and that this could be due to several factors. The BCIs provide better access to ILDs than interaural timing differences (ITDs) and hearing loss in childhood could disrupt binaural processing which is further exacerbated by delays to bilateral hearing that result in asymmetric auditory function between pathways from the left versus right ear. Although ILDs are available to children with BCIs, they take longer than normal to respond to them, suggesting increased listening effort. In the present study, we hypothesized that cortical and behavioral access to ILDs can be measured using an oddball task in children with BCI; that these measures are related to one another, and that task repetition improves both cortical and behavioral responses to ILDs. **Objectives:** to measure cortical access and behavioral responses to interaural level differences (ILDs) in children using bilateral cochlear implants (BCIs); to determine the role of attention on ILD access; and to assess effects of task repetition on ILD access. **Methods:** Twelve children with bilateral CIs participated (3F:9M). Age at testing was 14.51 ± 2.21 years (mean age ± SD); they received their first CI at 3.6 ± 2.19 years of age and had an inter-implant delay of 1.64 ± 4.86 years. Eight were simultaneously implanted and 4 sequentially implanted (3 implanted on L side first). A group of typically developing peers (5F:7M, age at test 15.33 ± 1.18 years) were also recruited. Children listened to bilateral stimuli in an oddball paradigm in which frequent stimuli (70% of trials) had ILD=0 and deviations (30% of trials) were ILD=16 dB. They were asked to press a button whenever they heard the deviant stimuli. Trials of 50 stimuli were presented in blocks and 5 blocks were completed. Accuracy and reaction time were measured and cortical responses to all stimuli were recorded using a 64 channel EEG recording system. Passive EEG responses to each of the stimuli were also recorded and presented interspersed with oddball attention blocks in random order. Global mean field power across the recording channels were assessed for amplitude differences from baseline or between conditions objectively by measuring the area under the curve for time windows of 50 ms from -200 ms to 800 ms latency. **Results:** Results revealed clear obligatory responses to

bilateral stimuli which were large in amplitude in the active oddball than passive control conditions in both groups. The oddball paradigm revealed larger amplitudes for the deviant ILD bilateral stimuli compared to the frequent at latencies of 250-450 ms in children with normal hearing and slightly later, at 300-500 ms in children using BCIs. Amplitudes to deviant stimuli showed a significant positive correlation with response accuracy (t = 2.8, df = 5, p-value = 0.037) and near significant negative correlation with response time (t = -2.3, df = 5, p-value = 0.07) in the BCI group, but not in the typically developing group (accuracy: t = -0.2, df = 6, p-value = 0.9; response time: t = -0.9, df = 6, p-value = 0.4). Behavioral accuracy increased (3-way interaction: F (4,115) = 6.1, p = <0.0001) and response time decreased (3-way interaction: F (4,115) = 9.2, p = <0.0001) with increasing oddball block presentation in both groups. Cortical amplitudes to deviant stimuli with increasing block and relation to behavioral data are being assessed. **Conclusion:** Results demonstrate that children with BCIs can use attention to access ILDs. This access is tied to the activation of cortical networks. Importantly, repetition of the oddball task reveals short term learning effects. These results suggest that there may be a role for practise to improve access to ILDs and perhaps spatial hearing in children with BCIs.

23. Hannah Whitehead; Applied Psychology and Human Development

Supervisor: Dr. Kaja Jasińska

SYMBOLIC AND NONSYMBOLIC MAGNITUDE PROCESSING AND THEIR RELATIONS TO MATH SKILLS: NEUROCOGNITIVE INSIGHTS FROM RURAL CÔTE D'IVOIRE

Whitehead HL, 1; Bugden S, 2; Tanoh F, 3; Wolf S, 4; Ogan A, 5; Kembou S, 6; Jasińska KK, 1,7

1 Ontario Institute for Studies in Education, University of Toronto, Toronto, Ontario, Canada; 2 Department of Psychology, University of Winnipeg, Winnipeg, Manitoba, Canada; 3 Department of Sociology, Université Péléfero Gon Coulibaly, Korhogo, Côte d'Ivoire; 4 University of Pennsylvania, Philadelphia, Pennsylvania, United States; 5 Carnegie Mellon University, Pittsburgh, Pennsylvania, United States; 6 Lausanne University, Écublens, Vaud, Switzerland; 7 Haskins Laboratories, New Haven, Conneticut, United States

Introduction: Research conducted in the Global North has found that both symbolic (e.g., Arabic numerals) and non-symbolic (e.g., dot arrays) magnitude processing predict mathematics achievement. However, in studies that account for both symbolic and non-symbolic magnitude processing, the relations between non-symbolic processing and mathematics achievement are reduced or eliminated suggesting a critical role of symbolic number processing in developing mathematical skills. Recent research from Ghana and Côte d'Ivoire found that non-symbolic processing was a significant and unique predictor of mathematics achievement, even when children were more accurate on the symbolic task. These diverging patterns between Global North and Global South countries suggest the precursors of mathematics are not universal. **Objective:** We used functional near-infrared spectroscopy (fNIRS) to understand the neural mechanisms that underlie context-based differences in precursors to mathematics. **Methods**: We assessed symbolic and non-symbolic magnitude processing in school-aged children in rural Côte d'Ivoire (N=188, Mage=8.89, SDage= 1.43) using a magnitude comparison task. Participants were instructed to select the larger magnitude within pairs of dot arrays (non-symbolic) and Arabic numerals (symbolic). **Results:** Our preliminary analyses revealed activation in prefrontal and left temporal regions for non-symbolic processing and right inferior frontal gyrus activation for symbolic processing. **Conclusion:** Activation of left temporal regions, not typically seen in Global North samples, suggests a potential neural basis for behavioral differences between Global North and Global South context. Brain-behaviour correlations and their relations to mathematics achievement will be discussed. Results from this study will inform how context influences the neurocognitive development of numerical skills.

COMPUTATIONAL NEUROSCIENCE

24. Dyla Dindwell; Department of Medical Biophysics

Supervisor: Dr. Charles Cunningham

MODELLING ISOTOPE EXCHANGE IN HYPERPOLARIZED CARBON-13 MRI OF THE BRAIN

Dingwell DA, 1,2*; Cunningham CH, 2,1

1 Department of Medical Biophysics, University of Toronto, Toronto, Ontario, Canada; 2 Physical Sciences, Sunnybrook Research Institute, Toronto, Ontario, Canada

Introduction: Fitting physiological parameters to in vivo hyperpolarized carbon-13 (HP 13C) MR neuroimaging data is complicated by the large variety of factors affecting 13C signal dynamics. Notably, in HP 13C MR brain scans, metabolic conversion of injected 13C-pyruvate produces 13C-lactate, but compensatory reactions involving endogenous metabolite pools can result in zero net flux of total pyruvate. This isotope exchange at equilibrium obscures the true metabolic rate. **Objective:** Develop a computational model of the interplay between HP 13C MR imaging parameters and metabolic signal mechanisms. Validate this model by refining results against in vitro spectroscopic measurements under realistic conditions. **Methods:** A novel particle-based model of HP 13C MRI was developed by integrating a quaternion-rotation-based forward solution of the classical Bloch equations with a Brownian dynamics-based biochemical simulator capable of implementing molecular motion, surface interactions, and enzymatic reactions. Simulated signal time courses were compared to spectrophotometric and MR spectroscopic measurements of bidirectional interconversion of pyruvate and lactate mediated by lactate dehydrogenase. **Results:** Simulated data indicated that isotope exchange, rather than net flux, was the predominant mechanism when high levels of endogenous lactate were present, despite the fact that increasing 12C-lactate always increased 13C-lactate signal. While accurately replicating spectroscopic results, the model's particle-level output metrics thus provided more detail than can be obtained in vitro, in vivo, or from conventional kinetic modelling. **Conclusions:** 13C-lactate signal in HP MRI is not a straightforward biomarker of neurometabolism, and needs to be understood in the context of the different local equilibria of the brain's complex cellular architectures.

25. Romesa Khan; Department of Psychology

Supervisor: Dr. Matthias Niemeier

PERFORMANCE-ENHANCING EFFECTS OF MEDIUM-RANGE FEEDBACK IN A GRASPING NEURAL NETWORK

Khan R, 1; Zhong H, 2; Das S, 2; Cai J, 3; Niemeier M, 4,5

1 Department of Psychology Scarborough, University of Toronto, Toronto, Ontario, Canada; 2 Department of Computer Science,

University of Toronto, Toronto, Ontario, Canada; 3 Department of Electrical and Computer Engineering, University of Toronto, Toronto, Ontario, Canada; 4 Centre for Vision Research, York University, Toronto, Ontario, Canada; 5 Vision: Science to Applications, York University, Toronto, Ontario, Canada

Introduction: Top-down predictions from generative models in the brain are conveyed through cortical layer-specific feedback connections during visual perceptual tasks. However, there is a dearth of understanding of the contribution of feedback when visual input is used for action planning, such as object grasping. Recent evidence shows that advanced object shape and movement representations during grasping also involve the reactivation of earlier visual areas, indicating that feedback connections carry information from downstream stages of visuomotor processing to the earlier stages in the visual stream. **Objectives and Methods:** We investigated the contribution of such neural feedback to the visuomotor control of grasping by using convolutional neural networks, trained to compute grasp positions for real-world objects, as a modelling framework. To make these models computationally and structurally more similar to the human cortex, we added generative feedback loops to a custom feedforward backbone, carrying advanced representations to early layers of the network. **Results:** When evaluated on images with additive Gaussian noise, after multiple forward and backward passes through the network, we observed an improvement in performance for the network with predictive coding dynamics in comparison to the feedforward baseline. We also find that this performance-enhancing effect under adverse conditions (1) is optimal for intermediate distance between the feedback source and target layers (medium-range feedback), and (2) relies on a balance between the relative contributions of local recurrence and top-down feedback. **Conclusion:** To conclude, our simulations show that introducing biologically plausible predictive coding dynamics improves model robustness to noisy visual stimuli in a neural network model optimised for grasp prediction.

26. Frank Mazza; Department of Physiology

Supervisor: Dr. Etay Hay

STRATIFYING DEPRESSION PATIENTS USING IN-SILICO EEG BIOMARKERS OF SST INTERNEURON INHIBITION

Mazza F, 1,2; Hay E, 1,2,3

1 Krembil Centre for Neuroinformatics, Centre for Addiction and Mental Health, 2 Department of Physiology, University of Toronto, 3 Department of Psychiatry, University of Toronto

Introduction: Depression is a leading cause of disability with a large proportion of patients being treatment-resistant. Recent postmortem studies in depression patients have implicated cellular mechanisms of reduced cortical inhibition by somatostatin-expressing interneurons (SST+INs). However, establishing the link between the cellular changes and diagnostic brain signals such as electroencephalography (EEG) is currently not possible in living humans. **Objective:** To overcome the experimental limitations, we characterized in-silico EEG biomarkers of SST+IN inhibition using detailed models of human cortical microcircuits. **Methods:** We trained an artificial neural network (ANN) to estimate SST+IN inhibition in microcircuit models of known inhibition reduction with good accuracy. We then applied the ANN to estimate patient inhibition from the EMBARC study (n = 113). **Results:** We identified a subset of depression patients exhibiting consistent high estimated reduced SST+IN inhibition compared to healthy controls, and showed that the estimated inhibition correlated strongly with depression severity score. **Conclusion:** Our study pioneers estimating cell-specific inhibition from patient EEG using machine learning and in-silico biomarkers, which will serve to improve mechanistic stratification of depression patients.

27. Faraz Moghbel; Department of Physiology

Supervisor: Dr. Etay Hay

DERIVING LARGE-SCALE NEURONAL CONNECTIVITY FROM MICROCIRCUIT ACTIVITY

Moghbel F, 1,2; Hassan T, 1; Guet-McCreight A, 1; Hay E, 1,2,3

1 Krembil Centre for Neuroinformatics, Centre for Addiction and Mental Health, Toronto, ON M5T 1R7, Canada; 2 Department of Physiology, University of Toronto, Toronto, ON M5S 1A1, Canada; 3 Department of Psychiatry, University of Toronto, Toronto, ON M5S 1A1, Canada

Introduction: Inferring detailed cortical microcircuit connectivity is essential for uncovering how information is processed in the brain. Whereas previous studies developed and applied methods for deriving putative monosynaptic connections from short lag correlations, they used simplified or small network models that did not address several key confounds of physiological large-scale networks. **Objectives and Methods:** We tested connectivity derivation methods on ground-truth spiking data from detailed models of human cortical microcircuits in different layers. **Results:** We showed that physiological oscillations in the large-scale microcircuits imposed confounds on derivation, and we developed methods to overcome the confounds. We showed that connection derivation was poor in cortical layer 2/3 (L2/3) microcircuits compared to layer 5 (L5), due to low firing rates and inactive neurons. General activation strategies for L2/3 microcircuits led to only a moderate improvement in derivation performance, due to a trade-off between the proportions of inactive neurons and overactive neurons, indicating the need for more sophisticated strategies. Lastly, we showed that inhibitory connections targeting distal dendrites required derivation over a longer timescale of cross-correlation lags. **Conclusion:** Our results elucidate key physiological challenges in deriving putative monosynaptic connections in large-scale realistic human neuronal networks and provide methods to improve accuracy and thus derive a fuller microcircuit connectivity.

28. Khashayar Namdar; Institute of Medical Science

Supervisor: Dr. Farzad Khalvati

MULTICLASS MACHINE LEARNING MODELS FOR MOLECULAR SUBTYPE IDENTIFICATION OF PEDIATRIC LOW-GRADE NEUROEPITHELIAL TUMORS USING BI-INSTITUTIONAL MRIS FOR PRECISION MEDICINE

Namdar K, 1,2,4,10; Wagner MW, 1,2,5; Hawkins C, 6; Tabori U, 7; Ertl-Wagner BB, 1,2,3,4; Khalvati F, 1,2,3,4,8,9,10

1 Department of Diagnostic Imaging & Image-Guided Therapy, The Hospital for Sick Children (SickKids), Toronto, ON, Canada; 2 Neurosciences & Mental Health Research Program, SickKids Research Institute, Toronto, ON, Canada; 3 Department of Medical Imaging, University of Toronto, Toronto, ON, Canada; 4 Institute of Medical Science, University of Toronto, Toronto, ON, Canada; 5 Department of Diagnostic and Interventional Neuroradiology, University Hospital Augsburg, Germany; 6 Department of Paediatric Laboratory Medicine, Division of Pathology, The Hospital for Sick Children, University of

Toronto, Canada; 7 Department of Neurooncology, The Hospital for Sick Children, Toronto, ON, Canada; 8 Department of Computer Science, University of Toronto, Toronto, ON, Canada; 9 Department of Mechanical and Industrial Engineering, University of Toronto, Toronto, ON, Canada; 10 Vector Institute, Toronto, ON, Canada

Introduction: Pediatric Low-Grade Neuroepithelial Tumor (PLGNT) is the most common type of brain tumor in children. Previously, we showed that radiomics-based machine learning (ML) models are effective for determining the presence of BRAF fusion and BRAF V600E mutation in PLGNT. **Objective**: Aligned with precision medicine goals, we propose ML pipelines to achieve per-patient predictions. **Methods**: Our REB-approved retrospective study included 495 children from 1999 to 2023. The local hospital dataset consisted of brain MRIs of patients with BRAF fusion (n=190), BRAF V600E mutation (n=95), and other molecular subtypes (n=169), while the external dataset included patients with BRAF fusion (n=32) and BRAF V600E mutation (n=9). Tumor segmentations were provided by a pediatric neuroradiology fellow and verified by a senior pediatric neuroradiologist. PyRadiomics was used for extracting the radiomics features from the Regions of Interest (ROI) on MRI Fluid-Attenuated Inversion Recovery (FLAIR) image volumes. We created 27 radiomics datasets using 3 sets of radiomics extraction hyperparameters and 9 image normalization methods, and utilized Random Forests (RF) as the classifiers, and repeated the validations (hyperparameter tuning and model initialization) 100 times. We then employed leave-one-out (LOO) validation method to achieve per-patient test results for the entire dataset, and evaluated the pipeline using the Area Under ROC Curve (AUC). **Results**: Overall, using the combination of radiomics and clinical variables, the average one-vs-the-rest (OvR) AUC was 0.819 with 95% CI [0.791, 0.848]. The AUC performance of the pipeline was 0.812, and 0.825 for males and females, respectively. Supratentorial cases had an AUC of 0.751 compared with 0.749 for infratentorial cases. Using only the clinical variables, we achieved an average AUC of 0.715 and radiomics alone resulted in AUC of 0.795. The difference between the performance levels of radiomics and clinical variables used individually, compared to when they were combined was statistically significant (p-value < 0.001). **Conclusion:** Our bi-institutional retrospective study shows radiomics-based ML models differentiate BRAF fusion, V600E mutation, and other molecular subtypes of PLGNT with high diagnostic accuracies. Also, we showed combining clinical variables and radiomics improves such models. Our per-patient model inferences facilitate group-based performance analysis (e.g., performance for different institutes, genders, tumor locations, and time spans).

29. Fatemeh Shomal Zadeh; Institute of Biomedical Engineering

Supervisor: Dr. Kei Masani

INVESTIGATING ANKLE MUSCLE STIFFNESS MODIFIED BY NEUROMUSCULAR ELECTRICAL STIMULATION USING SHEAR WAVE ELASTOGRAPHY

Shomal Zadeh F, 1,2; Lee JW, 1,2; Lim D,1,2; Fok KL, 1,2; Lee J, 1,2; Kumbhare DA, 1,2; Masani K, 1,2

1 KITE - Toronto Rehabilitation Institute, University Health Network, Toronto, Ontario, Canada; 2 Institute of Biomedical Engineering, University of Toronto, Toronto, Ontario, Canada

Introduction: Individuals with incomplete spinal cord injury (iSCI) often have impaired balance ability resulting in frequent falls. Controlling plantar flexors (i.e., soleus (SOL)) and dorsiflexors (tibialis anterior (TA)) are crucial for maintaining balance, which are often deteriorated after iSCI. An essential aspect of balance maintenance involves regulating ankle joint stiffness, which involves dynamically adjusting the stiffness of the SOL and TA muscles relative to joint angle/muscle length and the applied torque. We have developed a functional electrical stimulation therapy for standing balance using neuromuscular electrical stimulation (NMES) on SOL and TA, which showed a promising performance in a pilot study. Further details such as the ability of NMES on modifying ankle joint torque and ankle muscle stiffness need to be further studied to enhance the therapeutic effect of the proposed system. **Objective**: In this study, we aimed to investigate the ability of NMES in modifying the ankle muscle stiffness using shear wave elastography (SWE). **Methods**: To date, two female able-bodied were positioned on an isometric electro-dynamometer (Biodex-3) with the fully extended knee and the ankle at 90°. An ultrasonic probe using a custom-made holder was used to acquire SWE-images (Acuson-S2000 Siemens). During plantar- and dorsi-flexion, SWE of SOL and TA as well as the ankle joint torque were recorded at 1) relax, 2) voluntary contraction, 3) contraction induced by NMES, and 4) combination of 2) and 3). From the SWE-images, the Young's elastic modulus was calculated as a surrogate of stiffness for each image using shear modulus, shear wave velocity and muscle density (1090 kg/m3). Pearson's correlation was calculated between ankle torque and muscle stiffness for each condition. **Results**: SWE can detect variations in muscle stiffness resulting from voluntary and artificially induced contractions. Analyzing the association between increased ankle muscle stiffness due to voluntary versus artificially induced muscle contraction can provide insights into determining the required stimulation intensity using NMES in therapy for balance maintenance. Moreover, there was an approximately linear correlation between changes in ankle torque and ankle muscle stiffness under the aforementioned conditions (2, 3, and 4). These findings align with previous research suggesting that ankle stiffness fluctuates significantly with operational conditions, influenced by joint torque and position changes mediated by alterations in muscle activity. **Conclusion**: While data collection is ongoing, these initial findings indicate that SWE holds potential as a tool for quantifying muscle stiffness, which may contribute to ankle stiffness and, consequently, postural stability. Next, the impact of NMES on enhancing postural stability will be evaluated using this tool, particularly in individuals with iSCI.

30. Bernice Tang; School of the Environment

Supervisor: Dr Brad Bass

COMPARING THE EFFICACY OF TREATMENT REGIMENS FOR GLIOBLASTOMA MULTIFORME WITH REAL-LIFE MRI DATA USING THE COBWEB SIMULATION SOFTWARE

Tang B, 1,2,4; Mahanujam A, 1,2,3; Zhu C1,2,5; Thayaparan P, 1,2,3; Bass B, 1,2*

1 COBWEB Lab at Gerstein Science Information Centre, University of Toronto, Toronto, Ontario, Canada; 2 School of the Environment, University of Toronto, Toronto, Ontario, Canada; 3 Department of Neuroscience, University of Toronto Scarborough, Toronto, Ontario, Canada; 4 Bishop Strachan School, Toronto, Ontario, Canada; 5 Lawrence Park Collegiate Institute, Toronto, Ontario, Canada;

Introduction: Glioblastoma multiforme (GBM) is a Stage IV brain cancer, with less than 5% of patients surviving five years after diagnosis. Its aggressive nature and treatment difficulty is attributed to angiogenesis, rapid resistance to treatment, and its web-like growth preventing its complete removal during resection. The Stupp Protocol is the golden standard of care, consisting of maximal resection, chemotherapy with Temozolomide and radiation therapy, and has been proven to lengthen overall survival by 2.5 months. However, since its implementation, survival hasn't improved significantly and recurrence is still inevitable. Recently, emerging human trials have explored the post-resection addition of localized Temozolomide to the Stupp Protocol demonstrating its promise, and only mice trials exploring the use of a chemo immunotherapy hydrogel consisting of localized TMZ and anti-CD47 antibody, have been reported. **Objective:** Test the efficacy of a novel GBM treatment (Stupp Protocol with localized Temozolomide and anti-CD47 antibody) in comparison to other established treatments (control, Stupp Protocol, and Stupp Protocol with localized Temozolomide). Using our proprietary software, Complexity and Organized Behavior within Environmental Bounds (COBWEB), simulated efficacy was evaluated by comparing it to real-life MRI data from the LUMIERE dataset consisting of 91 patients. **Methods:** COBWEB agent-based simulation software was used to model efficacy of different treatments on different patients. 400 randomized controlled trials were performed, 100 trials for each treatment group - control, Stupp Protocol, Stupp Protocol with localized Temozolomide, and Stupp Protocol with TMZ-antiCD47 hydrogel. Seven agents were modeled: healthy cells, GBM tumor cells, tumor stem cells, Temozolomide, radiation therapy, Anti-CD47 antibody, and macrophages. The tumor is initiated at tick 50, and the number of weeks (n) is determined using the formula n=(t-50)/62. The model considered genetic factors, side effects, neural behaviour, interactions, immune responses, resistance, and mutations based on extensive literature consultation. Dependent Variables were identified as Healthy cell percentage, number of tumor-affected brain regions (symptoms). MRI data obtained from the LUMIERE dataset was used to validate the simulation's accuracy in representing treatment plans. **Results:** Using COBWEB, our findings indicate that the % of healthy cells was highest to lowest after treatment as follows: Stupp with TMZ > Stupp with Anti-CD47 > Stupp > Control. Remarkably, the tumor affected regions showed an inverse correlation with the % healthy cells: Stupp with Anti-CD47 < Stupp with TMZ < Stupp < Control. Using the Stupp protocol, the predicted Mean of healthy cell percentages (91.6)% was lower than that of actual healthy cell percentage (98.7%), suggesting further improvement to the study for more accurate predictability. **Conclusions:** Our findings encourage patients to start early palliative care, and model an aggressive cancer's treatment predicted outcomes. Through COBWEB, it was found that for simulated human patients with GBM, applying TMZ-antiCD47 hydrogel along with the Stupp Protocol significantly decreased ($p<0.05$) the number of tumor-affected regions compared to other treatments, however, it showed a slightly lower healthy cell percentage than the Stupp Protocol with TMZ. Our findings align with our hypothesis and animal trials, suggesting the hydrogel's higher efficacy compared to existing regimens.

CONCUSSION AND BRAIN INJURIES

31. Jing Lin; Rehabilitation Sciences Institute

Supervisor: Dr. Nancy Salbach

EXPLORING THE PERCEPTIONS OF INPATIENTS WITH STROKE, CAREGIVERS, AND STROKE TEAM OF IMPLEMENTING A VIDEO-BASED EXERCISE PROGRAM DESIGNED TO IMPROVE MOBILITY IN THE INPATIENT STROKE REHABILITATION SETTING: A THEORY-INFORMED QUALITATIVE STUDY

Lin J, Salbach N

Rehabilitation Sciences Institute, University of Toronto, Toronto, Ontario, Canada; Department of Physical Therapy, University of Toronto, Toronto, Ontario, Canada

Introduction: In the inpatient rehabilitation setting, stroke patients often spend a significant portion of their time sedentary due to mobility limitations. Task-specific training has been emphasized as crucial for enhancing mobility and quality of life post-stroke. However, there's a scarcity of evidence regarding non-therapist-led, group-based exercise programs targeting mobility, especially during non-therapy hours. **Objective:** This qualitative study aims to explore the perspectives of inpatients with stroke, caregivers, and stroke team members on implementing a video-based exercise program, TIMETM at Home, adapted for inpatient stroke rehabilitation. **Methods:** Utilizing the Knowledge to Action Framework and Theoretical Domains Framework, this study will investigate barriers and facilitators to program implementation and identify strategies for successful integration. **Results and Conclusion:** Findings will inform the development of an exercise program prototype and implementation strategy, potentially enhancing understanding of barriers and facilitators for implementing exercise interventions in stroke rehabilitation settings, thereby promoting continued participation in exercise beyond the inpatient setting.

32. Andie Ovcjak; Department of Physiology

Supervisor: Dr. Zhong-Ping Feng

ADVANCING STANDARD CARE FOR INFANTS WITH HYPOXIC-ISCHEMIC ENCEPHALOPATHY: EXPLORING THERAPEUTIC HYPOTHERMIA AND DANTROLENE INTEGRATION

Ovcjak A, 1; Miller SP, 2; Sun HS, 1,3; Feng ZP, 1

1 Department of Physiology, University of Toronto, Toronto, Ontario, Canada; 2 Department of Pediatrics, University of British Columbia, Vancouver, British Columbia, Canada; 3 Department of Surgery, University of Toronto, Toronto, Ontario, Canada

Introduction & Objective: Therapeutic hypothermia (TH) administered in the first 6 hours of life is the standard of care for neonatal hypoxic–ischemic encephalopathy (HIE), yet mortality and morbidity remain significant. Hence, an ongoing focus of research has been adjunct

therapies to enhance the protective effects of TH. Recently, we reported that inhibiting ryanodine receptor mediated-calcium release via Dantrolene pre-treatment, conferred pronounced neuroprotection in a neonatal HI model. Here, we hypothesized that TH combined with adjuvant drugs would be more efficacious than TH alone, and further, that Dantrolene may be an effective adjunct to TH. **Methods**: To evaluate the efficacy of combination therapy, meta-analysis of clinical studies evaluating HIE infants treated with combination therapy versus TH alone was carried out. To evaluate the effects of Dantrolene combined the TH, the in vivo Rice-Vannucci HI brain injury model was performed on postnatal day 7 mouse pups. Assessments of brain infarction volume and short-term neurobehavior were carried out and compared between Sham, HI-vehicle, HI-TH, HI-Dantrolene and HI-TH+Dantrolene mice. **Results**: 16 studies met inclusion criteria for meta-analysis. HIE infants totaled 1288 from included studies - 642 received a form of combination therapy, while 646 received TH alone. Length of hospitalization was significantly reduced in infants treated with combination therapy compared to those treated with TH alone. Risk of mortality and neurodevelopmental impairment did not differ. In our preclinical study, Dantrolene was found to have a therapeutic window of 1 hr-post HI as well as reduce brain infarction volume and neurobehavioral deficits to the same extent as TH alone. These effects were largely conserved when stratified by sex. **Conclusions**: This meta-analysis highlights the need for preclinical trials to conduct drug development studies in hypothermic settings. In doing so, our subsequent preclinical study demonstrates that although Dantrolene does not augment hypothermic-mediated neuroprotection, it may be an alternative treatment for infants who are unable to receive TH within its strict therapeutic window.

33. Kevin Solar; Neurosciences & Mental Health, SickKids Research Institute

Supervisor: Dr. Ben Dunkley

REPETITIVE SUBCONCUSSION LEADS TO ABNORMAL NEURONAL ACTIVITY IRRESPECTIVE OF CONCUSSION HISTORY

Solar KG, 1; Ventresca M, 1; Zamyadi R, 1; Zhang J, 2; Vartanian O, 2; Rhind SG, 3,2; Dunkley BT, 1,4,5,6

1 Neurosciences & Mental Health, SickKids Research Institute, Toronto, Ontario, Canada; 2 Defence Research and Development Canada, Toronto Research Centre, Toronto, Ontario, Canada; 3 Faculty of Kinesiology and Physical Education, University of Toronto, Toronto, Ontario, Canada; 4 Department of Medical Imaging, University of Toronto, Toronto, Ontario, Canada; 5 Department of Diagnostic and Interventional Radiology, Hospital for Sick Children, Toronto, Ontario, Canada; 6 Department of Psychology, University of Nottingham, Nottingham, England, United Kingdom

Introduction: Concussion represents a public health emergency that causes a neurochemical cascade of changes in the brain, which can have life altering consequences. Subconcussions are seen as less problematic and were neglected until recently, but we now know that repetitive subconcussions can lead to severe neurological impairments. They are prevalent in contact sports, and the military where specific members are exposed to varying repetitive occupational blast overpressure. Postmortem investigations of athletes show that total play time and impact force are more reliable than concussion history for predicting the presence and severity of chronic traumatic encephalopathy – a progressive and fatal neurodegenerative tauopathy, distinct from concussion, likely caused by repetitive head impacts, and only diagnosable after death – thus, an in vivo predictive biomarker would groundbreaking. Magnetoencephalography offers precise temporal imaging of neuronal electrochemical action, linking neural slowing to tauopathy, while functional MRI associates connectivity with tauopathy patterns. Therefore, both imaging modalities could offer a surrogate biomarker of tauopathy. **Objective**: This cross-sectional study aimed to understand interactions between lifetime blast exposure, neurobehavioural symptoms, mental health, and brain function outcomes in Canadian Armed Forces and Royal Canadian Mounted Police personnel and Veterans exposed to repetitive subconcussions from blast overpressure, controlling for concussion and traumatic stress history. **Methods**: Eight-one participants were divided into 'high' and 'low' blast exposure groups using a median split based on the Generalized Blast Exposure Value: n=41 high blast (26.4–65.7 years; 4 females); n=40 low blast (28.0–63.3 years; 8 females). We examined blast-related group differences in concussion symptoms, depression, anxiety, and post-traumatic stress disorder (self-reported questionnaires), and neuronal activity (magnetoencephalography) and functional connectivity (magnetoencephalography, functional MRI). **Results**: Magnetoencephalography demonstrated abnormal neuronal activity in participants with a worse history of repetitive subconcussions, including neural slowing (elevated delta activity) in the right fronto-temporal and subcortical regions (hippocampus, amygdala, caudate, pallidum, thalamus), and functional dysconnectivity in the posterior default mode network (low and high gamma). Importantly, these abnormalities were independent of concussion and traumatic stress history, and only magnetoencephalography, not functional MRI, detected dysconnectivity. Besides disrupted activity in crucial brain hubs, individuals with worse blast exposure had poorer somatic and cognitive outcomes, with no blast-related mental health differences and no associations between symptoms and neuronal activity. **Conclusion**: This research suggests that repetitive subconcussions have insidious effects on the brain and that magnetoencephalography may provide an effective strategy for both treatment by isolating targets in the brain and prevention by identifying individuals at risk of cumulative subconcussive neurotrauma.

DEPRESSION AND MENTAL HEALTH

34. Noah Chisamore; Department of Pharmacology and Toxicology

Supervisor: Dr. Joshua Rosenblat

REAL WORLD EFFECTIVENESS OF INTRAVENOUS KETAMINE FOR TREATMENT-RESISTANT DEPRESSION IN TRANSITIONAL AGE YOUTH

Chisamore N, 1,2; Danayan K, 1; Rodrigues N, 1; Mcintyre R, S1,3; and Rosenblat JD, 1,2,3

1 Mood Disorder Psychopharmacology Unit, UHN, Toronto, Ontario; 2 Department of Pharmacology, University of Toronto; 3 Department of Psychiatry, University of Toronto

Introduction: Treatment-resistant depression (inadequate response to ≥2 antidepressants) is associated with significantly greater overall depression symptoms, risk of suicidality, and disability. Ketamine is an emerging treatment for TRD associated with rapid, robust improvements in depressive symptoms and suicidality. However, the efficacy and safety of ketamine in transitional age youth (TAY; age 18-25) populations remains understudied. **Objective**: To compare the antidepressant efficacy of intravenous ketamine between transitional age youth and general adults. **Methods**: In this retrospective analysis,

TAY patients (n=52) who received ketamine for TRD at a treatment centre in Toronto, Ontario, were matched for sex, primary diagnosis, baseline depression severity and treatment resistance with a general adult (GA) sample (age 30-60). Patients received four ketamine infusions over two weeks (0.50-0.75 mg/kg over 40 minutes). The primary outcome was the change in Quick Inventory of Depressive Symptomatology Self-Report 16-item (QIDS-SR16) over time. Secondary outcomes were changes in QIDS-SR16 suicidal ideation (SI) item, anxiety [Generalized Anxiety Disorder 7-item (GAD-7)] and adverse effects. **Results**: A significant main effect of infusions on reduction of total QIDS-SR16 ($p<0.001$), QIDS-SR16 SI ($p<0.001$), and GAD-7 ($p<0.001$) scores was observed in the TAY group with moderate effect sizes, indicative of clinically significant improvements in depression, anxiety and suicidality. There were no significant differences between TAY and GA groups on these measures over time, suggesting comparable improvements. Safety and tolerability outcomes were also comparable between groups with only mild, transient adverse effects observed. **Conclusion**: Ketamine was associated with comparable clinical benefits, safety and tolerability in a TAY sample as compared to a matched GA TRD sample.

35. Katharina Göke; Institute of Medical Science

Supervisor: Dr. Daniel Blumberger

COGNITIVE SUBGROUPS IN TREATMENT-RESISTANT LATE-LIFE DEPRESSION AND THEIR IMPACT ON rTMS TREATMENT OUTCOMES

Göke K, 1,2; McClintock SM, 3; Mah L, 2,4,5, Rajji TK, 1,2,4,6; Lee HH, 4,7; Nestor SM, 2,4,7; Downar J, 1,2,4; Noda Y, 8; Daskalakis ZJ, 9; Mulsant BH, 1,2,4; Blumberger DM, 1,2,4

1 Temerty Centre for Therapeutic Brain Intervention and Campbell Family Research Institute, Centre for Addiction and Mental Health, Toronto, Ontario, Canada; 2 Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada; 3 Division of Psychology, Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas, Texas, United States; 4 Department of Psychiatry, Temerty Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada; 5 Rotman Research Institute, Baycrest Health Sciences, Toronto, Ontario, Canada; 6 Toronto Dementia Research Alliance, University of Toronto, Toronto, Ontario, Canada; 7 Harquail Centre for Neuromodulation, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada; 8 Department of Neuropsychiatry, Faculty of Medicine, Keio University School of Medicine, Tokyo, Japan; 9 Department of Psychiatry, University of California, San Diego Health, California, United States

Introduction: Late-life depression is often accompanied by cognitive impairment, yet substantial variability exists in the cognitive presentation among older adults with depression. Current data on the extent of cognitive impairments is inconclusive, particularly in patients with treatment-resistant depression. Repetitive transcranial magnetic stimulation (rTMS) is an evidence-based treatment for depression. However, the effectiveness of rTMS in patients with varying cognitive profiles remains unclear. **Objective**: This study aimed to investigate the heterogeneity in cognitive functioning of older adults with treatment-resistant depression by identifying distinct cognitive subgroups. Additionally, we examined whether cognitive subgroups differentially responded to treatment with bilateral rTMS. **Methods**: 165 older adults with treatment-resistant depression completed measures of executive function, information processing speed, verbal learning, and memory before undergoing treatment with bilateral rTMS. Cluster analysis was conducted to identify subgroups based on cognitive scores. Demographic and clinical variables, as well as outcomes with bilateral rTMS were compared between cognitive subgroups. **Results**: A three-cluster solution emerged, including "Cognitively Intact" (n = 89), "Cognitively Diminished" (n = 29), and "Impaired Memory" (n = 47) subgroups. Both the "Cognitively Diminished" and "Impaired Memory" subgroups had more severe anxiety symptoms than the "Cognitively Intact" subgroup. No significant differences were observed in other demographic or clinical variables, nor in the outcomes to rTMS treatment. **Conclusion**: Cognitive functioning in late-life depression was heterogeneous. The identified cognitive subgroups were related to differing levels of anxiety severity but not to rTMS treatment outcome. Future research should examine the relationship of cognitive subgroups with further cognitive decline and neurodegenerative processes.

36. Kateryna Maksyutynska; Institute of Medical Science

Supervisor: Dr. Mahavir Agarwal

DOES THE KETOGENIC DIET IMPROVE OUTCOMES IN SEVERE AND PERSISTENT MENTAL ILLNESS AND NEUROCOGNITIVE DISORDERS? A SYSTEMATIC REVIEW

Maksyutynska K, 1,2; Arnold C, 1; De R, 1,2; Smith E, 1,2; Panganiban K, 1,2; Humber B, 1,2; Besa R, 1; Cunnane S, 3; Agarwal SM, 1,2; Hahn MK, 1,2

1 Centre for Addiction and Mental Health (CAMH), Toronto, ON, Canada; 2 University of Toronto, Toronto, ON, Canada; 3 Université de Sherbrooke, Sherbrooke, QC, Canada

Introduction: The established safety and efficacy of the ketogenic diet in the treatment of epilepsy and other neurological disorders support its potential as a treatment option for individuals with psychiatric and neurocognitive disorders. **Objective**: We sought to identify and analyze results from all primary research investigating the impact of the ketogenic diet on clinical outcomes for individuals with severe and persistent mental illness and/or neurocognitive disorders. **Methods**: We searched English-language articles in Medline, Embase, PsycINFO, Cochrane Database of Systematic Reviews, Cochrane Central, Cochrane Methodology Register, CAB Abstracts, and Web of Science from database inception to August 18, 2023. Studies were included that reported on psychiatric or cognitive outcomes in individuals with a major mood disorder, schizophrenia spectrum, or cognitive disorder, who were treated with a ketogenic diet or ketone supplement. A narrative synthesis of the findings from the included studies was organized by target population. **Results**: A total of 3,038 articles were identified of which 67 met inclusion criteria for full analysis: 52 were in individuals with a cognitive disorder, 8 in mood disorders (6 in bipolar disorder, 2 in depression), 5 in schizophrenia spectrum disorders, and 2 in mixed populations. An analysis of included reports identified significant improvements in cognitive performance in individuals with cognitive disorders, with some reports showing improvements in positive and negative symptoms in schizophrenia and mood disorders. Reports capture treatment duration ranging from 6 weeks to 12 years. Most of the articles included in the review were case reports and case series, with few published controlled studies. **Conclusion**: This systematic review highlights promising findings from studies of the ketogenic diet in improving cognitive and mood outcomes in populations with severe mental illness and neurocognitive disorders. High-quality primary research (e.g. randomized controlled trials) is needed to replicate these effects in controlled settings to better establish the clinical efficacy of the ketogenic diet in these populations.

LEARNING AND MEMORY

37. Megan Lozzi; Department of Psychology

Supervisor: Dr. Robert Rozeske

DEFENSIVE BEHAVIOUR REPRESENTATIONS IN THE LATERAL PERIAQUEDUCTAL GREY

Lozzi M, 1; Rozeske RR, 1

1 Department of Psychology, University of Toronto Scarborough, Toronto, Ontario, Canada

Introduction: The ability of an organism to generate context-appropriate defensive responses to threat is essential for survival. It is proposed that defensive behaviour is regulated by the periaqueductal grey (PAG) along a dorsal-ventral (DV) continuum in which the former (dPAG) regulates active behavioural responses (e.g., escape), and the latter (vPAG) controls passive responses (e.g., freezing) (DeOca et al., 1998). **Objectives:** The functional role of the lateral PAG (lPAG) is less characterized, but given its position between the dPAG and vPAG, we hypothesized that it also controls expression of defensive responses. **Methods and Results:** To test this, we developed a learned fear test in which mice undergo training in two contexts; one context is paired with shock and the other is not. During the test, mice can freely move between the threatening and neutral contexts and we simultaneously record bulk calcium-evoked fluorescence in the lPAG with fiber photometry. With these data we will quantify dynamic changes in lPAG activity as mice move between threatening and neutral contexts. We will use deep learning and recurrent neural network tools to define and analyze the expression pattern of defensive behaviour poses. The synchronization of neural recording and behavioural data allows us to determine the association between behavioural poses expressed in the aversive vs neutral context and lPAG activity. **Conclusion:** These results will uncover brain-behaviour relationships during varying threat-levels, with implications for anxiety and other related disorders in which threat is ambiguous.

MENTAL DISORDERS

38. Riddhita De; Institute of Medical Science

Supervisor: Dr. Margaret Hahn

SEMAGLUTIDE FOR THE TREATMENT OF ANTIPSYCHOTIC ASSOCIATED WEIGHT GAIN IN PATIENTS NOT RESPONDING TO METFORMIN: A CASE SERIES

De R, 1,2; Prasad F, 1,2; Korann V, 1,2; Chintoh AF, 1,2,3; Remington G, 1,2,3; Ebdrup BH, 4,5,6,7; Siskind D, 8,9; Knop FK, 10,11,12,13; Vilsbøll T, 10,11,12,13; Fink-Jensen A, 14,15; Hahn MK, 1,2,3,16; Agarwal SM, 1,2,3,16

1 Schizophrenia Division, Centre for Addiction and Mental Health (CAMH), Toronto, Canada; 2 Institute of Medical Sciences, University of Toronto, Toronto, Canada; 3 Department of Psychiatry, University of Toronto, Toronto, Canada; 4 Center for Neuropsychiatric Schizophrenia Research, Mental Health Centre Glostrup, University of Copenhagen, Glostrup, Denmark; 5 Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark; 6 Center for Clinical Metabolic Research, Gentofte Hospital, University of Copenhagen, Copenhagen, Denmark ; 7 Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research (CINS) Glostrup, Denmark ; 8 Faculty of Medicine, The University of Queensland, Brisbane, QLD, Australia; 9 Metro South Addiction and Mental Health Service, Brisbane, QLD, Australia; 10 Center for Neuropsychiatric Schizophrenia Research, Mental Health Centre Glostrup, University of Copenhagen, Glostrup, Denmark ; 11 Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark; 12 Steno Diabetes Center Copenhagen, Copenhagen, Denmark; 13 Novo Nordisk Foundation Center for Basic Metabolic Research, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark; 14 Center for Neuropsychiatric Schizophrenia Research, Mental Health Centre Glostrup, University of Copenhagen, Glostrup, Denmark; 15 Psychiatric Centre Copenhagen, Rigshospitalet, Mental Health Services – Capital Region of Denmark, Copenhagen, Denmark; 16 Banting and Best Diabetes Centre, University of Toronto, Toronto, Canada

Introduction and Objective: While antipsychotic (AP) medications are considered the cornerstone of treatment in schizophrenia and other psychiatric conditions, contributing effects of these medications on weight gain have been well-established. Comorbid obesity among individuals with severe mental illness (SMI) have been associated with poorer quality of life, barriers to social engagement, worse adherence, and impaired cognition. Despite this, the available treatment strategies for managing this growing problem are significantly lacking. At present, metformin has the most evidence for modest weight gain mitigation in individuals with SMI who experience antipsychotic associated weight gain (AAWG). However, it is effective in only approximately 20% of patients, with no clear recommendations for the subgroup failing to respond to metformin. Among agents approved for chronic weight management in Canada, glucagon-like peptide-1 receptor agonists (GLP-1RAs) are associated with reductions in cardiovascular mortality, with the recent addition of once-weekly semaglutide for this indication. The long-acting, once-weekly formulation has shown promising preliminary evidence for both effectiveness and tolerability. Therefore, in this case series involving the SMI population, the primary objective was to study changes in weight over 12 months following the initiation of semaglutide among metformin non-responders. **Methods:** A retrospective chart review was conducted for individuals between 2019 and 2021, in the Mental Health and Metabolism clinic at the Center for Addiction and Mental Health (CAMH) in Toronto, Canada. The inclusion criteria consisted of patients who were on a stable dose of an antipsychotic medication, who failed to lose >5% body weight on metformin (highest tolerated dose) at the end of 3 months or those who continued to meet criteria for metabolic syndrome at the end of 3 months. They were then initiated on semaglutide of up to a 2 mg dose per week. All demographics and metabolic data were collected at baseline, 3, 6 and 12 months. **Results:** Twelve patients in total were included with a mean age of 36.09 ± 13.32 years, who were on a mean semaglutide dose of 0.71 ± 0.47 mg/week at the end of 12 months. At baseline, the mean weight was 111.4 ± 31.7 kg, and the BMI was 36.7 ± 8.2 kg/m2 with a mean waist circumference of 118.1 ± 19.3 cm. After initiation of semaglutide, weight loss of 4.56 ± 3.15 kg ($p < 0.001$) was noted at 3 months, 5.16 ± 6.27 kg ($p = 0.04$) at 6 months, and 8.67 ± 9 kg ($p = 0.04$) at 12 months. No serious adverse events were reported on the medication, with some experiencing tolerable gastrointestinal side-effects which subsided with time.**Conclusion:** This case series from a naturalistic, clinical setting suggests that among metformin non-responders, semaglutide appears to be effective in reducing AAWG. However, well-powered randomized control trials investigating semaglutide for AAWG in the SMI population are required.

NEUROANATOMY

39. Stefanie Bradley; Department of Biomedical Engineering

Supervisor: Dr. Tom Chau

CASE STUDY OF A STRUCTURAL MRI ANALYSIS OF 6-YEAR-OLD CHILD WITH CEREBRAL PALSY PRE- AND POST-PHYSIOTHERAPY-ASSISTED EXOSKELETON THERAPY

Bradley S, 1,2; Wright FV, 1,3; Chau T, 1,2

1 Bloorview Research Institute, Holland Bloorview Kids Rehabilitation Hospital; 2 Department of Biomedical Engineering, University of Toronto; 3 Department of Physical Therapy, University of Toronto

Introduction: Newly developed robotic gait technologies can offer upright supported mobility opportunities for children with gait limitations. The Trexo Plus is an overground pediatric lower limb exoskeleton that guides and powers children's leg movements, providing individualized access to new walking-based activities during physiotherapy. There are wide gaps in knowledge about how the body and brain respond to exoskeleton-mediated motor rehabilitation in children with cerebral palsy (CP), especially those with more compromised gross motor function. **Objective**: Our study explores the neuroplastic outcomes of a physiotherapy-based motor learning treatment paradigm with the Trexo exoskeleton. **Methods**: Pre/post case study of one participant from a larger pre-/post-test feasibility study (n=10). The Trexo-based physiotherapy intervention was administered twice weekly for 6 weeks in our outpatient center. The 6-year-old, right-handed child had a diagnosis of mixed cerebral palsy (spastic and dystonic) with bilateral involvement, and no independent ambulation (GMFCS Level IV). Awake magnetic resonance imaging (MRI) head scanning was done in a 3-Tesla MRI scanner, pre- and post-intervention. MRI structural preprocessing of T1-weighted images was done with a longitudinal pipeline (Freesurfer Software). A priori regions of interest (ROIs) included right/left motor cortices (precentral gyrus) and right/left primary somatosensory cortices (postcentral gyrus). **Results**: Left hemisphere (LH) and right hemisphere (RH) volumes are reported separately. ROI deltas were calculated by subtracting pre-intervention from post-intervention volumes. Cortical gray matter (GM) volume (% of original volume) (LH, RH) increased in the precentral gyrus (+3.53, +3.19) and increased in one hemisphere of the postcentral gyrus (+6.15, -0.70). Whole brain cerebral white matter (WM) volume (% of original volume) increased in the LH (+2.12) and decreased in the RH (-1.21). Total brain gray matter volume decreased post intervention (-0.65%). **Conclusion**: Following the exoskeleton-mediated physiotherapy intervention, volume increases in cortical GM ROIs and cerebral WM were more pronounced in the participant's LH. Analyses with a larger cohort will further elucidate these changes. Characterization of experience-dependent neuroplasticity in children with CP may help clinicians and stakeholders better understand the relationship among physiotherapy, neurological changes, and clinical outcomes. Further investigation into clinical significance is on-going/warranted.

NEURODEGENERATIVE DISEASES

40. Dustin Loren Almanza; Department of Medical Biophysics

Supervisor: Dr. Bojana Stefanovic

HIGH CARBOHYDRATE HIGH FAT DIET IMPROVES NEURONAL METABOLISM AND FUNCTIONAL HYPEREMIA IN EARLY STAGE OF AD PATHOLOGY

Almanza DLVA, 1,2; Koletar MM, 1; Lai AY, 3; Lam WW, 1; Hill ME, 3; Stanisz GJ, 1,2; McLaurin J, 3,4; Stefanovic B, 1,2

1 Physical Sciences Platform, Sunnybrook Research Institute, Toronto, Canada; 2 Department of Medical Biophysics, University of Toronto, Toronto, Canada; 3 Biological Sciences Platform, Sunnybrook Research Institute, Toronto, Canada; 4 Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Canada

Introduction: While obesity has been linked to both increased and decreased rate of cognitive decline in Alzheimer's Disease (AD) patients, the interaction between obesity and AD remains largely unknown. In the present study, transgenic rat model of Alzheimer's Disease (TgF344-AD) was used to investigate the effects of high carbohydrate, high fat (HCHF) diet on brain glucose metabolism and brain hemodynamics in the presence or absence of AD transgenes, in presymptomatic vs. symptomatic stages of AD progression using non-invasive brain imaging. **Objective**: To investigate the effect of obesity in presymptomatic (6-month-old) and symptomatic (12-month-old) TgF344-AD rats. **Methods:** The TgF344-AD rats exhibit amyloidogenesis, tau pathology, neuronal loss, and cognitive decline. For 3 months prior to imaging, TgF344-AD rats and their nTg littermates were given either CHOW or cafeteria diet (CHOW supplemented with a variety of human food items and 12% sucrose in water resulting in consistently elevated carbohydrate, salt and fat content). In the presymptomatic-AD (6-months) and established-AD (12-months) stages, the rats underwent 7T MRI neuroanatomy and neurometabolism, quantifying glucose uptake, resting perfusion, functional hyperemia, and myelin content. **Results**: Compared to their 6-month-old counterparts, 12-month-old nTg and TgAD rats showed decreased ($p=0.002$) hippocampal glucose uptake (by 161±40% and 84±30%), and perfusion reduction ($p=0.024$, by 11±3% and 15±2%). Hippocampal myelin was reduced by AD ($p=0.006$): by 10±2% at 6 months and by 6.5±1.0% at 12 months. Obese 12-month-old TgADs showed hippocampal glucose uptake elevation of 390±30% when compared to 6-month-old TgADs ($p<0.001$) and 433±40% when compared to the 12-month-old nTgs ($p=0.004$). Their resting perfusion, functional hyperemia, and myelin content levels were indistinguishable, but functional hyperemia in either genotype was elevated by obesity ($p=0.006$): by 38±5% at 6 months and by 43±5% at 12 months. Our findings indicate that a high caloric diet in the early stages of symptomatic AD can have propitious effects on neurophysiological and cerebrovascular function, in support of our findings that the HCHF diet stabilizes executive function in this model of AD in the early symptomatic stage of the disease. **Conclusion**: AD progression resulted in hippocampal atrophy and attenuation of hippocampal glucose uptake, resting perfusion, and myelin content. Induction of obesity in AD rescued hippocampal glucose uptake, resting perfusion, and myelin content, while elevating the level of functional hyperemia. The observed beneficial effects of obesity in the established AD, but not in normal aging, are speculated to result from increased metabolite availability being propitious for the metabolically dysregulated AD brain.

41. Ari Belotserkovsky; Department of Laboratory Medicine and Pathobiology

Supervisor: Dr. Gerold Schmitt-Ulms

BRAIN TARGETED AAV DELIVERY OF CRISPR-CAS9 TECHNOLOGY FOR PRNP KNOCKOUT

Verkuyl C, 1,2; Zhu S, 1,2; Zhao W, 1,2; Zerbes T, 1,2; Schmitt-Ulms G, 1,2

1 Tanz Centre for Research in Neurodegenerative Disease, University of Toronto, Toronto, Ontario, Canada; 2 Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Ontario, Canada

Introduction: Any strategy that can lower brain levels of the cellular prion protein (PrPC) selectively and persistently is expected to be effective for the treatment of prion diseases. Patients bearing disease-causing mutations within the prion gene may benefit the most from interventional gene editing-based therapy. Recent breakthroughs in generating brain-specific adeno-associated viruses (AAVs) have prompted us to explore if an all-in-one recombinant AAV (rAAV) packaged with a CRISPR-Cas system can be devised to functionally ablate the prion gene. **Objective and Methods:** To this end, we developed a plasmid that codes for a high-fidelity small Cas endonuclease, whose expression is controlled by a truncated neural cell adhesion molecule 1 (NCAM1) promoter active in PrPC expressing cells, and a prion gene-specific guide RNA (gRNA). In parallel, we established a robust and scalable rAAV assembly pipeline that has consistently yielded titres exceeding 1 x 1013 vg/mL. We compared several known engineered AAV capsids with tropism for the brain to determine which variant has superior blood-brain barrier penetrance and neuronal bias. Finally, we assembled our all-in-one therapeutic rAAV vector in the capsid which showed the most promise for brain-wide distribution. **Results:** We report on the results of proof-of-concept prion gene editing experiments using this therapeutic rAAV vector in human cells as a precursor to prion disease survival extension experiments. **Conclusion:** Future work will need to establish the relative efficacy and safety of this approach for the treatment of prion diseases.

42. Lauren Joe; Department of Laboratory Medicine and Pathobiology

Supervisor: Dr. Janice Robertson

INVESTIGATING THE EFFECTS OF COFILIN ON PHENOTYPES IN MODELS OF C9ORF72 HAPLOINSUFFICIENCY

Joe L, 1,2; Robertson J, 1,2

1 Tanz Centre for Research in Neurodegenerative Disease, University of Toronto, Toronto, Ontario, Canada; 2 Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Ontario, Canada

Introduction: Amyotrophic lateral sclerosis (ALS) is a crippling and fatal neurodegenerative disease caused by the gradual loss of motor neurons in the brain and spinal cord. This results in muscle paralysis and death, typically within 2-5 years of diagnosis. ALS shares clinical and neuropathological features with Frontal Temporal Dementia (FTD); the two diseases represent the extremes of a disease spectrum. The most common genetic cause of both diseases is hexanucleotide (G4C2) intronic repeat expansion in C9orf72 (chromosome 9 open reading frame 72). These repeats give rise to C9orf72 haploinsufficiency through transcriptional downregulation of C9orf72 mRNA, and consequent loss of C9orf72 protein. The function of C9orf72 is unclear but has been shown to interact with the actin-binding protein, cofilin, which regulates actin dynamics. Loss of C9orf72 causes inactivation of cofilin through phosphorylation at serine 3 by LIM domain kinase 1 (LIMK1). It has been shown that C9orf72 knockout (C9KO) mice exhibit changes in synaptic plasticity and deficits in nucleocytoplasmic transport associated with generation of neuronal-specific cytoplasmic granules containing importin-β1. ALS disease progression occurs rapidly and there is yet to be an effective treatment. My current research will be crucial to provide specific insight on the relationship between C9orf72 and cofilin. Furthermore, it will identify the regulation of cofilin activity as a potential therapeutic target for the treatment of C9orf72-linked ALS. **Objective:** My objective is to characterize the correlation between cofilin and C9orf72-linked ALS in mouse models. **Methods:** Effects of loss of C9orf72 on the actin cytoskeleton and cofilin in HeLa cells. On Day 0, parental (Par) and C9 knockout (KO3 and KO19) HeLa cells were plated at ~75% confluence on coverslips in 12-well plates. Cells were grown for 24h and were then harvested into either RIPA buffer Western Blot analysis, LAS2 buffer for G-actin/F-actin in Vivo Assay (Cytoskeleton, #BK037) as per the manufacturer's instructions, or fixed in 4% PFA for immunocytochemistry. Effects of cofilin expression on actin cytoskeleton in C9orf72 HeLa cells. On Day 0, parental (Par) and C9 knockout (KO3 and KO19) HeLa cells were plated at ~75% confluence on coverslips in 12-well plates. The following day, cells were transfected with either eGFP, eGFP-tagged wildtype (WT) cofilin, constitutively active cofilin (Ser3 mutated to alanine; S3A), or constitutively inactive cofilin (Ser3 mutated to aspartic acid; S3E). Cells were allowed to express the constructs for 24h and were then fixed in 4% PFA for immunocytochemistry. Effects of WT, S3A, and S3E cofilin expression on importin-B1 granules in hippocampal and cortical neurons in WT and C9orf72 KO mice. cDNA constructs expressing eGFP-tagged WT, S3A, and S3E cofilin were generated. These constructs were cloned into AAV9 viral vectors under control of the human synapsin 1 promoter to give neuronal specific expression in vivo. Heterozygous C9orf72 (C9) knockout mice were crossbred to generate WT, heterozygous C9 knockout (C9-Het) and homozygous C9 knockout (C9-homo) mice. Neonatal pups (P1) received intracerebral ventricular injections of the AAV9 viral vectors encoding the cofilin constructs, using the AAV9 backbone expressing eGFP as control. Mice were euthanized at 3 months of age using transcardiac perfusion (with PBS). Brain and spinal cords were dissected out and processed for immunohistochemistry (fixation in formalin and paraffin embedded; FFPE) and biochemistry (flash frozen in liquid nitrogen). FFPE sections of 6uM were cut onto slides and stained for: eGFP, to assess levels and distribution of cofilin expression, and importin-β1, to assess rescuing of synaptic and nuclear phenotypes in C9 knockout mice. **Results:** Results indicate increased levels of endogenous phosphorylated cofilin and filamentous actin in KO3 and KO19 HeLa cells. Exogenous expression of cofilin does not significantly impact the actin cytoskeleton in Par or KO HeLa cells. In mouse brain, expression patterns of wildtype (WT) and mutant (S3A; active, and S3E; inactive) cofilin and importin-β1 vary regionally in terms of morphology and structure labelling. **Conclusion:** To conclude, I have successfully investigated 1) the effects of endogenous cofilin expression on the actin cytoskeleton in C9KO HeLa cells, 2) the effects of exogenous cofilin expression on the actin cytoskeleton in Par and C9KO HeLa cells, and 3) the effects of exogenous expression of WT cofilin and its mutants on importin-β1 granules in hippocampal and cortical neurons in WT and het-/homo-C9KO mice. Future experiments should investigate the effects of WT, S3A, and S3E cofilin on TDP-43 and GluA1 levels in forebrain of WT and C9KO mice.

43. Bryan Kartono; Department of Laboratory Medicine and Pathobiology

Supervisor: Dr. Janice Robertson

ELUCIDATING THE ROLE OF C9ORF72 IN THE SYNAPSE

Kartono B, 1,2; Robertson J, 1,2

1 Tanz Centre for Research in Neurodegenerative Disease, University of Toronto, Toronto, Ontario, Canada; 2 Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Ontario, Canada

Introduction: Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease characterized by the loss of motor neurons from the brain and spinal cord, resulting in complete paralysis and death. ALS is often characterized by persistent synaptic dysfunction, manifesting as disruptions in neuronal structure, neurotransmitter systems, and ion channel regulation, driven by abnormalities in glutamatergic signaling and neuronal hyperexcitability. The most common genetic cause of ALS is a hexanucleotide repeat expansion in a non-coding region of C9orf72, leading to reduced expression of the C9orf72 protein. Despite our limited understanding of the pathological consequences of C9orf72 loss due to our incomplete understanding of its function, there is a growing understanding that genes associated with ALS, such as C9orf72, may contribute to the maintenance of normal synaptic function, as mutations in these genes frequently result in synaptic dysfunction. **Objectives, Methods and Results:** In this study, we demonstrate changes in the morphology of mouse primary cortical neurons in the context of C9orf72 haploinsufficiency, particularly alterations to neuronal branching and the composition of glutamate receptor subunits. Additionally, we found impaired protein pathways associated with synaptic function in the context of C9orf72 deficiency, including the Arf6-LIMK-Cofilin and PI3K-AKT-mTOR pathways. Furthermore, we show that inhibition of the anaplastic lymphoma kinase (ALK) by lorlatinib rescues abnormal neuronal branching and the composition of glutamate receptor subunits. **Conclusion:** Our findings shed light on the intricate mechanisms underlying synaptic dysfunction in in the context of C9orf72 deficiency. Furthermore, our discovery that ALK inhibition can rescue synaptic dysfunction associated with C9orf72 deficiency highlights a promising avenue for future research and treatment development.

44. Laura Kondrataviciute; Department of Biomedical Engineering

Supervisor: Dr. Suneil Kalia

DEPRESSIVE-LIKE PHENOTYPE INDUCED BY AAV-MEDIATED OVEREXPRESSION OF HUMAN α-SYNUCLEIN IN MIDBRAIN DOPAMINERGIC NEURONS

Kondrataviciute L, 1,2,3; Kapadia M, 2; Chau H, 2; George J.; Valiante T, 1,2,4,5; Milosevic L, 1,2,4,5; Kalia L, 1,6,7; Kalia S, 2,4,5,8,9

1 Institute of Biomedical Engineering, University of Toronto, Canada; 2 Krembil Research Institute, Toronto Western Hospital, University Health Network, Toronto, ON, Canada; 3 Physical Intelligence Department, Max Planck Institute for Intelligent Systems, 70569, Stuttgart, Germany; 4 KITE, Toronto Rehabilitation Institute, University Health Network; 5 CRANIA, University Health Network and University of Toronto, Toronto, Canada; 6 Division of Neurology, Department of Medicine, University of Toronto, Toronto, ON, Canada; 7 Tanz Centre for Research in Neurodegenerative Diseases, University of Toronto, Toronto, ON, Canada; 8 Institute of Medical Sciences, University of Toronto, Canada; 9 Department of Surgery, University of Toronto, Canada

Introduction: Parkinson's disease (PD), as the most prevalent neurodegenerative motor disorder, presents a complex spectrum of symptoms encompassing both motor impairments (bradykinesia, resting tremor, freezing of gait) and non-motor manifestations (depression, anosmia, anxiety). Robust animal models that faithfully replicate this multifaceted pathology are indispensable for comprehensive PD research. **Objective:** This study aims to investigate if depressive-like behaviour, prominent in up to 40% of PD patients (Laux, 2022), emerges in the bilateral human mutated alpha-synuclein (A53T) rat model of PD. **Methods:** 40 adult Sprague-Dawley rats were bilaterally injected into substantia nigra with either empty AAV1/2 vector or AAV1/2-expressing human mutated A53T-alpha synuclein. (Paxinos & Watson, 2013). Sucrose preference (Liu et al., 2018) and novelty suppressed feeding (Blasco-Serra et al., 2017) tests were performed on week 3 and week 6 post virus injection. Immunofluorescence staining for TH+, alpha-synuclein, DAPI was done to confirm neurodegeneration on week 6. **Results:** Both groups of rats showed a preference for the 20% sucrose solution with no statistically significant difference between groups on week 3 ($p=0.313$, t test). Statistically significantly lower preference for sucrose was exhibited on week 6 by alpha-synuclein expressing animals compared to control group ($p=0.0099$). Reduced responsiveness to highly palatable food consumption has also been observed in novelty suppressed feeding test, but statistically significant differences between A53T and EV have not been reached at any timepoint. **Conclusion:** Our findings suggest that the A53T-alpha synuclein rat model manifests depressive-like behavior, evidenced by diminished responsiveness to palatable stimuli. This model holds promise for investigating non-motor pathologies associated with PD.

45. Sonika Kumari; Institute of Medical Science

Supervisor: Dr Ann Yeh

RELATIONSHIPS BETWEEN FACTORS AT THE INDIVIDUAL-LEVEL AND THE BUILT ENVIRONMENT, AND THEIR IMPACT ON DEPRESSION IN PEDIATRIC-ONSET MULTIPLE SCLEROSIS

Kumari S, 1,2; Stephens S, 1; Yoo PY, 1,2; Arbour-Nicitopoulos K, 3; Feldman B, 4; Finlayson M, 5; Marie RA, 6; Motl R, 7; To T, 8; Yeh A, 1,2

1 Division of Neurology, Department of Pediatrics, Neurosciences and Mental Health (RI), The Hospital for Sick Children; 2 Temerty Faculty of Medicine, The University of Toronto; 3 Faculty of Kinesiology & Physical Education, University of Toronto; 4 Divison of Rheumatology, The Hospital for Sick Children; 5 School of Rehabilitation Therapy, Queen's University; 6 Max Rady College of Medicine, University of Manitoba; 7 Univeristy of Illinois, Chicago; 8 Child Health Evaluative Sciences Department, The Hospital for Sick Children

Introduction: Individual factors such as self-efficacy and goal setting are associated with depression in healthy children3. Furthermore, access to green spaces– i.e. the "built environment"— mitigates risks for poor mental health outcomes in healthy children 4. Over 30% of children with multiple sclerosis (MS) experience depression1,2. However, the relationships among self-efficacy, goal setting, the built-environment and depression in children with MS are unknown; understanding these relationships may have implications for interventional strategies for depression in this population. **Objectives**: To examine associations between built-environment features and depressive symptoms in children with MS. To examine associations between depressive symptoms, exercise goal setting, and physical activity self-efficacy in children with MS. **Methods**: Children (≤18 years) with MS attending a clinic at The Hospital for Sick Children completed three questionnaires: 1) The Centre for Epidemiological Studies Depression Scale for Children (CES-DC [score range 0-60], score >15 suggests significant depressive symptoms)5, 2) Exercise Goal Setting Scale (EGS[0-50])6, and 3) Physical Activity Self-Efficacy (PASES[0-

2])7. Built-environment features were accessed via the CANUE repository using postal codes8-11. Facility Richness Index and Proximity to Parks range from 0 (no access) to 1 (maximum access). Walk score (0-100), higher values indicate greater pedestrian accessibility. The normality of distribution was assessed using Shapiro-Wilk test and Spearman's rho correlation was conducted. **Results**: Most participants (n=56, age median 16±3 years (33 female (60%)) reside in areas with low park proximity (≤ 0.25, 100%), poor facility richness (≤ 0.1, 93%), and low walk scores (≤60, 88%). No significant correlations were observed between depression scores (median =13±14) and facility richness (rs=-0.174, p=0.204), proximity to park (rs=-0.034, p=0.820), or walk score (rs=-0.143, p=0.292). In a subset (n=41), lower depression scores were associated with higher goal setting scores (rs= -5.41, p<0.001) and self-efficacy scores (rs=-0.57, p<0.001). A Mann-Whitney test showed that males (median=35.4) had significantly higher EGS scores than females (median=25.7), p=0.005. **Conclusions**: Access to environmental facilitators of physical activity is limited in children with MS. We also found lower goal setting and self-efficacy in children who had higher depression scores, aligning with previous research findings in children without MS.

46. Jonathan Monteiro; Department of Immunology

Supervisor: Dr. Véronique Miron

MICROGLIA REGULATE SPONTANEOUS RECURRENT AGE-DEPENDENT DEMYELINATION

Monteiro JK, 1,2; McNamara NB, 4; Munro DA, 4; Rose J, 4; Holloway RK, 1,2; Hoffmann A, 1,2; Pridans C, 4; Priller J, 4; Miron VE, 1,2,3,4

1 Keenan Research Center for Biomedical Science, Unity Health Toronto, Toronto, Ontario, Canada; 2 BARLO Multiple Sclerosis Center, St. Michael's Hospital, Toronto, Ontario, Canada; 3 Department of Immunology, University of Toronto, Toronto, Ontario, Canada; 4 UK Dementia Research Institute, University of Edinburgh, Edinburgh, United Kingdom

Introduction: Multiple sclerosis (MS) is an autoimmune central nervous system (CNS) disorder against myelin, lipid-rich membranes that aid in neuronal impulse propagation. Adaptive immune responses targeting oligodendrocytes, myelin-producing cells, lead to myelin damage (demyelination) and lesion formation, which is associated with motor, cognitive, and sensory defects. MS is characterized by recurrent bouts of demyelination, followed by repair of myelin, or remyelination. Myelin can be regenerated (termed remyelination), but this process eventually fails in MS, leading to chronic demyelination and clinical decline. The lack of therapies to prevent progression highlights the need to elucidate mechanisms driving MS disease. Microglia, CNS-resident macrophages, are promising candidates as they regulate myelin health, and are dysregulated in MS brains at sites considered to be pre-lesions, suggesting a role in demyelination initiation. We asked whether microglia have a role in regulating myelin pathology relevant to MS. **Objective**: We sought to determine the role of microglia in regulating myelin health by studying transgenic mice that lack microglia (Csf1r-FIREΔ/Δ). **Methods**: Brains from Csf1r-FIREΔ/Δ and wildtype mice in youth (3, 6 months) and middle age (12, 18 months) were analyzed for myelin health via electron microscopy and immunofluorescence. **Results**: We discover that myelin dynamics in Csf1r-FIREΔ/Δ mice mimic MS. While no change in myelinated axons was observed at 3 months of age, we observed small, focal areas of demyelination at 6 months, remyelination at 9 months, and recurrent demyelination at 12 months that was maintained until 18 months, suggesting remyelination failure. Demyelination initiation was preceded by the emergence of an oligodendrocyte subpopulation which subsequently declined in association with oligodendrocyte loss. T cell infiltration was absent in youth, yet was observable by 18 months, indicating a potential secondary autoimmune response to spontaneous demyelination. **Conclusion**: We show that microglia are required to prevent spontaneous focal demyelination and recurrent, chronic demyelination with aging. We propose that microglia prevent the appearance of a pathological oligodendrocyte subpopulation whose death may drive initiation of demyelination, and a subsequent secondary response by autoimmune T cells in middle-age that may contribute to chronic demyelination. This highlights the importance of microglia in maintaining myelin health and preventing demyelination, pointing to microglia as novel therapeutic targets in MS.

47. Roseanne Nguyen; Neurosciences and Mental Health, SickKids Research Institute

Supervisor: Dr. Julien Muffat

USING HUMAN PLURIPOTENT STEM CELL-DERIVED NEURO-IMMUNE ORGANOIDS TO MODEL CENTRAL NERVOUS SYSTEM DEMYELINATION

Nguyen R, 1,2; Millar D, 1,2; Sun F, Bhattacharya A, 1,2; Torres-Perez MS, 1,2; Barkhouse K, 1,2; McNairn J, 1,2; Mohsin H, 1,2; Long C, 1,2; Cobo D, 1,2; Jan-Ahmadnejad M, 1,2; Stout E, 1,2; Naimi F, 1,2; Ju Y, 1,2; Li Y, 1,2; Muffat J, 1,2

1 The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada; 2 Department of Molecular Genetics, University of Toronto, Toronto, Ontario, Canada

Introduction: Demyelinating disorders are presently incurable, as details of their etiology and disease course remain unclear. One of the most prevalent demyelinating diseases is multiple sclerosis, and millions of individuals around the world live with the debilitating condition. **Objective**: I focus on the role of brain resident macrophages, the microglia, as I hypothesize that they are deleterious agents during demyelination but can paradoxically promote regeneration. There are currently no human in vitro models of demyelination that include microglia. **Methods**: I engineered a novel model of demyelination using human pluripotent stem cells (hPSCs) that I differentiate into neuro-immune 3D cultures. My demyelination model is integrated into our study of X-linked adrenoleukodystrophy (ALD), a monogenic demyelinating disease. This disease is poorly understood, but it leads the way in the development of cellular and gene-based therapies while remaining incurable. To generate the 3D cultures, I differentiated hPSCs using patterning factors to promote myelin formation. **Results**: These organoids contain neurons, astrocytes, oligodendrocytes and microglia. I used CRISPR gene editing to generate ALD mutant cultures and their isogenic controls. I successfully demonstrated that acute treatment with lysophosphatidylcholine (LPC) resulted in significant MBP loss and fragmentation and observed increased astrogliosis and elevation of NFL levels in the medium following 24 hours of treatment. Using multi-omics profiling, I will monitor microglial state changes upon LPC treatment and the impact of their presence on the demyelination process. I discovered that mutant microglia display abnormal lipid droplets. I hypothesize that ALD mutant organoids are more susceptible to induced demyelination than controls, owing to the dysfunctional lipid management in oligodendrocytes and microglia. **Conclusion**: This system will allow us to screen for therapeutic interventions modulating microglial reactivity, with the aim of limiting

demyelination and mitigating metabolic anomalies in microglia. This platform also provides an exciting opportunity to assess cellular and chemical interventions that promote remyelination.

48. Syeda Hania Qamar; Department of Laboratory Medicine and Pathobiology

Supervisor: Dr. Naomi Visanji

CREATING AN IN VIVO MODEL OF PROGRESSIVE SUPRANUCLEAR PALSY

Qamar SH, 1,2,3; Ferry R, 1; Mao A, 1; Thapa S, 1; Tanaka H, 1; Martinez-Valbuena I, 1;Visanji NP, 1,2,3,4

1 Tanz Centre for Research in Neurodegenerative Diseases, University of Toronto, Toronto, Ontario, Canada; 2 Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Ontario, Canada; 3 Krembil Brain Institute, 60 Leonard Avenue, Toronto, ON, M5T 0S8, Canada; 4 Rossy Progressive Supranuclear Palsy Centre, Toronto Western Hospital, 399, Bathurst St, Toronto ON, M5T 2S8, Canada

Introduction: Progressive Supranuclear Palsy (PSP) is a rare and fatal neurodegenerative disease in which tau protein misfolds and aggregates in three key regions of the brain, the striatum (CPu), globus pallidus (GP) and substantia nigra (SNr). To date, no animal model exists that can mimic the cytopathologic in conjunction with the anatomic specificity that characterizes PSP to help understand the underlying mechanisms and patterns of disease pathogenesis. **Objective**: Our overall aim is to develop an animal model that replicates the anatomical and cytopathologic hallmarks, spatiotemporal spread of pathology and progressive neurodegeneration that characterize PSP using human PSP brain derived tau. As a first step, here we compare the effects of five different tau extraction methods from human PSP brain inoculated in mice that express all six isoforms of human tau (6hTau). **Methods**: 10% w/v raw homogenate extracts, PBS soluble extracts as well as 0.1%, 1% and 2% sarkosyl insoluble (SI) tau extracts were prepared from human PSP brain. The tau yield per mg of tissue from each preparation was analyzed using ELISA. 6hTau mice were each inoculated in three key nuclei implicated in early stages of PSP (CPu, GP and SNr). Locomotor behaviour was assessed monthly and tau cytopathologies were examined at 3- and 6-months post inoculation (mpi) using immunohistochemistry (IHC) for phosphorylated tau (AT8). **Results**: The PSP 10% w/v raw homogenate extract yielded the greatest amount of total tau, followed by the PBS soluble extract, 0.1% SI, 1% SI and 2% SI extract, which had the lowest total tau yield of all preparations. The brains of 10% w/v raw homogenate and PBS soluble tau inoculated animals were negative for AT8 IHC at 3mpi and 6mpi. 2% SI tau inoculation resulted in AT8 positive neurons and neurites at 3mpi, which appeared to have increased by 6mpi. Analysis of additional timepoints and extract preparations are ongoing. Analysis of inoculation feasibility demonstrates that 1g of human PSP frontal cortex only yields sufficient 2% SI tau to induce moderate tau pathology in the CPu, GP and SNr of a single animal. Thus, our next steps involve amplification of PSP tau to create a reproducible and scalable animal model of PSP. **Conclusion**: Although 10% w/v raw homogenate tau extraction yielded the highest amount of total tau, inoculation in animals did not result in pathology. Conversely, inoculation with 2% SI tau, which had the lowest yield, induced abnormal neuronal tau deposition reminiscent of early pathology in PSP. These data demonstrate the importance of determining the optimal tau extraction method from human brain as a first step in developing an animal model of PSP pathology.

49. Can Sarica; Institute of Medical Science

Supervisor: Dr. Andres M. Lozano

LOCAL FIELD POTENTIAL CORRELATES OF TRANSCRANIAL FOCUSED ULTRASOUND NEUROMODULATION IN PATIENTS WITH PARKINSON'S DISEASE

Sarica C, 1,2; Darmani G, 2; Ramezanpour H, 3; Chen R, 2,4; Lozano AM, 1,2

1 Division of Neurosurgery, Department of Surgery, University of Toronto, Toronto, Ontario, Canada; 2 Krembil Research Institute, University of Toronto, Toronto, Ontario, Canada; 3 Centre for Vision Research, York University, Toronto, Ontario, Canada; 4 Division of Neurology, Department of Medicine, University of Toronto, Toronto, Ontario, Canada

Introduction: Transcranial Focused Ultrasound Stimulation (tFUS) represents a cutting-edge neuromodulation technique, recently demonstrated to be safe in patients with Parkinson's Disease (PD). However, the impact of tFUS on basal ganglia local field potentials (LFP), which could potentially serve as a crucial biomarker for optimizing treatment, remains unexplored. **Objective:** The aim of this study is to investigate the potential modulation of subthalamic nucleus (STN) LFPs in patients with PD following tFUS applied to the primary motor cortex (M1) and globus pallidus internus (GPi). **Methods:** Seventeen PD patients in the medication-on state participated in 2 or 3 visits, during which they were exposed to one of four conditions: Active M1, active GPi, active sham (applied to the occipital cortex), and passive sham. Ten subjects were randomly assigned to each active condition, while all subjects underwent the passive sham condition. tFUS was administered to each hemisphere for 2 minutes using a theta burst protocol, consisting of 20-ms bursts of ultrasound (0.5MHz) repeated at 5Hz. LFPs were recorded from the STN in 5-minute epochs using the Percept PC deep brain stimulation (DBS) system at five time points: baseline, online (during sonication), and post-sonication at 10, 30, and 45 minutes. **Results:** During GPi sonication, there was a significant increase in LFP power within the high beta frequencies (20-25 Hz) observed during both online and post-sonication conditions compared to baseline. While a similar trend of increase was noticed during passive and active sham conditions, the magnitude of change was notably less pronounced than during active GPi stimulation. Conversely, M1 sonication resulted in increased power within the theta and alpha bands, with no significant change observed within the beta band. **Conclusion:** The theta burst tFUS protocol applied to the GPi demonstrates an increase in beta band frequency power in PD patients. To translate this finding into clinical treatment, one may consider either selecting a different target area (such as the dorsal striatum or substantia nigra) or modifying the sonication protocol. Alternatively, given its potential efficacy in augmenting neural activity, theta burst tFUS might be better suited for conditions characterized by hypofunction, such as depression or addiction.

50. Raghav Sharma; Department of Laboratory Medicine and Pathobiology

Supervisor: Dr. Janice Robertson

SINGLE-NUCLEUS ANALYSIS OF CELL TYPE-SPECIFIC CHANGES IN THE HIPPOCAMPUS DUE TO C9ORF72 HAPLOINSUFFICIENCY

IN AMYOTROPHIC LATERAL SCLEROSIS AND FRONTOTEMPORAL DEMENTIA

Sharma R, 1,2; Robertson J, 1,2

1 Tanz Centre for Research in Neurodegenerative Disease, University of Toronto, Toronto, Ontario, Canada; 2 Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Ontario, Canada

Introduction: Amyotrophic lateral sclerosis (ALS) is an adult-onset neurodegenerative disease characterized by the degeneration of both upper and lower motor neurons, resulting in progressive muscle wasting and paralysis. ALS is linked with frontotemporal dementia (FTD) which is a group of disorders characterized by progressive damage to the frontal and temporal lobes of the brain. Both ALS and FTD are most commonly caused by a GGGGCC hexanucleotide repeat expansion (HRE) in a non-coding region of C9orf72 (C9). The HREs cause transcriptional downregulation of the C9orf72 mRNA resulting in lowered levels of C9orf72 protein in disease affected brain regions. The function of C9orf72 remains poorly understood, although has been linked with membrane trafficking events and autophagy through its proposed activity as a GTPase activating protein. Studies from our lab using heterozygous (C9-HET) and homozygous (C9-KO) C9orf72 knockout mice have identified roles for C9orf72 in synaptic remodeling, particularly in the hippocampus, and in regulation of nucleocytoplasmic transport. In addition to intrinsic neuronal mechanisms, multiple cell types contribute to the pathogenesis of ALS/FTD, including microglia, astrocytes, and oligodendrocytes. Using a multiome analysis of snRNA and snATAC-seq analyses will allow for capturing and isolating cell-type specific effects across clusters, while examining changes in the transcriptome and epigenome to discover novel gene-regulatory networks that may be implicated in disease. **Objective:** To increase the understanding of loss of C9orf72 function to the pathomechanisms underpinning ALS/FTD, I propose applying an integrative analysis of the cell subtype-specific transcriptomic and epigenomic changes caused by loss of C9orf72 in mouse brain. **Methods:** The hippocampus and frontal cortex were dissected from 12 mice at 3 months of age (4 C9-WT, 4 C9-HET, 4 C9-KO), these were sex balanced (2 males and 2 females per genotype). Nuclei suspensions from the hippocampus were performed using iodixanol density gradient purification, then analyzed using 10X Chromium Single Cell Multiome Assay for Transposase-Accessible Chromatin (ATAC) + Gene Expression (v1). This data provides a per-cell barcoded count matrix corresponding to the expression of genes and open chromatin. Frontal cortex nuclei were isolated using the 10X Chromium Nuclei Isolation kits (10X Genomics) and then libraries were prepared from the same multiome kit as above (v1). Established quality control (QC) metrics previously described for snRNA-seq and for snATAC-seq were used, filtering nuclei that did not pass cutoffs to ensure high quality nuclei were retained. Established integration methods such as reciprocal principal component analysis for the snRNA-seq data, and reciprocal latent semantic indexing for snATAC-seq were performed, and annotation of the dataset was performed using a random forest classifier NSForest from marker genes derived from the snRNA-seq dataset. Differentially expressed genes (DEGs) were obtained using the MAST R package and contextualized using the Gene Ontology Biological Processes pathway enrichment. Differentially accessible regions (DARs) were identified using the logistic regression model and motif accessibility was assessed using the chromVAR package. **Results:** A total of 48854 nuclei were retained and 39 subclass clusters were identified and collapsed to 26 major class cell-type annotations encompassing the hippocampus, entorhinal cortex, and subiculum. We observe that a majority of DEGs are down-regulated in C9-HET mice (~92%), whereas C9-KO show a lower proportion of down-regulation (~58%) and more up-regulated transcripts. In the DG cells of C9-KO mice, genes in pathways associated with synaptic membrane adhesion, pre-and post-synaptic membrane organization, and glutamatergic synaptic transmission are up-regulated. The CA3-CA1 regions additionally show depletion in synaptic plasticity. However, there are also down-regulated genes in pathways associated with synaptic plasticity, synaptic organization, ionotropic glutamate receptor signaling, and ligand-gated ion channel pathways. In the CA4-1 subfields of C9-KO mice, we see up-regulation of transmembrane transport, suggesting increased membrane transport may contribute to hyperexcitability. The CA1 in C9-KO shows downregulation of neuron projection organization and dendrite development. In the CA4, CA3, CA1, and DG subfields of C9-HET mice, significant GO terms are predominantly down-regulated and associated with regulation of transporter activity, cation transport/channel activity, and synaptic organization. These down-regulated pathways in C9-HET overlap with up-regulated terms in C9-KO, suggesting these cell types are differentially vulnerable to excitotoxicity between genotypes. Oligodendrocytes are especially vulnerable due to loss of C9, with oxidative phosphorylation and aerobic respiration being the most enriched GO terms, suggesting deficiency in ATP production and myelin biogenesis and is further supported by snATAC-seq data showing oligodendrocytes having loss of expression across genomic regions. **Conclusion:** Cell type-specific changes can be seen at the transcriptomic level due to C9orf72 haploinsufficiency and complete knockout, where C9-HET mice neurons show downregulation of transmembrane transporter activity, specifically cation transmembrane transporters, and dysfunction of calcium-signaling whereas C9-KO mice neurons show the opposite, with upregulation of transmembrane transporter activity, glutamate synaptic transmission, and synapse organization. CA1 and DG also show loss in synaptic plasticity, indicating that synaptic dysregulation is occuring across excitatory neurons. Oligodendrocytes are the most effected glial cell-type, with prominent dysfunction of mitochondrial processes, and show further dysregulation at epigenomic level suggesting that oligodendrocytes are some of the first cells to show impairment under loss of C9. Overall, we found both cell subtype-specific genes affected by C9orf72 deficiency and identified both transcriptomic and epigenomic drivers. Furthermore, the murine hippocampal atlas will fill a gap for other researchers who require high quality annotations for their own single nucleus datasets to help them identify what cells they have recapitulated.

51. Sandra Shenouda; Department of Laboratory Medicine and Pathobiology

Supervisor: Dr. Janice Robertson

INVESTIGATING THE THERAPEUTIC POTENTIAL OF JRMS TARGETING TDP-43 AGGREGATION IN ALS

Shenouda S, 1,2; Shenouda M, 1,2; Robertson J, 1,2

1 Tanz Center for Research in Neurodegenerative Diseases, University of Toronto; 2 Department of Laboratory Medicine and Pathobiology, University of Toronto

Introduction: Amyotrophic lateral sclerosis (ALS) is an adult-onset neurodegenerative disease characterized by the loss of motor neurons causing progressive paralysis, and eventually death due to respiratory failure within 2 to 5 years of diagnosis. Currently, ALS remains with no cure or effective treatment. The pathological hallmark in 97% of all ALS cases is the presence of cytoplasmic aggregates of TAR DNA-binding protein 43 (TDP-43) in disease affected neurons. TDP-43 is a

conserved RNA/DNA-binding protein normally confined to the nucleus. In disease, TDP-43 is mislocalized to the cytoplasm where it forms aggregates, accompanied by presence of truncated lower molecular weight C-terminal fragments, such as TDP-35 and TDP-25. TDP-43 mainly aggregates through its C-terminal low complexity glycine-rich domain (LCD), which is also present in the truncated fragments. **Objectives:** My project aims to validate small molecule 'JRMS' on its ability to prevent and reverse TDP-43 aggregates. JRMS was tested in cellular models and a mouse model to evaluate its efficacy on reducing TDP-43 aggregation. **Methods and Results:** Immunocytochemistry and immunoblot analysis were employed to assess the effects on various TDP-43 isoforms, aiming to reduce insoluble aggregated TDP-43 as a positive outcome. **Conclusion:** The overall goal is to validate JRMS as a small molecule with therapeutic benefit for eventual clinical testing.

52. Ella Bing Xin Song; Department of Pharmacology and Toxicology

Supervisor: Dr. Krista Lanctôt

EXAMINING THE RELATIONSHIP BETWEEN ANGIOPOIETIN-2 AND COGNITION IN EARLY ALZHEIMER'S DISEASE

Song BX, 1,2; Beroncal E, 1; Andreazza AC, 1; Gallagher D, 1,2,3; Marzolini S, 5; Rapoport M, 1,3; Charles J, 1,3; Herrmann N, 1,2,3; Oh PI, 5; Kiss A, 2; Swardfager W, 1,2; MacIntosh BJ, 1,2; Rajji TK, 1,4; Marotta G, 3; Siddiqui M, 2; Vieira D, 2; Kusumo R, 1,2; Lanctôt KL, 1,2,3,5

1 University of Toronto, Toronto, ON, Canada; 2 Sunnybrook Research Institute, Toronto, ON, Canada; 3 Sunnybrook Health Sciences Centre, Toronto, ON, Canada; 4 Centre for Addiction and Mental Health, Toronto, ON, Canada; 5 KITE Research Institute, Toronto Rehabilitation Institute, Toronto, ON, Canada

Introduction: Angiopoietin-2, which regulates endothelial permeability and angiogenesis functions, is emerging as a potential biomarker for early Alzheimer's disease (AD). Elevated levels of cerebrospinal fluid angiopoietin-2 concentrations have been found in early AD and may be associated with the breakdown of blood-brain barrier that can contribute to cognitive decline. There is a lack of research on blood angiopoietin-2 levels and cognition in early AD. **Objective**: To examine the association between serum angiopoietin-2 and global cognition. **Methods**: Participants were diagnosed with mild cognitive impairment (MCI) due to AD or mild Alzheimer's dementia using the Diagnostic and Statistical Manual of Mental Disorders 5 criteria for mild or major neurocognitive disorder. Serum angiopoietin-2 concentrations (ng/mL) were measured and analyzed using enzyme-linked immunosorbent assays. Global cognition was assessed by the Montreal Cognitive Assessment (MoCA). Linear regression analyses were used to assess the association between angiopoietin-2 levels and cognition adjusting for covariates selected a priori: age and the presence of cardiovascular risk factors or disease (cardiovascular status). Angiopoietin-2 levels were log-transformed prior to analyses due to significant departure from normality in Shapiro-Wilk tests. **Results**: Of 30 participants [17 (57%) male, 21 (70%) MCI, 22 (73%) with cardiovascular risk factors or disease], the mean (SD) age was 74.8 (8.7), years of education was 16.3 (2.2), MoCA total score was 21.9 (3.4), and angiopoietin-2 levels were 4.0 (3.6) ng/mL. Higher angiopoietin-2 was associated with better cognition [$F(3,26) = 6.7$, $p = .002$, $R2 = .44$]. Controlling for age and cardiovascular status, one log angiopoietin-2 unit was associated with a 4.2 (SE= 2.0) higher score in global cognition ($p = .048$, $f2 = .10$). **Conclusion**: In this sample, higher serum angiopoietin-2 concentrations were associated with better global cognition, controlling for age and cardiovascular status. This relationship supports the potential involvement of angiogenesis in cognitive functions and neurodegenerative diseases and suggests the need for further research to explore cardiovascular functions and cognition in early AD.

53. Claire Verkuyl; Department of Laboratory Medicine and Pathobiology

Supervisor: Dr. Gerold Schmitt-Ulms

A PROOF-OF-CONCEPT AAV-DELIVERED GENE-EDITING TRIAL FOR THE TREATMENT OF PRION DISEASE

Verkuyl CE, 1,2; Belotserkovsky A, 1,2; Zhu S, 1,2; Zhao W, 1,2; Zerbes T, 1,2; Eid S, 1,2; Watts JC, 1,3; Schmitt-Ulms G, 1,2

1 Tanz Centre for Research in Neurodegenerative Disease, University of Toronto, Toronto, Ontario, Canada; 2 Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Ontario, Canada; 3 Department of Biochemistry, University of Toronto, Toronto, Ontario, Canada

Introduction: Prion diseases are fatal neurodegenerative diseases that lack an effective treatment. In each case, disease begins with infectious prions (PrPSc) that act as templates and induce the normal cellular prion protein (PrPC) in the brain to convert to PrPSc through a conformational change. As this templated conversion spreads through the brain, the accumulation of toxic PrPSc results in neuronal loss, gliosis, and spongiform encephalopathy. All available data suggests that reducing PrPC levels would be a safe, effective approach to slowing prion disease progression and extending survival. Accordingly, mice lacking the prion gene (Prnp) cannot contract prion disease, and Prnp heterozygosity has been shown to double disease survival time. The function of PrPC remains debated, but Prnp ablation in both mice and cattle does not lead to severe phenotypic changes. Moreover, humans with only one functioning prion allele can live to old age in good health. **Objectives**: We hypothesize that recent advances in the virus-mediated delivery of gene editing tools can be harnessed to generate an effective gene therapy for prion diseases. **Methods:** By quieting the expression of the prion gene, we will extend survival and improve symptoms of patients with prion disease. Aim 1: Assemble an all-in-one rAAV vector that can generate a functional knockout of the prion gene using CRISPR-Cas9 technology. Aim 2: Construct a second all-in-one rAAV reporter vector for monitoring prion gene-editing efficacy. Aim 3: Generate a robust rAAV assembly pipeline and transduce wild type, healthy mice to establish if gene editing remains effective in vivo. **Results**: A therapeutic all-in-one rAAV plasmid that codes for a Prnp-specific guide RNA and a high-fidelity, small Cas endonuclease was constructed using Gibson assembly and site-directed mutagenesis. In parallel, a fluorescent 'traffic light' reporter plasmid that encodes red and green fluorescent proteins separated by the segment of the Prnp gene targeted by our therapy was assembled. In vitro transfection studies proved that our therapeutic construct could achieve a reduction of PrPC, then both plasmids were packaged separately into AAV9 capsids. These rAAVs were intrathalamically injected into healthy, wild-type mice, and allowed to incubate for three weeks before tissues were analyzed for PrPC levels or gene-editing events visualized with the help of our fluorescent reporter. Results from these preliminary studies indicate that this therapy can induce a knockout in the Prnp gene, which could improve symptoms and extend survival for those with prion disease. **Conclusions**: The key components of an rAAV-delivered gene therapy that generates a

functional knockout of the prion gene are in place, with future trials in additional models aiding the enhancement of the efficacy and safety of this approach. If successful, this therapy will provide a treatment for a class of fatal and devastating neurodegenerative diseases that typically lead to death within 1-2 years.

NEUROIMAGING

54. Gloria Tian; Faculty of Music – Music and Health Research Collaboratory / Keenan Research Centre for Biomedical Science, Li Ka Shing Knowledge Institute

Supervisor(s): Dr. Michael Thaut and Dr. Tom A. Schweizer

MUSIC-EVOKED VERSUS PHOTO-EVOKED AUTOBIOGRAPHICAL MEMORIES: AN FMRI STUDY IN OLDER ADULTS WITH NEURODEGENERATION AND COGNITIVE IMPAIRMENT

Tian GLJ, 1,2,3; Graham S, 7,8; Churchill N, 3; Fornazzari L, 5; Fischer C, 3,5,6; Schweizer TA, 3,4; Thaut MH, 1,2

1 Music and Health Science Research Collaboratory (MaHRC), Faculty of Music, University of Toronto; 2 The Academy of Neurologic Music Therapy; 3 Keenan Research Centre for Biomedical Science, Li Ka Shing Knowledge Institute; 4 Department of Surgery, Division of Neurosurgery, University of Toronto;5 Geriatric Psychiatry, St. Michael's Hospital, Toronto; 6 Department of Geriatric Psychiatry, Institute of Medical Science, University of Toronto; 7 Sunnybrook Research Institute, Sunnybrook Hospital, Toronto; 8 Department Medical Biophysics, Institute of Medical Science, University of Toronto

Introduction: Previous findings have demonstrated that preserved neural networks and structures in Alzheimer's disease pathology overlap with musical memory, emotions, and autobiographical memory associations. Music has the capacity to elicit positive memories and increased recollection of autobiographical memories. Music also holds the powerful potential to enhance overall cognitive performance. **Objective:** The aim of the current study is to examine the potential benefits of daily exposure to long-known, autobiographical music compared to photographs in older adults with cognitive impairment. Furthermore, the study intends to develop a deeper understanding of how functional network activity, and changes associated with the intervention, may differ in the brain during autobiographically-salient auditory (music) versus visual (photograph) tasks. **Methods:** Participants aged 65 years and older will be recruited from St Michael's Hospital Memory Clinic. Individuals will be randomised into music (n = 10) versus photograph (n = 10) conditions. Data acquisition includes MRI scans at baseline and pre- and post-intervention period (4 weeks), and cognitive testing. **Results:** Results from the study are expected to provide empirical support for music as a short and meaningful treatment. **Conclusion:** Changes associated with daily exposure to music could potentially alter functional neural networks – providing objective evidence for implementation of music-related therapies in neurodegenerative diseases.

NEUROLOGICAL DISEASES

55. Natasha Benn; Rehabilitation Sciences Institute

Supervisor: Dr. Kristin Musselman

A SYSTEMATIC REVIEW OF PHYSICAL INTERVENTIONS FOR THE REHABILITATION OF UPRIGHT BALANCE CONTROL AND BALANCE CONFIDENCE IN PEOPLE WITH CHRONIC, MOTOR INCOMPLETE SPINAL CORD INJURY/DISEASE

Benn NL, 1,2; Jervis Rademeyer H, 3; De Souza W, 2; Pakosh M, 2; Musselman KE, 2,4

1 Rehabilitation Sciences Institute, University of Toronto, Toronto, ON, CAN; 2 KITE, Toronto Rehabilitation Institute, University Health Network, Toronto, ON, CAN; 3 Faculty of Medicine, University of Alberta, Edmonton, AB, CAN; 4 Physical Therapy Dept, University of Toronto, Toronto, ON, CAN.

Introduction: To assist with clinical decision-making, evidence syntheses are needed to demonstrate the efficacy of available interventions and guide who and how the intervention can be applied. **Objective**: This systematic review and meta analysis describes the efficacy and dosage of interventions targeting upright balance control and/or balance confidence in adults with motor incomplete spinal cord injuries/diseases (SCI/D). **Methods:** A search strategy following the PICO framework was developed. Six databases were searched: APA PsychInfo, CINAHL, Embase, Emcare Nursing, Web of Science CC, and Medline. Title, abstract and full-text screening were conducted by two researchers independently. Inclusion criteria were: 1) adults with chronic, motor-incomplete SCI/D; 2) physical intervention targeting standing and/or walking; and 3) clinical and/or biomechanical measures of upright balance control and/or balance confidence. Participant characteristics, balance intervention details, adverse events and study results were extracted. The Downs and Black Checklist assessed methodological quality. Meta-analyses on pre-post intervention outcomes and a meta-regression of dosage were completed. **Results:** The search returned 1,664 unique studies; 26 were included. Methodological quality was moderate to good. Participants were 500 individuals with SCI/D, aged 18-74 years (males: females = 2.4:1). Minor adverse events were reported in eight studies (e.g. muscle soreness, fatigue). Clinically significant improvements in Berg Balance Scale were seen with Body-Weight Supported Treadmill Training, Standing/Walking Virtual Reality, Visual Feedback Balance Training (with or without FES), and Underwater Treadmill Training. Walking interventions had a significant pooled effect size on improving standing balance control and balance confidence. There were no significant findings on dosage response. **Conclusions:** Several interventions resulted in clinically significant improvements in standing balance control. However, walking-specific therapies, in particular, show promise in improving upright balance control post-SCI/D.

56. Avery Cameron; Institute of Medical Science

Supervisor: Dr. Aylin Reid

INVESTIGATING CELL TYPES RESPONSIBLE FOR INCREASED SEIZURE GENERATION IN A MODEL OF NEUROFIBROMATOSIS TYPE 1

Cameron AR, 1,2; Yang MD, 2; Sadek M, 2; Reid AY, 1,2,3

1 Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada; 2 Krembil Research Institute, University Health Network, Toronto, Ontario, Canada; 3 Division of Neurology, University Health Network/University of Toronto, Toronto, Ontario, Canada

Introduction: Neurofibromatosis type 1 (NF1) is a genetic neurocutaneous disorder with increased prevalence of seizures and epilepsy compared to the general population. Our lab previously showed increased seizure susceptibility and epileptogenesis in a mouse model of NF1 (Nf1+/- mice). As these mice do not have

intracranial lesions, the increased seizure susceptibility appears to be related to the genetic mutation itself, a possibility also supported by reports from patients. However, the mechanism behind this remains unknown. ~75% of NF1 patients with epilepsy necessitate multiple anti-seizure medications, potentially leading to severe side effects. Even with multiple medications, up to 40% of NF1 patients with epilepsy continue to have seizures and are medically refractory. Understanding the mechanism of seizures in NF1 is crucial for targeted therapy development for this population and could also benefit the treatments of other populations with epilepsy. NF1 is caused by a heterogeneous mutation of the Nf1 tumor suppressor gene, resulting in decreased levels of the protein neurofibromin which plays a crucial role in regulating cellular growth, division, and migration. Loss of neurofibromin disrupts these processes through overactivity of the Ras-ERK and PI3K-mTOR pathways. Seizures are traditionally considered to be a result of an increase in neuronal excitation verses inhibition, though some studies have shown increased inhibitory activity can initiate seizure activity. Nf1+/- mice and patients with NF1 have increased GABAergic activity due to altered ERK signaling, which may play a role in increased seizure susceptibility. In this study, I will investigate the roles of excitatory verses inhibitory neurons in seizures and epilepsy in NF1 and determine whether drugs targeting the ERK and mTOR pathways can reverse increased seizure susceptibility. **Objectives:** Determine: 1) which cell type is responsible for the increased seizure susceptibility observed in Nf1+/- mouse 2) if MEK or mTOR inhibition will decrease seizure susceptibility. **Methods:** I generated mice with cell-specific deletions of Nf1 by crossing Nf1flox/flox mice with mice expressing Cre recombinase under the control of the parvalbumin (PV; inhibitory neurons) or vesicular glutamate transporter (vGlut; excitatory neurons) promoter. Controls include wild-type (Nf1+/+) and Nf1+/- (Nf1 mutation present in all cell types) mice, crossed with PV-Cre or vGlut-Cre mice to control for the presence of Cre. Aim 1: Young adult male and female mice of the different genotypes are implanted with intracranial electrodes and undergo 4 days of continuous video-EEG monitoring to detect spontaneous epileptiform abnormalities and seizures. Following this monitoring, they receive an i.p. injection of 10 mg/kg kainic acid, and a further 180 minutes of video and EEG signals are recorded. This data is being analyzed for latency to first epileptiform spike, first electrographic seizure activity, behavioral seizure severity, and total seizure duration. Aim 2: Pharmacologic rescue experiments will be performed in WT and Nf1+/- mice, plus groups demonstrating increased seizure susceptibility in the previous aim. Implanted mice will receive a daily dose of 5mg/kg s.c. U012669 (MEK inhibitor) or 1 mg/kg i.p. everolimus (mTOR inhibitor) for two weeks. Video-EEG monitoring and kainic acid-induced seizure susceptibility testing will be completed as previously described to determine the effects of pharmacological treatment. **Results:** My preliminary results for Aim 1 show a decreased latency to first spike and first seizure and increased seizure duration in Nf1flox/vGlut mice versus Nf1flox/PV mice, suggesting that excitatory cells drive the altered seizure susceptibility we previously reported in Nf1+/- mice. **Conclusion:** Based on our preliminary results, altered seizure susceptibility in NF1 seems to be driven by vGlut+ excitatory neurons, as evidenced by the decrease in first spike and seizure latency and increase in total seizure duration. Experiments are currently ongoing to complete Aim 1 and confirm if the findings are statistically significant. Following the completion of Aim 1, I will be investigating if the altered seizure susceptibility is mediated by altered activity in the MEK or mTOR pathways.

57. Jerry Li; Institute of Medical Science

Supervisor: Dr. Mojgan Hodaie

HIPPOCAMPAL SIGNATURES OF ACCELERATED BRAIN AGING IN TRIGEMINAL NEURALGIA

Li J, 1,2; Latypov TH, 1,2; Srisaikaew P, 1; Hodaie M, 1-3

1 Division of Brain, Imaging & Behaviour, Krembil Brain Institute, University Health Network, Toronto, Ontario, Canada; 2 Institute of Medical Science, Temerty Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada; 3 Division of Neurosurgery, Temerty Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada

Introduction: Can pain modify aging? Trigeminal neuralgia (TN) is the most common form of chronic neuropathic facial pain. Despite up to 50% of patients requiring surgical intervention, there are almost no biomarkers or predictors for prognosis. To address this, the biological age of the brain, or brain age, has been computed using machine learning on whole-brain metrics. Patients with TN had significantly greater brain ages than healthy counterparts, and brain ages differed between patients who responded well to pain-relieving surgery versus those who did not. Hippocampal abnormalities in TN also appear to normalize following successful surgery. **Objective**: Brain age may be an objective and non-invasive biomarker for TN patients. Given the impact of chronic pain on the hippocampus and the hippocampus' intrinsic link with aging, we hypothesize that hippocampal subfields may be effective predictors of brain age. Since the hippocampus can recover following successful surgery, accelerated brain aging may also be mitigated. **Methods:** Multiple support vector regression (SVR) models were trained on 522 healthy subjects to predict their chronological age, or "brain age". MRI scans of whole brains were segmented into constituent and hippocampal subfield volumes, upon which separate SVRs were trained and optimized. Models then predicted the brain age of 123 TN patients. **Results:** An SVR built on hippocampal subfields performed nearly as well as one built on whole-brain segmentations. Another SVR built on a combination of these volumes outperformed all previous models (R^2 = 0.95; MAE = 3.3 years). This combined model predicted the ages of patients with TN (R^2 = 0.83; MAE = 4.8 years) and found their mean brain age, 62.1 ± 0.9 years, to be significantly greater than their actual mean age of 59.6 ± 1.3 years (q = 0.022). Surgical responders, females, and right-sided TN pain cohorts had significantly greater brain ages than chronological ages (q = 0.046, 0.047, 0.047) than their respective counterparts before surgery. **Conclusions:** Across several diseases, a biologically older brain robustly correlates with negative health trajectories. Accordingly, patients with TN, a debilitating manifestation of chronic neuropathic facial pain, appear to have biologically older brains, with differential profiles based on surgical response, sex, and pain laterality. Our methods promote quicker validation and translation of brain age into clinical tools for prognostication and optimization of therapeutic avenues to expedite treatment timelines.

58. Rafi Matin; Institute of Medical Science

Supervisor: Dr. George M. Ibrahim

EFFECTS OF DEEP BRAIN STIMULATION OF THE CENTROMEDIAN THALAMIC NUCLEUS ON GABA IN A MOUSE MODEL OF EPILEPSY

Matin RM, 1,2; Zhang KK, 1,2; Gorodetsky C, 1,3; Venetucci-Gouveia F, 1; Ibrahim GM, 1,2,4

1 Neuroscience and Mental Health, The Hospital for Sick Children, Toronto, Ontario, Canada; 2 Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada; 3 Division of Neurology, The Hospital for Sick Children, Toronto, Ontario, Canada; 4 Division of Neurosurgery, Hospital for Sick Children, Toronto, Ontario, Canada

Introduction: Despite the best available medical interventions, individuals with refractory epilepsy continue to experience debilitating seizures. Deep brain stimulation (DBS) offers a promising avenue, involving the surgical implantation of electrodes to modulate neural circuitry through electrical stimulation. While DBS targeting the centromedian nucleus of the thalamus (CM-DBS) has shown clinical promise for refractory epilepsy, its neurobiological mechanisms remain elusive, hindering personalized treatment development. Furthermore, while previous studies demonstrate DBS's ability to increase γ-Aminobutyric acid (GABA) levels, a critical inhibitory neurotransmitter in epilepsy, this has not been explored in the context of CM-DBS. **Objective:** In this study, we used mouse models to determine whether CM-DBS increases GABA levels within the CM-connected brain network. Additionally, considering clinicians adjust stimulation settings to optimize therapeutic efficacy, we assessed the effects of various CM-DBS settings on GABA levels. We hypothesized that CM-DBS with clinically effective settings would increase GABA levels within the CM-network. **Methods:** C57BL/6J mice (n=18, healthy control) and Cntnap2-KO mice (n=18, epilepsy model) were randomly assigned to 4 experimental groups: 1) CM-DBS high frequency (clinically effective stimulation), 2) CM-DBS low frequency (clinically ineffective stimulation), 3) Sham (receiving DBS electrode but no stimulation), 4) Naive (no surgery). Microdialysis was concurrently performed during CM-DBS to assess changes in GABA levels at the CM. Additionally, tissue samples from various brain regions within the CM network (i.e., thalamus, basal ganglia, hippocampus, amygdala) were collected following stimulation. GABA levels from the microdialysis and tissue extraction samples will be quantified with mass spectrometry. **Results:** Although the experiments are complete, analysis with mass spectrometry and final results are pending. Our data will enable us to evaluate the impact of stimulation on GABA and confirm whether clinically effective stimulation parameters correlate with increased GABA in the CM network. **Conclusions:** Our findings will provide insight into how CM-DBS achieves its therapeutic effects. Future studies can further explore additional mechanisms at the molecular, cellular, and network levels to obtain a comprehensive understanding of this technique. Ultimately, this line of research will enhance our understanding of how CM-DBS achieves seizure suppression and facilitate tailored treatment optimization for patients.

59. Elina Provad; Rehabilitation Sciences Institute

Supervisor: Dr. Kristin Musselman

BARRIERS AND FACILITATORS TO IMPLEMENTING FUNCTIONAL ELECTRICAL STIMULATION COMBINED WITH VISUAL FEEDBACK AS A BALANCE INTERVENTION IN NEUROREHABILITATION, FROM THE PERCEPTIVE OF END USERS

Provad E, 1,2; Patel T, 3; Benson K, 2; Chan K, 2; Lee JW, 2,4; EL, 1,2,3; Wolfe DL, 5; Masani K, 2,4; Musselman KE, 1,2,3

1 Rehabilitation Sciences Institute, University of Toronto, Toronto, Canada; 2 KITE Research Institute-Toronto Rehabilitation Institute, University Health Network, Toronto, Canada; 3 Department of Physical Therapy, University of Toronto, Toronto, Canada; 4 Institute of Biomedical Engineering, University of Toronto, Toronto, Canada; 5 Parkwood Institute, Lawson Health Research Institute, London, Canada

Introduction: There is an increased risk in individuals with neurological injury or disease to experience falls, calling attention to the need for effective balance interventions. A novel intervention that supports balance training is a combination of functional electrical stimulation and visual feedback balance training (FES+VFBT). This intervention has shown promise but is currently lab-based and needs re-designing to be more clinically useful. **Objective**: To uncover end users' perspectives on potential challenges and solutions to utilizing the FES+VFBT system as an intervention for balance training. **Methods**: Three semi-structured focus group sessions were conducted to discover participants' viewpoints on the challenges and solutions of using FES+VFBT as part of their neurorehabilitation programs. The focus groups were comprised of two participants with spinal cord injury, one with stroke, two physiotherapists and a hospital administrator. A deductive-inductive content analysis method was used to analyze the interview transcripts. The predefined levels of the Social Ecological Model (SEM) served as the basis for deductive analysis. Interview categories and codes were derived using an inductive method. **Results**: The themes covered each of the four levels of the SEM: intrapersonal, interpersonal, organizational/training environment and society/policy. Identified categories included potential challenges connected to the intrapersonal (e.g., lack of knowledge, tolerance of user) and organizational/training environment (e.g., cost, need for space and time, technical challenges) levels. Additionally, the identified categories also included possible solutions mapped to all four levels of the SEM: intrapersonal (e.g., reading and research), interpersonal (e.g., practicing together), organizational/training environment (e.g., tailoring system parameters, social support), and society/policy (e.g., create guidelines, provide cost options). **Conclusion**: The findings will be employed to improve the design of the FES+VFBT system and to support its implementation into neurorehabilitation practices.

NEUROLOGICAL REHABILITATION

60. Nicole Cesca; Rehabilitation Sciences Institute

Supervisor: Dr. Kristin Musselman

PHYSICAL INTERVENTIONS USED TO IMPROVE GAIT ADAPTABILITY FOR INDIVIDUALS WITH NON-PROGRESSIVE NEUROLOGICAL IMPAIRMENTS: A SCOPING REVIEW

Cesca N, 1,2; Heffernan MG, 1,2; Winokur S, 3; Chan K, 2; Pakosh M, 4; Musselman KE, 1,2,5

1 Rehabilitation Sciences Institute, Temerty Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada; 2 KITE- Toronto Rehabilitation Institute, University Health Network, Toronto, Ontario, Canada; 3 Faculty of Kinesiology and Physical Education, University of Toronto, Toronto, Ontario, Canada; 4 Library & Information Services, Toronto Rehabilitation Institute, University Health Network, Toronto, Ontario, Canada; 5 Department of Physical Therapy, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada

Introduction: Gait adaptability (i.e., ability to modify walking patterns to the environment/task), is essential for safe community ambulation. Yet, there is limited literature that systematically summarizes interventions aimed at improving gait adaptability for individuals with non-progressive neurological impairments. **Objective:** To synthesize quantitative studies that assessed the effects of gait adaptability interventions on individuals with non-progressive neurological impairments. **Methods:** A comprehensive search was conducted in six databases: CINAHL Complete, Embase, Emcare Nursing, Medline ALL, PEDro, and Web of Science Core Collection. Studies were included if: a) participants were

adults with a non-progressive neurological injury/disease, b) walking was involved in the training intervention, c) the environment/task changed during the intervention, d) gait/walking adaptability was a target of the intervention, and e) participants completed more than two training sessions. Data regarding study and participant characteristics, details of gait interventions, and outcomes were extracted. **Results:** From the 25 included studies, 553 adults (456 stroke, 97 motor incomplete spinal cord injury), completed various gait adaptability interventions: overground walking with real-world obstacles (n=6), treadmill training with virtual/augmented reality (n=7), combined treadmill and overground walking with added tasks (n=6) and treadmill training with extra tasks (n=3). Sixteen studies employed randomized control trials. Common outcome measures: 10-meter walk test, 6-minute walk test, and Berg Balance Scale. Results showed improvements in walking speed, endurance, and balance control, with varying efficacy compared to control groups. **Conclusion:** Gait adaptability interventions improved walking-related outcomes in individuals with non-progressive neurological injuries however, conclusive evidence regarding their superiority over alternative training methods remains lacking.

NEUROPHARMACOLOGY

61. Tian Kong; Department of Physiology

Supervisor: Dr. Lu-Yang Wang

INNOVATING POSITIVE ALLOSTERIC MODULATORS OF POTASSIUM CHANNELS TO TREAT EPILEPSY

Kong T, 1; Arsenault J, 2; Weng OW, 1; Wang LY, 1,2

1 Department of Physiology, Faculty of Medicine, University of Toronto, Toronto, Canada; 2 Program in Neurosciences & Mental Health, Sick Kids Research Institute, Toronto, ON, M5G 1X8, Canada

Introduction: Epilepsy is one of the most common neurological diseases that affects around 50 million people worldwide and 1 in 200 children in Canada. The core substrate underlying the pathogenesis of epilepsy can be ascribed to an excitation and inhibition (E/I) imbalance at synaptic, circuit or system levels. Among numerous genetic mutations associated with epilepsy, ion channelopathy represents one of the leading causes for E/I imbalance by disrupting ion homeostasis and neuronal excitability. Loss-of-function (LOF) mutations of the KCNA2 gene, encoding potassium channel Kv1.2, causes neurological diseases including severe epileptic encephalopathy, episodic ataxia type 1 (EA1), seizures and autism spectrum disorder. Nonetheless, no drugs are available to treat its LOF mutations. We discovered a new class of positive allosteric modulators (PAMs), e.g. Compounds C1, C2 and C3, that potentiate Kv1.2 activity at nanomolar range. **Objective:** In the stable Kv1.2-GFP Chinese Hamster Ovary (CHO) cell-line, we investigated the effect of C1, C2 and C3 on Kv1.2 activity, expression, and localization. **Methods:** Electrophysiological recordings and in silico docking revealed that C2 has the highest potency among the analogs. Chronically, C2 and C3 promotes Kv1.2 trafficking to cytoplasmic membranes from the intracellular pool. **Results:** Through in silico simulation and site-directed mutagenesis, we defined a novel binding cavity on the Kv1.2 channel for C2 and its structural analogs. To explore the utility of C2 in epilepsy, we examined its effect on phosphatase and tensin homolog (PTEN) knockout (KO) human iPSCs derived neurons because PTEN mutations have been linked to drug-resistant epilepsy. With multi-electrode array (MEA) recordings, we found Compound C2 (100 nM) showed robust therapeutic efficacy in supressing the hyperexcitability and burst activities in this epileptic model. **Conclusion:** This project rationalizes Kv1.2 PAMs as a viable approach to rectify the E/I imbalance in epilepsy and it will bring a new class of AEDs to treat epilepsy and potentially other neurodevelopmental disorders as a result of Kv1.2 channelopathy.

62. Isaak Kuk; Department of Pharmacology and Toxicology

Supervisor(s): Dr. Bernard Le Foll and Dr. Christine Wickens

THE INFLUENCE OF AGE ON DRIVING-RELATED CANNABIS EFFECTS: EXPLORING CANNABIS USE FREQUENCY AND RELATED FACTORS

Zaweel A, 1,2; Kuk I, 1,2; Brands B, 1,3; DiCiano P, 1,2,3; Kaduri P, 4,5; Stoduto G, 3; Le Foll B, 1,2,3,4,5; Wickens C, 1,2,3,6

1 Department of Pharmacology and Toxicology, University of Toronto, Toronto, Ontario, Canada; 2 Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto, Ontario, Canada; 3 Institute of Mental Health Policy Research, Centre for Addiction and Mental Health, Toronto, Ontario, Canada; 4 Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada; 5 Addictions Division, Centre for Addiction and Mental Health, Toronto, Ontario, Canada; 6 Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada

Introduction: Since the national legalization of recreational cannabis use in Canada, incidences of driving under the influence of cannabis (DUIC) have also risen. In surveys, individuals who report DUIC are twice as likely to be involved in a collision in the past year than those who do not. Risks associated with DUIC are believed to vary across age groups due to differences in cognitive development and driving experience, as well as physiological and behavioural responses to cannabis. Therefore, it is in the interest of road safety to better understand the behavioural differences associated with DUIC as it relates to various demographic groups, including age. **Objective:** Using a driving simulator system, our project aims to assess the impact of smoked cannabis on driver performance as a function of age. **Methods:** Occasional and regular cannabis users, aged 19-25 or 35-45 years, will be recruited from the community to participate in our mixed-design, double-blind, placebo-controlled randomized trial. Eligible participants will be asked to come into the Centre for Addiction and Mental Health (CAMH) for two exposure sessions (placebo and active cannabis). Participants will drive the simulator and undergo cognitive testing before smoking and at two time points after smoking. Vital signs and blood samples will also be collected before and at various time points after cannabis exposure. **Results and Conclusion:** Our goal is to understand potential differences in how cannabis affects driver behaviour and performance in young (19-25) and middle-aged (35-45) drivers. A secondary aim is to explore the effects in frequent (≥6 days/week) vs occasional (≤1 day/week) cannabis users.

63. Emma Russo; Department of Pharmacology and Toxicology

Supervisor: Dr. Ali Salahpour

CHARACTERIZATION OF A NOVEL MOUSE MODEL OF DOPAMINE TRANSPORTER DEFICIENCY SYNDROME

Russo E; Rezayof A; Beerepoot P; Milenkovic M; Chow DW; Ramsey AJ; Salahpour A

Department of Pharmacology and Toxicology, University of Toronto, Toronto, ON, Canada School of Biology, University of Tehran, Tehran, Iran National Institute of Health, Maryland, USA

Introduction: Neurotransmission of dopamine is crucial for various behaviors including motivation, learning, and locomotion. The dopamine transporter (DAT) plays a pivotal role in regulating dopamine signaling by transporting extracellular dopamine back into the presynaptic neuron. Dysfunctions in the DAT protein can lead to Dopamine Transporter Deficiency Syndrome (DTDS), characterized by impaired trafficking, reduced expression, and function of DAT. **Objective:** Here, we present the characterization of a novel mouse model of DTDS (A313V-knock-in), mimicking the human DTDS-causing variant A314V. **Results:** Our study demonstrates that A313V mice express only 20% of mature DAT protein compared to wild-type mice. Notably, we observe the retention of immature DAT in the endoplasmic reticulum in the A313V mice, a phenomenon not previously reported in a mammalian brain in vivo for a DTDS-causing variant. Additionally, A313V mice exhibit basal hyperactivity, which can be attenuated with aMPT, an inhibitor of the dopamine synthesis enzyme tyrosine hydroxylase. **Conclusion:** These findings closely resemble clinical and molecular features of DTDS in humans, laying groundwork for potential pharmacological interventions for this disorder.

64. Jianmeng Song; Institute of Medical Science

Supervisor: Dr. Philip Gerretsen

THE ASSOCIATION BETWEEN TDCS RELATED CHANGES IN REGIONAL CEREBRAL BLOOD FLOW AND IMPROVED ILLNESS AWARENESS IN SCHIZOPHRENIA

Song J, 1,2; Kim J, 1,2; Ueno F, 1,2; Carmona-Torres E, 1,2; Kambari Y, 1,2; Amaev A, 1,2; Abdoli zadeh A, 1,2; Koizum T, 1,2; De Luca V, 2,3,4; Blumberger D, 2,3; Remington G, 2,3,4; Pollock B, 2,3,4; Graff-Guerrero A, 1,2,3,4; Gerretsen P 1,2,3,4

1 Multimodal Imaging Reserach Group, Brain Health Imaging Centre, Centre for Addiction and Mental Health, Toronto, Ontario, Canada; 2 Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada; 3 Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada; 4 Schizophrenia Division, Centre for Addiction and Mental Health, Toronto, Ontario, Canada

Introduction: Impaired illness awareness (IIA) occurs in up to 98% of patients with schizophrenia and leads to negative clinical outcomes. Previous functional MRI studies suggest that IIA may be related to interhemispheric imbalance in the posterior parietal area (PPA). Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation that applies a weak current passed between anodal and cathodal electrodes placed on the scalp. Recent studies support the potential value of tDCS to improve IIA in schizophrenia. Arterial spin labeling (ASL) is a brain imaging technique that provides an absolute measure of regional cerebral blood flow (CBF). We investigated the effect of tDCS on regional CBF and changes in IIA. **Objective:** The study aimed to assess whether tDCS can increase IIA in participants with schizophrenia and change regional CBF at region-of-interest. **Methods:** A total of 19 participants with schizophrenia with moderate-to-severe IIA were randomized to receive either bilateral PPA active (n=11) or sham (n=8) 2mA tDCS for 20 sessions. IIA was measured using the VAGUS, Self-report (VAGUS-SR). Regional CBF underneath the electrodes was measured using pseudo-continuous ASL (pCASL) pre- and post-tDCS and extracted using REX toolbox. **Results:** The mean age was 43.4 (SD=13.6) and 21% were female. The baseline mean VAGUS-SR score was 4.7/10 (SD=2.2). Regional increases in CBF with 20 sessions of bilateral tDCS of the PPA in the active treatment group were associated with improved IIA when controlling for baseline illness severity ($p<0.05$). **Conclusion:** The results indicate that increases in regional CBF beneath the anode with bilateral PPA tDCS may represent a neuroimaging biomarker of treatment associated improvements in IIA.

65. Lola Zovko; Department of Pharmacology and Toxicology

Supervisor: Dr. Ali Salahpour

THE EFFECTS OF ENDOCANNABINOID MODULATION ON AN ACUTE MOUSE MODEL OF PARKINSON'S DISEASE

Zovko LE, 1; Mielnik CA, 1; Ruth RA, 1; Salahpour A, 1

1 Department of Pharmacology and Toxicology, University of Toronto, Toronto, Ontario, Canada

Introduction: Parkinson's Disease (PD) is a neurological disorder marked by Lewy body formation and loss of dopamine neurons projecting to the striatum, resulting in symptoms like resting tremor, bradykinesia, and postural instability. L-DOPA, the precursor to dopamine, is the gold standard treatment for PD, but long-term use or high chronic doses may result in a debilitating condition named L-DOPA Induced Dyskinesia (LID), characterized by involuntary movements. The endocannabinoid system (ECS) modulates dopamine in the striatum by releasing endocannabinoids like 2-arachidonoyl-glycerol (2-AG) and activating pre-synaptic CB1 receptors, altering neurotransmitter release. Dysfunction of the ECS in PD is increasingly recognized, with alterations in CB1 receptor expression and endocannabinoid levels observed in patients. **Objective:** This study aims to identify therapies targeting the ECS to prolong L-DOPA efficacy without inducing dyskinesias, given its role in modulating dopamine transmission in the striatum. **Methods:** We employed an acute Parkinson's mouse model by inhibiting tyrosine hydroxylase with alpha-methyl-p-tyrosine (aMPT) in dopamine transporter knockout (DAT-KO) mice, resulting in full dopamine depletion and extreme PD-like symptoms. L-DOPA administration bypasses TH inhibition and restores locomotor activity. This model is known as the Dopamine Deficient Dopamine Transporter Knockout (DDD) model. Adult DAT-KO mice were administered with aMPT (250 or 125 mg/kg i.p.), endocannabinoid modulators (see below, i.p.), and L-DOPA (25 or 12.5 mg/kg s.c.). Locomotor activity was assessed acutely, or chronically where injections were repeated for 14 days with locomotor testing done every other day. MAGL (monoacylglycerol lipase, 2-AG metabolizing enzyme) inhibitors MJN110 (5 mg/kg i.p.) and ABX-1431 (5 mg/kg i.p.) have been tested acutely, with ABX-1431 tested chronically as well. DAGL (diacylglycerol lipase, 2-AG synthesizing enzyme) inhibitor DO34 (30 mg/kg i.p.) and CB1 receptor inverse agonist rimonabant (3 mg/kg i.p.) were also tested in the acute paradigm. Data were analyzed with 3-way R-ANOVA (drug, sex, time) with post-hoc Sidak's test. **Results:** Acutely, MAGL inhibitors potentiated L-DOPA induced locomotor effects. A combination of MAGL (5 mg/kg) and L-DOPA (12.5 mg/kg) results in comparable locomotor effects to a higher L-DOPA dose alone (25 mg/kg). This enhanced response with MAGL inhibitors was blocked by the CB1 receptor inverse agonist rimonabant. DO34 treatment alone reduced L-DOPA locomotor response. Our results show that increases in 2-AG enhance L-DOPA responses, while reductions in 2-AG reduce L-DOPA responses. Chronic administration of L-DOPA in mice resulted in reduced horizontal locomotor activity and increased vertical activity. Vertical activity is a proxy measure of dyskinesia, and drugs that

reduce dyskinesia in humans are shown to reduce vertical activity in chronically L-DOPA treated mice. Mice treated with a combined dose of ABX-1431 (5 mg/kg) and L-DOPA (12.5 mg/kg) had a delayed onset of vertical activity compared to mice treated with L-DOPA alone, implying delayed onset of LID. **Conclusions:** Acute enhancements of L-DOPA locomotor effects via increased 2-AG with MAGL inhibitors is likely mediated via CB1. Conversely, reducing 2-AG levels with DAGL inhibition reduces the L-DOPA induced locomotor effects. This highlights the potential for MAGL inhibition as a concomitant therapeutic used in conjunction with L-DOPA to delay, or prevent, LID.

NEUROPHYSIOLOGY

66. Bojing Gui; Institute of Biomedical Engineering

Supervisor: Dr. Kei Masani

SPINAL AND CORTICOSPINAL PATHWAY MODULATION DUE TO BALANCE AND POSTURE

Gui B, 1,2; Fok KL, 1,2; Kaneko N, 3; Masani K, 1,2

1 Institute of Biomedical Engineering, University of Toronto, Toronto, ON, Canada; 2 KITE Research Institute, University Health Network, Toronto, ON, Canada; 3 Department of Life Sciences, Graduate School of Arts and Sciences, The University of Tokyo, Tokyo, Japan

Introduction: Postural control involves integration of sensory inputs and motor commands within the spinal cord and brain. While studies have investigated the role of descending corticospinal commands and spinal reflexes in maintaining balance using methods such as motor evoked potentials (MEPs) using transcranial magnetic stimulation (TMS) and H-reflexes using peripheral nerve stimulation, the exact pathways involved remain unclear. **Objectives:** We aim to contribute to this understanding by exploring the effects of posture on spinal motoneurons by utilizing F-waves as a direct measure of their excitability. Furthermore, we wish to further investigate corticospinal and spinal pathways by isolating the effects of body position and both voluntary and postural muscle activity to understand the specific factors influencing postural control. **Methods:** Data collection from healthy participants is ongoing. Participants performed four tasks: natural standing, supported standing with voluntary muscle contraction, supported standing, and sitting. Electromyographic signals from the soleus, medial head of gastrocnemius, and tibialis anterior muscles was recorded. Visual feedback was used to ensure consistent muscle activity during voluntary contraction to match natural standing. Soleus F-waves, H-reflexes, and MEPs were measured. Values including F-wave persistence, F/M-max ratio, H-max/M-max ratio, and MEP amplitude mean and variability were extracted from these measurements. **Results:** Preliminary results from two participants indicate that while the H-reflex is inhibited during standing, consistent with previous results indicating the effect on body position on the spinal reflex pathways, the F-wave is posture invariant, indicating spinal motoneuronal excitability is not affected by body position and postural control. MEPs were found to be consistent during different resting positions, while being facilitated by both voluntary and postural activity. This indicates similar cortical contribution to both voluntary and postural activity. **Conclusion:** Increased knowledge of the control of standing balance will aid in developing effective rehabilitation therapy for individuals with balance disorder.

67. Alicia N. Harracksingh; Department of Physiology

Supervisor: Dr. Zhong-Ping Feng

PROFILING THE VISUAL SYSTEM OF LYMNAEA STAGNALIS AS A NOVEL MODEL FOR INVESTIGATING PHOTORECEPTIVE BEHAVIORS AND RETINAL PROCESSING IN INVERTEBRATES

Harrackingh AN, 1; Bandura J, 1; Morizumi T, 2; Monnier PP, 1,3; Henderson JT, 4; Feng ZP, 1

1 Department of Physiology, Temerty Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada;

2 Department of Biochemistry, Temerty Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada;

3 Department of Ophthalmology and Vision Sciences, Temerty Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada; 4 Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada

Introduction: To navigate the external world, animals perceive and react to light using complex visual system machinery. To date, diverse animal models have been employed to explore visual system function and potential mechanisms in both physiological and pathophysiological states. While invertebrate models have been instrumental in elucidating visual properties, few have been established to investigate photoreceptive behaviors and retinal processing. As well, our current understanding of the cellular and molecular mechanisms that underlie photoreception across the animal kingdom is limited, highlighting the need to establish new animal models for studying the fundamentals of vision. **Objectives:** In this study, we capitalized on valuable features of L. stagnalis, along with recent transcriptomic work, to establish a platform for assessing visual system function through anatomical and histological evaluations of the L. stagnalis eye, functional analysis of phototaxis behaviors, and phylogenetic assessments of core molecules involved in phototransduction. **Methods and Results:** First, to understand the laminar retinal organization in the L. stagnalis eye and determine whether rhodopsin-positive cells where present and distributed throughout discrete retinal layers, we employed TEM and histological screens to uncover for the first time the presence of rhodopsin-positive sensory photoreceptor cells that may be associated with light sensitivity. Next, to characterize the functional outputs of photosensation, we created a novel neurobehavioral test to assess snail phototaxis in vivo using DeepLabCut software. By extrapolating locomotory features such as trajectory length, speed, acceleration, and tortuosity, neurobehavioral assessments revealed that most animals in a cohort exhibit positive phototaxis behaviors. Lastly, to elucidate the molecular basis of phototransduction in L. stagnalis, we conducted transcriptomic mining of the L. stagnalis CNS transcriptome, identifying three novel putative rhodopsin-like genes. Using phylogenetic assessments and AlphaFold2 structural predictions, we revealed the evolutionary conservation and structural similarity of L. stagnalis rhodopsin-like proteins to higher-order animal rhodopsins. Our transcriptome mining further uncovered a rich repertoire of genes for both vertebrate Gt-coupled and invertebrate Gq-coupled phototransduction signaling pathways in the CNS. This allowed us to predict the signaling pathways underlying photosensation in L. stagnalis. **Conclusion:** Taken together, this study offers valuable insights into the conservation of photoreception processes and distinctive visual mechanisms in L. stagnalis, setting the stage for additional exploration of this model organism in vision research. The importance of this study lies in establishing L. stagnalis as a crucial model for understanding vision sciences, laying the groundwork for

future investigations into the molecular and evolutionary facets of photosensitivity and phototaxis behaviors.

68. Dallas Leavitt; Institute of Biomedical Engineering

Supervisor: Dr. Luka Milosevic

AUDITORY ODDBALL RESPONSES IN THE HUMAN SUBTHALAMIC NUCLEUS AND SUBSTANTIA NIGRA PARS RETICULATA

Leavitt D, 1,2,3; Alanazi FI, 3,4; Al-Ozzi TM, 3,4; Cohn M, 3; Hodaie M, 3,5,6; Kalia SK, 3,5,6; Lozano AM, 3,5,6; Milosevic L, 1,2,3,7,8; Hutchison WD, 3,4,5,6

1 Institute of Biomedical Engineering, University of Toronto, Ontario, Canada; 2 University of Toronto – Max Planck Centre for Neural Science, University of Toronto, Ontario, Canada; 3 Krembil Brain Institute, University Health Network, Toronto, Ontario, Canada; 4 Department of Physiology, University of Toronto, Ontario, Canada; 5 Department of Surgery, University of Toronto, Ontario, Canada; 6 Division of Neurosurgery, Toronto Western Hospital – University Health Network, Toronto, Ontario, Canada; 7 Center for Advancing Neurotechnological Innovation to Application (CRANIA), Toronto, Ontario, Canada; 8 Knowledge, Innovation, Talent, Everywhere (KITE) Research Institute, University Health Network, Toronto, Ontario, Canada

Introduction: The auditory oddball is a mainstay in research on attention, novelty, and sensory prediction. How this task engages subcortical structures like the subthalamic nucleus and substantia nigra pars reticulata is unclear. **Objective:** To identify neural correlates of attended, infrequent tones in the subthalamic nucleus and substantia nigra pars reticulata. **Methods:** We administered an auditory OB task while recording single unit activity (35 units) and local field potentials (57 recordings) from the subthalamic nucleus and substantia nigra pars reticulata of 30 patients with Parkinson's disease undergoing deep brain stimulation surgery. **Results:** We found tone modulated and oddball modulated units in both regions. Population activity differentiated oddball from standard trials from 200 ms to 1000 ms after the tone in both regions. In the substantia nigra, beta band activity in the local field potential was decreased following oddball tones. **Conclusion:** The oddball related activity we observe may underlie attention, sensory prediction, or surprise-induced motor suppression.

69. Suha Sagheer; Faculty of Dentistry

Supervisor: Dr. Iacopo Cioffi

A NOVEL BRAIN CIRCUIT REGULATING THE JAW MOTOR RESPONSE TO STRESS

Sagheer S, 1,2; Mouseli P, 1,2; Moayedi M, 1,2; Cioffi I, 1,2

1 Centre for Multimodal Sensorimotor and Pain Research, Faculty of Dentistry, University of Toronto, Toronto, Ontario, Canada; 2 University of Toronto Centre for the Study of Pain, University of Toronto, Toronto, Ontario, Canada

Introduction: Muscular temporomandibular disorders (mTMD) are the second most common cause of musculoskeletal pain and chronic facial pain. Oral behaviors, such as wake-time tooth clenching and grinding, are the strongest predictor of these disorders. Oral behaviors are also a coping behavior for stress. The amygdala is implicated in modulating limbic activity, including stress-related behaviors. A recent rodent study identified a brain circuit linking the central nucleus of the amygdala (CeA) to the trigeminal motor nucleus (5M), which controls the muscles of mastication. Our lab has resolved the CeA-5M circuit in humans in vivo for the first-time using MRI; however, the circuit's functional role in humans has yet to be explored. **Objective:** To determine whether the CeA-5M circuit regulates the activation of the muscles of mastication in response to stress in humans. Here, we tested whether experimentally induced stress activates this circuit in healthy adults. **Methods:** 50 healthy adults (27 F, 23 M) completed questionnaires (State-Trait Anxiety Inventory, Pain Catastrophizing Scale, Somatosensory Amplification Scale, and Oral Behaviors Checklist) and performed a validated experimental stress-inducing task. This stress-inducing task involves presenting neutral and aversive images from the International Affective Picture System in separate runs to participants in a laboratory setting, and again while undergoing functional MRI (fMRI). During this stress-inducing task, participants provided self-reported stress ratings on numeric rating scales (0: no stress; 10: most stress they have ever felt) during stressful and neutral runs. Surface electromyography (EMG) was used to assess masseter muscle activity in response to stress in the laboratory. Results:The stress ratings were (mean±SD) 3.9±2.6 for stressful runs, and 0.7±1.2 for the neutral runs. A power spectral density (PSD) analysis of masseter activity showed that the stressful runs were associated with a greater PSD than the neutral runs for frequencies between 100-300Hz ($p<0.05$). A general linear model of fMRI data showed co-activation of the right CeA and 5M during the stressful runs as compared to neutral runs (cluster-corrected $p<0.05$). **Conclusions:** Experimentally induced stress activates the muscles of mastication, and both the CeA and 5M, indicating that CeA-5M is likely related to stress-coping oral behaviours. This is the first study to functionally characterize a novel brainstem circuit related to stress-related oral behaviours, and thus may lay the groundwork for understanding the neural underpinnings of mTMD pathophysiology.

70. Shirin Tajali; University Health Network

Supervisor: Dr. Kei Masani

INVESTIGATION OF LOWER LIMB SPINAL MOTOR EVOKED POTENTIALS ACROSS POSTURES USING TRANSCUTANEOUS SPINAL CORD STIMULATION

Tajali S, 1; Fok KL, 1,2; Kaneko N, 1,2,3,4; Sayenko DG, 5; Masani K, 1,2

1 KITE Research Institute – University Health Network, Toronto, ON; 2 Institute of Biomedical Engineering, University of Toronto, Toronto, ON; 3 Japan Society for the Promotion of Science, Tokyo; 4 Department of Life Sciences, Graduate School of Arts and Sciences, The University of Tokyo, Tokyo; 5 Department of Neurosurgery, Center for Neuroregeneration, Houston Methodist Research Institute, Houston, Texas

Introduction: Transcutaneous spinal cord stimulation (TSCS) is a valuable tool for the neurophysiological assessment of spinal circuitries and modulation of spinal network excitability. To date, several reports have described the characteristics of the spinal motor evoked potentials (SMEPs) across various spinal levels and electrode configurations. However, the effects of posture on SMEPs are not very well understood. **Objective:** The purpose of this study was to investigate the characteristics and modulation of SMEPs by applying lumbar TSCS across commonly used postural conditions. **Methods:** Eight neurologically intact individuals participated in this study and double-pulse stimulations with 1-ms pulse durations and with 50-ms intervals were applied at the level of L1-L2 in the following postural conditions: (1) standing, (2) supported standing (SS), (3) sitting, and (4) supine lying.

In the SS condition, the participant stood on a standing frame by which the leg muscles were relaxed while keeping the same standing posture. Surface electromyogram signals were recorded from the soleus (SOL), medial head of gastrocnemius (MG), tibialis anterior (TA), rectus femoris (RF), vastus lateralis (VL), and biceps femoris (BF) muscles in the dominant leg. The recruitment properties include the peak-to-peak amplitude of the first and second responses, and maximal post-activation depression (DMAX). **Results & Conclusion:** We found that the second SMEPs were significantly smaller than the first one in all muscles across postures, indicating that transsynaptic activation of motor pools projecting to the lower limb muscles can be achieved via lumbar TSCS across commonly used postural conditions. We also found that the highest DMAX was recorded in the supine condition and it was significantly higher in SOL, MG, and BF than in quadriceps (RF &VL). This may indicate that TSCS applied at the caudal level of the spinal cord can preferentially evoke responses in these postural anti-gravity muscles. In addition, no significant difference in the post-activation depression was found between SS and standing supporting similar activation of lumbosacral spinal networks with TSCS in the SS and standing conditions. This can maximize the therapeutic potential of TSCS when applied in SS in individuals with muscle paralysis.

PAIN AND NOCICEPTION

71. Emili Adhamidhis; Institute of Medical Science

Supervisor: Dr. Mojgan Hodaie

DYNAMIC CHANGES IN CORTICAL THICKNESS IN CHRONIC PAIN PATIENTS FOLLOWING PAIN RELIEF

Adhamidhis E, 1,2; Srisaikaew P, 2; Li J, 1,2; Noorani A, 3; Mikulis D, 1,2,3; Davis K, 1,2; Hodaie M, 1,2,3,4*

1 Institute of Medical Science, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada; 2 Division of Brain, Imaging & Behaviour, Krembil Brain Institute, Toronto Western Hospital, University Health Network, Toronto, Ontario, Canada; 3 Temerty Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada; 4 Division of Neurosurgery, Krembil Neuroscience Centre, Toronto Western Hospital, University Health Network, Toronto, Ontario, Canada

Introduction: Trigeminal neuralgia (TN) is a chronic neuropathic pain disorder characterized by severe, unilateral, facial pain. Although surgical treatment is considered highly effective for this group, 20% of TN patients remain in pain following treatment. The mechanisms underlying the effect of surgical treatment, and why some patients remain non-responsive, are unknown. **Objective:** The present study aims to uncover how gray matter composition potentially modifies following surgical pain relief. Regions of interest were defined a priori according to literature that identified fourteen regional predictors of surgical response in TN patients. This study distinctly investigates how these regional predictors modify after surgery, and which of them are more relevant, in order to (1) understand the neural underpinnings of pain relief and (2) validate these identified regions as predictors of response. **Methods:** Retrospective imaging data was acquired from 119 surgically naÃ¯ve TN patients that underwent Gamma Knife Radiosurgery (GKRS) at Toronto Western Hospital. These patients underwent both pre- and post- surgical magnetic resonance imaging (MRI) scans and reported their pain intensity levels before and after surgery on the Barrow Neurological Institute (BNI) scale. Surgical response was defined as â‰¥ 75% pain relief following treatment. **Results:** Six regions had significant changes in cortical thickness in the responder group following surgical treatment. In responders with both left- and right-sided TN pain, the same six regions normalized towards the level of healthy controls, indicating a shared mechanism underlying pain relief from GKRS treatment. No significant changes in cortical thickness were observed in non-responders, indicating that pain relief directly causes the observed gray matter modifications. **Conclusion:** Our findings identify key regions that had significant response-dependent changes in cortical thickness and thus support their use as predictors of treatment response in trigeminal neuralgia patients. Normalization of these regions may underlie the effect of pain relief, and future studies should investigate these regions in other chronic pain conditions.

72. Rima El-Sayed; Institute of Medical Science / Krembil Brain Institute

Supervisor: Dr. Karen Davis

RELATIONSHIP BETWEEN ALPHA BRAIN ACTIVITY AND CONDITIONED PAIN MODULATION RESPONSE

El-Sayed R, 1,2; Cheng JC, 1,2; Rogachov A, 1,2; Osborne NR, 1,2; Besik A, 2; Sanmugananthan VV, 1,2; Hemington KS, 1,2; Kim JA, 1,2; Bosma RL, 2; Mills EP, 2; Dunkley BT, 3,4,5; Davis KD, 1,2,

1 Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada; 2 Division of Brain, Imaging, and Behaviour, Krembil Brain Institute, University Health Network, Toronto, Ontario, Canada; 3 Diagnostic Imaging, The Hospital for Sick Children, Toronto, Ontario, Canada; 4 Neurosciences & Mental Health Program, The Hospital for Sick Children Research Institute, Toronto, Ontario, Canada; 5 Department of Medical Imaging, University of Toronto, Toronto, Ontario, Canada; 6 Department of Surgery, University of Toronto, Toronto, Ontario, Canada

Introduction: Conditioned pain modulation (CPM) reflects the capacity of a remote noxious conditioning stimulus (CS) to modulate the pain evoked by a test stimulus (TS). Some people exhibit decreased TS pain (inhibitory) during a CS, others experience greater TS pain (facilitatory) or no change (noCPM). This is paradigm-dependent in healthy individuals (noCPM and facilitatory CPM with heat vs. inhibitory CPM with pressure stimuli). Previously, we found higher power and slower frequency in the alpha band (8-13 Hz in the dynamic pain connectome (DPC) in people with chronic pain compared to healthy individuals. However, it is not known whether alpha power relates to individual variability in CPM in healthy individuals. **Objective**: This study aims to explore brain-behavioural links underlying CPM in healthy individuals using resting state magnetoencephalography (MEG), with a focus on alpha activity in the key regions of interest (ROIs) in the DPC previously associated with CPM. **Methods:** A total of 68 right-handed healthy individuals (39 females, 29 males) underwent CPM testing using heat TS and CS and a 5-minute resting state MEG scan (Elekta Neuromag TRIUX system). The CPM effect was calculated as a %change in pain intensity evoked by a painful TS on one forearm due to a concurrent painful CS delivered to the other forearm (Qsense, Medoc Inc). In this study we compared 4 alpha metrics between the 3 CPM groups (facilitatory, inhibitory, and noCPM): total alpha power from the area under the power-frequency curve (AUC alpha power), power at 10 Hz (mid-alpha power), frequency where alpha power peaks (PAF), and power at PAF (PAF power). GraphPad Prism was used for group statistical testing with the Benjamin-Hochberg method at FDR 0.05 used to correct for multiple comparisons across ROIs. **Results:** Of

the 68 participants, 32% had inhibitory CPM (-37.1% +/- 26.2%; 17 F, 5 M), 49% had facilitatory CPM (26.2% +/- 17.4%; 18 F, 15 M), and 19% had noCPM response (0% +/- 0%; 4 F, 9M). There was no significant age difference between the inhibitory, facilitatory and noCPM groups. The most prominent MEG finding was that the noCPM group had significantly higher mid-alpha, AUC alpha, and PAF power compared to the facilitatory CPM group in the right thalamus, medial prefrontal cortex (mPFC), and dorsolateral prefrontal cortex bilaterally (dlPFC). Right hemispheric differences were strongest (thalamus, dlPFC). Additionally, in the mPFC, the inhibitory CPM group had higher alpha power in all 3 power measures compared to the facilitatory CPM group. There were no significant group differences in PAF that passed multiple comparisons corrections, however PAF in the inhibitory group was negatively correlated with CPM in the right dlPFC and bilateral thalamus. **Conclusion:** Our novel finding of alpha power differences between individuals with facilitatory CPM and noCPM highlights the importance of distinguishing these CPM effects, often not done in CPM studies. The greater thalamic and dlPFC alpha power found in the noCPM group may reflect a reduced sensory gating from the thalamus that produces sensory information overflow to the dlPFC of the salience network (SN). Since the SN is engaged when pain is attended to and that distraction strengthens CPM, great attention to pain could act to block CPM. Also, different mPFC alpha activity across CPM groups could reflect the capacity of the descending pathway to modulate pain. Finally, the relationship between weaker inhibitory CPM with slower PAF aligns with other studies in healthy individuals linking pain sensitivity with slower PAF. Thus, brain-CPM relationships were characterized by alpha power in the DPC and relationships between alpha frequency and CPM strength in the inhibitory CPM group. CPM has potential clinical utility to predict chronic pain treatment response and whether pain-free individuals develop postoperative chronic pain. Increased understanding of mechanisms underlying CPM will provide insight into pain modulation that in the future may be a predictor for treatment response.

73. Janet Li; Institute of Medical Science

Supervisor: Dr. Karen Davis

INDIVIDUAL DIFFERENCES IN CONDITIONED PAIN MODULATION ARE ASSOCIATED WITH STATIC FUNCTIONAL CONNECTIVITY WITHIN THE DESCENDING ANTINOCICEPTIVE PATHWAY

Li JZ, 1,2; Mills EP, 2; Osborne NR, 1,2; Cheng JC, 1,2; Sanmugananthan VC, 1,2; El-Sayed R, 1,2; Besik A, 2; Kim JA, 1,2; Hemington K, 1,2; Bosma R, 1,2; Erpelding N, 2; Rogachev A, 1,2; Davis KD, 1,2,3

1 Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada; 2 Krembil Brain Institute, Division *of Brain, Imaging, and Behaviour, University Health Network, Toronto, Ontario, Canada; 3 Department of Surgery, University of Toronto, Toronto, Ontario, Canada*

Introduction: Pain perception and coping ability is widely variable amongst people. These individual differences may in part be attributed to strength of a key pathway within the dynamic pain connectome (DPC), the descending antinociceptive pathway (DAP). Functional connectivity (FC) is a measure of synchronous activity between brain areas and, as such, it can provide insight into the efficacy or strength of functionality within a brain pathway. Conditioned pain modulation (CPM) is the effect of a painful conditioning stimulus applied to one body area on the pain evoked by a test stimulus applied to a different body area. It is thought to be a surrogate measure of endogenous pain modulation capacity. **Objective:** To examine brain-behaviour relationships between CPM and FC within the DAP. Specifically, to determine whether an individual's capacity to exhibit conditioned pain modulation (CPM) (changes in test stimuli (TS) pain due to a conditioning stimulus (CS)) reflects static functional connectivity (FC) of the descending antinociceptive pathway (DAP). My hypothesis was that CPM is associated with stronger FC within the DAP. **Methods:** CPM was assessed using painful heat test and conditioning stimuli (TS, CS) applied to the volar forearms. Subjects also underwent resting-state functional MRI (rs-fMRI) and FC was determined between the subgenual anterior cingulate cortex (sgACC), periaqueductal gray (PAG), and rostroventral medulla (RVM). **Results:** In 151 healthy participants (72 males, 79 females), three types of CPM effect were identified: 1) Antinociception: TS pain attenuated (38% of participants), 2) No-CPM: no significant change in TS (32% of participants), and 3) Pronociception: increased TS pain (30% of participants). Resting-state functional MRI determined FC between the subgenual anterior cingulate cortex (sgACC), periaqueductal gray (PAG), and rostroventral medulla (RVM). The correlation of sgACC - RVM FC had a medium effect size with CPM effect magnitude in the Pronociception group. Women, compared to men, were more likely to be categorized as Pronociceptive. **Conclusion:** This thesis suggests that FC of the DAP may reflect or contribute to CPM.

74. Nikou Kelardashti; Institute of Medical Science

Supervisor: Dr. Karen Davis

BRAIN-BEHAVIOR RELATIONSHIPS BETWEEN ALPHA OSCILLATIONS AND BEHAVIORAL PHENOTYPES RELATED TO PAIN-ATTENTION INTERACTION

Kelardashti N, 1,2; El-Sayed R, 1,2; Sanmugananthan VV, 1,2; Kim JA, 1,2; Osborne NR, 1,2; Cheng JC, 1,2; Hemington KS, 1,2; Rogachov A, 1,2; Bosma RL, 1,2; Besik AE, 1; Davis KD, 1,2,3

1 Division of Brain, Imaging and Behavior, Krembil Brain Institute, Krembil Research Institute, University Health Network, Toronto, Ontario, Canada; 2 Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada; 3 Department of Surgery, University of Toronto, Toronto, Ontario, Canada

Introduction: Attention is one of the key factors influencing our experience of pain, yet the interaction between attention and pain is complex and not well understood. The Davis lab has previously defined two behavioral phenotypes related to pain-attention interactions. The first phenotype is determined based on an intrinsic attention to pain (IAP) score, which quantifies the degree to which a person attends to pain (high IAP) or mind-wanders away from pain (low IAP). The second phenotype classifies individuals based on how pain impacts cognitive performance during an attention-demanding task (pain dominates (P-type), attention to task dominates (A-type)). MRI-based imaging has identified structural and functional brain features within the dynamic pain connectome (DPC)—a system that includes the ascending nociceptive pathway, descending antinociceptive pathway, default mode network, and salience network—in the IAP and A/P phenotypes. However, the fine temporal dynamics of brain activity is not discernible using the hemodynamic-based fMRI approach. Magnetoencephalography (MEG) offers high temporal resolution to examine resting-state neural oscillations within the DPC with millisecond precision. The alpha oscillation band has been linked to attention. Peak alpha frequency (PAF)—the frequency in the alpha

range (8-13 Hz) with the greatest power—has been linked to acute pain sensitivity and shown to be aberrant in individuals with chronic pain.**Objective:** The overall goal of this project was to explore brain-behavior relationships between alpha oscillations in the DPC and behavioral pain-attention phenotypes in healthy individuals. **Methods:** Resting state MEG was acquired from 50 healthy individuals (mean age ±SD=26.9±6.4; 27F, 23M). Power spectra analyses were done for alpha band activity in regions of interest (ROIs) of the DPC. The A/P phenotype was designated based on cognitive interference task performance with and without concurrent pain. An IAP score was determined from an experience sampling task of mind-wandering away from vs attention to painful stimuli.**Results:** 1) The relationship between measures of alpha oscillations (total alpha power, PAF power, PAF) in nodes of the DPC and the IAP and A/P phenotypes was not apparent using inferential p-value statistics. 2) Individuals with low IAP had higher theta power compared to those with high IAP in the nodes of ascending nociceptive pathway and default mode network. **Conclusion:** The finding that IAP and A/P Phenotype subgroups did not differ in alpha power suggests that alpha activity in the DPC is responsive to various attentional demands, rather than being specifically attuned to pain. Lower theta power in low IAP compared to high IAP individuals may be due to strong internally-oriented attention in people who tend to mindwander away from pain.

75. Matthew Mockford; Faculty of Dentistry

Supervisor: Dr. Massieh Moayedi

FUNCTIONAL CONNECTIVITY OF THE EXTRASTRIATE BODY DURING VISUAL ILLUSIONS IN PATIENTS WITH COMPLEX REGIONAL PAIN SYNDROME

Mockford MR; Lewis JS; Moayedi M

1 Centre for Multimodal Sensorimotor and Pain Research, Faculty of Dentistry, University of Toronto, Toronto, Ontario, Canada; 2 University of Toronto Centre for the Study of Pain, University of Toronto, Toronto, Ontario, Canada; 3 School of Health and Wellbeing, University of the West of England, Bristol, United Kingdom

Introduction: Complex regional pain syndrome (CRPS) is a chronic pain disorder with neuropathic features that can occur following trauma to a limb. It is accompanied by pain, motor disturbances, and vascular abnormalities, and is of unknown etiology with poor treatment outcomes. Patients with CRPS often report that their affected limb is distorted—i.e., body perception disturbances (BPD). Visual illusions that modify conscious body perception can reduce pain in clinical populations such as knee osteoarthritis and CRPS, but the mechanisms underlying these analgesic responses are not understood. However, we have shown that illusions which modulate body image are mediated by the extrastriate body area (EBA) and its connectivity to the posterior parietal cortex. **Objective:** Our objective was to investigate differences in brain connectivity of the EBA between patients with CRPS and pain-free individuals during a visual hand morph illusion using functional magnetic resonance imaging (fMRI). **Methods**: 47 participants (23 upper limb CRPS, 24 healthy; 9 males, 38 females) aged (mean ± SD) 52.1 ± 13.4 years consented to procedures approved by NIHR and UWE ethics. Participants underwent a multisensory hand morph illusion using the MIRAGE setup while undergoing an fMRI scan. Participants underwent 4 runs of the task, with 10 trials each (5 active morphs, 5 sham morphs). The illusion had a morph phase where the hand was changed, lasting 3 seconds, followed by a hold phase where participants viewed their new hand shape for 3 seconds. We investigated psychophysiological interactions between the extrastriate body area (EBA) and the rest of the brain during the morph and hold phase of the illusion in patients with CRPS and healthy controls. Analysis was carried out using FEAT (FMRI Expert Analysis Tool) Version 6.00, part of FSL (FMRIB'S Software Library). Given the exploratory nature of the study, significance was set to an uncorrected Z>3.1. **Results:** We discovered that the left and right EBA both had increased functional connectivity with the left dorsolateral prefrontal cortex (dlPFC) during the hand morph illusion task. The left EBA also had increased functional connectivity with the caudate during the hand morph illusion task. **Discussion:** While experiencing illusions that modulate bodily perception, individuals with CRPS shows increased connectivity of the EBA with the left dlPFC and caudate compared to healthy individuals. The dlPFC has been implicated in the cognitive dimension of the pain experience, so its functional coupling with a brain region involved in processing body image in patients with CRPS is logical. The caudate has also been implicated in pain processing, more specifically in pain avoidance behaviour and pain suppression. Further research is required to identify the role these brain regions have in the mechanisms of body perception and pain interactions. This will allow for better treatments that alleviate BPD and pain symptoms in individuals with CRPS. **Conclusion:** EBA functional connectivity during a visual illusion task differs between patients with CRPS and healthy controls, proposing mechanisms of treatment for visual illusions.

SYNAPTIC PLASTICITY

76. Samuel Fung; Graduate Department of Pharmaceutical Sciences

Supervisor: Dr. Robert Bonin

ARC AS A REGULATOR OF SPINAL CORD SYNAPTIC PLASTICITY AND RECONSOLIDATION

Fung SW, 1; Bonin RP, 2

1 Graduate Department of Pharmaceutical Sciences, Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada; 2 University of Toronto Centre for the Study of Pain, University of Toronto, Toronto, Ontario, Canada

Introduction: The spinal cord is a critical hub for sensory processing, where external stimuli can modulate the synaptic strength of sensory pathways. This dynamic modulation, known as synaptic plasticity, can be regulated by the trafficking and subunit composition of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) on the post-synaptic membrane. Nociceptive pathways in the spinal dorsal horn (SDH) can undergo synaptic reconsolidation, where reactivation of synaptic pathways will lead to a brief window of malleability before consolidation. Within this window, disrupting spinal reconsolidation by inhibiting protein synthesis can weaken previously potentiated pathways by synaptic depotentiation. However, the mechanism underlying synaptic depotentiation during disrupted reconsolidation has not yet been elucidated. **Objectives and Methods:** Here, we modelled spinal reconsolidation using peripheral Capsaicin injections to induce mechanical hyperalgesia as well as activate and reactivate nociceptive pathways in the SDH. **Results:** We discovered that Arc is acutely expressed in the SDH after Capsaicin injection, with high synaptic membrane expression. During reconsolidation blockade, mutant (MUT) mice with impaired Arc mRNA dendritic trafficking did not experience reversal of hyperalgesia compared to wild-type mice. MUT mice exhibited altered protein expression of AMPAR scaffolding proteins in

the SDH. Inhibiting Arc interaction with endocytic machinery during disrupted reconsolidation was also sufficient to prevent reversal of hyperalgesia. **Conclusion:** These findings suggest that Arc may play a key role in modulating spinal synaptic plasticity via AMPAR trafficking.

TRANSLATIONAL RESEARCH

77. Sun Eui (Sunny) Choi; Department of Medical Biophysics

Supervisor: Dr. Brian Nieman

THE BRAIN IMPACT OF SYSTEMIC METHOTREXATE CHEMOTHERAPY IN A JUVENILE MOUSE MODEL

Choi S, 1,2,3; Ayoub T, 1,2,3; Yeung J, 1,2,3; Nieman BJ, 1,2,3,4

1 Mouse Imaging Centre, Hospital for Sick Children, Toronto, Ontario, Canada; 2 Translational Medicine, Hospital for Sick Children Research Institute, Toronto, Ontario, Canada; 3 Department of Medical Biophysics, University of Toronto, Toronto, Ontario, Canada; 4 Ontario Institute for Cancer Research, Toronto, Ontario, Canada

Introduction: MTX is the backbone of chemotherapy for pediatric acute lymphoblastic leukemia (ALL) and is delivered through all phases of treatment. While five-year survival rates exceed 90%, survivors may display late neurocognitive deficits affecting quality of life. **Objective:** To evaluate brain volume changes after systemic methotrexate (MTX) treatment in a juvenile mouse model. **Methods:** CD-1 mice were split into two groups, MTX-treated (n=22) and saline-treated (n=21). Mice were given MTX (5 mg/kg) or saline intravenously under isoflurane anaesthesia at postnatal day 17 (P17) and P19. In vivo manganese-enhanced magnetic resonance imaging (MEMRI) was used to evaluate longitudinal brain volume changes in mice at timepoints P14, P24, P42, and P63. A linear mixed-effects model was used to model structural changes across images and included fixed-effect terms for age, treatment, administration route, and their interactions. Random-effect terms accounted for individual and litter variability. **Results:** Widespread brain volume loss was seen immediately after systemic MTX administration (98/183 structures showed volume decrease at P24). Most structures showed a trend to an increased growth rate such that volumes recovered by P63. The increased growth rate was statistically significant in the striatum and frontal cortex. **Conclusion:** Systemic MTX treatment causes acute volume loss followed by a gradual recovery. This may have implications for the brain impact of MTX in childhood cancer survivors. Additional comparison of CNS-targeted MTX will be important to form a full picture of MTX's potential impacts.

78. Sahara Haylestrom; Music and Health Science Research Collarboratory, Faculty of Music

Supervisor: Dr. Michael Thaut

THE LONG-TERM PHYSICAL AND PSYCHOLOGICAL EFFECTS OF A SPEECH AND MOTOR NEUROLOGIC MUSIC THERAPY (NMT)® PROTOCOL FOR THE TREATMENT OF DYSTONIA

Haylestrom ST, 1; Yuan VR, 1; Hurt-Thaut C, 1; Thaut M, 1

1 Music and Health Science Research Collaboratory, Faculty of Music, University of Toronto, Toronto, Ontario, Canada
Introduction: Dystonia is a neurological movement disorder characterized by involuntary repetitive muscle contractions. The neuroanatomical mechanisms and pathology are only partially understood with a need for continued research investigating the role of various brain regions and networks. Current available treatments encompass medications, chemodenervation with botulinum toxin infections, physical therapy, deep brain stimulation, and surgical procedures. The effect of music on dystonic symptoms has been examined through case studies, observations, and experimental studies, showing evidence of positive impacts. **Objective:** This clinical research project aimed to study the long-term changes of a targeted Neurologic Music Therapy (NMT)® protocol on a small group of dystonic participants. We predicted that at cessation of the 12-week treatment cycle, data collected from our pre- and post-treatment cycle standardized assessments – the Cervical Dystonia Impact Profile (CDIP-58), measuring dystonic symptoms, and the Vocal Handicap Index, measuring perceived voice function – will show no significant changes in test scores between week 0 and week 12. This result will demonstrate our NMT protocol's potential to preserve function and contribute to reducing the rate of decline in this group of dystonic participants. **Methods:** Using a targeted clinical protocol of speech and motor NMT techniques over the course of 12 weekly group synchronous virtual 60-minute sessions, the long-term changes in participants' symptoms were measured through administration of two standardized assessments pre- and post- treatment cycle. The Cervical Dystonia Impact Profile (CDIP-58) and the Vocal Handicap Index (VHI), both standardized and validated self-report assessment scales, were employed to measure physical, emotional, and psychosocial levels of functioning in participants before and after participation in the 12-week treatment cycle. Participants were adults diagnosed with dystonia (n = 2-6, varying per week), with a mean age of 74 (SD = 8.52), and weekly sessions were co-led by 3 student therapists and supervised by an accredited Music Therapist with NMT certification. The session protocol utilized a defined set of NMT techniques, progressing in the same order each week: Warm up, Vocal Intonation Therapy (VIT)®, Oral Motor and Respiratory Exercises (OMREX)®, Therapeutic Singing (TS), Patterned Sensory Enhancement (PSE)®, Rhythmic Auditory Stimulation (RAS)®, Cool down (PSE), and closing song. Materials utilized included laptops, microphone, Zoom software, keyboard pianos, guitars, and percussion instruments, chairs and tables. Using the Wilcoxon signed rank test for paired samples, statistical analysis was conducted using R statistical software (Version 4.3.1). **Results:** Findings show a maintenance effect across the 12-week treatment cycle, denoting no long-term changes for this group. 10 weeks have been completed, therefore to conclusively analyze data the treatment cycle must be concluded with all final data collected (as of April 4th, 2024). **Conclusions:** This clinical protocol shows promise as an adjunct treatment modality to support individuals with dystonia in the maintenance of their disorder. It is expected that perceptions of psychosocial function, and quality of life will increase in the post CDIP and VHI assessments. Limitations to the study design included diverse participant diagnoses, symptoms, and circumstances leading to limited ability to draw generalizable conclusions. Also, varied weekly attendance created inconsistent group sizes week to week, with limited ability to track individuals over time. The virtual setting also limited clinical observation and assessment of participant presentation, symptoms, and speech and motor function. Additionally, the small sample size made the options for data analyses narrow. Future directions encompass completion of this 12-week treatment cycle, as well as further research on differential effects of speech vs. motor NMT techniques, virtual vs. in-person sessions, and group vs. individual sessions. An emphasis on continued robust research of dystonic populations is needed to more specifically investigate the use of music as a clinical treatment for individuals affected by this neurological disorder.

79. Kristoffer Panganiban; Institute of Medical Science

Supervisor: Dr. Margaret Hahn

GUT MICROBIOME AND METABOLIC DYSFUNCTION IN ANTIPSYCHOTIC NAÏVE PATIENTS

Panganiban K, 1,2; Lee J, 1,2; Costa-Dookhan K, 1,2; De Palma 3; Agarwal SM,1,2; Hahn M, 1,2

1 Schizophrenia Division, Centre for Addiction and Mental Health (CAMH); 2 Institute of Medical Science, University of Toronto; 3 Faculty of Health Sciences, McMaster University

Introduction: Psychosis spectrum disorders (PSDs) comprise a debilitating series of mental disorders that have a prevalence rate of 3% and are observed to have a significantly higher risk of developing metabolic disorders. Antipsychotics (APs), the cornerstone of treatment for PSDs, are known to contribute to the risk of metabolic disorders. Although the mechanisms underlying PSD pathophysiology are largely unknown, the gut microbiome (GMB) may be a contributing factor as it has been observed to be dysregulated in other psychiatric illnesses. **Objectives:** (1) Identify whether there are GMB differences between healthy controls and patients and (2) whether there are differences at baseline between patients who gain ≥ 7% weight at the 12 week follow-up. **Methods:** The current study design is cross-sectional, case control and longitudinal. The cross-sectional, case-control aspect of the study involved 21 minimally treated AP patients (defined as AP usage of 3 weeks or less in the past 3 months) with PSDs and 19 healthy controls matched for age, sex, BMI and highest level of parental education. The longitudinal aspect included 14 patients that were followed for 3 months. Alpha and beta diversity measures were used to quantity GMB diversity. **Results:** The results showed that there is no significant difference in alpha diversity between patients and controls. However, there is a significant difference in beta diversity, with controls showing higher diversity than patients. It was observed that controls had higher proportions of Prevotella and Bacteroides while having lower proportions of Ruminococcus and Bifidobacterium. **Conclusion:** The patients showing lower levels of beta diversity indicates that they have an unhealthier gut as more diverse GMBs are historically thought to be healthier. In addition, the proportions of the taxa seen in patients may contribute to psychopathology and metabolic dysfunction.

80. Katarzyna Pieczonka; Institute of Medical Science

Supervisor: Dr. Michael Fehlings

CHARACTERIZING INDUCIBLE OLIGODENDROGENICALLY-BIASED NEURAL PROGENITOR CELLS IN SPINAL CORD INJURY

Pieczonka K, 1,2; Khazaei M, 2; Fehlings M, 1,2,3

1 Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada; 2 Krembil Research Institute, University Health Network, Toronto, Ontario, Canada; 3 Department of Surgery, University of Toronto, Toronto, Ontario, Canada

Introduction: Spinal cord injury (SCI) is associated with the loss of oligodendrocytes, which play key roles in myelination and in modulating interactions between glia and neurons. Neural progenitor cells (NPCs) are a promising source of cells for SCI treatment, due to their ability to replace the lost oligodendrocytes, neurons and astrocytes. However, the differentiation of NPCs into oligodendrocytes is often inefficient, whereby the majority of the cells differentiate into astrocytes following transplantation. **Objective:** We aimed to enhance oligodendrocyte differentiation by generating an inducible oligodendrogenic NPCs (ioNPCs) in which the extent of oligodendrocyte differentiation could be carefully regulated. **Methods:** Human ioNPCs were prepared by engineering NPCs to express Olig2 under the control of the conditional doxycycline-inducible tet-ON promoter, in which doxycycline administration regulates Olig2 expression. The cells were then treated with doxycycline for 3, 7 or 10 days. Next, the cells were characterized in vitro using a combination of qRT-PCR analysis, immunostaining, and bulk RNA sequencing. **Results:** qRT-PCR analysis revealed that the expression of several genes involved in oligodendroglial lineage determination, including OLIG1, OLIG2 and PDGFRA, progressively increased with longer doxycycline treatment timelines. Immunostaining showed the ratio of O1+ oligodendrocytes was significantly higher in the ioNPCs (39.44 ± 16.5%) compared to NPCs (24.73 ± 6.5%). Bulk RNA sequencing revealed that a total of 521 genes were differentially expressed between ioNPCs and NPCs. Oligodendroglial genes such as OLIG1, PDGFA, and MYRF, as well as neuronal and astrocyte genes such as TUBB3, MAP2 and S100B, were amongst the differentially expressed genes. Gene set enrichment analysis revealed an enrichment in the gene expression signatures of distinct subpopulations of oligodendroglial lineage cells, including oligodendrocyte precursor cells and mature oligodendrocytes, in the ioNPCs. **Conclusion:** In conclusion, our study suggests that ioNPCs are a promising source of cells that exhibit enhanced oligodendrocyte differentiation.

81. Victoria Yuan; Music and Health Science Research Collaboratory, Faculty of Music

Supervisor: Dr. Michael Thaut

THE SHORT-TERM EFFECTS ON PAIN, TENSION, AND MOOD OF A SPEECH AND MOTOR NEUROLOGIC MUSIC THERAPY(NMT)® PROTOCOL FOR THE TREATMENT OF DYSTONIA

Yuan VR, 1; Haylestrom ST, 1; Hurt-Thaut C, 1; Thaut M, 1

1 Music and Health Science Research Collaboratory, Faculty of Music, University of Toronto, Toronto, Ontario, Canada

Introduction: This clinical research project examined the short-term effects of a targeted clinical protocol of speech and motor Neurologic Music Therapy (NMT)® techniques for the treatment of dystonia. Dystonia is a complex neurological movement disorder characterized by involuntary sustained or repetitive muscle contractions, with diverse clinical manifestations and causes. Current treatment is individualized, and research continues to investigate the roles of various brain regions and networks underlying this condition. Music has been shown to have beneficial effects on dystonia symptoms, including reducing pain and tension, and increasing mood. NMT is an emerging and promising adjunct treatment for individuals with dystonia and this study contributed to deepening the understanding of dystonia and the use of NMT in its treatment for adults living with the condition. **Objective:** The objective of the study was to examine the efficacy of a targeted NMT clinical protocol during synchronous virtual sessions on adults diagnosed with dystonia by collecting clinical data measuring short-term changes in perceived pain, tension, and mood over the course of each session. It was predicted that there would be significant short-term, temporary reductions in pain and tension and an increase in mood from pre- to post-session. **Methods:** This study used a pre-post design and a targeted clinical protocol of speech and motor NMT techniques over the course of 12 synchronous virtual group sessions held once per week for 60 minutes via Zoom. Sessions were co-led by 3 student therapists and supervised by an accredited Music Therapist

with NMT certification. Participants included adults diagnosed with dystonia (n = 2-6, varying per week); the mean age of participants was 74 years (SD = 8.52). The clinical intervention protocol consisted of a warmup, Vocal Intonation Therapy (VIT)®, Oral Motor and Respiratory Exercises (OMREX)®, Therapeutic Singing (TS), Patterned Sensory Enhancement (PSE)®, Rhythmic Auditory Stimulation (RAS)®, a PSE-based cool down, and a closing song. The short-term changes in participants' symptoms were measured through self-report assessments pre- and post-session for every session during the intervention period. The pre-post session assessments consisted of 7-item Likert scales on perceived levels of pain, tension, and mood. Materials included laptops, microphones, Zoom software, chairs, tables, keyboard pianos, guitars, and percussion instruments. Statistical analysis was performed using the Wilcoxon signed rank test for paired samples using R statistical software (Version 4.3.1). **Results:** Preliminary analyses of results suggested that the NMT intervention contributed to a significant decrease in perceived pain and tension, and a significant increase in perceived mood, from pre- to post-session. From the 10 sessions completed thus far, 3 out of 30 measures showed statistically significant changes pre- to post-session ($p < 0.05$). 20 out of 30 measures showed clinically meaningful changes pre- to post-session. There were no significant overall changes over the course of the 12-week period, suggesting the intervention provided a temporary short-term beneficial effect and a maintenance effect of symptoms over time. **Conclusion:** For this group, the clinical protocol was effective in improving symptoms short-term. Participants met treatment goals of decreasing pain and tension, and increasing mood, by at least 1 level in 60-70% of sessions thus far. Additional clinical implications of using music in group settings included increased social interaction, motivation, and emotional wellbeing. Limitations included participants' diverse diagnoses, symptoms, and circumstances; voluntary and varied weekly participant attendance, small sample sizes, and the virtual platform. This study provides insight into the effectiveness of NMT in dystonia treatment. Continued research is needed to enhance understanding of NMT as a viable intervention for individuals with dystonia. The maintenance effects and short-term benefits of this NMT protocol provide evidence supporting the continued use of this clinical protocol and the potential for music-based intervention as an accessible, cost-effective, low-risk and geographically inclusive adjunct therapy, thereby contributing to clinical practices and translational research to improve clinical outcomes in dystonia.

OTHER: NEUROPHYSICS

82. Xin Mu; Max Planck Institute of Microstructure Physics / Department of Electrical & Computer Engineering

Supervisor: Dr. Wesley Sacher

INTEGRATION OF MICROFLUIDICS INTO SILICON PHOTONIC NEURAL PROBES

Mu X, 1,2; Chen FD, 1,2; Chameh HM, 3; Movahed M, 3; Straguzzi JN, 1; Rosko DA, 1,2; Kumar P, 1; Luo X, 4; Chua H, 4; Lo GQ, 4; Valiante TA, 3,5,6,7; Poon JKS, 1,2; Sacher WD, 1*

1 Max Planck Institute of Microstructure Physics, Weinberg 2, 06120 Halle, Germany; 2 Department of Electrical and Computer Engineering, University of Toronto, 10 King's College Road, Toronto, Ontario M5S 3G4, Canada; 3 Krembil Brain Institute, University Health Network, Toronto, Ontario, Canada; 4 Advanced Micro Foundry Pte Ltd, 11 Science Park Road, Singapore Science Park II, 117685, Singapore; 5 Division of Neurosurgery, Department of Surgery; 6 Toronto Western Hospital, University of Toronto, Toronto, Ontario, Canada; 7 Institute of Biomedical Engineering, University of Toronto, Toronto, Ontario, Canada

Introduction: Due to the unique cell-type selectivity, optogenetic tools are important to study brain functions and brain disorders. Despite the capability of delivering light to neurons with optogenetic neural interfaces, electrical recording sites are also used for simultaneous electrophysiology studies.For fundamental neuroscience research, the delivery of pharmacological agents into deep brain regions can help dissect complex neural circuits and neurotransmitter/receptor systems, promising for the treatment of neurodegenerative diseases. **Objectives:** Based on the state-of-art of optogenetic and microfluidic tools for neuroscience research, we implemented a multifunctional optogenetic neural interface with comprehensive integration of multimodalities for simultaneous optical stimulation, electrical recording, and drug delivery. **Methods and Results:** The microfluidic neural probes were fabricated on a 200-mm wafer at Advanced Micro Foundry. The probe is thinned down to around 100 μm, consisting of a 2.7 mm long by 3 mm wide probe base and a 4 mm long probe shank. The probe shank width is about 100 μm, which is comparable to the neuron size. The small cross-section of the shank can reduce tissue damage during probe implantation. 16 grating emitters are located near the shank tip with an electrode in the adjacency of each optical emitter. Light can be guided to each optical emitter through the edge couplers with the customized 16-core fiber and scanning system. Microfluidic inlet/outlet formed by deep etch is defined in the vicinity of grating emitters and electrodes. We used the microfluidic neural probes to conduct chemical stimulation via direct injection, optogenetic stimulation, and in vivo electrophysiology recordings in an awake head-fixed setup on Thy1-ChR2-eYFP mice. **Conclusion:** The integration of grating emitters, electrodes, and microfluidics channels in one neural probe enables high-resolution optogenetic stimulation, neurotransmitter delivery and electrophysiology recording in real time.

Oral Presentations

SESSION I

BEHAVIORAL NEUROSCIENCE

Zeenat Ladak; Applied Psychology & Human Development

Supervisor: Dr. Richard Volpe

EQUITY IN PRENATAL HEALTHCARE SERVICES GLOBALLY: AN UMBRELLA REVIEW

Ladak Z, 1,4; Grewal N, 2; Kim MO, 2; Small S, 1; Leber A, 1; Hemani M, 3; Sun Q, 2; Hamza DM, 2; Laur C, 1,4; Ivers NM, 1,4,5; Falenchuk O, 1; Volpe R, 1

1 University of Toronto, Toronto, Canada; 2 University of Alberta, Edmonton, Canada; 3 McMaster University, Hamilton, Canada; 4 Women's College Hospital Institute for Health System Solutions & Virtual Care, Toronto, Canada; 5 Women's College Hospital, Toronto, Canada

Introduction: Timely, appropriate, and equitable access to quality healthcare during pregnancy is proven to contribute to better health outcomes of birthing individuals and infants following birth. Equity is conceptualized as the absence of differences in healthcare access and quality among population groups. Healthcare policies are guides for front-line practices, and despite merits of contemporary policies striving to foster equitable healthcare, inequities persist. **Objective:** The objective of this umbrella review is to identify prenatal healthcare practices, summarize how equities/inequities are reported in relation to patient experiences or health outcomes when accessing or using services, and collate equity reporting characteristics. **Methods:** For this umbrella review, six electronic databases were searched (Medline, EMBASE, APA PsychInfo, CINAHL, International Bibliography of the Social Sciences, and Cochrane Library). Included studies were extracted for publication and study characteristics, equity reporting, primary outcomes (prenatal care influenced by equity/inequity) and secondary outcomes (infant health influenced by equity/inequity during pregnancy). Data was analyzed deductively using the PROGRESS-Plus equity framework and by summative content analysis for equity reporting characteristics. The included articles were assessed for quality using the Risk of Bias Assessment Tool for Systematic Reviews. **Results:** The search identified 8065 articles and 236 underwent full-text screening. Of the 236, 68 systematic reviews were included with first authors representing 20 different countries. The population focus of included studies ranged across prenatal only (n = 14), perinatal (n = 25), maternal (n = 2), maternal and child (n = 19), and a general population (n = 8). Barriers to equity in prenatal care included travel and financial burden, culturally insensitive practices that deterred care engagement and continuity, and discriminatory behaviour that reduced care access and satisfaction. Facilitators to achieve equity included innovations such as community health workers, home visitation programs, conditional cash transfer programs, virtual care, and cross-cultural training, to enhance patient experiences and increase their access to, and use of health services. There was overlap across PROGRESS-Plus factors. **Conclusion:** This umbrella review collated inequities present in prenatal healthcare services, globally. Further, this synthesis contributes to future solution and action-oriented research and practice by assembling evidence-informed opportunities, innovations, and approaches that may foster equitable prenatal health services to all members of diverse communities.

Linda Marchesano; Ontario Institute for Studies in Education

Supervisor: Dr. C. Marchesano

THE NEURAL NETWORKS OF MATHEMATICS AND DECISION-MAKING

Marchesano L, 1; Umeya S, 2; Marchesano C, 3

1 Ontario Institute for Studies in Education (OISE), University of Toronto, Toronto, Ontario, Canada; 2 Independent Researcher, Toronto, Ontario, Canada; 3 Faculty of Arts and Sciences, University of Toronto, Toronto, Ontario, Canada

Introduction: Mathematics and decision-making similarly involve manipulating items in space to perform calculations and assess options for comparison and evaluation. Anatomical evidence suggests these processes occupy overlapping brain regions and engage similar neural networks which develop with age and activity-dependent factors. Research shows that engaging in mathematics has a significant impact on the development of the brain. Differences in the strength of white matter connectivity between central regions implicated in mathematical and executive function processes existed between students who continued their mathematical education during high school and those who did not. Controlling for initial discrepancies between the students, higher concentrations of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) were also found. Mathematical processes hold an evolutionary importance evidenced in dedicated cells distributed throughout the peripheral and central nervous system for goal-directed behaviour and can inform the basics of mathematical abilities. Signs of mathematical abilities are seen in infants as young as 3 months old. In research, implications of mathematical success mostly focus on future academic achievements including employment prospects in science, technology, engineering and mathematics (STEM) fields. However, fewer studies have been conducted regarding the use of mathematics and contributions to future behavioural outcomes such as executive decision-making paradigms in a social setting. **Objective:** The current study aims to demonstrate the importance of engaging in mathematics in cognitive and behavioural development which constitutes better decision-making in the future. The overall objective of my research is to utilize data regarding ontogenetically and phylogenetically conserved brain processes to inform teaching in mathematics to enhance cognition in students. **Methods:** I created a survey measuring high school math engagement and decision-making approaches. Emotional and cognitive-based decisions were distinguished based on evidence of distinct developmental pathways (ie mesocortical and mesolimbic systems). Participants (N=52) were recruited via a secured online platform. Analysis was conducted using Statistical Package for the Social Sciences (SPSS) v.28. **Results**: A Pearson correlation coefficient showed a significant and strong positive relationship between high school math engagement and cognitive-based decision-making in adulthood $r(50) = .592$, $p < .001$. **Conclusion:** This study demonstrates that engaging in mathematics during adolescence predicts future cognitive-based decision-making during adulthood. Alternatively, those with less mathematical engagement during adolescence make more emotional-based decisions later in life.

CELLULAR AND MOLECULAR NEUROSCIENCE

Raphael Chan; Department of Physiology

Supervisor: Dr. Lu-Yang Wang

MOLECULAR AND ULTRASTRUCTURAL BASES OF DISTINCT RELEASE MODALITIES AT A CENTRAL SYNAPSE

Chan R, 1,2; Gurma M, 1,2; Darbandi A, 3; Schalek RL, 4; Lichtman JW, 4; Trimble WS, 5; Zhen M, 1,3,6; Wang LY, 1,2*

1 Department of Physiology, University of Toronto, Toronto, Ontario, Canada; 2 Program in Neurosciences & Mental Health, The Hospital for Sick Children, Toronto, Ontario, Canada; 3 Nanoscale Biomedical Imaging Facility, The Hospital for Sick Children, Toronto, Ontario, Canada; 4 Center for Brain Science, Harvard University, Cambridge, Massachusetts, United States; 5 Program in Cell Biology, The Hospital for Sick Children, Toronto, Ontario, Canada; 6 Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, Ontario, Canada

Introduction and Objectives: Sensory experience and cognitive ability are made possible by the diverse strength and plasticity of synapses in the brain. Yet, we lack a fundamental understanding of the mechanisms underlying functional synaptic heterogeneity. We address this at the calyx of Held glutamatergic synapse in the mouse brainstem, where morphologically diverse nerve terminals contain main stalks and a variable number of bouton-like swellings. Our previous work suggests that the filamentous protein Septin 5 (Sept5) differentiates spatial coupling of calcium influx to neurotransmitter release at active zones (AZs) in stalks and swellings, diversifying whole-terminal release probability. Sept5 binds the SNARE protein syntaxin-1 to inhibit synaptic vesicle (SV) exocytosis, potentially acting as a wedge that prevents full zippering of SNAREs. **Methods:** We designed two membrane-permeable TAT-peptides conjugated with putative binding motifs from Sept5 to disrupt its interaction with SNARE complex assembly and SV release. We recorded miniature excitatory postsynaptic currents (mEPSCs) in diverse WT and Sept5-KO synapses with treatment of TAT-peptides or their scrambled controls. To examine postsynaptic contributions to heterogeneity, we used super-resolution expansion microscopy (ExM) to analyze the topography of postsynaptic AMPARs at stalks and swellings. These are being complemented by ultrastructural investigation via automated tape-collecting ultramicrotome scanning electron microscopy (ATUM-SEM) to analyze the nanoscale organization of SVs at AZs in stalks and swellings of 3D-reconstructed calyces. **Results:** Preliminary data indicate that differences in mEPSC amplitude distribution between morphological extremes likely arise from differences in AMPAR cluster size at stalks and swellings, and this difference in mEPSC amplitudes is eliminated in Sept5-KO synapses. One of two peptides mirroring Sept5 interface motifs shifted mEPSC amplitude distribution in WT but not Sept5-KO synapses. We propose that differences in molecular organization at distinct morphological compartments endows a single synapse population with diverse quantal output. **Conclusion:** Ongoing ultrastructural analyses will elucidate the precise molecular determinants of functional synaptic heterogeneity. Supported by CIHR and NSERC.

Madeleine Falby; Institute of Medical Sciences / Krembil Research Institute

Supervisor: Dr. Taufik Valiante

THE COLLAPSE OF DEGENERACY: HOW A LOSS OF INTRINSIC BIOPHYSICAL DIVERSITY IN DEEP SUBICULUM PYRAMIDAL NEURONS PAVES THE WAY FOR SEIZURE ACTIVITY

Falby M, 1,2; Moradi Chameh H, 1; Tripathy S, 1,4; Zhang L, 1,2; Valiante TA, 1-3,5,6*

1 Krembil Research Institute, Division of Clinical and Computational Neuroscience, Toronto, Ontario, Canada; 2 Institute of Medical Sciences, University of Toronto, Toronto, Ontario, Canada; 3 Department of Surgery, Division of Neurosurgery, University of Toronto, Toronto, Ontario, Canada; 4 Krembil Centre for Neuroinformatics, Centre for Addiction and Mental Health, Toronto, Ontario, Canada; 5 Institute of Biomaterials and Biomedical Engineering, University of Toronto, Toronto, Ontario, Canada; 6 Electrical and Computer Engineering, University of Toronto, Toronto, Ontario, Canada

Introduction: A neurological insult has the potential to bring about an epilepsy phenotype, while at other times a healthy physiological state in the brain is preserved. This phenomenon is yet to be understood, presenting a challenge for the development of effective epilepsy therapeutics. The concept of degeneracy, the ability of distinct entities to compensate for one another and adapt to unpredictable changes, provides an elegant solution to explain the homeostatic protective mechanisms that maintain healthy functioning of the brain when threatened by epileptogenic insults. **Objective:** However, a degenerate system requires heterogeneous components and may collapse when variability of these components is reduced. We, therefore, hypothesized that a loss of neuronal heterogeneity, a precondition to degeneracy, underlies the failure of homeostatic protective mechanisms leading to an increased vulnerability to epileptogenic insults and the emergence of seizure activity. **Methods:** Using the kainic acid model of epilepsy, we investigated the heterogeneity of intrinsic biophysical properties of deep subiculum neurons, an essential participant in the propagation of seizure activity. **Results:** By comparing whole-cell patch-clamp recordings, we found a significant loss of heterogeneity in the spike threshold property of subiculum neurons engaging in seizure-activity ($p < 0.0001$). This finding was not found to be influenced by inter-animal variability or accompanied by a significant difference in the mean threshold value. **Conclusions**: The loss of heterogeneity in the threshold property suggests that deep subiculum pyramidal neurons are more selectively tuned to respond to a tight range of inputs. This may reflect a lack of excitability to perturbations presented by seizure activity and explain the subiculum's role in propagating seizure activity. While the exact mechanisms underlying this loss of heterogeneity have yet to be investigated, this finding underscores a potential collapse of degeneracy that accompanies epilepsy.

CONCUSSION AND BRAIN INJURIES

Chloe Buso; Institute of Medical Sciences

Supervisor: Dr. Charles Tator

PATHOPHYSIOLOGY AND TREATMENT OF COMPUTER SCREEN INTOLERANCE IN PATIENTS WITH PERSISTING CONCUSSION SYMPTOMS

Buso C, 1,2; Tator C, 1,2

1 Institute of Medical Science, University of Toronto; 2 Canadian Concussion Centre, Toronto Western Hospital, University Health Network

Introduction: Many concussion patients suffer from computer screen intolerance (CSI), a symptom of unknown pathophysiology that significantly impairs ability to view computer, cell phone and TV screens. **Objectives**: To determine if patients with CSI are less symptomatic after reading or watching a video on a Flicker-Free screen than a conventional flickering computer screen. **Methods:** Patients were randomized into two groups: Group 1 used the Flicker Screen in Visit 1 and the Flicker-Free Screen in Visit 2; and Group 2 used the screens in reverse order. Subjects performed reading and video tasks. Symptoms were recorded using the Sports Concussion Assessment Tool at baseline, after reading, and after the video. **Results:** We have tested 44 patients, with our targeted number being 50. Thus, the study is ongoing, we remain blinded, and refer to the screens as Screens 1 and 2. With Screen 1 reading significantly increased the total number ($p = 0.0057$) and severity of symptoms ($p=0.0001$). With Screen 2, reading also significantly increased the total number ($p = 0.0051$) and severity of symptoms ($p=0.0081$), but the video also significantly increased the total number of symptoms ($p = 0.0135$). However, to date, there is no significant difference in number or severity of symptoms between Screens 1 and 2. **Conclusions:** To date, the Flicker-Free computer screen has not been proven to be a useful therapeutic intervention for CSI patients. We are considering additional measures to treat CSI and also conducting studies to elucidate its pathophysiology.

Marc Khoury; Institute of Medical Sciences

Supervisor: Dr. Tom Schweizer

HISTORY OF TRAUMATIC BRAIN INJURY IS ASSOCIATED WITH INCREASED GREY-MATTER LOSS IN PATIENTS WITH MILD-COGNITIVE-IMPAIRMENT

Khoury MA, 1,2; Churchill NW, 1; Di Battista A, 3; Graham SJ, 4; Symons S, 5; Troyer AK, 6; Roberts A, 7,8,9; Kumar S, 10,11; Tan B, 12; Arnott SR, 12; Ramirez J, 13; Tartaglia MC, 14; Borrie M, 15,16; Pollock B, 17,18; Rajji TK, 17,18; Pasternak SH, 16,19; Frank A, 20,21; Tang-Wai DF, 22; Scott CJM, 13,23; Haddad SMH, 24; Nanayakkara N, 24; Orange JB, 7,24; Peltsch A, 25; Fischer CE, 1,2,26; Munoz DG, 1,2,27; Schweizer TA, 1,2,28,29

1 Keenan Research Centre for Biomedical Science, the Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto; 2 Institute of Medical Science, Temerty Faculty of Medicine, University of Toronto, Toronto; 3 Defence Research and Development Canada, Toronto Research Centre, Toronto; 4 Physical Sciences Platform, Sunnybrook Research Institute, Toronto; 5 Department of Medical Imaging, Sunnybrook Health Sciences Centre, Toronto; 6 Neuropsychology and Cognitive Health Program, Baycrest Hospital, Department of Psychology, University of Toronto; 7 School of communication Sciences and Disorders, Western University, London; 8 Department of Computer Science, Western University, London; 9 Canadian Centre for Activity and Aging, Toronto; 10 Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto; 11 Department of Psychiatry, Faculty of Medicine, University of Toronto; 12 Rotman Research Institute, Baycrest Health Sciences, Toronto; 13 Sunnybrook Research Institute, Sunnybrook Health Sciences Centre, Toronto; 14 Tanz Centre for Research in Neurodegenerative Diseases, University of Toronto; 15 Schulich School of Medicine and Dentistry, University of Western Ontario, London; 16 St. Joseph's Healthcare Centre, London; 17 Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto; 18 Department of Psychiatry, University of Toronto; 19 Department of Clinical Neurological Sciences, London Health Sciences Centre, London; 20 Bruyère Research Institute, Ottawa; 21 University of Ottawa; 22 Division of Neurology, Department of Medicine, University of Toronto; 23 L.C. Campbell Cognitive Neurology Research Unit, Hurvitz Brain Sciences Research Program Sunnybrook Health Sciences Research Program, Sunnybrook Health Sciences Centre, Toronto; 24 University of Western; 25 Queen's University, Kingston; 26 Department of Psychiatry, University of Toronto; 27 Department of Laboratory Medicine and Pathobiology, University of Toronto; 28 Institute for Biomedical Engineering, Science & Tech (iBEST), a Partnership between St. Michael's Hospital and Ryerson University, Toronto; 29 Division of Neurosurgery, Faculty of Medicine, University of Toronto

Introduction: To date, there remains an incomplete understanding of the impact of traumatic brain injury (TBI) in pathological aging and its associations with clinical outcome. **Objectives**: The following study investigates whether patients with Mild-cognitive impairment (MCI) and a history of TBI show greater declines in cortical thickness and measures of executive function over a 2-year period. **Methods**: 85 patients with mild cognitive impairment (MCI) were identified from the Ontario Neurodegenerative Research Initiative, 26 of which had a self-reported history of traumatic brain injury (MCI-TBI) and 59 without (MCI-noTBI). Cortical thickness was evaluated using T1-weighted MRI scans, segmented using freesurfer's longitudinal pipeline. Bayesian multilevel modelling was used to evaluate group differences in cortical thickness cross-sectionally and longitudinally, as well as group differences in neuropsychological measures of executive function. **Results**: Compared to MCI[TBI-], MCI[TBI+] patients had, cross-sectionally, less grey matter at baseline within the right entorhinal, left medial orbitofrontal and inferior temporal cortex bilaterally. Longitudinally, the left rostral middle frontal, the left caudal-middle frontal and left lateral orbitofrontal showed greater grey matter loss over the span of 2 years, relative to controls (Median = 1-2%, 90%HDI [-0.01%: -0.001%], Probability of Direction = 90-99%). Of the neuropsychological measures, MCI[TBI+] participants primarily displayed longitudinal decline in Trails-Making-Test (TMT)-derived ratio (Median: 0.737%, 90%HDI: [0.229%: 1.31%], PD=98.8%) and differences scores (Median: 20.6%, 90%HDI: [-5.17%: 43.2%], PD=91.7%). **Conclusions**: Our findings indicate that patients with MCI and a history of TBI are at risk of accelerated neurodegeneration, displaying greater cortical atrophy in areas vulnerable to TBI-related mechanical injury, relative to MCI patients without prior TBI. Importantly, these findings shed light on the extent to which TBI may affect the progression of neurodegeneration in pathological aging and may help establish MCI-TBI as a unique, diagnostic category associated with clinical outcome.

SESSION II

COGNITIVE NEUROSCIENCE

Lauren Cole; Music and Health Sciences Research Collaboratory

Supervisor: Dr. Michael Thaut

AND ASSOCIATED SYSTEM-LEVEL BRAIN PLASTICITY OF MEMORY FUNCTION AND VERBAL LEARNING IN AMNESTIC MILD COGNITIVE IMPAIRMENT

Cole L, 1,2; Thaut M, 1*; Alain C, 1,2*; Henry M, 1,3*

1 Music and Health Sciences Research Collaboratory, University of Toronto, Toronto, Ontario, Canada; 2 The Alain Lab, Baycrest Centre, Toronto, Ontario, Canada; 3 Neural and Environmental Rhythms Research Group, Max Planck Institute for Empirical Aesthetics, Frankfurt, Hesse, Germany

Introduction: Amnestic Mild Cognitive Impairment (aMCI) is a neurological disease characterized as a pathological disorder of cognitive impairment, primarily in memory function, and the prodrome of AD. Cognitive rehabilitation has become a primary approach for intervention for this population, with a considerable number of studies demonstrating the older adult brain to be capable of plastic changes. Memory training which induces neuroplasticity demonstrates potential benefits. Specifically, studies consistently find music-assisted learning to be an effective aid for verbal memory, though focusing primarily on Alzheimer's Disease (AD), neglecting aMCI. **Objective:** The present study intends to determine whether this influence of musical mnemonics is apparent in this transitional stage between healthy older adults and AD. **Methods:** The study protocol is reciprocal to that of Thaut et al., 2014, involving the administration of an ordered word-list task while participants simultaneously undergo electroencephalography (EEG) recording. This within-subject paradigm will measure behavioural differences in memory recall of an ordered word list, presented either sung as a musical mnemonic, rhythmical spoken or spoken. EEG will be utilized for noninvasive task-related imaging, with high temporal resolution of the brainwave measures. Time-frequency analyses will determine the effects of musical mnemonics as an aid in verbal memory, in amalgamation with the associated system-level brain plasticity. **Results**: Anticipated results are older adults with aMCI will exhibit improved verbal learning, and short-term memory of an ordered word list using musical mnemonics, and significantly different topographies of neural synchronization between conditions, with increased learning-related alpha band coherence for short-term recall in music conditions. **Conclusion:** A proactive approach to early interventions for aMCI is needed to prevent deterioration in cognition. Fewer AD cases will have a positive domino effect on our public health system, creating more space and availability for resources and clinicians.

Hsin-Yun (Angel) Hsieh; Neurosciences & Mental Health, SickKids Research Institute

Supervisor: Dr. Benjamin Dunkley

FREQUENCY-SPECIFIC ALTERATIONS TO NEURAL SYNCHRONIZATION IN MILITARY-RELATED PTSD

Hsieh HY, 1; Ali M, 1; Ventresca M, 1; Zamyadi R, 1; Zhang J, **; Vartanian O, **; Rhind SG, **; Dunkley BT, 1,2,3,4*

*1 Neurosciences & Mental Health, SickKids Research Institute, Toronto, ON, Canada; 2 Department of Medical Imaging, University of Toronto, Toronto, ON, Canada; 3 Department of Diagnostic and Interventional Radiology, Hospital for Sick Children, Toronto, ON, Canada; 4 Department of Psychology, University of Nottingham, Nottingham, UK; 5 Faculty of Kinesiology and Physical Education, University of Toronto, Toronto, ON, Canada; ** Defence Research and Development Canada, Toronto Research Centre, Toronto, ON, Canada*

Introduction: Posttraumatic stress disorder (PTSD) is a serious psychiatric challenge with symptom clusters that comprise of intrusive thoughts, emotional withdrawal and avoidance, negative alterations to cognition and mood, and maladaptive hypervigilance. PTSD can be severely life limiting and is difficult to treat, in part due to cross-patient heterogeneity in presentation, with distinctive subtypes. PTSD is prevalent in military personnel compared to the wider Canadian public, partly due operational stressors and an increased exposure to traumatic stress. The neurobiological basis of PTSD remains unsolved, but prominent ideas include the tri-network model theory, which implicates dysfunctional connectivity between the Default Mode (DMN), Salience (SAL) and Central Executive Networks (CEN) as explaining primary symptoms. **Objective:** This cross-sectional study explored neurophysiological circuit functioning in PTSD in the CEN, DMN and SAL networks and mental health outcomes in Canadian Armed Forces and Royal Canadian Mounted Police personnel and Veterans with and without a diagnosis of PTSD, using resting state magnetoencephalography (rs-MEG), which offers a high-resolution tool to image neuronal electrochemical circuits. **Methods:** One-hundred and sixteen participants were recruited (avg age 46.2 & 91% male): n=62 with PTSD; and n=54 without PTSD, stratified by a clinical diagnosis of PTSD and being subclinical or symptomatic on the day of assessment (Symptomatic PTSD group Checklist score > 34). We also collected outcome data on depression and anxiety and measured neuronal activity using rs-MEG. Neural synchronization, a mechanism for functional connectivity and network communication through coherence, was defined by the weighed phase-based index (wPLI). **Results:** Those with PTSD exhibited poorer secondary outcomes of mental health, including significantly increased depression and anxiety symptoms. MEG demonstrated abnormal neuronal network activity in PTSD, including reduced low-frequency neural synchrony across the CEN and SAL networks ($p < .05$) but not the DMN ($p > 0.05$); conversely, the PTSD group also exhibited high-frequency hypersynchronization across the CEN, SAL and DMN ($p < .05$). A follow-up analysis showed this hyperconnectivity includes frontal areas such as the ventrolateral, ventromedial, dorsal inferior, and rostral medial prefrontal cortex. **Conclusion:** This research suggests that PTSD is in part mediated by abnormal connectivity in brain circuits, including frequency specific alterations to neural synchronization – a mechanisms for brain communication and information processing. Interestingly, the differential patterns of connectivity included reduced synchronisation at low-frequency, and hyperconnectivity at high frequencies. This study provides novel clinical targets for non-invasive precision brain stimulation. Future studies will explore the link between moral injurious events, PTSD and neurobiology, and for a basis for subtyping military-related PTSD.

Kai Ian Leung; Rehabilitation Sciences Institute

Supervisor: Dr. Monika Molnar

A META-ANALYSIS OF LANGUAGE AND COGNITION IN THE DEVELOPING BILINGUAL BRAIN: FROM INFANCY TO ADOLESCENCE

Leung KI; Tremblay P; Rochon E; Molnar M

Rehabilitation Sciences Institute, University of Toronto, Toronto, Ontario, Canada; Department of Speech-Language Pathology, University of Toronto, Toronto, Ontario, Canada; Department of Rehabilitation, Université Laval, Quebec City, Canada, CERVO Brain Research Center, Quebec City, Canada

Introduction: Behavioral neuroimaging studies focusing on language and cognition in developing populations offer insights into functional brain plasticity. However, these studies have predominantly focused on monolinguals, overlooking the significant proportion of bilingual individuals worldwide. Investigating the experience of learning two languages from a young age could provide valuable insights into brain-behavior relationships. **Objective:** This systematic review and exploratory meta-analysis of functional magnetic resonance imaging (fMRI) and functional near-infrared spectroscopy (fNIRS) studies aimed to address two research questions: (i) what brain areas are activated when typically developing bilingual children engage in language and/or cognitive tasks? (ii) how do these activated brain regions in bilingual children compare with those identified in monolingual children from the same studies? **Methods:** Following PRISMA guidelines, we searched for peer-reviewed, primary articles with bilingual and monolingual participants under 18 years old, reporting brain activity (fMRI [x,y,z] coordinates) for language and/or cognitive tasks. Studies were appraised for quality using the JBI Checklist. Coordinate-based activation likelihood estimation of fMRI studies was utilized in an exploratory meta-analysis to compare within-and between-group areas of activation. Heterogeneity in data reporting standards across fNIRS studies precluded their inclusion in the meta-analysis.

Results: Out of 23 studies meeting inclusion criteria, six fMRI studies were included in the exploratory meta-analysis. Our synthesis and meta-analyses suggest that: (1) young bilinguals' neural correlates of language and cognition recruited classic language and control networks, notably the frontal (prefrontal cortex, inferior frontal gyrus), parietal (inferior parietal lobule), temporal (superior temporal gyrus) cortices; (2) functional differences between bilinguals and monolinguals were identified in the left inferior frontal gyrus through meta-analysis. **Conclusion:** Findings imply similar language and cognitive networks across developmental stages for bilinguals. However, more research is needed; collaborative efforts involving researchers, clinicians, and community members are essential to enhance our understanding of how the language environment influences brain function and lateralization.

COMPUTATIONAL NEUROSCIENCE

Niki Akbarian; Institute of Medical Science

Supervisor: Dr. James Kennedy

DOES NEUROTICISM PROTECT AGAINST LATE-LIFE COGNITIVE DECLINE? A GENOMIC ANALYSIS

Akbarian N, 1,2; Santos FC, 2; Afjeh SS, 2; Zai C, 1,2,3; Kennedy JL, 1,2,3*

1 Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada; 2 Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto, Ontario, Canada; 3 Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada

Introduction: Mounting evidence suggests an association between neuroticism, defined as the predisposition to experience frequent negative emotions, and risk of late-life cognitive decline, possibly due to shared genetic contribution. **Objective**: This study examined the relationship between genetic liability to neuroticism and late-life cognitive decline. **Methods:** Data from 11,415 UK Biobank participants (4951 females, mean age = 63.4(SD=2.71)) aged 60 or above, with white British ancestry and no dementia history were analyzed. All the participants completed cognitive tests of Fluid Intelligence, Symbol Digit Substitution (processing speed), Trail Making (executive function), and Pairs Matching (memory) during the baseline (2014-2015) assessment, and 675 participants completed the same tests during the follow-up (2021-2022). Genetic liability to neuroticism was determined using polygenic risk score (PRS), computed through clumping and thresholding. Statistical analysis employed mixed effect modeling, adjusting for covariates including sex, age, baseline cognitive score, and first 10 principal components. Significance threshold was set to $p<0.05$, adjusting p values via Tukey method. **Results:** Individuals with higher neuroticism PRS demonstrated less decline in the fluid intelligence (estimate =1.26×10-2, $p<0.001$). Similar trend was observed for Symbol Digit Substitution (estimate =2.64×10-2, $p=0.002$) and Trail Making (estimate=-0.031, $p<0.001$). However, no association was found between changes in Pairs Matching over time and neuroticism PRS. **Conclusion**: The results suggest that a higher genetic liability to neuroticism is related to a lesser decline in fluid intelligence, processing speed, and executive functioning in older adults over time. However, caution is needed in interpretation due to small effect sizes and limitations such as incomplete longitudinal data and a homogeneous British ancestry sample, limiting generalization.

Heng Kang Yao; Department of Physiology

Supervisor: Dr. Etay Hay

IMPAIRED DENDRITIC INPUT PROCESSING IN SIMULATED HUMAN CORTICAL MICROCIRCUITS WITH LOSS OF INHIBITION AND SPINES IN DEPRESSION

Yao HK, 1, 2; Hay E, 1,2,3

1 Krembil Centre for Neuroinformatic, Centre for Addiction and Mental Health, Toronto, Ontario, Canada; 2 Department of Physiology, University of Toronto, Toronto, Ontario, Canada; 3 Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada

Introduction: Major depressive disorder (depression) is associated with altered dendritic mechanisms in excitatory cortical pyramidal (Pyr) neurons due to decreased inhibition from somatostatin (SST) interneurons and a loss of spines. Dendrites are vital to signal processing as they receive the majority of synaptic inputs, and exhibit nonlinear properties such as backpropagating action potentials that contribute to coincidence detection of signals. However, it is currently unclear how dendritic changes in depression impact dendritic integration of signals, particularly in the human context. **Objectives and Methods:** Here, we expanded our previous data-driven models of human cortical microcircuits in health and depression to include active dendritic properties that enable backpropagating action potentials as measured in human neurons, and spine loss in depression in terms of

synapses loss and altered intrinsic property. **Results:** We showed that the altered intrinsic properties in spine loss abnormally increase the amplitude of the backpropagating action potential and abolished nonlinear integration of signals. Furthermore, we showed that reduced SST interneuron inhibition and spine loss in depression increased baseline circuit activity (noise) and decreased responses (signals) to result in reduced signal-to-noise ratio and increased stimulus detection errors. **Conclusion:** Our study thus mechanistically links cellular changes in depression to impaired dendritic processing in human cortical microcircuits.

NEUROIMAGING

Kevan Clifford; Institute of Medical Science

Supervisor: Dr.Yuliya Nikolova

NEUROSTRUCTURAL EFFECTS OF NOVEL POLYGENIC RISK SCORES FOR MOLECULAR BRAIN AGING

Clifford KP, 1,2; Dos Santos F, 2; Abdelhack M, 2; Felsky D, 2,3; Sibille E, 2,3,4; Nikolova YS, 2,3

1 Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada; 2 Centre for Addiction and Mental Health (CAMH), Toronto, Ontario, Canada; 3 Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada; 4 Department of Pharmacology and Toxicology, University of Toronto

Introduction: Healthy and pathological brain aging are associated with distinct changes in brain structure. Abnormal trajectories of brain aging may, in part, be driven by deviations from typical gene expression patterns. **Objective:** Here, we evaluated the neurostructural effects of novel polygenic risk scores (PRSs) capturing shifts towards older-age-like expression in age-dependent genes (AGE-PRS) in a large non-clinical population. **Methods:** Lists of age-dependent genes and corresponding cis-eQTL variants were based on in-house transcriptomic data from postmortem cortical tissue across the adult lifespan (n=209, 20-92y). Genetic and Freesurfer-extracted regional cortical thickness (CT) measures were obtained from the UK-Biobank (n=31,384, 44-73y). We computed 25 inter-related AGE-PRSs, comprising 123-2614 genes, based on 5 distinct thresholds for each gene's association with cis-eQTL variants nested within 5 thresholds for genes' associations with age. Linear regressions on regional CT (FDR-corrected across 62 regions) were conducted with PRS-AGE as the independent variable, controlling for demographics, 10 genetic components, and study site.**Results:**The AGE-PRS comprising 1124 age-dependent genes showed strongest phenotypic effects. It was associated with greater CT in the left precentral gyrus (pFDR=0.05), left insula (pFDR=0.05), as well as the right precentral (pFDR=0.05) and right supramarginal (pFDR=0.05) gyri, and right precuneus (pFDR=0.05). Greater CT associations also occurred at trending levels in both left and right caudal middle frontal gyri (pFDR=0.052 and pFDR=0.078, respectively) and the right insula (pFDR=0.078). **Conclusion:**Greater CT in frontotemporal regions co-occurring with genetic shifts toward older-age-like gene expression may reflect compensatory processes, or neurostructural phenotypes resembling those observed in major depressive disorder and initial stages of neurodegenerative disease.

SESSION III

NEUROANATOMY

Savina Cammalleri; Department of Biomedical Engineering

Supervisor: Dr. Aaron Wheeler

UNDERSTANDING MICROGLIA HETEROGENEITY USING DISCO

Cammalleri SR, 1,2; Scott EY, 2,3; Wheeler AR, 1,2,3

1 Institute of Biomaterials and Biomedical Engineering, University of Toronto, Toronto, Ontario, Canada; 2 Donnelly Centre for Cellular and Biomolecular Research, University of Toronto, Toronto, Ontario, Canada; 3 Department of Chemistry, University of Toronto, Toronto, Ontario, Canada

Introduction: The project will build upon past work by implement the recently developed cutting-edge methodology - ex vivo digital microfluidic isolation of single cells for Omics (evDISCO) - to study transcriptomic and proteomic profiles of microglia in defined physiological states. This novel method is capable of isolating single cells from highly heterogeneous populations using digital microfluidics which are then able to be used in multi-omics and capture image-based data for downstream analysis. **Objective:** The project will focus on the functional consequences of neuronal inputs to microglia. Microglia are specialized immune cells that play a crucial role in maintaining CNS homeostasis and functioning. Evidence suggests that microglia also have a regulatory role in brain function, responding to neuronal inputs and feeding back regulatory information via chemical messengers and cell-cell contacts. Their role as physiological regulators of brain function, by receiving specific input from surrounding neurons and feeding back regulatory information via chemical messengers and cell-cell contacts. **Methods:** To this end, I will comparatively profile microglia (i) from transmitter-secretion-deficient brains (organotypic Unc13 KO brain slices) to determine how overall circuit activity affects microglia states, and (ii) from multiple brain regions (e.g. frontal cortex, visual cortex, hippocampus, striatum, a.o.) to systematically assess how the specific neuronal environment defines specific microglia states. As the evDISCO approach circumvents the requirement of complex additional reporter lines (e.g. RiboTag or BioID), we expect that the planned PhD-project will rapidly provide deep insights into how microglia interact with neurons to co-define circuit function. **Results and Conclusion:** Understanding the biology of these interactions requires a deep characterization of microglia's transcriptomic and proteomic profiles in defined physiological states. The goal of the project is to understand the underlying biology by using evDISCO in microglia report mouse lines focusing on the effects of neuronal signaling on microglia transcriptomes and proteomes in defined brain regions and single cells.

Babishaa Sauntharrajan; Department of Laboratory Medicine and Pathobiology

Supervisor: Dr. Yeni H Yucel

ELUCIDATING THE SUPRACHOROIDAL DRAINAGE PATHWAY: A NOVEL FRONTIER IN GLAUCOMA MANAGEMENT

Sauntharrajan B, 1,2; Gupta N, 1,2,3,4; Zhou X, 2; Gumeler E, 5; Koletar M, 6; Lam WW, 6; Stanisz G, 6,7; Yucel YH, 1,2,3,4

1 Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, ON, Canada; 2 Keenan Research Centre for Biomedical Science, St Michael's Hospital Li Ka Shing Knowledge Institute, Toronto, ON, Canada; 3 Department of Ophthalmology and Visual Sciences, University of Toronto, Toronto, ON, Canada; 4 Department of Ophthalmology and Visual Sciences, The University of British Columbia, Vancouver, BC, Canada; 5 Department of Neuroradiology, Faculty of Medicine, Hacettepe University, Ankara, Turkey; 6 Department of Physical Sciences, Sunnybrook Health Sciences Centre, Toronto, ON, Canada; 7 Department of Medical Biophysics, University of Toronto, Toronto, ON, Canada

Introduction: The suprachoroidal space serves as a compartment for delivering biologics, nanoparticles, and genes to the posterior segment of the eye. However, the routes of drainage of solutes and fluid from this space remains elusive. **Objective**: The present study aims to map and characterize the drainage pathway from the suprachoroidal space by injecting a near-infrared fluorescent nanoparticle tracer injection. **Methods**: A near-infrared fluorescent nanoparticle tracer, CF770 conjugated with bovine serum albumin (MW:70kDa, 0.5µL), was injected into the suprachoroidal space (10nl/s) of the right eye in adult mice (C57BL/6J; n=8). Sham-injected left eyes were utilized as controls. In vivo and ex vivo fluorescence images of the eye and neck lymph nodes were captured using a scanning laser ophthalmoscope at 10-, 15-, and 20-minute intervals post-injection. Mice were euthanized 20 minutes after injection, and their tissues were processed for histological validation. Sagittal sections of the orbit, 20µm thick, were double labeled with podoplanin and podocalyxin, marking lymphatic vessels and blood vessels' endothelial cells, respectively. Tissue sections without primary antibodies served as negative controls. Immunofluorescence-stained sections were imaged using a confocal scanning laser microscope and a near-infrared epifluorescence microscope at 20x and 63x magnifications. **Results**: In vivo fluorescent imaging depicted the presence of a lymphatic network with a tendency for the nasal region in the orbit. Near-infrared epifluorescence microscopy revealed that the tracer drains through the sclera and orbit. Immunofluorescence analysis identified podoplanin-positive lymphatic vessels in the choroid with a central lumen, distinct from blood vessels. Furthermore, a near-infrared tracer was detected in the lumen of podoplanin-positive lymphatic channels in the conjunctiva. Ex vivo imaging demonstrated that the tracer injected into the right suprachoroidal space drains into the right accessory submandibular neck lymph node. **Conclusion**: This study provides the first evidence that fluid and nanoparticles exit the eye through a nasal route into the sclera and orbit from the suprachoroidal space and subsequently, drain into the ipsilateral accessory submandibular lymph node. It presents evidence of lymphatic vessels in the choroid and demonstrates tracer draining into conjunctival lymphatic channels. A better understanding of this intricate pathway originating from the suprachoroidal space holds significant implications for designing new therapeutic modalities for glaucoma such as novel drainage devices or drug delivery strategies targeting the suprachoroidal space.

NEURODEGENERATIVE DISEASES

Anthaea-Grace Patricia Dennis; Institute of Medical Science

Supervisor: Dr. Antonio Strafella

USE OF MACHINE LEARNING FOR IDENTIFICATION OF PARKINSON'S DISEASE AND MILD COGNITIVE IMPAIRMENT THROUGH NEUROIMAGING AND BIOFLUID BIOMARKERS: A STUDY FROM THE PPMI COHORT

Dennis A-GP, 1,2; Strafella AP, 1,2,3

1 Edmond J. Safra Parkinson Disease Program, Neurology Division, Toronto Western Hospital & Krembil Brain Institute, University Health Network, University of Toronto; 2 Institute of Medical Science, Temerty Faculty of Medicine, University of Toronto; 3 Brain Health Imaging Centre, Centre for Addiction and Mental Health, University of Toronto

Introduction: Parkinson's Disease (PD) is a neurodegenerative disorder resulting in both motor symptoms, such as bradykinesia, rigidity, tremor, and gait difficulties, and a variety of nonmotor symptoms, like cognitive impairment and behavioural complications. During PD progression, cognitive ability declines, resulting in mild cognitive impairment (MCI). PD and MCI have been explored with neuroimaging-based biomarkers; however, relying on these biomarkers alone can sometimes be ineffective because of large individual differences in brain activity. Thus, combining biofluid biomarkers, allowing also for proteomic differences, can help in a better biological definition of the disease. **Objective**: Since current diagnostic tests for PD and MCI focus on individual biomarkers, misdiagnoses can be frequent. This research aims to combine neuroimaging and biofluid data as biomarkers for PD and MCI progression, with the goal of developing a more efficient method of predicting disease states and symptoms. **Methods**: Using the support vector machine and random forest machine learning techniques, models were created based on neuroimaging and biofluid biomarkers for a subset of PD and healthy subjects from the Parkinson's Progression Markers Initiative (PPMI) dataset. Striatal binding ratios (SBRs) of the caudate and anterior putamen extracted from DaT-SPECT imaging were used as neuroimaging biomarkers. Proteomic concentrations of beta-amyloid-42, alpha-synuclein, total-tau, phosphorylated-tau, and neurofilament light derived from cerebrospinal fluid (CSF) represented the biofluid biomarkers. **Results**: When differentiating subjects with PD from healthy subjects, both the random forest and support vector machine techniques perform with high accuracy when using SBRs as biomarkers. In comparison, these techniques did not perform as well when using proteomic biomarkers from CSF. **Conclusion**: Based on these results, diagnostic performance may be improved through combining DaT-SPECT imaging with data from CSF-based biomarkers to distinguish subjects with PD from healthy subjects and subjects with MCI from subjects with normal cognitive abilities. This study's next steps involve developing machine learning models that combine both neuroimaging and biofluid-based biomarkers.

Nafia Mirza; Institute of Medical Science

Supervisor: Dr. Tom Schweizer

THE NEURAL CORRELATES OF THE PORTEUS MAZE TASK IN HEALTHY AND PATHOLOGICAL AGING

Mirza NJ, 1,2; Churchill NW, 1; Rashidi-Ranjbar N, 1; Tam F, 3; Fischer CE, 1,2,4; Graham SJ, 3,5; Schweizer TA, 1,2,6,7

1 Keenan Research Centre for Biomedical Science, St. Michael's Hospital, Toronto, ON, Canada; 2 Institute of Medical Sciences, University of Toronto, Toronto, ON, Canada; 3 Physical Sciences Platform, Sunnybrook Research Institute, Toronto, ON, Canada; 4 Department of Psychiatry, Faculty of Medicine, University of Toronto, Toronto, ON, Canada; 5 Department of Medical Biophysics, Faculty of Medicine, University of Toronto, Toronto, ON, Canada; 6 Division of Neurosurgery, St. Michael's Hospital, Toronto, ON, Canada; 7 Institute of Biomaterials and Biomedical Engineering, University of Toronto, Toronto, ON, Canada

Introduction: The Porteus Maze Test (PMT) assesses executive functioning, planning, and processing speed. While the PMT has been used to assess prefrontal cortex function in various neurological conditions, its neural basis in healthy aging and Mild Cognitive Impairment (MCI) remains unexplored. **Objective:** This study aims to characterize the neural substrates of the PMT in MCI using a novel MR-compatible tablet and stylus, with real-time visual feedback. **Methods**: Twenty-nine healthy controls and eleven MCI patients (69 ± 9 yrs., 16 female) underwent fMRI using a 3T MRI system at St. Michael's hospital. Participants used a MR-compatible tablet and stylus in the MRI to perform the PMT, along with a control task that involved tracing a solved maze. Functional MRI captured brain activity during both tasks, and task completion times were recorded. At the subject level, voxel-wise general linear model (GLM) analyses measured brain activity for maze and control tasks relative to a fixation condition. T-tests were used to generate group level activation maps of brain areas engaged during task performance, in patients with MCI and the healthy aging cohort, and activations were compared between groups. **Results**: In the maze task, both healthy control and MCI groups exhibited widespread frontal-parietal activity during both the PMT and control task. However, MCI patients demonstrated increased activation in the middle temporal, hippocampus, orbitofrontal, and cuneus during the PMT when compared to the healthy aging cohort. **Conclusion**: This study characterized the impact of MCI on PMT and task-related brain activity. Overall, this study identified increased activity seen in frontal-parietal regions of the brain. This study also indicated a distinct functional brain response for in individuals with MCI, providing new insights into this widely-used neurocognitive assessment.

NEURODEVELOPMENT

Tariq Ahmed; Institute of Medical Science

Supervisor: Dr. Mahavir Agarwal

METFORMIN FOR ANTIPSYCHOTIC-INDUCED WEIGHT GAIN IN ADULTS WITH INTELLECTUAL AND/OR DEVELOPMENTAL DISABILITIES

Ahmed T, 1,2; Papoulias M, 1; Stogios N, 1,2; Desarkar P, 1,2; Lin HY, 1,2; Lunsky Y, 1,2; Hahn M, 1,2; Agarwal SM, 1,2

1 Centre for Addiction and Mental Health, Toronto, Ontario, Canada; 2 Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada

Introduction: Close to 50% of adults with intellectual and/or developmental disabilities (IDD) are overweight or obese. One third of patients with IDD are prescribed antipsychotic medications, which are known to cause significant weight gain, leading to obesity and other related diseases like diabetes. Weight gain is associated with poorer quality of life, decreased social engagement, worse medication adherence, and poorer brain function. Unfortunately, current treatments for managing obesity and other related risk factors for heart disease are inadequately studied in individuals with IDD. Research has shown that the drug metformin helps to reduce the weight gain associated with antipsychotic drugs, but this has not yet been tested in adults with IDD. Our early findings show that metformin may be quite effective in reducing the weight gain associated with taking antipsychotic medication in adults with IDD. We plan to study patients with IDD who are overweight or obese and are taking antipsychotic medication to test metformin's ability to reduce body weight, and improve heart health. **Objectives:** Primary) To assess whether metformin is effective over 24 weeks in reducing weight in overweight or obese adults with ID

receiving APs. Secondary) To examine the effect of metformin on waist circumference, measures of glucose metabolism, and tolerability. Exploratory) To explore if sex, and AP type (clozapine and olanzapine vs. others) moderate the effect of metformin. **Methods:** Stable outpatients, between the ages of 18-65 years, with an IDD diagnosis, on treatment with an AP (stable dose for ≥3 months), BMI of ≥30 kg/m^2, or 27 kg/m^2 with at least one weight-related comorbidity will be randomized in a 1:1 ratio to add-on daily metformin (500-1500 mg/d) or placebo for 24 weeks in a double-blind manner (N=50 in each arm; our N provides 86% power to detect a clinically significant difference of 5% weight loss, and allows for 30% dropouts). Participants will be excluded if they have uncompensated cardiovascular, endocrine, haematological, hepatic, renal, or pulmonary disease or history of treatment with metformin. Both arms will receive diet and lifestyle advice. Participants will undergo a screening visit at study start which includes assent and informed consent procedures, collection of demographic data, comprehensive medical history, physical exam, and fasting blood work (including glucose, insulin, HbA1c, and lipids). During the 24-week RCT phase, participants are titrated up to 2000mg per day and seen once every four weeks. Weight, blood pressure, and waist circumference will be assessed at each study visit. Other outcomes will be assessed at baseline, mid- , and endpoint. After the 24-week double-blind period, all participants will have the option of being treated with open-label metformin for an additional 24 weeks. **Results:** This trial is currently underway with recruitment having begun in September 2023. Four participants are currently enrolled in the trial. Primary endpoint data is not yet available. However, a case series published in 2023 from the Centre for Addiction and Mental Health has shown that metformin has promise in treating antipsychotic-induced weight gain (AIWG) in individuals with IDD, with additional adaptive reductions observed for fasting glucose, glycated hemoglobin (HbA1c) and various lipid levels. It is expected that this trial will produce similar results. **Conclusion:** This trial will examine the possibility of adding a potent tool in the limited armament against obesity in adults with ID. Generating efficacy data for a very accessible and scalable intervention will support guideline development and help improve clinical management of a recalcitrant health problem in adults with IDD.

NEUROIMMUNOLOGY

Robert Duba-Kiss; Department of Pharmacology and Toxicology

Supervisor: Dr. David Hampson

Duba-Kiss R, 1; Hampson DR, 1,2*

1 Department of Pharmacology & Toxicology, University of Toronto, Toronto, Ontario, Canada; 2 Faculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada

A STUDY OF THE IMMUNOGENICITY OF CAS9 IN THE DEVELOPING AND MATURE MOUSE CENTRAL NERVOUS SYSTEM

Introduction: Adeno-associated virus (AAV) gene therapies are being assessed as potential treatments for a variety of neurological genetic disorders. Some AAV therapies in development rely on the expression of proteins which are not endogenously produced by the patient, such as Cas9 nucleases used in gene editing. A drawback of such strategies is the risk of triggering an inflammatory immune response directed against the exogenous polypeptide, in this case a prokaryotic protein. AAV therapies for some neurodevelopmental disorders may require the treatment of newborns or infants who have immature immune systems; it is generally thought that they exhibit weaker immune responses compared to older children and adults. Inflammatory responses against foreign transgenes might therefore be mitigated by early postnatal vector administration. **Objective:** This study seeks to elucidate differences in the immune response to Cas9 expressed in the CNS between newborn and mature mice, with the goal of determining whether early postnatal expression of Cas9 results in lower inflammation and toxicity compared to adults. **Methods:** AAV-Cas9 was administered to the CNS of early postnatal mice via intracerebroventricular injection and to adult mice via intra-cortical injection; the degree of neurotoxicity and inflammation elicited in each cohort was quantified one-month post-treatment. Several key controls were included in our study. Analyses of neuroinflammation were also performed three months after neonatal treatment to assess whether any degree of immune tolerance to Cas9 observed at the 30-day post-injection time point is maintained after full maturation of the mouse brain and immune system. **Results:** Mice administered Cas9-encoding AAVs as neonates showed lower levels of inflammation, higher neuronal density, and higher Cas9 expression, than mice administered the same AAVs as adults. Additionally, Cas9 expression persisted for three months following early postnatal AAV injection and was well tolerated at this timepoint. **Conclusion:** Our results support the hypothesis that expression of transgenic Cas9 in the brain shortly following birth is safer from an immunological standpoint than when the onset of expression is in the adult CNS. These findings have implications for the use of non-self proteins in gene therapies for neurodevelopmental and other disorders.

SESSION IV

LEARNING AND MEMORY

Julia Bandura; Department of Physiology

Supervisor: Dr. Zhong-Ping Feng

DISTINCT PROTEOMIC BRAIN STATES UNDERLYING LONG-TERM MEMORY FORMATION IN AVERSIVE OPERANT CONDITIONING

Bandura J, 1; Chan C, 2; Sun HS, 3; Wheeler AR, 2,4,5; Feng ZP, 1

1 Department of Physiology, University of Toronto, Toronto, Ontario, Canada; 2 Department of Chemistry, University of Toronto, Toronto, Ontario, Canada; 3 Department of Surgery, University of Toronto, Toronto, Ontario, Canada; 4 Donnelly Centre for Cellular and Biomedical Research, University of Toronto, Toronto, Ontario, Canada; 5 Institute of Biomedical Engineering, University of Toronto, Toronto, Ontario, Canada

Introduction: Long-term memory (LTM) formation relies on de novo protein synthesis driven by learning-dependent regulation of translation initiation. However, the identities of newly synthesized proteins and the mechanisms by which they regulate consolidation and maintenance of LTM remain unclear. One common approach to identify the targets of learning-induced novel protein synthesis has been to apply label-free quantification of protein abundance via shotgun proteomics, successfully identifying many differentially expressed proteins associated with LTM. However, analyzing differential protein expression by comparing animals subjected to conditioning or training with naïve or sham control counterparts introduces significant biological ambiguity. It remains unclear which differentially expressed proteins are essential for successful LTM formation following training or learning. **Objectives:** To address this, we sought to leverage a molluscan model of LTM formation, aversive operant conditioning of aerial respiratory behaviour in the pond snail Lymnaea stagnalis (L. stagnalis), which leads to a robust decrease in the animal's respiratory behaviour, but not uniformly, where animals are classified as either capable or incapable of learning based on their ability to form LTM. Therefore, in the current study, we sought to identify the proteins and pathways regulated by successful LTM formation following aversive operant conditioning in L. stagnalis, thus identifying pathways that may be crucial to LTM formation. **Methods:** Aversive operant conditioning of aerial respiratory behaviour was conducted as done previously (Dong & Feng 2017), with training yielding animals displaying LTM and no LTM, and yoking yielding yoke control animals. Aerial respiratory behaviour was measured 24 hours prior to (pre-test) and following (memory test) training, and whole CNS preparations were dissected immediately after the memory test. Protein lysates were prepared from four ganglia per group, cleaned of salts and detergents, and prepared into peptide digests for mass spectrometry. Liquid chromatography-mass spectrometry (LC-MS) was performed on peptide digests using nanoflow reversed-phase LC on an EASY-nLC 1200 ultra-high-pressure system coupled to a Q Exactive HF-X mass spectrometer equipped with a nano-electrospray ion source. Raw MS files were analyzed by DIA-NN, based on an in silico spectral library generated from predicted L. stagnalis protein-coding sequences (Dong, Bandura et al. 2021). Downstream differential enrichment analysis of DIA-NN output files was performed in R using the DEP BioConductor package and Clustergrammer was used to cluster proteins by differential expression profiles. Predicted L. stagnalis protein-coding sequences were annotated by homology using NCBI protein-protein BLAST against the mouse Uniprot proteome, and functional annotation and enrichment analysis was performed using gprofiler2 and Enrichr. Proteins, GO terms, and pathways were considered significantly differentially enriched if the adjusted p-value < 0.05. **Results:** Proteomic identification and quantification of L. stagnalis proteins in LTM, no LTM, and yoke CNS identified 3,274 predicted L. stagnalis proteins. 366 significant proteins uniquely differentially expressed between LTM and yoke control CNS as well as differentially expressed proteins common to both the LTM vs. yoke control and LTM vs. no LTM sets were identified as associated with the ability to form LTM, of which 88 were identified as "upregulated in LTM" (having strongly positive log2-fold changes for LTM vs. no LTM and LTM vs. yoke control and close to zero or negative log2-fold changes for no LTM vs. yoke control) and 36 proteins were identified as "downregulated in LTM" (having strongly negative log2-fold changes for LTM vs. no LTM and LTM vs. yoke control and close to zero or positive log2-fold changes for no LTM vs. yoke control). Functional annotation of these up- and downregulated protein sets identified several pathways to be enriched in both sets, as well as protein turnover-related terms within the upregulated in LTM set, while transcription-related terms were associated with the downregulated in LTM set. Together, these data suggest that transcription and translation following LTM formation in this model rely on tight regulation of the machinery responsible for both, and that inhibition of global transcription while specific transcription-related pathways are activated may be a key mechanism of LTM formation in this model. **Conclusion:** In conclusion, this study represents the first proteomic screen of LTM formation ability following aversive operant conditioning in L. stagnalis utilizing an improved transcriptome-guided protein sequence library, and collectively shows that LTM formation in this model induces changes in expression of proteins associated with protein synthesis, degradation, and transcription. Our results further imply that training induces specific proteomic brain states associated with successful and unsuccessful LTM consolidation that are distinct from yoke control brain states. Further studies will determine which identified proteins are critical for LTM formation, hence using the current study as a jumping off point for more detailed exploration of the involvement of a diverse set of protein signaling pathways in LTM, leading to discovery of novel mechanisms of regulation of neuronal function in learning and memory.

PAIN AND NOCICEPTION

David Rodriguez; Department of Pharmaceutical Sciences

Supervisor: Dr. Robert Bonin

PHARMACOLOGICAL ISOLATION OF NON-IONOTROPIC NMDA RECEPTOR SIGNALING REVERSES LONG-TERM POTENTIATION IN THE SPINAL CORD DORSAL HORN AND ATTENUATES PAIN HYPERSENSITIVITY IN VIVO

Rodriguez D, 1; Zhang H, 1; D'Souza A, 1; Zain M, 1; Fung S, 1; Bennett L, 1; He D, 2; Bonin RP, 1,3,4

1 Department of Pharmaceutical Sciences, Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada; 2 Department of Anesthesia, Temerty Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada; 3 Department of Cell and Systems Biology, University of Toronto, Toronto, Ontario, Canada

4 University of Toronto Centre for the Study of Pain, Toronto, Ontario, Canada

Introduction: Long-term potentiation (LTP) of synapses between primary sensory neurons and spinal cord dorsal horn neurons has been

closely associated with the development of pain hypersensitivity (i.e. hyperalgesia) in various pathological conditions. Synaptic plasticity is highly dependent on NMDA receptor (NMDAR) function; opening of this ligand-gated ion channel mediates calcium (Ca2+) influx into the cytosol, and the activation of calcium-sensitive signaling cascades that induce LTP and promote the sensitization of ascending pain pathways. Interestingly, recent investigations have described a novel, non-ionotropic NMDAR (NI-NMDAR) signaling mechanism in the brain that does not require channel opening, and which instead favours the processes of long-term depression (LTD) and dendritic spine shrinkage. **Objectives:** In this study, we test the hypothesis that NI-NMDAR signaling can be used to depotentiate previously-sensitized pathways in the spinal cord and to promote the reversal of hyperalgesia in rodent models of pathological pain. **Methods:** For electrophysiology experiments, C fiber-evoked postsynaptic field potentials (fPSPs) were recorded in acute spinal cord explants isolated from adult mice. Dorsal roots containing primary sensory afferents were stimulated using a bipolar electrode, and a recording electrode was inserted into the superficial dorsal horn of the spinal cord to measure postsynaptic responses. For behavioural experiments, hyperalgesia was induced via intraplantar injections of capsaicin or complete freund's adjuvant (CFA); Von Frey filaments were then used to measure mechanical pain sensitivity in the injected paw. **Results:** We found that pharmacological isolation of NI-NMDAR activity significantly decreased the overall magnitude of dorsal horn LTP in spinal cord explants. Importantly, this reversal of spinal LTP translated into significant decreases in mechanical pain sensitivity in vivo following capsaicin- or CFA-induced hyperalgesia. **Conclusion:** Our results identify NI-NMDAR signaling as a promising new target for the treatment of chronic pain.

SYNAPTIC PLASTCITY

Muchun Han; Department of Physiology

Supervisor: Dr. Graham L. Collingridge

BRIEF APPLICATION OF (S)-KETAMINE CAUSES LONG-TERM DEPRESSION OF NMDA RECEPTOR-MEDIATED SYNPATIC TRANSMISSION IN THE MOUSE HIPPOCAMPUS

Han M; Tidball P; Georgiou J; Collingridge GL

Department of Physiology, University of Toronto; Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital;Tanz Centre for Research in Neurodegenerative Diseases, University of Toronto

Introduction: Ketamine, an open-channel blocker of the N-methyl-D-aspartate receptor (NMDAR), has been shown to have rapid and sustained antidepressant effects after a single sub-anesthetic dose. Among its two enantiomers, (S)-ketamine acts more potently at NMDARs than (R)-ketamine, and its use as an antidepressant was approved by the FDA in 2019. **Objectives:** Given that the mechanism underlying ketamine's sustained antidepressant action remains unclear, we investigated if (S)-ketamine has any long-term effect on NMDAR-mediated synaptic transmission. **Methods and Results:** In extracellular recordings from the CA1 region of mouse hippocampal slices, we found that a 20 min application of 10 μM (S)-ketamine resulted in a long-term depression (LTD), lasting >2 h, of NMDAR-mediated synaptic responses recorded in low (0.2 mM) magnesium conditions. This LTD effect was eliminated when (S)-ketamine was applied in the presence of 1 mM magnesium, suggesting that binding of (S)-ketamine to the pore of NMDARs is required for its induction. In contrast, (S)-ketamine's effects were not dependent on the electrical stimulation protocol, since neither the acute nor long-term inhibition of NMDAR-mediated responses were affected by an increase or pause in test-frequency stimulation. Finally, we found that the LTD effect of (S)-ketamine was not reversed by a subsequent application of 1 mM magnesium, whereas the slow wash-out of memantine (another NMDAR channel blocker) was accelerated by magnesium. **Conclusion:** Together, our results suggest that brief exposure to (S)-ketamine can lead to long-lasting changes in NMDAR-dependent synaptic function, which may be relevant to ketamine's antidepressant action.

Quinn Pauli; Graduate Department of Pharmaceutical Sciences

Supervisor: Dr. Rob Bonin

DISTINCT ROLES FOR IONOTROPIC AND NON-IONOTROPIC NMDA RECEPTOR-MEDIATED SIGNALING IN SYNAPTIC DEPOTENTIATION IN THE RODENT HIPPOCAMPUS

Pauli Q, 1; Bonin R, 1, 2

1 Department of Pharmaceutical Sciences, University of Toronto, Toronto, ON; 2 University of Toronto Centre for the Study of Pain, University of Toronto, Toronto, ON

Introduction: Adaptive forgetting or memory modification can occur in the face of changing information. During memory formation, synapses in the hippocampus are strengthened, referred to as long-term potentiation. Reflecting the dynamic nature of memory, long-term potentiation can also be subsequently modified. There is evidence that weakening of previously strengthened synapses (depotentiation) may underlie forgetting. The NMDA receptor is critically involved in synaptic modification by recruiting distinct ion flux-dependent and -independent cascades. **Objectives:** Therefore, the aim of this project is to interrogate the involvement of NMDA receptor signaling in depotentiation. **Methods:** Electrophysiological recordings were obtained in hippocampal slices from male and female C57Bl/6 mice to monitor synaptic strength over time. Long-term potentiation was electrically induced at CA3-CA1 synapses. The susceptibility of different types of long-term potentiation to depotentiation was then assessed using a low frequency electrical stimulation pattern, and NMDA receptor antagonists were applied during depotentiation. **Results:** We confirmed that different types of long-term potentiation exhibit varying susceptibility to depotentiation. Additionally, we show that the ion flux-dependent and -independent NMDA receptor cascades recruited during depotentiation depend on the type of long-term potentiation induced. Similar results were obtained in hippocampal slices obtained from both male and female mice. Future experiments will aim to test the molecular mechanisms recruited during long-term potentiation that enable or prevent depotentiation. **Conclusions:** Our results show that the NMDA receptor pathways recruited during synaptic depotentiation may depend on the type of long-term potentiation induced. These results have important implications for how different types of memories are forgotten and why certain memories resist modification.

TRANSLATIONAL RESEARCH

Ilakkiah Chandran; Institute of Medical Science

Supervisor: Dr. Danielle Andrade

TRANSITION IN EPILEPSY: THE HEALTHCARE PRACTITIONER PERSPECTIVE

Chandran I, 1; Patel P, 2; Rubboli G, 3; Cross H, 4; Craiu D, 5; Tan CT, 6; Ali QZ, 1; Marques P, 1; Kerrigan B, 1; Ji C, 1; Kija E, 7; Siddiqui M, 8; Jetté N, 9; Carrizosa J, 10; Nabbout R, 11; Andrade D, 1

1 Adult Genetic Epilepsy (AGE) Program, University Health Network, Toronto, Canada; 2 Montefiore Medical Center New York, USA; 3 University of Copenhagen, Copenhagen, Denmark; 4 The Prince of Wales Childhood Epilepsy, Pediatric Neurology at UCL Institute of Child Health, London, England; 5 Carol Davila University of Medicine, Bucharest, Romania; 6 Department of Medicine, University of Malaya, Malaysia; 7 Muhimbili University of Health and Allied Sciences, Tanzania; 8 University of Alberta, Canada; 9 Department of Clinical Neurosciences, University of Calgary, Canada; 10 Pediatric Neurology Service, Pediatric Department, University of Antioquia, Columbia; 11 Necker-Enfants Malades Hospital, Paris, France

Introduction: Approximately 1.1 million children with epilepsy become adults every year. Moving from the pediatric to adult health care can be troublesome, and transition guidelines have been suggested, although not implemented in most places. The International League Against Epilepsy (ILAE) has set a Transition from Pediatric to Adult Care Task Force, and their first goal was to review the current situation in different parts of the world.**Objective**: This study aimed to understand the perspectives and attitudes of healthcare practitioners on the challenges of transitioning epilepsy patients to adult care. By understanding these perspectives, we aim to identify the barriers preventing satisfactory transition while examining the elements needed for successful transitions. **Methods**: A questionnaire was distributed to practitioners worldwide through ILAE Chapters in 8 languages. The responses were then analyzed through descriptive analyses and qualitative summaries. **Results**: 306 practitioners from 55 countries responded to our questionnaire. 52% of respondents were adult neurologists and 45% were child neurologists. 58% of respondents describe the availability of an adult neurologist with knowledge of the condition impacts patient transition. The three most common practitioner-perceived barriers to building and sustaining transition programs found were: Lack of multidisciplinary teams (90%); Patients feel attached to the childcare system (89%); Limited education and training for transition in epilepsy (81%); Respondents also perceived adult practitioners as less comfortable treating childhood epilepsies (67%) and likely not comfortable following patients with complex epilepsies, multiple comorbidities, and previously failed treatments as a barrier to transition (68%). **Conclusions**: This ILAE Transition Task Force survey highlights the views of a large number of HCP in 38 countries about transition in epilepsy. It also identifies perceived barriers such as lack of funding, multidisciplinary teams, and accessibility, which can help policymakers target specific issues to make structured transition programs possible.

Xinyang Zhang; Department of Physiology

Supervisor: Dr. Hong-Shuo Sun

TRPM7 KINASE INHIBITION EXERTS NEUROPROTECTIVE EFFECTS ON NEONATAL HYPOXIC-ISCHEMIC BRAIN INJURY

Zhang X, 1,2; Luo Z, 1,2; Ovcjak A, 1; Feng ZP, 1; Sun HS, 1,2

1 Department of Physiology, Temerty Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada; 2 Department of Surgery, Temerty Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada

Introduction: Hypoxic-ischemic brain injury (HIBI) describes deleterious brain damage occurring perinatally, leading to significant neonatal mortality and disability worldwide, yet with limited therapeutics available. Involved in mediating ischemic and hypoxic brain damage, transient receptor potential melastatin 7 (TRPM7) includes both a divalent cation channel and an atypical α-kinase domain, thus functioning as a channel-kinase. Compared to its channel function, TRPM7 kinase activity is not well understood in the pathophysiology of HIBI. **Objective**: To evaluate whether TG100-115, a novel and potent pharmacological inhibitor of TRPM7 kinase, provides both short- and long-term neuroprotection against HIBI in vivo. **Methods:** We surgically established the HIBI model in postnatal day 7 CD-1 mice, and quantified brain injury using both histological and morphological measurements. Neurobehavioral assessments were conducted to detect functional recovery. Multiple doses of TG100-115 were administered to identify the optimal dose, which was then given at various time points to ascertain the therapeutic window. **Results**: TG100-115 pre-HIBI-30-min-treatment significantly reduced cerebral infarction at 24 hours post-HIBI, with 2.5 mg/kg identified as the optimal dose based on three effective doses (1, 2.5, and 5 mg/kg). Post-treatments up to 3 (1, 2, and 3) hours after HIBI also decreased infarction volume. Pre-HIBI-30-min- and post-HIBI-1-hour-treatment enhanced cliff avoidance, geotaxis, righting reflex, grip strength, and increased mouse body weight during a 7-day observation following HIBI onset. Furthermore, these treatments diminished brain liquefaction volume and mass loss, preserving brain morphology. Four weeks post-HIBI, neurobehavioral performances (accelerated rotarod, novel object recognition, and passive avoidance), body weight, and brain morphology were improved by post-HIBI-1-hour-treatment, illustrating long-term neuroprotection. **Conclusion**: TG100-115 exerts neuroprotection against HIBI and the TRPM7 kinase domain holds potential as a therapeutic target for HIBI.

SESSION V

NEUROPHARMACOLOGY

Christina Pereira; Institute of Medical Science

Supervisor: Dr. Stefan Kloiber

FATTY ACID AMIDE HYDROLASE LEVELS IN SOCIAL ANXIETY DISORDER: A REPLICATION PET STUDY WITH THE TRACER [11C]CURB

Pereira CF, 1,2; Ahmed M, 3; Firdiawati R, 1; Rusjan PM, 4; Tyndale RF, 1,5,6; Husain MI, 1,6; Le Foll B, 1,2,5,6,7,8; Zai G, 1,2,6; Boileau I, 1,2,5,6; Kloiber S, 1,2,5,6

1 Centre for Addiction and Mental Health, Toronto, Ontario Canada; 2 Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada; 3 Schulich School of Medicine and Dentistry, University of Western Ontario, London, Ontario, Canada; 4 Department of Psychiatry, McGill University, Montreal, Quebec, Canada; 5 Department of Pharmacology and Toxicology, University of Toronto, Toronto, Ontario, Canada; 6 Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada; 7 Translational Addiction Research Laboratory, Toronto, Ontario, Canada; 8 Department of Family and Community Medicine, University of Toronto, Toronto, Ontario, Canada

Introduction: Novel interventions are needed for social anxiety disorder (SAD) given the magnitude of non-responders. Fatty acid amide hydrolase (FAAH), the metabolizing enzyme of anandamide, is an emerging treatment target as FAAH inhibition decreases rodent anxiety and enhances sociability. FAAH inhibitors are now being explored to treat SAD, however little is known about this enzyme in humans. Our institution, CAMH, developed a radiotracer ([11C]CURB) to quantify human brain FAAH using positron emission tomography (PET). Brain FAAH was 8.8% elevated in SAD in a preliminary study, suggesting FAAH's potential involvement. However, the SAD sample was small, and healthy controls' (HCs) social anxiety was not characterized. **Objective:** This project aims to replicate this in a larger sample compared to HCs with low social anxiety. Methods: Participants completed a [11C]CURB PET scan with assessments and genotyping for the FAAH C385A polymorphism. PET data were analyzed producing a reliable indicator of FAAH levels, lk3. Mean brain FAAH was calculated using nine regions. **Results**: Individuals with SAD [n=4; M/F:1/3; age:27.8(±5.9)] and HCs [n=11; M/F:6/54; age:24.7(±3.3)] completed the study. No difference in mean brain FAAH (lk3) emerged across the whole sample (SAD mean = 0.169; HC mean = 0.169). Although, when correcting for FAAH C385A, individuals with SAD had 3.5% higher brain FAAH (n=3; mean = 0.176) compared to HCs (n = 8; mean = 0.170). Statistical analysis is pending with larger sample. **Conclusion:** PET imaging offers the unique ability to quantify this enzyme in SAD. These findings can improve our understanding of SAD neurobiology. If FAAH is elevated in SAD, this information can guide the potential use and development of endocannabinoid-targeting treatments in SAD.

Nayaab Punjani; Institute of Medical Science

Supervisor: Dr. Michael G. Fehlings

NEUROPROTECTIVE SUBCOMMISSURAL ORGAN– SPONDIN DERIVED PEPTIDE FOR TISSUE REPAIR AND FUNCTIONAL RECOVERY IN CERVICAL TRAUMATIC SPINAL CORD INJURY

Punjani N, 1,2; Lemarchant S, 3; Altamentova S, 2; Chio JCT, 4; Hong J, 2; Wang J, 2; Godfrin Y, 3,5; Fehlings MG, 2,6

1 Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada; 2 Genetics and Development, Krembil Research Institute, University Health Network, Toronto, Ontario, Canada; 3 Axoltis Pharma, Lyon, France; 4 Tulane University School of Medicine, New Orleans, Louisiana, United States of America; 5 Godfrin Life-Sciences, Caluire-et-Cuire, France; 6 Division of Neurosurgery and Department of Surgery, University of Toronto, Toronto, Ontario, Canada

Introduction: Spinal cord injury (SCI) limits sensory and motor function at and below the level of the injury, with 60% of cases occurring at the cervical level, often with more severe complications including impaired respiratory function, as well as urinary and bowel incontinence. The initial physical injury is followed by secondary cascades including disruption to the blood-spinal cord barrier, inflammation, and scar formation, further impacting neuron cell survival and regeneration. NX is a 12 amino acid peptide derived from the subcommissural organ (SCO)-spondin, a protein proposed to be involved in vertebrate spinal cord regeneration. **Objective**: Evaluate the efficacy of NX to promote functional recovery and tissue repair in a rat cervical traumatic SCI model. **Methods**: Female adult Wistar rats received a clip compression-contusion injury at the C6/C7 level of the spinal cord to model incomplete traumatic SCI in humans. Injured rats were randomized into 4 groups, to receive one daily dose of either NX (8mg/kg) or vehicle intraperitonially, starting 4 hours (h) or 8h post-SCI (n=16-17/group). 12 sham rats received a laminectomy and vehicle treatment beginning at 4h post-surgery. Neurobehavioral tests were performed for up to 8 weeks post-injury, and rats were then sacrificed for histological assessments. **Results**: Early initial administration of NX increased forelimb grip strength and improved several aspects of locomotion including regularity index and base of support of the forelimbs (CatWalk). Delaying initial administration of NX to 8h, promoted weight gain, accelerated bladder control recovery from 14 to 9 days post-injury, and improved trunk balance (inclined plane) as early as one-week post-injury. Using histology (n=6/group) greater white matter preservation, reduced cavity size, as well as higher synaptic and neuronal soma counts were observed with NX beginning at 8h post-injury. **Conclusion**: NX targets various aspects of SCI, improving motor function, bladder control, white matter preservation, and neuronal counts, with more benefits observed at the later initial injection timepoint. We anticipate that this study will provide a strong proof of concept for its use as a treatment for acute SCI patients, with the delayed timepoint allowing for translational ease of administration.

Emily Smith; Institute of Medical Science

Supervisor: Dr. Margaret Hahn

DYSGLYCEMIA ASSOCIATED WITH ANTIPSYCHOTIC USE: A SYSTEMATIC REVIEW AND META-ANALYSIS

Smith E, 1,2; Panganiban K, 1,2; Maksyutynska K, 1,2; Lee J, 1; Prasad P, 1; Pereira S, 1,2; Monteiro J, 3; Kaushik V, 1; Fuller K, 4; McCarthy M, 5; Ballon J, 6; Prestwood T, 6; Correll C, 7; Agarwal SM, 1,2,8; Freyberg Z, 9; Hahn M, 1,2,8

1 University of Toronto, Toronto, Ontario, Canada; 2 Centre for Addiction and Mental Health, Toronto, Ontario, Canada; 3 McMaster University, Hamilton, Ontario, Canada; 4 St. Francis Xavier University, Antigonish, Nova Scotia, Canada; 5 University of California San Diego, San Diego, California, USA; 6 Stanford University, Stanford, California, USA; 7 Zucker School of Medicine, Hempstead, New York, USA; 8

Banting & Best Diabetes Centre, Toronto, Ontario, Canada; 9 University of Pittsburgh, Pittsburgh, Pennsylvania, USA

Introduction: Antipsychotics (APs) are the cornerstone of treatment for schizophrenia spectrum disorders (SSDs) and are approved for the treatment of affective disorders including bipolar disorder (BD) and major depressive disorder (MDD). However, AP use is associated with severe metabolic consequences including weight gain, dyslipidemia, and dysglycemia. Although studies indicate that glucose dysfunction can occur independently of weight gain, glycemic changes associated with AP use are usually considered to be a consequence of AP-induced weight gain. **Objective**: Therefore, the aims of this review are to 1) specifically clarify the effect of APs on glucose homeostasis independently of weight gain and 2) determine whether APs similarly impact glycemic control independently of drug class and treatment duration. **Methods**: We searched MEDLINE, EMBASE, PsychINFO, CENTRAL, CINAHL, and Web of Science from inception to August 2023 to identify all randomized controlled trials (RCTs) that compared the effect of APs on glucose metabolism to placebo (PBO), with no restriction on psychiatric diagnosis. Glucose dysfunction was examined using a random effects meta-analysis, with subgroup analyses for study length, AP type, and age (child/adolescent vs. adult). Where possible, meta-regression analyses were conducted to explore the effects of weight gain, study length, and AP dose on changes in glucose parameters. **Results:** Of 20954 references identified in our search, 92 RCTs in patients with SSDs (N=49 studies), BD (N=38 studies), and MDD (N=5 studies) met our inclusion criteria. Across all diagnoses, AP use was associated with a significantly greater increase in blood glucose compared to placebo when considering all available data (mean difference (MD) = 0.05 mmol/L [0.03, 0.07], p<0.00001, I2=21%, n=20124 AP vs. n=10637 PBO) and when only considering values collected under fasting conditions (MD = 0.05 mmol/L [0.03, 0.07], p<0.0001, I2=23%, n=16723 AP vs. n=8546 PBO). Similarly, AP-treated patients were more likely than PBO-treated patients to experience hyperglycemia, defined as fasting glucose ≥126 mg/dl (odds ratio = 1.29 [1.01, 1.64], p=0.04, I2=0%, n=5199 AP vs. 3019 PBO). Study length, AP type, and age did not alter either of these findings. Plasma insulin was also significantly increased by AP exposure (MD all values = 12.37 pmol/L [6.68, 18.06], p<0.0001, I2=35%, n=7518 AP vs. n=3640 PBO; MD confirmed fasting = 11.44 pmol/L [5.20, 17.69], p=0.0003, I2=37%, n=6499 AP vs. n=2974 PBO), with significant subgroup differences according to AP type and age but not study length. Importantly, the strength of the effect of different APs on blood glucose did not appear to follow the established hierarchy of weight gain liabilities outlined in the literature. Specifically, so-called 'weight neutral APs' such as ziprasidone and lurasidone produced comparable dysglycemia to APs traditionally associated with significant weight gain like olanzapine (p=0.28, I2=17.4%). Subsequent meta-regression analyses found that AP-associated increases in fasting glucose may be independent of change in weight, change in BMI, study length, mean AP dose, and cumulative AP dose (all p > 0.05) and that increases in fasting insulin may be independent of study length and AP dose (mean and cumulative) (all p > 0.05). **Conclusion**: Our review demonstrates that both short- and long-term exposure to APs are associated with a significant increase in dysglycemia risk as indicated by AP-induced elevations in blood glucose and insulin. Furthermore, all APs cause some degree of glucose dysregulation regardless of exposure time and established propensities for AP-induced weight gain. Further studies are required to better understand how AP use contributes to dysglycemia, including temporal changes throughout the treatment course, and how these effects could potentially be mitigated using metabolic interventions.

NEUROPHYSIOLOGY

Kayla Baker; Institute of Medical Science

Supervisor: Dr. Gaspard Montandon

IDENTIFYING THE ROLE OF GABAERGIC CELLS IN THE PERIAQUEDUCTAL GREY AND THE PREBOTZINGER COMPLEX IN BREATHING AND RESPIRATORY DEPRESSION BY OPIOIDS

Baker KS, 1,2; Scarpellini C, 2; Montandon G, 1,2,3

1 Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada; 2 Keenan Research Center for Biomedical Science, St. Michael's Hospital, Unity Health Toronto, Toronto, Ontario, Canada; 3 Division of Respirology, Department of Medicine, University of Toronto, Toronto, Ontario, Canada

Introduction: Breathing is an essential process that is maintained by brainstem regions that are vulnerable to drugs such as opioids to cause respiratory depression. Opioids are widely prescribed analgesics, but this respiratory side effect can be lethal and limits the use of opioids safely. To understand how opioids depress breathing it is critical to identify the neural circuits that control respiratory rhythms and how they overlap with analgesia. Two key brain regions in this pathway are the preBötzinger Complex (preBötC) which generates inspiratory activity, and the periaqueductal grey (PAG) which is involved in analgesia. Inhibitory GABA cells in these brain regions express the mu-opioid receptor meaning they can be targeted by opioids, but the role of these GABA cells in the control of breathing and respiratory depression is unknown. **Objectives:** We aim to identify the role of the GABAergic preBötC and PAG cells in breathing and respiratory depression using in vivo optogenetics and hypothesize that optogenetic activation of inhibitory preBötC and PAG neurons will depress breathing. **Methods:** To stimulate GABA neurons, we stereotaxically injected a cre-dependent adeno-associated virus expressing either the excitatory channelrhodopsin or the inhibitory archaerhodopsin in the region of interest of vesicular GABA transporter (vGAT)-cre mice. We measured breathing using diaphragm activity in anesthetized mice and whole-body plethysmography in freely behaving mice while we stimulated GABA cells with blue light and inhibited cells with green light. **Results and Conclusions**: We found that preBötC vGAT cell excitation depresses breathing and inhibition can trigger inspiratory activity. These data suggest that the inhibitory preBötC cells are involved in modulating inspiration timing. Current studies focus on identifying the role of PAG GABA cells in breathing. Determining the role of GABA cells in respiration allows us to better understand what is occurring in the brain when breathing is depressed by opioids.

Hanne Bartels; The Hospital for Sick Children

Supervisor: Dr. Karen Gordon

CORTICAL EFFECTS OF COCHLEAR IMPLANTATION IN CHILDREN WITH PRELINGUAL ASYMMETRIC HEARING LOSS

Bartels H, 1; Gordon K, 1

1 Archie's Cochlear Implant Laboratory, The Hospital for Sick Children, Toronto, ON, Canada

Introduction: As children with asymmetric hearing loss (AHL) face various academic challenges, cochlear implants (CI) have become the standard treatment. However, achieving true binaural hearing continues to be a challenge. It is unknown whether the cortical and behavioral effects of AHL are different for children with left versus right-sided

deafness, or whether the protection provided by the CI might be different. We hypothesize that left-sided deafness (a right-ear advantage) results in stronger effects on cortical processing. **Objective:** The objective of the present study was to investigate whether the behavioral and cortical effects of early cochlear implantation are different for children with deafness in the left versus right ear. **Methods:** To test this hypothesis, 69 children who received a CI following limited durations of prelingual unilateral severe hearing loss [mean (±SD) = 2.07 (±1.52)] were included in this study. Children had normal hearing in the contralateral ear [(n = 42 (60.9%)] or used a hearing aid for a mild to moderate hearing loss [PTA < 60dB, n = 27 (39.1%)] and 39 (53.6%) had a left cochlear implant. Cortical auditory evoked potentials (CAEPs) could be measured in 61 children (average of 2.85 recordings per child) using multi-channel electroencephalography at initial (≤ 2 weeks, n = 33), early (1-3 months, n = 49) and after chronic CI use (≥3 months, n = 96). Stimuli consisted of 36ms trains of acoustic clicks/biphasic electric pulses at a rate of 250 Hz, repeated at 1 Hz and were presented unilaterally to the CI and acoustic hearing ear (AH-ear) alone, as well as bilaterally. Localization of early auditory detection was performed using the time-restricted artifact and coherent source suppression (TRACS) beamformer. Measurements were peak dipole moments and corresponding latencies. Cortical lateralization and aural preference were calculated from dipole moments in left and right auditory cortex, with more positive values indicating stronger right hemispheric dominance and contralateral ear preference, respectively. **Results:** Immature auditory detection measured by peak dipole moments were significantly larger in the right compared to the left auditory cortex ($p < 0.001$), and was weaker for stimulation of the CI-ear alone than the AH-ear ($p < 0.001$) alone or bilateral stimulation ($p = 0.005$). Peak latency decreased with time ($p < 0.001$) and was shorter for stimulation of the AH-alone than CI-alone ($p < 0.001$) or bilateral condition ($p = 0.001$). At initial CI-use, cortical lateralization [median (IQR) = 11.14% (-21.73% - 40.19%)] was not weighted to either hemisphere and showed no correlation to side of deafness ($p = 0.85$) or stimulation mode ($p = 0.53$). Interestingly, chronic CI-use revealed proportional shifts in hemispheric lateralization across all conditions. Linear regression indicated a significant inverse relationship between initial CL values and slope of evolution of CL over time ($p < 0.001$). **Conclusion:** By investigating the cortical effects of cochlear implantation and comparing outcomes between left- and right-sided deafness, this study helps improve our understanding of the benefit of a CI in children with AHL. Our results demonstrate no clear ear-dependent differences in cortical processing in children with asymmetric hearing at initial CI-use, revealing altered auditory processing from each ear. This occurs for children with either left or right sided deafness. However, cortical shifts with ongoing cochlear implant use reveal plasticity to bilateral input and ongoing work will assess effects of deprivation related cortical plasticity and consistency of cochlear implant use on the cortical changes with cochlear implant use reported here.

Darshan Panesar; Developmental Psychology & Education; Applied Psychology and Human Development, Ontario Institute for Studies in Education

Supervisor: Dr. Kang Lee

NOVEL CONTACTLESS MONITORING OF SLEEP PSYCHOPHYSIOLOGY

Panesar D, 1; Lee K, 1

1 Applied Psychology and Human Development, Ontario Institute for Studies in Education, University of Toronto

Introduction: Sleep is essential for a healthy life. Our current understanding of sleep psychophysiology is still limited, due to the fact that conventional measures are disruptive and impractical to measure natural sleep. **Objectives:** This pilot study examined a novel method of contactless psychophysiological monitoring called infrared-video photoplethysmography (IR-VPPG) in comparison with conventional sleep physiological (e.g., BIOPAC) and observational measures. We predicted that IR-VPPG measurements of psychophysiology would demonstrate strong agreement and strong correlation with conventional measures of psychophysiology. **Methods:** We assessed 11 adult participants (Mage = 24.18 years) during a short rest/sleep in a lab environment. We monitored participants during their nap using specialized infrared recording, ECG and respiratory monitoring. Using specialized video processing and machine learning models we extracted a wide range of psychophysiological activities (e.g., Heart Rate, Breathing, Stress, Emotion etc.) from the collected data. We then contrasted this data to the conventional sleep physiologicaal and observational measures. **Results:** Our results for heart rate and breathing demonstrated low error and a high agreement between our method and the conventional monitoring methods. As a first, our method measured both stress and emotion of participants during sleep. **Conclusion:** This study provides preliminary evidence for a revolutionary contactless method to monitor sleep naturalistically and accurately. We hope to provide this contactless tool to users, researchers, and clinicians to monitor and measure psychophysiological features during sleep. Potential applications of this technology in psychophysiological research and other fields are discussed.

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