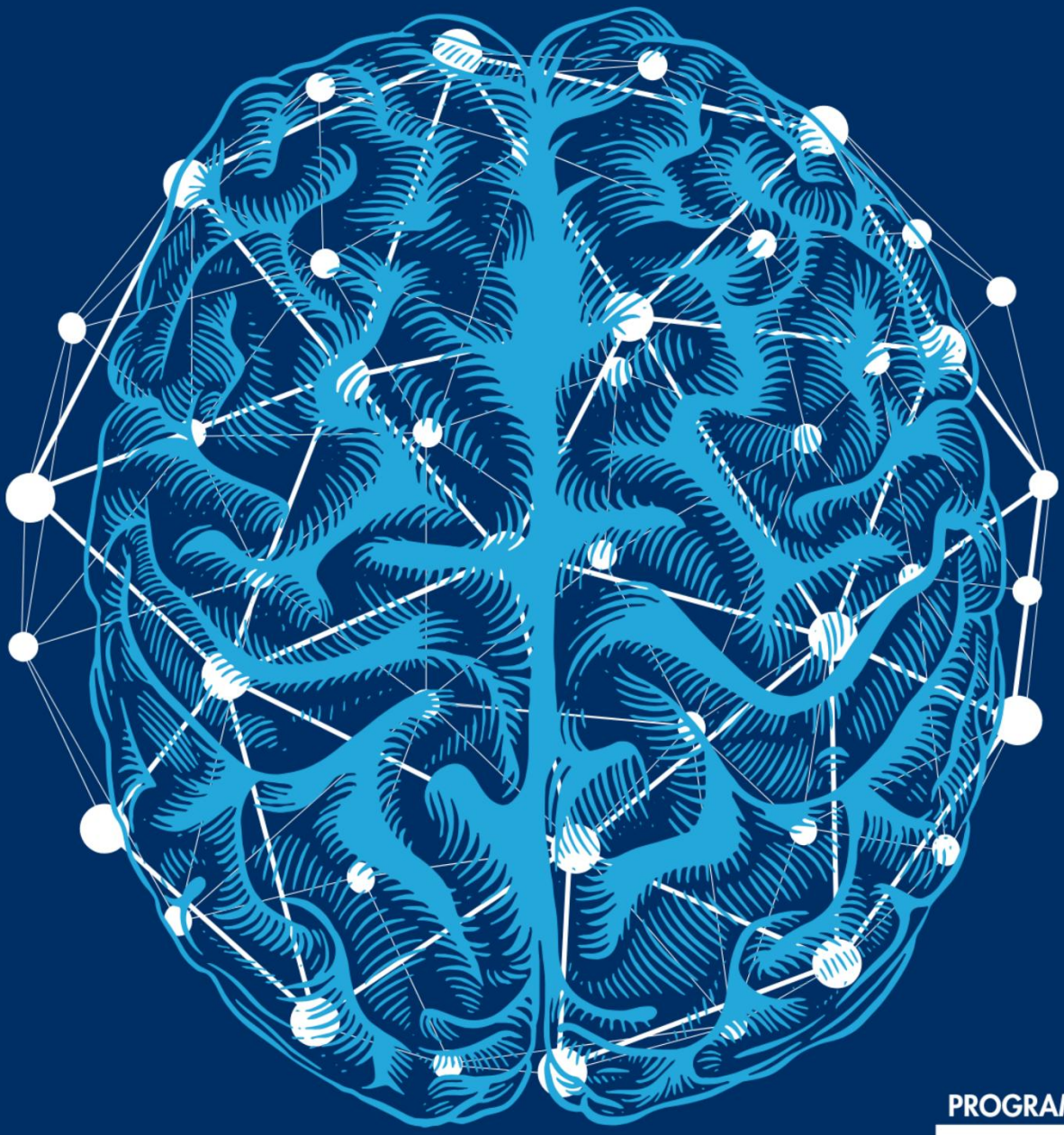
COLLABORATIVE PROGRAM IN NEUROSCIENCE (CPIN)

UNIVERSITY OF TORONTO 2025 CPIN RESEARCH DAY



PROGRAM SCHEDULE

MEETING PROGRAM

JUNE 24, 2025, 9AM
MEDICAL SCIENCE BUILDING,
1 KING'S COLLEGE CIRCLE, TORONTO, ON

COVER ART: ANGENELLE EVE ROSAL

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Collaborative Program in Neuroscience (CPIN)

2025

CPIN RESEARCH DAY

Tuesday, June 24th, 2025

Medical Sciences Building (MSB), 1 King's College Circle, Toronto, ON

Program Schedule

9:00 AM	**Registration, Poster Setup, and Poster Viewing**	Stone Lobby
10:00 AM	**Welcome and Opening Remarks** Dr. Zhong-Ping Feng	MSB2158 JJR Macleod Auditorium
10:15 AM	**Speaker I:** Dr. Derek Van Der Kooy – *"How to Make a Mammalian Eye"* **Moderator:** Dr. Jeffrey Henderson	
11:00 AM	**Speaker II:** Dr. John Peever – *"REM Sleep in Health and Disease"* **Moderator:** Dr. Kaori Takehara	
11:45 AM	**CPIN Trainee Poster Presentation/Evaluation** (lunch will be provided for early registrants)	Stone Lobby
1:30 PM	**Workshop:** Dr. Gabor Kovacs – *"Introduction to Neuropathology and AI in understanding Neurodegenerative Disorders"* **Moderator:** Dr. Ain Kim	MSB2158 JJR Macleod Auditorium
2:30 PM	**CPIN Trainee Oral Presentation/Evaluation Session I** Section I. *Clinical & Translational Neuroscience* Section II. *Integrative Social, Behavioral, and Computational Neuroscience* Section III. *Molecular Neuroscience & Neurodegenerative Disorders* Section IV. *Pain, Sensation, and Neural Circuits* Section V. *Psychiatric Disorders*	MSB2158 JJR Macleod Auditorium MSB2170 MSB2171 MSB2173 MSB3278
3:15 PM	**CPIN Trainee Oral Presentation/Evaluation Session II** Section I. *Clinical & Translational Neuroscience* Section II. *Integrative Social, Behavioral, and Computational Neuroscience* Section III. *Molecular Neuroscience & Neurodegenerative Disorders* Section IV. *Pain, Sensation, and Neural Circuits* Section V. *Psychiatric Disorders*	MSB2158 JJR Macleod Auditorium MSB2170 MSB2171 MSB2173 MSB3278
4:00 PM	**Keynote Speaker:** Dr. Daniel Drucker – *"Will GLP-1 medicines change the neuroscience landscape?"* **Moderator:** Dr. Hong-Shuo Sun	
5:00 PM	**Awards Ceremony & Closing** *Jonathan Dostrovsky Awards in Neuroscience* *Trainee Presentation awards* Dr. Zhong-Ping Feng Dr. Jeffrey Henderson Dr. Ain Kim	MSB2158 JJR Macleod Auditorium
5:30 PM	**Reception**	Stone Lobby

Keynote Speaker

Daniel Drucker, OC, MD, FRCPC, FRSC, FRS. Professor, Department of Medicine, University of Toronto.

"Will GLP-1 medicines change the neuroscience landscape"

Dr. Daniel Drucker is a clinician-scientist internationally recognized for his groundbreaking work in endocrinology and metabolic research, and a recent recipient of the 2025 Breakthrough Prize in Life Sciences. He will deliver a keynote lecture at the 2025 CPIN Research Day titled "Will GLP-1 medicines change the neuroscience landscape?" His research has focused on discovery and characterization of GLP-1 and understanding how GLP-1 regulates blood sugar, appetite, as well as gastrointestinal and brain function.

Featured Speakers

Derek Van Der Kooy, PhD. Professor, Department of Molecular Genetics and Institute of Medical Science, University of Toronto.

"How to Make a Mammalian Eye"

Dr. Van Der Kooy's work first established the presence of adult neural stem cells within the mammalian brain. His work laid the foundation for the mechanism by which embryonic stem cells directly differentiate into neural stem cells and provided the first demonstration of stem cells within the adult mammalian eye, in addition to work on learning and memory, mechanisms of opiate reward and pancreatic stem cells. Dr. van der Kooy is a prior recipient of the Heinz Lehmann and Till & McCulloch Awards and a member of Royal Society of Canada.

John Peever, PhD. Professor, Department of Cell & Systems Biology, University of Toronto Vice-Dean, Students, School of Graduate Studies; President, Canadian Sleep Society.

"REM Sleep in Health and Disease"

Dr. John Peever is an expert in the neural control of sleep, with a special focus on mechanisms governing REM sleep. His work uncovers how REM sleep contributes to cognitive function, emotional regulation, and brain health — and how its disruption can contribute to neurological and psychiatric disease. He also leads initiatives supporting graduate student development and sleep health across Canada.

Professional Development Workshop Speakers

"Introduction to Neuropathology and AI in understanding Neurodegenerative Disorders"

Gabor G. Kovacs, MD, PhD, FRCPC. Professor, Department of Laboratory Medicine and Pathobiology Consultant Neuropathologist/Neurologist, UHN Principal Investigator, Tanz Centre for Research in Neurodegenerative Disease.

Dr. Gabor Kovacs' major research interest is the neuropathology of neurodegenerative diseases. He has published more than 380 peer-reviewed papers, earning him an H-index above 69, and edited two books on Neuropathology. Dr. Kovacs's aim is to use his expertise in the neuropathology of neurodegenerative diseases to enhance the excellent Neuropathology team at LMP, to probe the molecular mechanisms underlying neurodegenerative proteinopathies using state-of the-art methodologies and to facilitate collaborative research on neurodegenerative disorders at the Krembil Brain Institute and Tanz Centre for Research in Neurodegenerative Disease.

Ain Kim, PhD. Post-Doctoral Researcher, Tanz Centre for Research in Neurodegenerative Disease, University of Toronto.

Dr. Ain Kim's research explores the application of artificial intelligence (AI) to transform and deepen our understanding of neurodegenerative diseases, with a particular emphasis on the morphological, biochemical, and cytopathological characterization of these diseases.

Poster Presenter Groups

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	20	Sarah Eide		37	Kristoffer Panganiban
	28	Alexandra Koch-Liu		38	Jane Paterson
	42	Angenelle Rosal		53	Meng Yang
	44	Can Sarica		57	Sampson Zhao
	48	Ruth Tran		59	Lola Zovko
Behavioral & Social Neuroscience	25	Kendall Mar	Pain & Sensory Disorders	1	Spencer Abssy
	33	Silvia Margarian		21	Rima El-Sayed
	34	Liv McIsaac		27	Kakeru Kimura
	41	Charlotte Romain		31	Julia Beth Kowaleski
	52	Bozhi Wu		39	Daniel Phan
	54	Meeraal Zaheer		45	Ariana Seyed Makki
	55	Sofiya Zbaranska		51	Abigail Wolfensohn
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	11	Sima Buchnak		17	Riddhita De
	14	Andrew Cheon		22	Kanak Gupta
	18	Joel Diaz		30	Vittala Korann
	24	Samantha Jackson Blodgett		43	Simran Sandhu
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Room	Theme	Abstract #	Name
MSB2158	Clinical & Translational Neuroscience	1	Regina Annirood
		2	Ruobing Chen
		3	Kevan Clifford
		4	Federico Gaiti
		5	Barbara Gundi
		6	Kathrin Mertel
		7	Elina Nezon
		8	Yutong Sun
MSB2170	Integrative Social, Behavioral, and Computational Neuroscience	9	Mryam Ali
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		11	Madison Fedele
		12	Talia Fiaani
		13	Annelies Hoorn
		14	Zeenat Ladak
		15	Jiya Shah
		16	Rossi Tomin
MSB2171	Molecular Neuroscience & Neurodegenerative Disorders	17	Ilakkiah Chandran
		18	Dipa Chatterjee
		19	Bianca Hill
		20	Ahmad Israwi
		21	Shinwon Kang
		22	Munkyeong Kwon
		23	Jonathan Monteiro
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MSB2173	Pain, Sensation, and Neural Circuits	25	Irina Alymova
		26	Matthew Cormie
		27	Omar Khalil
		28	Faraz Moghbel
		29	Pedram Mouseli
		30	Huseyin Taskin
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MSB3278	Psychiatric Disorders	33	Katharina Göke
		34	Danica Johnson
		35	Shannen Kyte
		36	Kateryna Maksyutynska
		37	Ayesha Rashidi
		38	Alexandra Sas
		39	Earvin Tio
		40	Yutong Wang

Event Organizers

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Zhong-Ping Feng (Chair)
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Hong-Shuo Sun
Kaori Takehara
Ain Kim (Post-Doctoral Lead)
Sarah Eide (Student Co-Lead)
Irina Alymova (Student Co-Lead)

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Kai Ian
Mehvish Jamal
Sofia Gentile
Aysu Kollu
Zuhal Olomi
Angenelle Eve Rosal
Rayan Saghian
Muhammad Shan Sohail
Ryan Yip

Featured Speakers
Daniel Drucker (Keynote Speaker)
Derek Van Der Kooy
John Peever

Trainee Workshop
Gabor G. Kovacs
Ain Kim

Poster Presentation Judges
Robert Bonin
Patricia Di Ciano
Jimmy Fraigne
Jeff Henderson
Tatiana Lipina
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Shraddha Pai
Martin Ralph
Filsy Samuel
Gerold Schmitt-Ulms
Muhammad Shoaib
Nicolette Stogios
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Kaori Takehara
Naomi Visanji
Yuanye (Phoebe) Yan
Tara Zeitoun
Wenda Zhao

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Jeffrey Henderson (Co-Chair)
Baohua Liu
Hong-Shuo Sun
Kaori Takehara
Doug Tweed

Oral Presentation Judges
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Patricia Di Ciano
Zhong-Ping Feng
Carla Elena Mezo Gonzalez
Seojin Lee
Tatiana Lipina
Maxwell Shafer
Muhammad Shoaib
Kaori Takehara
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Ain Kim
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Institute of Biomedical Engineering | Warren Chan; Milos Popovic
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
Immunology | Chao Wang; J.C. Zúñiga-Pflücker
Institute of Medical Science | Albert Wong; Mingyao Liu
Laboratory Medicine and Pathobiology | Janice Robertson; Rita Kandel
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 | Doug Tweed; Scott Heximer
Physiology | Zhong-Ping Feng (CPN Director; Chair of Committees)
Psychology | Kaori Takehara; Elizabeth Page-Gould
Rehabilitation Science Institute | Karl Zabjek; Angela Colantonio

Poster Presentations

1. Spencer Abssy; Faculty of Dentistry

Supervisor: Dr. Massieh Moayedi

Theme: Pain & Sensory Disorders

ABNORMAL BRAIN RESPONSES TO INNOCUOUS MULTISENSORY STIMULATION IN ADOLESCENTS WITH CHRONIC MUSCULOSKELETAL PAIN

Abssy SS, 1,2; Pascual-Diaz S, 3; Ritacca LG, 1; Mouseli P, 1,2; Biggs E, 4; Hoeppeli ME, 5,6; White J, 4; Angst MS, 4; Aghaeepour N, 4; Gaudillière B, 4; King C, 5,6; Coghill RC, 5,6; Simons LE, 4; López-Solà M, 3; Stinson J, 7; Moayedi M, 1,2*

1 Centre for Multimodal Sensorimotor and Pain Research, University of Toronto Faculty of Dentistry, Toronto, Ontario, Canada; 2 Centre for the Study of Pain, University of Toronto, Toronto, Ontario, Canada; 3 Serra Hunter Programme, Department of Medicine, University of Barcelona, Barcelona, Spain; 4 Department of Anesthesiology, Perioperative and Pain Medicine, Stanford University School of Medicine, Stanford, California, USA; 5 Pediatric Pain Research Center (PPRC), Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA; 6 Department of Pediatrics, University of Cincinnati, Cincinnati, Ohio, USA; 7 Department of Anesthesia and Pain Medicine, The Hospital for Sick Children, Toronto, Ontario, Canada

Introduction: Up to 25% of adolescents suffer from chronic musculoskeletal (MSK) pain, impairing physical, emotional, and social functioning. While altered sensory processing has been observed in adult chronic MSK pain and juvenile fibromyalgia, whether such abnormalities exist in adolescent MSK pain remains unknown. Here, we investigated brain responses to a non-painful multisensory task in adolescents with MSK pain compared to pain-free controls. We hypothesize that MSK pain will have reduced activation in primary sensory cortices, and heightened responses in higher order and integrative cortex, compared to controls. **Methods**: Sixty-nine adolescents with chronic MSK pain and 32 pain-free controls underwent fMRI using a multisensory paradigm (simultaneous auditory tones, visual checkerboards, tactile finger-tapping). Participants rated their unpleasantness after each block, and bodily pain intensity, extent, unpleasantness, task interference at the end of the run. Ratings were compared between groups with a t-test (significance at $p < .05$). Functional MRI were preprocessed in FSL. Task-evoked brain activity was compared between groups (corrected $p < .05$, and uncorrected $p < .001$). **Results**: Controls had significantly lower unpleasantness ratings, and lower pain ratings across all measures ($p < .05$). Controls had higher activation than MSK patients in the left secondary somatosensory, primary and secondary auditory cortices (S2, A1, A2, respectively). Uncorrected images showed bilateral A1 and A2 activation. **Conclusion**: These findings parallel sensory processing deficits observed in adults with fibromyalgia, suggesting shared neural mechanisms across chronic pain conditions. This study provides the first evidence of multisensory cortical alterations in adolescent MSK pain. As the largest fMRI study of multisensory processing in adolescent MSK pain, these findings advance understanding of brain contributions to pediatric chronic pain and underscore the need for longitudinal studies to evaluate neural predictors of clinical outcomes.

2. Ariya Ahona; Department of Pharmacology & Toxicology

Supervisor: Dr. Meghan J. Chenoweth

Theme: Psychiatric Disorders

USING MENDELIAN RANDOMIZATION TO EXPLORE POTENTIAL CAUSALITY UNDERLYING SCHIZOPHRENIA-SMOKING COMORBIDITY

Ahona AN, 1; Giratallah H, 1; Tyndale RF, 1,2; Chenoweth MJ, 1,2*

1 Department of Pharmacology & Toxicology, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada; 2 Centre of Addiction and Mental Health, Toronto, Ontario, Canada

Introduction: Tobacco use disorder (TUD) and schizophrenia (SCZ) are highly comorbid and heritable conditions. Recent studies show shared genetic risk factors between the two disorders, but it remains unclear whether there is any causal relationship underlying this comorbidity. Randomized controlled trials are infeasible due to ethical limitations in populations with these disorders. Mendelian randomization (MR) offers a natural, alternative causal inference approach to discerning potential causality between these disorders. **Objective:** We will explore bidirectional causal relationships between SCZ and TUD using two-sample MR analyses. **Methods:** Summary statistics from published genome-wide association studies (GWAS) were leveraged in two-sample MR analyses between SCZ and two TUD representative traits: cotinine (COT) levels, a biomarker of smoking heaviness, and cigarettes smoked per day (CigDay), a self-reported measure of smoking heaviness. Causal estimation was performed using Steiger-filtered inverse-variance weighted (IVW) fixed effects meta-analysis. Sensitivity analyses assessed instrument validity and robustness of causal estimates. **Results:** Evidence of a causal effect of higher COT levels on higher likelihood of SCZ was indicated by a significant positive causal estimate ($\beta=0.0899$, $p=0.0011$). There was also evidence suggesting a causal effect of SCZ on greater CigDay ($\beta=0.0194$, $p=2.236e-7$). In contrast, MR of SCZ on COT ($\beta=0.0208$, $p=0.4348$) and MR of CigDay on SCZ ($\beta=0.0568$, $p=0.5041$) showed no significant causal effects. No evidence of directional horizontal pleiotropy was detected as all MR Egger regression intercepts were non-significant (ps > 0.18), suggesting our findings were robust. Further sensitivity analyses generally supported the main findings. **Conclusion:** These findings revealed weak, inconsistent causal inferences among SCZ and TUD representative traits. Further instrument filtering, validation, and expanded sensitivity analyses are needed. Leveraging data from additional TUD phenotypes may help clarify SCZ-TUD comorbidity.

3. Alessia Alicandro; Department of Cell and Systems Biology

Supervisor: Dr. Kaori Takehara

Theme: System & Circuits Neuroscience

COMPARISON OF THE PROJECTION DENSITY TO THE LATERAL ENTORHINAL CORTEX AMONG PREFRONTAL CORTICAL SUBREGIONS IN MICE

Alicandro A,1,2; Margarian S, 2,3; Hui T, 3,4; Takehara-Nishiuchi K, 1,2,3

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Introduction The prefrontal cortex (PFC) is involved in a diverse array of cognitive and affective functions, with each function potentially being mediated by distinct subregions. In particular, the role of the PFC in learning and memory relies on close interactions with the hippocampus and the lateral entorhinal cortex (LEC). However, the anatomical organization supporting this interaction is incompletely understood. Therefore, we compared the density of projections to the LEC originating from four subregions of the PFC: the orbitofrontal cortex (OFC), prelimbic cortex (PL), infralimbic cortex (IL), and anterior cingulate cortex (ACC) in mice. **Objective**: To visualize PFC cells projecting to the LEC, retrograde viral vectors carrying EGFP gene were infused into the LEC. **Results**: Between the examined PFC subregions, the highest density of labeled cells was detected in the OFC. Furthermore, the density of labeled cells in the superficial compared to the deep layers were significantly greater in the OFC but not the other subregions. In parallel, variations in viral spread within the LEC, ranging from the superficial layers only to both superficial and deep layers, had a significant correlation with the labeling density in the OFC. Conversely, labeled cells were very sparce in the PL, IL, and ACC when the LEC infection was limited to the superficial layers compared to both the superficial and deep layers. **Conclusion**: These findings reveal that the PFC subregions exhibit distinct patterns in the intensity and targeting of efferents to the LEC, such that the OFC uniformly targets the superficial and deep layers of the LEC, but the PL, IL, and ACC preferentially target the deep layers. These anatomical differences may provide a foundation for the varying involvement of PFC subregions across different stages of memory processes (encoding, consolidation, retrieval) and the content of memory (aversive, appetitive).

4. Dustin Loren Almanza; Department of Medical Biophysics

Supervisor: Dr. Bojana Stefanovic

Theme: Aging & Neurodegenerative Disorders

RESCUE OF ATTENUATED HIPPOCAMPAL NEUROVASCULAR COUPLING IN A RAT MODEL OF ALZHEIMER'S DISEASE FED WITH HIGH CALORIC DIET

Almanza DL, 1,3; Trevisiol A, 1; Koletar M, 1; Hil MI, 2; Stanisz G, 1,3,4; McLaurin J, 2,5; Stefanovic B, 1,3

1 Physical Sciences Platform, Sunnybrook Research Institute, Toronto, Canada; 2 Biological Sciences Platform, Sunnybrook Research Institute, Toronto, Canada; 3 Department of Medical Biophysics, University of Toronto, Toronto, Canada; 4 Department of Neurosurgery and Pediatric Neurosurgery, Medical University, Lublin, Poland; 5 Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Canada

Introduction: Alzheimer's disease (AD) patients exhibit hippocampal dysfunction and atrophy. Vascular comorbidities (e.g., with obesity) are highly prevalent and increase the risk of developing dementia. The interaction of AD pathology and obesity is difficult to study in humans due to the slow course of AD and array of copathologies. Experimental AD models incorporating obesity are needed to establish sensitive and translational imaging assays. **Objective**: To characterize hippocampal functional hyperemia using non-invasive MRI technique in TgF344-AD rat model (TgAD) comorbid with obesity. **Methods**: TgAD rats and their non-transgenic littermates were given three months ad lib access to high carbohydrate, high fat (HCHF) food items before MR imaging them at 12 months of age (established AD). Pseudo continuous arterial spin labeling (pCASL) MRI was utilized to establish an assay of hippocampal neurovascular compromise and its sensitivity to AD/obesity. **Results**: In CHOW-fed cohorts, hippocampal CBF response to forepaw stimulation was attenuated in TgAD rats (7 ± 14 ml/100g/min) relative to nTg rats (49 ± 21 ml/100g/min). In contrast, this CBF response was enhanced with HCHF diet (60 ± 26 ml/100g/min) (diet-genotype, P=0.001). Similarly, volume of activation was attenuated in TgAD rats (0.03 ± 0.08) compared to nTg rats (0.34 ± 0.14, P<0.001); yet enlarged with HCHF diet (0.25 ± 0.15, P<0.001) (diet-genotype, P<0.001). Present neurophysiological improvements were accompanied by restoration of executive function and spatial learning on Barnes maze in additional rats. **Conclusion**: The observed rescue of functional hyperemia with HCHF in established AD, but not in normal aging, is speculated to result from metabolically dysregulated AD brain profiting from calorie-dense food consumption. We have established an assay of hippocampal neurovascular function in AD and its vascular comorbidities with high translational potential. This approach benefits from ease of delivering somatosensory stimuli, minimal impact of aging/neurodegeneration on somatosensation, and recognition that confounding impairments in AD impede patients' ability to perform functional tasks.

5. Lauren Altomare; Institute of Medical Science

Supervisor: Dr. Mojgan Hodaie

Theme: Molecular & Cellular Neuroscience

UNRAVELLING THE EPIGENOMIC LANDSCAPE AND ACCELERATED AGING IN TRIGEMINAL NEURALGIA USING MACHINE LEARNING

Altomare L[1-3]; Li J[2,3*]; Wang J[4]; Yefet L[4]; Agyekum T[3]; Srisaikaew P[3]; Adhamidhis E[2,3]; Sun J[3,6]; Wolfensohn A[2,3]; Wu M[3]; Nassiri F[3-5]; Hodaie M[2-4]

1 Division of Engineering Science, Faculty of Applied Science & Engineering, University of Toronto, Toronto, Ontario, Canada; 2 Institute of Medical Science, Temerty Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada; 3 Krembil Brain Institute, Toronto Western Hospital, University Health Network, Toronto, Ontario, Canada; 4 Division of Neurosurgery, Department of Surgery, Temerty Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada; 5 Princess Margaret Cancer Centre, University Health Network, Toronto, Ontario, Canada; 6 Department of Psychology, Faculty of Arts & Science, University of Toronto, Toronto, Ontario, Canada

Introduction: Trigeminal neuralgia (TN) is a debilitating chronic neuropathic facial pain condition. Among many other environmental factors, chronic pain alters DNA methylation, a form of epigenetic regulation used to estimate the biological age of the body, termed epigenetic age. Epigenetic age reflects the molecular and physiological well-being of biological systems and their components, which has clinical relevance as it can predict health trajectories and outcomes. Using machine learning (ML), we have previously shown that accelerated brain aging is present in TN. However, the impact of TN on the rest of the body and whether epigenetic aging is accelerated in TN remain unclear. Pain-relieving surgery for TN is highly effective. Thus,

the presence of TN pain is a modifiable environmental factor. We hypothesized that epigenetic aging is present in TN and will largely affect the DNA methylation profiles of genes related to the nervous system. **Objective**: To determine epigenetic signatures associated with TN and their roles in biological systems and pathways. **Methods**: Saliva samples (2 mL) were collected from 15 TN patients before they underwent pain-relieving surgery. Saliva data from 32 healthy controls (HC) were obtained from external databases. Saliva samples underwent DNA extraction, extension through polymerase chain reaction, and DNA methylation analysis using Illumina Infinium MethylationEPIC 850K arrays. Principal component analysis (PCA) and differential methylation analysis were used to identify significant genomic loci across the samples. The functions of the ten most significant loci from these analyses were highlighted using Ensembl Genome Browser 114. DNA methylation profiles were also fed into several epigenetic clocks to predict epigenetic ages. **Results**: The first two PCA components explained 25.2% and 21.6% of variance, for a total of 46.8%, across TN and HC methylation patterns. 37 components explained 95% of variance in the data. Genomic loci that highly contributed to these two components included genes associated with neuroplasticity, stress responses, and chromatin remodeling (GRIA4, TAOK3, TJP1, WDR46, ARHGEF3, DIS3L2). Differential methylation analysis between TN and HC identified 203 significantly differing genomic loci ($q < 0.05$). In TN, there was hypermethylation at oncogenic and inflammatory genes (PVT1, RASA2, PTPRU) and hypomethylation of neuroprotective and homeostasis regulators (HDAC4, GRIN2D, E2F1). LncRNAs and intergenic regions exhibited high methylation variability between TN and HC, suggesting regulatory disruption in non-coding regions. Multiple epigenetic clocks determined that epigenetic aging was accelerated in TN compared to HC (PhenoAge, Horvath1, HRSInChPhenoAge, Lin, VidalBralo, Zhang2019: $q < 0.001$; Horvath2: $q = 0.002$). **Conclusion**: Taken together, accelerated epigenetic aging in TN was associated with altered DNA methylation in genomic loci involved in regulating synaptic signaling, immune response, and chromatin architecture. Understanding the epigenetic landscape of TN may provide clinically relevant biomarkers at the intersection of chronic pain and aging. Adopting the perspective of pain as a modifiable environmental factor can push towards more proactive, personalized, and timely care for patients with TN.

6. Kayla Baker; Institute of Medical Science

Supervisor: Dr. Gaspard Montandon

Theme: System & Circuits Neuroscience

MIDBRAIN SOMATOSTATIN CELLS STIMULATE BREATHING AND MOTOR ACTIVITY IN RODENTS IN VIVO

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; 3 Departments of Medicine and Pharmacology & Toxicology, University of Toronto.

Introduction: Breathing is an essential function that is automatically generated by neural circuits in the medulla. Although breathing is mostly an automatic process, it is highly flexible and can change during behaviors requiring activation of respiratory muscles, such as sniffing or vocalization. Respiratory neural circuits receive projections from many brain regions so respiratory muscles can be modulated to accommodate motor behaviors. The periaqueductal grey matter (PAG) located in the midbrain sends projections to the medulla. While the PAG is not involved in the automatic production of breathing, it is involved in coordinating autonomic functions such as breathing with behaviours. However, the types of PAG neurons involved in breathing and their functions remain unclear. Somatostatin (SST), an inhibitory neuropeptide found in the medulla but also in the ventrolateral PAG (vlPAG) may be involved in modulating breathing. In addition, SST PAG cells are involved in neuropathic pain. **Objective**: Here, we aim to determine the role of SST vlPAG neurons in modulating respiratory rhythm and their role in motor behaviours such as motor response to pain. **Methods**: We used optogenetics to selectively activate SST vlPAG cells while measuring respiratory activity with whole-body plethysmography and motor behaviors with video recording in freely-behaving mice. **Results**: We observed that photostimulation of SST vlPAG cells stimulates breathing while simultaneously increasing locomotor activity. To determine whether changes in respiratory activity were due to increased motor activity, we performed the same experiments in anesthetized mice and found that photostimulation of SST vlPAG neurons increased respiratory activity. **Conclusion**: Our results suggest that stimulation of SST vlPAG neurons independently modulated respiratory and motor activity and may be involved in the modulation of respiratory muscle activity to produce non-respiratory behaviors.

7. Mary-Claire Ball; Ontario Institute for Studies in Education, Department of Applied Psychology & Human Development

Supervisor: Dr. Kaja Jasińska

Theme: Cognitive Neuroscience

EXPERIENCE WITH THE LANGUAGE OF INSTRUCTION IS RELATED TO CHILDREN'S LANGUAGE SKILLS AND HOW THEY LEVERAGE LANGUAGE FOR READING IN MULTILINGUAL COMMUNITIES IN CÔTE D'IVOIRE

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Introduction: Spoken language skills (e.g., phonological awareness, vocabulary) and their interactions, contribute to skilled reading (Harm & Seidenberg, 2004). Yet we know little about how this occurs for the 200 million children across the globe who are learning to read in an unfamiliar language (UNESCO, 2016). In rural Côte d'Ivoire, many children speak one, two, or more regional languages at home but attend school and learn to read in French (Jasińska & Guei, 2023). Research conducted in Global North contexts suggests that bilingual experience at home benefits language and reading skills (e.g., Jasińska & Petitto, 2018). Similarly, previous research from Côte d'Ivoire found that children from French-speaking bilingual homes demonstrated better language and reading skills in Ivorian languages and French compared to children from non-French-speaking monolingual homes (Ball et al., 2022). However, little research has explored the language and reading skills of children who speak two or more languages at home that do not include the language of instruction. **Objective**: In this

study, children (N=1382, M age=9.09, SD age=2.08) completed standardized French language and literacy assessments to examine how the home language environment relates to language and reading skills in the language of instruction, and how children leverage language skills for reading. **Methods**: Children were either monolingual speakers of one regional language, bilingual speakers of two regional languages or one regional language and French, or multilingual speakers of two or more regional languages and French. **Results:** Bilingual and multilingual children who spoke French at home significantly outperformed their monolingual and bilingual peers who did not speak French on language tasks. Further, bilingual children who spoke French leveraged their language skills more during reading tasks. However, the associations between language skills and reading were more complex for children who did not speak French and depended on their age and French proficiency. **Conclusion**: The results suggest that in this context, experience with multiple languages facilitates language and reading skill development only when they include the language of instruction.

8. Monica Bell Vila; Department of Medical Biophysics

Supervisor: Dr. Bojana Stefanovic

Theme: System & Circuits Neuroscience

WEARABLE IMPLANTS FOR THERAPEUTIC DELIVERY OF SUBCUTANEOUS ALTERNATING CURRENT STIMULATION IN A RAT MODEL OF STROKE RECOVERY

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Introduction: Recent research has highlighted the therapeutic potential of electrical stimulation across brain diseases, including stroke, Alzheimer's Disease, and Parkinson's Disease. Alternating current stimulation (ACS) is of particular interest given its low cost, portability, the ability to entrain neurons - i.e. synchronize their spiking to a phase of the stimulation waveform, thereby spurring synaptic remodeling. **Objective**: We set out to develop a wearable implant to deliver bihemispheric subcutaneous alternating current stimulation for rebalancing interhemispheric excitation-inhibition in a rat model of recovery from focal ischemia. **Methods**: Adult rats were anaesthetized with isoflurane; scalp was excised to expose the dorsal skull surface; the skull was thinned over the right sensorimotor cortex for subsequent creation of a photothrombotic lesion. A photothrombotic lesion was produced by illumination of Rose Bengal. 6 weeks post-stroke, the rats were anesthetized with isoflurane and a 3D-printed electrode holder was secured to the skull, with two pairs of silver electrodes targeting either hemisphere for delivery of electric stimulation. A small craniotomy was performed to implant a Neuropixels 1.0 probe into the primary sensorimotor cortex. Under propofol anesthesia (7.5mg/kg followed by 44 mg/kg/hr iv), electrophysiological activity was acquired at 30 kHz for 20 minutes. Following baseline recordings, ACS was delivered bilaterally for 20-minutes at 100μA, with 40 Hz applied ipsilaterally and 5 Hz contralaterally, and recordings were acquired for a subsequent 20-minutes following stimulation offset. Multi-unit activity was isolated and spike sorting was performed with Kilosort 4. **Results**: The electrode holders successfully allowed delivery of ACS in rats. In the chronic stage of recovery, we were able to record broadband activity from approximately 200-300 cortical neurons. Bihemispheric ACS increased perilesional neuronal synchronization during contralateral forepaw stimulation. **Conclusion**: Ongoing studies will evaluate the effects of chronic ACS combined with tray-reaching based rehabilitation on forelimb function recovery following photothrombotic stroke.

9. Laura Bennett; Graduate Department of Pharmaceutical Sciences

Supervisor: Dr. Robert Bonin

Theme: System & Circuits Neuroscience

AMYLOID-BETA DELIVERED BY A SPINAL HYDROGEL ALLEVIATES NEUROPATHIC PAIN IN A PRECLINICAL MODEL

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Introduction: Synaptic plasticity that allows for memory in the brain has mechanistic and functional parallels to synaptic plasticity that occurs between neurons in the spinal dorsal horn. The small peptide, amyloid-beta, is associated with memory loss in Alzheimer's disease but is present at endogenously low concentrations in brains of healthy individuals. We hypothesize that amyloid-beta contributes to synaptic plasticity and sensory processing in the spinal dorsal horn. **Objective**: Our overall aim is to modulate amyloid-beta in the spinal dorsal horn to improve hypersensitivity in pain models. **Methods**: We used Enzyme Linked Immunosorbent Assay (ELISA) to quantify amyloid-beta in the spinal cord and we tested mechanical sensitivity using von Frey. We intrathecally delivered synthetic amyloid-beta after inducing neuropathic pain by a spared nerve injury (SNI). Amyloid-beta was delivered by a hydrogel with nanoparticles for spatiotemporal control of the amyloid-beta peptide release. Microglia morphology was analyzed by immunohistochemistry and Imaris. **Results**: We observed that an intrathecal injection of synthetic amyloid-beta transiently improved the mechanical sensitivity of female mice but not male mice after SNI. To prolong the improvement in mechanical sensitivity, we delivered amyloid-beta via hydrogel which significantly decreased mechanical sensitivity up to ten days post SNI. Additionally, we found a significant change in microglia morphology in the spinal dorsal horn after hydrogel delivery of amyloid-beta in female mice. **Conclusion**: Taken together, our results thus far indicate modulation of amyloid-beta may play a role in the mechanical sensitivity attributed to a model of neuropathic pain at the level of the spinal cord.

10. Stefanie Bradley; Institute of Biomedical Engineering

Supervisor: Dr. Tom Chau

Theme: Development & Neurodevelopmental Disorders

STRUCTURAL CHARACTERIZATION OF THE BRAINS OF CHILDREN WITH CEREBRAL PALSY USING MANUAL AND AUTOMATED METHODS

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Introduction: Magnetic resonance imaging (MRI) in pediatric research studies is typically conducted without sedation. Awake scanning is particularly challenging with young children with cerebral palsy (CP) due to issues with tolerability and child motion. Motion artifacts impact image quality, which can render structural analysis inaccurate. The presence of underlying brain pathologies further complicates segmentation accuracy. While manual segmentation remains the gold standard for neuroanatomical delineation, it is often not feasible for large-cohort studies due to its labor-intensive and time-consuming nature. Thus, partially or fully automated neural segmentation pipelines is necessary. **Objective**: Compare manual and automated methods for cortical segmentation in children with CP, compared to an age-matched neurotypical (NT) brain template (National Institutes of Health) with little to no motion artifacts. **Methods**: Two participants with CP (spastic unilateral, 5 years old; spastic bilateral, 6 years old) underwent brain scans in a 1.5 Tesla MRI at Holland Bloorview Kids Rehabilitation Hospital. Grey and white matter delineations were done with Freesurfer Software and then reviewed by a pediatric neuroradiologist to assess the need for additional manual corrections. Cortical surface-based registration to an age-matched pediatric atlas (University of North Carolina) was used to annotate brain regions and subsequently obtain regional cortical thicknesses and grey matter volumes. **Results**: Freesurfer's automated white/gray matter delineation was deemed accurate for the NT pediatric template but inaccurate for CP scans in the following areas: anterior temporal poles, superior gyri, and posterior occipital lobe. Manual correction of the automated labeling of the white matter mask and voxel intensity normalization improved accuracy. For participants with a subsequent scan, a within-child unbiased template was used to reduce noise. In uncorrected scans, cortical thickness was underestimated by up to 11% in areas that included the temporal pole, superior parietal, and precuneus. Similarly, cortical gray matter volume was underestimated by up to 40% in areas that included the medial and lateral occipital, posterior temporal, and sensorimotor regions, compared to the manually corrected segmentations. **Conclusion**: Pediatric scans affected by motion or pathology (i.e., CP scans) require additional manual intervention when using automated segmentation tools, to ensure credible structural analysis. Rather than discarding motion-affected scans, these extra measures should be considered to promote inclusion of underrepresented populations in research studies.

11. Sima Buchnak; Institute of Biomedical Engineering

Supervisor: Dr. Douglas Cheyne

Theme: Cognitive Neuroscience

USING MEG TO INVESTIGATE SENSORIMOTOR DEFICITS IN PAEDIATRIC POST-STROKE DYSTONIA

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Introduction: Arterial Ischemic Stroke (AIS) occurs in about 1,000 North American children annually, often imposing lifelong motor impairments like dystonia. This condition, characterized by involuntary contractions and abnormal postures, occurs in 21% of children with basal ganglia strokes. While the mechanisms underlying its development remain unclear, impaired neural inhibition in the motor cortex is likely a key factor. Sensorimotor beta rhythms, which typically show event-related desynchronization (ERD) after movement, reflect these inhibitory functions. Our study examines beta ERD in the sensorimotor regions of children with post-stroke dystonia and its link to corticospinal tract integrity, a critical pathway for movement control. **Methods**: Structural MRI and functional MEG data were collected from 15 childhood AIS patients at SickKids, along with age- and sex-matched healthy controls. To examine movement-related activity and somatosensory-evoked responses, MEG recordings were obtained during a passive finger-lifting task. **Results**: Preliminary results suggest that individuals with dystonia exhibit weaker ERD for movements of their affected hand compared to non-dystonic individuals. For movements of their non-affected hand, they show stronger ERD than controls, but their ERD was similar to non-dystonic individuals. Additionally, lateralization of beta reactivity was altered in both dystonia and non-dystonic individuals compared to controls. **Conclusion**: For movements of their affected hand, individuals with dystonia exhibited similar neural inhibition in sensorimotor cortex to controls. This was decreased for the non-affected hand, suggesting altered lateralization of beta reactivity patterns in these patients.

12. Danielle Bukovsky; Institute of Medical Science

Supervisor: Dr. Philip Gerretsen

Theme: Aging & Neurodegenerative Disorders

SAFETY, FEASIBILITY, AND TOLERABILITY OF PSILOCYBIN IN OLDER ADULTS WITH AMNESTIC MCI: PRELIMINARY DATA FROM A SV2A PET IMAGING STUDY

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Introduction: Amnestic mild cognitive impairment (aMCI) is characterized by synaptic loss and cognitive decline and is considered a precursor to Alzheimer's Disease. Currently, there are no effective treatments for aMCI, and available treatments (i.e., cholinesterase inhibitors) do not appear to improve cognitive or functional outcomes. Psychedelics, including psilocybin, have regained interest for treatment of treatment-resistant neuropsychiatric disorders. Research suggests psilocybin's psychedelic and clinical effects may be due to interaction with the 5HT2A serotonin receptor (5HTA-R) in the brain. Cognitive impairments, such as memory decline, have been associated with lower 5HT2A-R density in the brain. Encouragingly, preclinical animal studies suggest that psilocybin may promote synaptogenesis in the brain, particularly in areas associated with learning and memory, likely

through its interaction with the 5HT2A-R. Psilocybin may represent a novel treatment to counter neurodegenerative progression and consequently improve cognitive outcomes in patients with aMCI. **Objective**: The objective of this study is to assess psilocybin's effect on synaptic density in the hippocampus and prefrontal cortex of patients with aMCI, and whether these changes are associated with improved cognitive outcomes. **Methods**: The present double-blind, placebo-controlled randomized PET study will use the radioligand [18F]SynVesT to assess psilocybin's effect on synaptic density in the hippocampus and prefrontal cortex of patients with aMCI. aMCI participants and sex-matched healthy controls will be randomized to receive either two doses of 25mg psilocybin or placebo one week apart. Participants will be monitored by a study physician and qualified therapist. PET scans are conducted pre- and one-week post-treatment. Clinical, safety, and neuropsychological assessments are done at baseline and 1-, 4-, and 12-weeks post-treatment. Safety measures include monitoring vital signs, suicidal ideation, and adverse events (AEs). **Results**: Pilot data from two aMCI participants (Male% = 50%, mean age = 71.0(±3.0), mean baseline MOCA = 22(±3.0)) and three healthy controls (Male% = 67%, mean age = 66.3(±5.1); mean baseline MOCA = 27.7(±1.5)) is available. All participants completed study procedures without issue. Psilocybin was well tolerated, with no unexpected or serious AEs. All expected AEs resolved without sequelae. Expected AEs included dizziness (n=4) and altered perception (n=3). Blinding remains in effect. **Conclusion**: The preliminary data suggest psilocybin is safe, well-tolerated, and can be feasibly investigated in a supervised medical setting in older adults as a prospective treatment for aMCI.

13. Jingxin (Jessie) Chen; Department of Pharmacology & Toxicology

Supervisor: Dr. Thomas Prevot

Theme: Neuropharmacology & Drug Development

PRO-COGNITIVE EFFECTS OF α5-GABAA POSITIVE ALLOSTERIC MODULATION IN A MOUSE MODEL OF ALZHEIMER'S DISEASE

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Introduction: Alzheimer's disease (AD) is a debilitating neurodegenerative disorder. Despite extensive drug development efforts, directly targeting amyloid and tau pathologies has yielded limited success, and current treatments fail to meaningfully improve patient life quality. Our research identifies the α5-GABAAR, a GABAergic receptor subunit essential for the regulation of cognitive function, as a promising novel therapeutic target. We developed a novel molecule that selectively enhances α5-GABAAR activity, reversing cognitive deficits and neuronal shrinkage induced by amyloid load in preclinical studies. However, the contribution of α5-GABAARs in the regulation of cognitive functions and their potential to reverse brain pathology has not been clarified by direct genetic approaches. **Objective:** This project proposes to demonstrate the necessary role of positive allosteric modulation at the α5-GABAARs in the regulation of cognitive functions in a mouse model of AD. We hypothesize that, following chronic treatment, the drug-sensitive strain will show better cognitive performance than the drug-insensitive strain, despite both groups having amyloid pathology. **Methods:** 5xFAD mice, as a model of progressive amyloid load, were crossed with a5 knock-in mice, who bear a point mutation rendering the allosteric site of the α5-GABAAR insensitive to drug binding. Double transgenic animals (n=12, 50% female) and their wildtype littermates (n=12, 50% female) underwent three weeks of drug treatment (GL-II-73, 30 mg/kg), administered through drinking water. Spatial cognition was subsequently assessed by Morris Water Maze. **Results:** Preliminary results show that chronic administration of α5-GABAAR positive allosteric modulator gave mice with amyloid deposition an advantage in the initial day of spatial learning in Morris Water Maze. This effect was only observed in the drug-sensitive wildtype group, and not the drug-insensitive a5 knock-in strain. **Conclusion**: Our early findings demonstrated potential for the symptomatic efficacy of α5-GABAA positive allosteric modulation in a mouse model of AD, specifically at improving spatial learning function. Further analysis will clarify the association in other facets of cognition and any potential sex differences.

14. Andrew Cheon; Department of Cell and Systems Biology

Supervisor: Dr. Junchul Kim

Theme: Cognitive Neuroscience

DISTINCT TEMPORAL DYNAMICS OF ANTERIOR OLFACTORY NUCLEUS ACTIVITY IN ODOR-CONTEXT MEMORY.

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Introduction: The anterior olfactory nucleus (AON) serves a central role in early olfactory processing, integrating bottom-up inputs from olfactory structures and top-down inputs from higher-order limbic structures to modulate odor-guided behaviors. We previously demonstrated that hippocampal projections to the AON form an experimentally tractable neural circuit model of odor-context memory, highlighting the AON as a repository for odor-context engrams. However, the temporal dynamics of AON activity during odor memory processes remain unknown. **Objective**: This study aims to characterize population-level AON activity dynamics as a simple odor memory develops into context-dependent odor memory. **Methods:** We coupled in vivo fiber photometry with our modular olfactory go/no-go paradigm to record from the dorsal and medial AON of Thy1-GCaMP6 mice during performance of context-independent and context-dependent go/no-go tasks. **Results:** We found that both AON subdivisions showed distinct temporal dynamics of activity depending on the complexity of the olfactory go/no-go task. Notably, the dorsal AON fires during the pre-odor interval in two-chamber but not single-chamber go/no-go, and this pre-odor activity is strongest when context-dependent odor memory is required. The medial AON shows relatively higher population-level activity under all task conditions, including the single-chamber go/no-go. Given the absence of odor cues during the pre-odor interval, we hypothesize that this form of AON activity is context-dependent. **Conclusion**: Our in vivo calcium imaging results align with our hypothesis that the AON stores odor-context memories. Future experiments will leverage one-photon calcium imaging to decode the information contained in AON activity corresponding to odor-context memory processes. This study provides novel insight into the

fundamental role of AON circuits in odor-context memory, which has significant implications for understanding how the brain processes sensory elements of episodic memory.

15. Annie Chu; Faculty of Music

Supervisor: Dr. Michael Thaut

Theme: Clinical & Translational Neuroscience

Exploring music-aid verbal learning and corresponding brain plasticity among patients with mild cognitive impairment

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Introduction: According to the World Health Organization, Alzheimer's disease has consistently ranked among the top seven causes of mortality. Approximately, one out of every thirteen elderly individuals aged 65 and above receives a diagnosis of dementia, with mild cognitive impairment (MCI) affecting 17.99% of this demographic. MCI is a condition marked by cognitive decline exceeding typical age-related changes and educational norms, yet it does not substantially hinder daily activities. The amnestic subtype of MCI may represent a prodromal stage of Alzheimer's disease (AD) and is highly likely to progress to the disease. Further research endeavours are warranted to assess interventions that are both ecologically valid and economically feasible while also being non-invasive and fun for this population. Music-based interventions have emerged as promising treatments for dementia by leveraging music's ability to evoke emotions and memories. Non-invasive MMT has demonstrated efficacy in enhancing learning and memory retention, particularly impacting verbal memory across various neurological conditions. MMT incorporates elements like rhythm, melody, and rhyme to facilitate information processing and memory enhancement. Engaging in MMT may enhance memory capabilities and promote neuroplasticity by improving neural network activity in compromised brains. However, research on similar therapies for MCI is limited, and existing studies primarily focus on English-speaking and Western cultures, raising questions about the translatability of MMT's effectiveness to Chinese-speaking populations. **Objective**: 1) To elucidate the underlying mechanisms through which MMT facilitates the encoding, storage, and retrieval processes. 2) To ascertain the applicability of MMT within Chinese-speaking cohorts and assess its efficacy in enhancing language acquisition and memory among patients with MCI. 3) To investigate the neuroplastic effects of MMT through the utilization of fMRI techniques. **Methods**: The study cohort consisted of 64 native Mandarin-Chinese speakers aged between 55 and 90 years, residing in Taiwan. The subjects will be stratified into two groups: matched healthy controls and those with MCI based on evaluation by a neurologist or psychologist. Inclusion Criteria for MCI Subjects: 1. Memory complaint validated by an informant. 2. Memory performance at least 1.5 SD below age-standardized norms 3. Absence of dementia diagnosis. 4. Functional independence intact. Exclusion Criteria: 1. Severe psychiatric disorders, head trauma, cerebrovascular disease, or neurological disorders. 2. Recent general anaesthesia within 6 months. 3. Use of brain-affecting medications or substances. 4. Conditions prohibiting MRI participation (e.g., pregnancy, claustrophobia, metal implants). All participants are randomly assigned to a "sung" (musical) or "spoken" (non-musical) condition. Using the Chinese Verbal Learning Test (CVLT), participants encoded and recalled two-character nouns while undergoing fMRI scanning. **Results**: The preliminary data suggests that musical mnemonics enhance long-term verbal memory in older Mandarin speakers, engaging neural regions linked to auditory and language processing. **Conclusion**: This study aims to provide evidence of neural pathway facilitation and potential mitigation of dementia risk. Extension of MMT benefits beyond English-speaking populations, for instance, its applicability in tonal language speakers, like Mandarin Chinese.

16. Bhavarth Dave; Institute of Medical Science

Supervisor: Dr. Sanjeev Kumar

Theme: Clinical & Translational Neuroscience

IMPACT OF PSYCHOTROPIC MEDICINES ON NEUROPSYCHIATRIC SYMPTOMS IN DEMENTIA: A LONGITUDINAL PERSPECTIVE.

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Introduction: In Canada, >650,000 individuals suffer from dementia and approximately 90% of these patients experience neuropsychiatric symptoms (NPS) such as aggression. Routine clinical practice often involves the prescription of multiple medications to manage NPS, leading to polypharmacy. **Objective**: The present study aimed to investigate the longitudinal relationship between psychotropic medications and aggressive behaviour in patients with dementia-related NPS. **Methods**: Data from the Standardizing Care for Neuropsychiatric Symptoms of Dementia (StaN) trial was analyzed. Aggressive behaviour was assessed using the Cohen-Mansfield Agitation Inventory (CMAI) – aggressive behavior scale at baseline (week 0), week 1, week 3, week 4, week 8, and exit (week 12). The number of psychotropic medications prescribed for agitation were recorded at the same time points. Linear Mixed Models (LMM) were used to evaluate this relationship, adjusting for age, gender, randomization (Integrated Care Pathway (ICP) or Treatment as Usual (TAU)), and baseline CMAI aggressive behavior scores. **Results**: The study included 185 participants with dementia and NPS. There was a significant association between baseline aggressive behavior ($p < 0.001$) and time ($p < 0.001$) with aggressive behavior. Furthermore, there was no significant association between number of psychotropic medications with aggressive behavior ($p = 0.930$). **Conclusion**: This study did not find evidence of the association between number of psychotropic medications and aggression indicating that psychotropic polypharmacy may not necessarily improve aggressive behavior in those with dementia and NPS. Future studies may examine causal relationships between polypharmacy, dose and specific classes of psychotropic medications, and adverse effects (AEs) with aggressive behaviour in dementia.

17. Riddhita De; Institute of Medical Science

Supervisor: Dr. Margaret Hahn

Theme: Psychiatric Disorders

THE EFFECT OF SEMAGLUTIDE ON ANTIPSYCHOTIC-INDUCED WEIGHT GAIN AND OTHER METABOLIC VARIABLES, AMONG A COHORT OF INPATIENTS AT THE CENTRE FOR ADDICTION AND MENTAL HEALTH: A CHART REVIEW

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Introduction: Individuals with severe mental illnesses including schizophrenia spectrum disorders (SSDs), major depressive disorder, and bipolar disorder, have a significantly reduced life expectancy of 15-20 years when compared to the general population due to cardiovascular disease. While antipsychotic (AP) drugs remain the cornerstone of treatment for SSDs, their use is associated with significant metabolic disruptions including weight gain, dyslipidemia and type 2 diabetes among others. At present, metformin is recommended as an appropriate first line pharmacological intervention in the context of AP-induced weight gain and dysmetabolism. However, close to 20% of individuals fail to respond to metformin, with limited evidence supporting alternative pharmacological interventions. Although evidence is still emerging, glucagon-like peptide-1 receptor agonists (GLP-1RAs) have shown efficacy and tolerability in SSDs. The current evidence is based on older, daily injectable agents, while efficacy and safety of newer and more promising medications, such as once weekly semaglutide, is lacking. **Objective**: This study aimed to explore the effectiveness of semaglutide over time, to help draw evidence-based conclusions from a sample of patients located in a controlled, hospital setting. **Methods**: A retrospective chart review was conducted examining psychiatric inpatients taking APs who have been initiated on semaglutide injections between 2018, post semaglutide approval in Canada and 2024 at the Center for Addiction and Mental Health (CAMH) in Toronto, Canada. All demographic, metabolic and anthropometric data were collected until they were discharged from the hospital, as long as they were within our protocol's approved timeframe. Given loss to follow-up post hospital discharge, only data from baseline, 3, 6, 9 and 12 months were analyzed. All demographic data have been shown either as a mean with standard deviation or as a percentage, while all model-specific data have been shown as a mean with their respective standard errors. **Results**: A total of 47 patients were included in our analysis, with a mean age of 42.96 years +13.23 years. Among this cohort, 59.6% were male, 85.1% of the sample was diagnosed with either schizophrenia or schizoaffective disorder and 66% of the sample was noted to have Type 2 diabetes at baseline. The mean weight was 113.15 ± 30.71 kg with a BMI of 40.18 ± 10.31 kg/m2. and a mean HbA1c of 7.3± 2.1% at baseline. Patients were on a mean semaglutide dose of 0.25 ± 0.18 mg/week at initiation (N=47), 0.90 ± 0.34 mg/week at 3 months (N=47), 1.23 ± 0.49 mg/week at 6 months (N=24), 1.12 ± 0.45 mg/week at 9 months (N=15), and 1.36 ± 0.55 mg/week at 12 months of follow up (N=11). The maximum dose that individuals were titrated to was 2 mg/week. After initiation of semaglutide and following adjustment of age, sex and baseline weight, a significant weight change was noted over time ($p<0.001$). There was a mean weight loss of 3.15 ± 0.74 kg at 3 months ($p<0.001$), 7.66 ± 1.04 kg ($p < 0.001$) at 6 months, 9.45 ± 1.62 kg ($p < 0.001$) at 9 months, and 12.71 ± 2.52 kg ($p < 0.001$) at 12 months. Additionally, a significant change from baseline was seen in HbA1c levels at all timepoints ($p<0.001$) with a mean reduction of 1.0± 0.2% at 3 months (N=23), 1.2± 0.3% at 6 months (N=16), 1.4 ± 0.3% at 9 months (N=11), and 1.3± 0.2% at 12 months (N=10). There were also improvements seen in lipid parameters in the cohort such as in triglycerides levels. While there were no major adverse events reported in this cohort, commonly occurring side effects included nausea and diarrhea, which however did not result in treatment discontinuation. **Conclusion**: This retrospective chart review offers both clinical and research insights, in relation to the effectiveness of semaglutide among individuals with severe mental illnesses and metabolic comorbidity. The study findings showcase the potential of semaglutide in antipsychotic-induced weight gain, with minimal side effects. Given these findings, studies involving semaglutide with both a larger sample size and the higher approved dose of semaglutide for chronic weight management are warranted.

18. Joel Diaz; Institute of Medical Science

Supervisor: Dr. Jamie Feusner

Theme: Cognitive Neuroscience

THE VERTICAL OCCIPITAL FASCICULUS DIFFERENTIALLY MODULATES ORIENTATION-DEPENDENT FACE PROCESSING IN BODY DYSMORPHIC DISORDER

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Introduction: Body dysmorphic disorder (BDD) is characterized by visual perceptual abnormalities, with previous studies demonstrating reduced global (holistic) processing and heightened attention to local features. This study examined the relationship between structural connectivity of the right vertical occipital fasciculus (rVOF)—a major fiber bundle connecting dorsal and ventral visual systems involved in global and local processing—and the face inversion effect (FIE) in individuals with BDD compared to controls. **Objective**: The VOF has been proposed as a structural bridge linking dorsal and ventral visual streams. Disruptions in this pathway may contribute to the global-local perceptual imbalances reported in BDD. We aimed to examine whether microstructural properties of the rVOF, as indexed by fractional anisotropy (FA), predict behavioral performance on face inversion tasks in BDD and controls. We hypothesized that stronger rVOF connectivity would be associated with heightened global interference during face inversion, with this relationship altered in BDD. **Methods**: Two independent datasets were analyzed: (i) 16 individuals with BDD and 19 healthy controls completed a sequential matching task, judging whether two sequentially presented upright or inverted face stimuli were the same or different; (ii) 28 individuals with BDD and 28 healthy controls completed a two-alternative forced choice (2AFC) match-to-sample task, selecting which of two simultaneously presented faces (upright or inverted) matched a previously viewed target face. The 2AFC task included both a fast (500 ms) and slow (5000 ms) stimulus presentation condition. FSL's XTRACT tool was used to isolate rVOF from diffusion MRI, with structural connectivity measured as its mean FA. Response times (RTs) were analyzed using a linear mixed-effects model with group, orientation, and mean FA as predictors. **Results**: Significant Group × Orientation × FA interactions were found in both

datasets, indicating that the relationship between rVOF structural connectivity and behavioral RTs differed by diagnostic group and stimulus orientation. In the sequential matching task, the interaction was significant (β=−.093, p=.024), with higher FA associated with faster RTs in controls but slower RTs in individuals with BDD. In the 2AFC matching task, a similar interaction emerged only for short-duration stimuli (β=−.184, p=.018), suggesting that rVOF microstructure plays a role in early-stages of face perception. **Conclusion**: Structural connectivity between dorsal and ventral visual regions differentially influences the FIE in individuals with BDD compared to controls. In controls, stronger rVOF connectivity was associated with increased global interference (larger inversion effect), whereas in BDD, this relationship is reversed (smaller inversion effect). These findings highlight rVOF as a predictor of perceptual biases in BDD and may hold prognostic or therapeutic relevance for addressing body image distortions.

19. Dylan Dingwell; Department of Medical Biophysics

Supervisor: Dr. Charles Cunningham

Theme: Molecular & Cellular Neuroscience

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Introduction: In hyperpolarized carbon-13 MRI, metabolic conversion of injected 13C-pyruvate generates 13C-lactate through a reversible enzymatic reaction dependent on the local balance between NAD (NAD+/NADH) coenzymes, while irreversible consumption of pyruvate in mitochondria fuels the tricarboxylic acid cycle, generating 13C-bicarbonate as a byproduct. Regional signal changes in frequency-selective images of these metabolites indicate that, in the brain, lactate oxidation precedes bicarbonate production, but the precise metabolic pathways followed in this reaction chain are unclear. **Objective**: Use biochemical modelling to characterize the extent to which lactate oxidation is a precursor step in bicarbonate production and whether this reaction takes place predominantly in the cellular cytosol. **Methods**: A 10 micron cubic volume representing a single brain cell with a spherical mitochondrial compartment comprising 10% of the cellular volume was modelled using the biochemical simulator Smoldyn with magnetic resonance modelling. Models of neuronal and astrocytic redox states were developed using hyperpolarized 13C-MRI data obtained in vivo to define rate parameters. **Results**: Modelling typical reactant concentrations and NAD distributions at cellular scale for neurons and astrocytes, and tuning conversion rate constants based on in vivo data, enabled tracking of pathways followed by individual 13C-labelled metabolites in simulation. In silico, 13C-bicarbonate was primarily produced from either non-converted pyruvate or lactate transported into mitochondria and then oxidized, with no condition showing a substantial contribution from cytosolic back-conversion. **Conclusion**: Lactate oxidation prior to bicarbonate production is significant and likely to be driven by mitochondrial coenzyme pools, consistent with the mechanism of mitochondria using lactate as an energy source.

20. Sarah Eide; Department of Physiology

Supervisor: Dr. Zhong-Ping Feng

Theme: Aging & Neurodegenerative Disorders

THE INTERSECTION OF VASCULAR DYSFUNCTION AND NEURODEGENERATION: THROMBIN-MEDIATED NEURODEGENERATION OF THE AGING NEUROVASCULAR UNIT VIA INHIBITION OF MITOCHONDRIAL RECYCLING

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Introduction: Vascular contributions to neurodegeneration are increasingly recognized, with early evidence implicating blood-derived proteins in the pathogenesis of Alzheimer's disease (AD). Thrombin, a central enzyme in the coagulation cascade, is elevated in individuals with neurodegenerative diseases and exerts cellular effects through activation of the PAR1 receptor. However, the specific effects of thrombin on the aging brain and the molecular mechanisms driving its potential neurotoxicity remain unexplored. **Methods**: To investigate thrombin's role in age-related neuronal dysfunction, we utilized in vitro models of senescent human neuronal cells. Neuronal responses to thrombin were assessed via cell viability assays and morphological analysis using immunofluorescence. Whole-cell proteomics was performed to identify induced signaling changes. Mitochondrial function was evaluated using reactive oxygen species (ROS) assays and semi-supervised machine learning-based classification of mitochondrial morphology. Western blot and pharmacological interventions were employed to dissect the mechanisms underlying thrombin-induced neurodegeneration and senescence. **Results**: Senescent neurons exhibited heightened sensitivity to thrombin, attributed to increased PAR1 expression. Thrombin exposure led to reduced neuronal viability and impaired neurite outgrowth. Proteomic analysis revealed significant alterations in mitochondrial protein expression. Thrombin inhibited mitophagy, elevated ROS production, and disrupted mitochondrial network integrity, resulting in the accumulation of dysfunctional mitochondria. These mitochondrial defects contributed to a neurodegenerative phenotype and promoted further induction of neuronal senescence with prolonged thrombin exposure. **Conclusion**: This study identifies thrombin as a key vascular-derived factor that accelerates brain aging and neuronal dysfunction by inducing senescence and impairing mitochondrial homeostasis. These findings suggest that thrombin may serve as an early molecular driver of neurodegeneration and a promising therapeutic target for the prevention or attenuation of age-related neurological diseases.

21. Rima El-Sayed; Institute of Medical Science

Supervisor: Dr. Karen Davis

Theme: Pain & Sensory Disorders

ALPHA OSCILLATIONS AND CONDITIONED PAIN MODULATION PREDICT PAIN RELIEF FROM SPINAL CORD STIMULATION

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Introduction: Neuropathic pain (NP) is a severe form of chronic pain associated with significantly reduced quality of life. Spinal cord stimulation (SCS) can provide significant pain relief but is ineffective in half of those treated, highlighting the importance of predictive markers of treatment outcome. **Objective**: Given previous studies showing abnormal alpha oscillations and altered conditioned pain modulation (CPM) in chronic pain, our aim was to determine whether alpha oscillations and CPM can predict pain relief from SCS. **Methods:** Patients with NP were evaluated before a 12-day SCS trial using pain self-reports, CPM, a magnetic resonance imaging (MRI) scan and a 5-minute resting state magnetoencephalography (MEG) scan to evaluate alpha oscillations (8-13Hz) in the dynamic pain connectome. Those with ≥30% pain reduction in a post SCS evaluation were considered treatment responders. Age- and sex-matched healthy controls (HC) also underwent CPM testing and MEG. **Results**: The analyses included 40 patients with NP (22F, 18M) and 29 HCs (17F, 12M). Approximately half of the patients were non-responders and pre-SCS testing of CPM revealed this group (but not the responders) to exhibit significantly diminished inhibitory CPM compared to HCs. Pre-SCS MEG revealed that lower peak alpha power throughout the ascending nociceptive pathway and salience network was correlated with greater pain relief. **Conclusion**: These data highlight abnormalities in alpha oscillations in the ascending nociceptive pathway and the health of the descending inhibitory control system in patients with NP that could provide predictive value when considering personalized pain management with SCS treatment.

22. Kanak Gupta; Institute of Medical Science

Supervisor: Dr. Liisa Galea

Theme: Psychiatric Disorders

CHARACTERIZING SEX DIFFERENCES IN FUNCTIONAL CONNECTIVITY DURING CHRONIC STRESS-INDUCES NEGATIVE COGNITIVE BIAS

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Introduction: Major Depressive Disorder (MDD) affects 20% of the population and affects females at twice the rate as males. MDD is characterized by several symptoms including cognitive symptoms, such as negative cognitive bias (NCB). NCB is the perception of ambiguous stimuli or situations as negative. Changes in network connectivity between limbic system regions, including the hippocampus, prefrontal cortex, amygdala, and nucleus accumbens, is implicated in MDD and can predict negative cognitive bias in MDD. **Objective**: Here we examined possible sex differences in activity of limbic and reward pathway regions as well as the functional connections within these regions in adult rats. **Methods**: Male and female Sprague-Dawley rats underwent either 21d of chronic unpredictable stress (CUS) to induce a depressive-like endophenotype or no CUS. Rats then underwent a cognitive bias task in which, after learning to discriminate between shocked context and a non-shocked context, they were exposed to an ambiguous context (with half the features of the shock vs no shock context) and freezing behaviors were recorded. Activated neurons were visualised using an immunofluorescent stain for immediate early gene (IEG) c-Fos protein, which is transcribed rapidly in response to stimuli, across 20 limbic/reward regions. We hypothesize that 1) activation patterns and relationship with NCB will differ by region and sex 2) functional connectivity patterns in response to CUS-induced negative cognitive bias will differ by sex. **Results**: Our data show that CUS increases activation in the hippocampus in females but lowers it in males. CUS also decreases activation in the central amygdala and ventral subiculum in both sexes. Functional connectivity analyses indicate that the role of different subregions in cognitive bias differs by sex and stress conditions. Compared to non-stressed (NS) females, CUS females show lower functional connectivity within the frontal cortex, while the subiculum and ventral hippocampus become more integral to the network. In CUS males the centrality of the dorsal hippocampus increases compared to NS males. Conversely to CUS females, CUS males maintain frontal cortex connectivity but lose functional connections to the subiculum. **Conclusion**: These results signify that there are sex differences in brain activation and functional connectivity patterns involved in negative cognitive bias.

23. Alicia Harracksingh; Department of Physiology

Supervisor: Dr. Zhong-Ping Feng

Theme: System & Circuits Neuroscience

MOLECULAR AND FUNCTIONAL PROFILING OF PHOTOSENSATION IN THE POND SNAIL LYMNAEA STAGNALIS

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Introduction: Animals rely on intricate visual system machinery to perceive and respond to light, allowing them to navigate their external environments Diverse animal models have been developed to investigate photoreception, however, there remains a pressing need for more integrative models. Invertebrate visual systems of early diverging species have advanced our understanding of photoreceptive behaviors and retinal processing, but models for invertebrate photoreception remain limited. **Objective**: To establish the pond snail Lymnaea stagnalis as an integrative invertebrate model for visual system research by investigating its anatomical, behavioral, and molecular mechanisms of photoreception, with the goal of advancing our understanding of photosensory processing and evolutionary diversity in visual systems. **Methods and Results**: Specifically, we characterized the retinal and dermal organization of Lymnaea stagnalis, identifying rhodopsin-positive photoreceptor cells in both ocular and non-ocular tissues. Using DeepLabCut software, we developed a neurobehavioral assay to assess phototaxis and observed positive phototactic responses in the majority of snails, likely mediated by the invertebrate Gq/PLC/TRP phototransduction pathway. Profiling a novel L. stagnalis rhodopsin further supported the role of Gq-coupled signaling in light sensation. Transcriptome analysis additionally revealed that L. stagnalis expresses genes associated with both vertebrate-like Gt-coupled and invertebrate-like Gq-coupled phototransduction pathways,

underscoring evolutionary divergence in visual signaling mechanisms. **Conclusion**: This study highlights L. stagnalis as a valuable model for research into photosensory systems, providing insights into photoreception and phototaxis mechanisms, and laying the groundwork for exploring molecular and evolutionary aspects of visual function and photoreceptor physiology.

24. Samantha Jackson Blodgett; Faculty of Music

Supervisor: Dr. Michael Thaut

Theme: Cognitive Neuroscience

VOICE REHABILITATION: A CASE STUDY IN POST-STROKE DYSPHONIA

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Objective: This case study examined the effectiveness of a short-term combined intervention using Vocal Intonation Therapy (VIT) and Therapeutic Singing (TS) in improving speaking voice quality in a stroke patient with unilateral vocal fold paralysis. **Methods**: The participant received eight weekly 60-minute sessions via Zoom. Voice samples were extracted from recordings. Voice quality was assessed pre- and post-intervention using the Acoustic Voice Quality Index (AVQI) and Acoustic Breathiness Index (ABI) in addition to other acoustic measures. Voice samples were analyzed using VOXplot. **Results:** Results indicated moderate improvements in AVQI and ABI scores, suggesting a positive impact on vocal function. **Conclusion**: These findings support the clinical potential of music-based interventions for post-stroke dysphonia and provide a foundation for further research.

25. Kendall Kendall; Department of Psychology

Supervisor: Dr. Junchul Kim

Theme: Behavioral & Social Neuroscience

A BEHAVIOURAL ASSAY FOR INVESTIGATING CUED CONFLICT BETWEEN ALLOCENTRIC AND EGOCENTRIC SPATIAL MEMORY WITH INSTINCTIVE ESCAPE IN MICE

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Introduction: Instinctive escape behavior is widely recognized as a reliable model for assessing spatial memory in mice. **Objective**: Here, we present a novel behavioral assay designed to evaluate how mice navigate toward a learned goal when confronted with conflicting egocentric and allocentric cues. **Methods**: Escape to a learned shelter was triggered by an innately aversive auditory stimulus in the presence of a proximal LED landmark. To assess cue preference (egocentric vs. allocentric), we introduced a cue-conflict situation where the allocentric LED cue was deliberately shifted away from the previously visited shelter location. In a no-conflict scenario, the LED stayed directly above the shelter. **Results**: Baseline tests in C57BL/6J mice showed a decreased reliance on allocentric cues as the LED landmark deviated further from the actual shelter. When the disparity between the LED cue and the shelter location exceeded a threshold, the mice began to favor egocentric strategies over allocentric ones. To demonstrate its utility, we applied the cue-conflict assay to test the 5xFAD Alzheimer's disease (AD) mouse model at the prodromal stage (2–3 months old). Escape profiles in AD and wild-type (WT) mice revealed a complex, genotype-dependent pattern of behavior across LED shift conditions, independent of disease progression. Notably, AD mice exhibited a higher incidence of allocentric (LED-directed) escapes than WT mice at both ages, particularly when the LED shift was small. **Conclusion**: Future studies using neural recording and manipulation techniques can further elucidate the circuit-level mechanisms underlying the cue conflict resolution.

26. John Kennedy; Department of Psychology

Theme: Development & Neurodevelopmental Disorders

PIAGET 3-MOUNTAINS TASK ANALYSIS: WITHOUT SINGLE COLUMNS, ROWS, DIAGONALS = 24 ARRANGEMENTS + 4 RESPONSES

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Introduction: Given a 3D arrangement of a cone, a sphere and a cube, tblind and sighted players identify a 2D triangle, circle & square array that fits a vantage point -- front, side, or rear. **Objective**: Describe the usable combinations. **Methods**: Given 3x3 slots, in rows and columns, the objects cannot be in a single column or row because the object nearest the vantage point would obscure the two behind and introduce ambiguity. Also, a diagonal arrangement would fit two sides, and thereby introduce ambiguity. What remains? A. An object in the left corner can be paired with an object in the middle column's far slot. The 3rd object then would be in the middle of the right column. One of 3 objects X one of 2 objects = 6 arrangements B. An object in the left column middle slot can be paired with an object in the middle column's far slot or its near slot. This allows for 6X2 = 12 arrangements. C. An object in the left column, far corner can be paired with an object in the middle column's near slot. The 3rd object must be in the middle of the right column: 6 arrangements. **Result**: In total 6x4 = 24 arrangements of the 3D objects and, given a cone, a circle and a square, response arrays can be laid out 6 ways but 2 do not fit any side -- they put the corner object in the middle of the 3 shapes, and corner objects cannot be in the middle of a response array. Therefore there are 2 impossible response arrays. **Conclusion**: The combinations are 24 3D-object arrangements and 4 2D-shape response arrays.

27. Kakeru Kimura; Institute of Biomedical Engineering

Supervisor: Dr. Kei Masani

Theme: Pain & Sensory Disorders

ANKLE QUASI-STIFFNESS DURING QUIET STANDING IN INDIVIDUALS WITH INCOMPLETE SPINAL CORD INJURY COMPARED TO ABLE-BODIED CONTROLS

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Introduction: Ankle joint stiffness plays a crucial role in maintaining balance during quiet standing. This study investigated ankle joint quasi-stiffness, a property that reflects the combined contributions of intrinsic and neural mechanisms. **Objective:** To compare ankle quasi-stiffness between individuals with incomplete spinal cord injury (iSCI) and able-bodied (AB) individuals, and to explore its relationship with postural sway. **Methods**: Fifteen individuals with iSCI and fourteen age- and sex-matched AB individuals completed 150 seconds of quiet standing under eyes open (EO) and eyes closed (EC) conditions. Ankle quasi-stiffness (Kqs) was computed as the slope of the ankle torque–angle relationship during postural sway. Values were normalized using each participant's mgh (mass × gravity × height of the center of mass [COM]). **Results:** The absolute value of Kqs was significantly higher in the iSCI group than in the AB group under the EC condition(p=0.027). The normalized value of Kqs also remained higher in the iSCI group under EC(p=0.022). Under the EC condition, Kqs and COM acceleration were positively correlated in the iSCI group(r=0.77, p=0.004). **Conclusion:** These results suggest that individuals with iSCI increased ankle quasi-stiffness under sensory-challenged conditions, i.e., the EC condition, as a compensatory response to sensory deficits, while it resulted in increased postural sway.

28. Alexandra Koch-Liu; Department of Pharmacology & Toxicology

Supervisor: Dr. Chao Zheng

Theme: Clinical & Translational Neuroscience

PRELIMINARY CHARACTERIZATION OF RHO-ASSOCIATED PROTEIN KINASE 2 RADIOLIGANDS FOR IMAGING TAUOPATHIES

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Introduction: Rho-associated coiled-coil kinase 2 (ROCK2), a serine/threonine kinase overactivated in Alzheimer's disease (AD) and non-AD tauopathies, contributes to impaired autophagy, tau aggregation, and amyloid-beta deposition. As a potential early biomarker, ROCK2 is the target of novel positron emission tomography (PET) radioligands under development by the Zheng laboratory: [11C]ROCK201 and [18F]ROCK202. **Objective**: This study aims to characterize the binding properties of [3H]ROCK201 in tauopathy rodent models and postmortem human AD tissue and evaluate the pharmacokinetics of [18F]ROCK202 in healthy rodents. **Methods**: In vitro autoradiography using [3H]ROCK201 (10 nM) and [18F]ROCK202 (10 nM) was performed with and without Fasudil·HCl (10μM) to assess total vs. non-specific binding in TgF344-AD rats, PS19 mice, and human AD tissue. Binding in the hippocampus, cortex, thalamus, and caudate putamen was analyzed using MCID software. In vivo PET imaging with [18F]ROCK202 evaluated tracer uptake and clearance kinetics in healthy rodents. **Results**: [3H]ROCK201 autoradiography revealed higher total binding in TgF344-AD rats compared to wild-type controls (n = 3; 4 slices/brain). Specific binding was significant in TgF344-AD rats (66 ± 5%), PS19 mice (72 ± 3%), and human AD tissue (49 ± 35%). In vivo [18F]ROCK202 PET imaging in healthy rodents demonstrated robust initial tracer uptake and gradual washout, indicating favorable pharmacokinetics. **Conclusion**: These findings support the specificity and potential of ROCK2-targeted radioligands for imaging AD-related pathology. Increased ROCK2 binding in AD models and promising in vivo kinetics of [18F]ROCK202 highlight its promise in translational science, bridging preclinical and clinical studies of tauopathies.

29. Tian Kong; Department of Physiology

Supervisor: Dr. Lu-Yang Wang

Theme: Molecular & Cellular Neuroscience

THE RESCUE OF NEURODEVELOPMENTAL DISORDERS (NDDS) WITH NOVEL POTASSIUM CHANNEL MODULATORS

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Introduction: Ion channelopathy is one of the leading causes for excitation-inhibition (E/I) imbalance and NDDs 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 epileptic encephalopathy, ataxia, seizures and autism spectrum disorder (ASD). In Fragile X Mental Retardation 1 (Fmr1) gene knockout (KO) mice, downregulation of presynaptic Kv1.2 in GABAergic interneuron terminals leads to excessive inhibitory overtone underlying behavioural deficits associated with Fragile X syndrome (FXS), which can be rectified by upregulating the level and function of Kv1.2. However, few drugs are available to treat its LOF mutations and hypoexpression. **Methods**: We discovered a new class of positive allosteric modulators (PAMs), e.g. C1, C2 and C3, that target Kv1.2 and potentiate its activity at nanomolar range. **Results:** In the stable Kv1.2-GFP CHO cell-line, electrophysiological recordings 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. In silico simulation and site-directed mutagenesis revealed a novel binding cavity of C2 and its analogs on the Kv1.2 channel. In the Fmr1KO cerebellum, C2 attenuated hyperexcitability of interneurons and enhanced the spike frequency of Purkinje neurons by reducing its inhibitory overtone. In vivo pharmacokinetic study showed that both C2 and C3 can pass the blood-brain barrier without toxicity. **Conclusion**: This project rationalizes Kv1.2 PAMs as a viable approach to rectify E/I imbalance. It will bring a new class of drugs for NDDs associated with Kv1.2 channelopathy.

30. Vittala Korann; Institute of Medical Science

Supervisor: Dr. Mahavir Agarwal

Theme: Psychiatric Disorders

THE DYSREGULATION OF THE GLYMPHATIC SYSTEM IN PATIENTS WITH PSYCHOSIS SPECTRUM DISORDERS

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Introduction: The pathophysiological mechanisms influencing psychosis spectrum disorders (PSDs) are largely unknown. The glymphatic system (GS), which is a brain's metabolic waste clearance pathway, has recently been implicated in its pathophysiology and has also been shown to be disrupted in various neurodegenerative and vascular diseases. Initial studies examining the glymphatic system in PSDs have reported disruptions, but the findings have been confounded by medication effects as they included antipsychotic (AP)-treated patients. Moreover, in patients with first-episode psychosis, task-based and resting-state functional imaging studies have reported that AP treatment can normalize functional dysconnectivity involving the frontal and temporal regions. **Objective**: As such, AP usage represents a potentially important confounding factor in this field of study. To avoid this confounding factor, we measured the functionality of the GS in a sample of AP-minimally exposed patients with PSDs and healthy controls (HCs) by utilizing the diffusion tensor imaging analysis along the perivascular space (DTI-ALPS) technique. **Methods:** The study included 13 AP-minimally exposed (≤2 weeks AP exposure in the past 3 months/lifetime) patients with PSDs and 114 HCs. The 64-direction diffusion weighted images (DWI) of both groups were processed by combining both FSL and MRtrix3 commands. The superior corona radiata (SCR) and the superior longitudinal fasciculus (SLF) were recognized as the projection and association fibers at the level of the lateral ventricle body, respectively, based on the JHU-ICBM-DTI-81-white-matter Labeled Atlas. The bilateral SCR and SLF areas were defined as spheres with a 5mm diameter, and these ROIs were applied to the diffusivity maps of all participants. The bilateral SLF and SCR diffusivity values were automatically computed along the x-, y-, and z-axis (i.e., Dxx, Dyy, and Dzz) for the DTI-ALPS calculation. We quantified water diffusion metrics along the x-, y-, and z-axis in both projection and association fibers to derive the DTI-ALPS index, a proxy for glymphatic activity. Between-group differences were analyzed using two-way ANCOVA controlling for age and sex. Partial correlations were used to assess the association between the ALPS index and clinical variables. **Results**: Analyses revealed that AP-minimally exposed patients had a significantly lower DTI-ALPS index of the left and right hemispheres and the whole brain compared to HCs, even after adjusting for age and sex (Falps_L = 11.09, $p = 0.001$; Falps_R = 10.92, $p = 0.001$; Falps = 13.06, $p < 0.001$). The effect sizes for the hemispheres and whole brain are: left ($\eta p2 = 0.112$), right ($\eta p2 = 0.134$) and whole brain ($\eta p2 = 0.142$). The diffusivities along the x-axis of both projection and association fibers, in both the left and right hemispheres, were also lower in AP-minimally exposed patients than in HCs (Fproj_L = 54.49, $p < 0.001$; Fproj_R = 70.268, $p < 0.001$; Fassoc_L = 36.02, $p < 0.001$; Fassoc_R = 56.01, $p < 0.001$). In addition, the diffusivities along the y-axis of projection fibers in both the left and right hemispheres were lower in AP-minimally exposed patients when compared to HCs (Fproj_L = 27.63, $p < 0.001$; Fproj_R = 30.87, $p < 0.001$). Furthermore, we did not find any significant correlations (all $p > 0.05$) between the DTI-ALPS index with age, BMI, symptomatology, and metabolic parameters. **Conclusion**: Overall, this study demonstrates that AP-minimally treated PSDs have a lower DTI-ALPS index compared to HCs. This indicates that patients have a lower metabolic waste clearance in the GS as proper brain functioning may require a normal waste clearance. Understanding the mechanisms that influence the GS may help to understand the pathophysiology of PSDs as proper metabolic waste clearance is needed for normal brain functioning.

31. Julia Beth Kowaleski; Faculty of Music

Supervisor: Dr. Michael Thaut

Theme: Pain & Sensory Disorders

INVESTIGATING THE EFFECTS OF AUDITORY STIMULI ON POSTURAL SWAY

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Introduction: Postural sway is the measurement of small movements the body makes to maintain balance while standing. Existing research shows that auditory and vestibular systems are both structurally and functionally linked. Research that investigates how auditory input impacts the vestibular system in humans are few but does provide basic behavioural evidence that auditory stimuli may influence postural sway. There is evidence that individuals with "autistic traits" have differences in sensory processing compared to neurotypical individuals10,11. **Objective**: To determine the impact of different auditory stimuli on the vestibular system when measuring postural orientation and investigate if peoples' sensory profiles influence their postural sway response in different sound conditions. **Methods:** This study recruited adults aged 18-34 with good or corrected vision and normal hearing. Participants stood on a stable surface force plate and performed the following tasks while listening to different auditory conditions: double leg stance eyes open (DLEO), double leg stance eyes closed (DLEC), single leg stance eyes open, single leg stance eyes closed. Sound conditions consisted of a 1000HZ constant pure tone (1000C), a looped ascending and descending tone pattern (MM), and a 1000HZ pure tone presented intermittently to match the rhythm of the melodic pattern (1000I). Sound conditions and tasks were randomized for each participant. Participants also completed sensory assessments. **Results**: Preliminary results showed that different sound conditions appear to have an influence on CoP measurements. Sway path length and sway velocity was notably reduced during the looping tone pattern compared to the other tone conditions. **Conclusion**: There are significant gaps in understanding the mechanisms of how auditory stimuli can affect postural sway. Gaining insight on how a predictable melodic pattern and other auditory stimuli influence postural sway deepens our understanding of how individuals engage with their world and has potential clinical applications.

32. Hayoung Kwon; Faculty of Music

Supervisor: Dr. Michael Thaut

Theme: Development & Neurodevelopmental Disorders

THE USE OF RHYTHMIC AUDITORY STIMULATION IN STROKE GAIT REHABILITATION : A CASE STUDY

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Introduction: Gait impairment is one of the most common and significantly affecting an individual's motor abilities, independence, and quality of life. Rhythmic Auditory Stimulation (RAS®) is a Neurologic Music Therapy (NMT™) technique that utilizes rhythmic auditory cues to enhance gait parameters such as cadence, velocity, and stride length in individuals with neurological impairments. **Objective**: This study examined the effects of RAS® gait training on a 57-year-old male stroke who experienced a right thalamic hemorrhage. **Methods**: The participant received ten individual RAS intervention sessions over a ten-week period. Pre- and post-assessments were conducted during the first and final sessions, measuring cadence, walking velocity, and stride length using the 10-Meter Walk Test. Balance was evaluated using the Berg Balance Scale (BBS) as a secondary outcome. **Results**: Descriptive data were recorded and analyzed using Microsoft Excel. Following the intervention, the participant demonstrated clinically meaningful improvements in both cadence and walking velocity, while stride length remained stable. The participant also showed a modest improvement in balance. **Conclusion**: These findings suggest that RAS may support gait and balance recovery in stroke rehabilitation.

33. Silvia Margarian; Department of Psychology

Supervisor: Dr. Kaori Takehara

Theme: Behavioral & Social Neuroscience

SUCCESS IN TRANSITIVE INFERENCE IS ASSOCIATED WITH THE ACTIVATION OF THE MEDIAL PREFRONTAL CORTEX IN MICE

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Introduction: Transitive inference (TI) allows to predict indirect relationships between items based on previously learned set of overlapping premises. Past lesion studies have shown that TI relies on the integrity of the medial prefrontal cortex (mPFC) and hippocampus in both humans and rodents. However, the precise anatomical pathways underlying this essential component of intelligence remain poorly understood. **Objective:** By combining gene-based circuit mapping with a newly developed automated TI task for mice, we investigated brain regions activated during the recall of direct and indirect item relationships. **Methods:** During the recall test, all mice chose correctly in the direct relationships; however, ~60% made correct transitive judgments on indirect relationships (good performers), while the remaining mice could not (bad performers). **Results:** Analyses of cFos expression revealed that the prelimbic and infralimbic subregions of the mPFC were more strongly activated in the good performers than the bad performers. In contrast, the cell activation in the CA1 subregion and dentate gyrus of the dorsal hippocampus was comparable between the two groups. All except dentate gyrus showed more robust cell activation in mice that underwent the test than those that stayed in their home cage. Currently, we are examining cFos expression in several other regions and overlaps between cFos expression and efferent projection targets. **Conclusion:** These results uncover the brain activity patterns associated with the ability to organize separately learned information into a mental model and use it for future adaptive behaviour.

34. Liv McIsaac; Faculty of Music

Supervisor: Dr. Michael Thaut

Theme: Clinical & Translational Neuroscience

THE EFFECTS OF MUSICAL VOICE TRAINING ON DYSPHONIA FOLLOWING A STROKE

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Introduction: In stroke rehabilitation, voice quality can be a significant area of concern for patients. Although some treatments currently exist, the effect of vocal training on voice quality rehabilitation is severely under-researched. **Objective**: By performing a seven-week long case study following the progress of a stroke patient undergoing vocal lessons to improve voice quality remotely, we hypothesized that a measureable improvement using a combination of three rating-based assessments could be attained. **Results**: Ultimately, all three assessments showed some degree of improvement, although some demonstrated a larger effect than others. **Conclusion**: We concluded that while the results indicate improvement, the degree was likely impacted by several key factors, namely the number of sessions.

35. Cory McKenzie; Department of Psychology

Supervisor: Dr. Paul Frankland

Theme: Development & Neurodevelopmental Disorders

CA3 INPUTS TO CA1 DRIVE THE EMERGENCE OF INHIBITORY SIGNALLING AND MEMORY SPECIFICITY

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Introduction: A bias towards memory generalization has been observed in both human children and juvenile mice. Children are more likely than adults to mistake a similar lure item for an identical target, while juvenile mice generalize contextual fear memories to similar, but distinct, contexts where an adult would exhibit fear memory only in the original training context. Although there are differences in these tasks and the rate of development, this developmental phenomenon appears

to be conserved in altricial mammals and provides an opportunity to study potential mechanisms underlying how our memory system develops. In particular, the hippocampus undergoes a critical period during the transition to greater memory specificity. This critical period has been associated with the maturation of interneurons in the CA1 of the hippocampus and is hypothesized to occur in an activity-dependent manner. Computational modelling also proposes that CA3 to CA1 projections are critical for the formation of specific episodic memories. **Objective**: The present study seeks to investigate the development of memory specificity in both human children and juvenile mice. **Methods**: A modified mnemonic similarity task (MST) was used to assess the development of memory specificity in humans. In mice a combination of contextual fear conditioning, neural projection tracing, and optogenetics were used to identify neurobiological mechanisms underlying memory specificity development. **Results**: We show that 1) human children and juvenile mice both show an increase in memory specificity with age, although at a different rate 2) CA3 projections to CA1 are immature in juvenile mice, particularly in their connection to interneurons 3) in mice, the development of memory specificity can be accelerated or delayed by manipulating the activity of CA3 to CA1 projections. **Conclusion**: These findings suggest that the development of memory specificity relies on the activity-dependent maturation of CA1 interneurons.

36. Tahir Muhammad; Institute of Medical Science

Supervisor: Dr. John B. Vincent

Theme: Molecular & Cellular Neuroscience

FUNCTIONAL AND COMPUTATIONAL ANALYSIS OF THE CHROMATIN MODIFIERS CHD2 AND CHD8 GENES IN NEURODEVELOPMENTAL DISORDERS

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Introduction: Autism spectrum disorder (ASD) and Intellectual Disability (ID) are neurodevelopmental disorders (ND) affecting social interaction, communication, cognition and behavior. They are characterized by a wide range of symptoms and severity, affecting 1 in 36 and 2-3 in 100 children, respectively. ND are of critical concern due to the extensive resources needed for intervention and treatment, as well as its lasting impact on the health and well-being of children, youth, adults, and their families and communities. The etiology of ND includes genetic mutations in many genes, including a number of chromatin-modifying genes (e.g. CHD2, CHD8, and MECP2). Chromatin modifiers regulate the expression of many genes. While mutations in these genes are known to cause neurodevelopmental phenotypes, the specific underlying cellular and molecular mechanisms are remaining unknown. **Objective**: We hypothesize that missense variants in CHD2, and CHD8 affect the DNA-binding dynamics, protein interactions, chromatin organization, and/or degradation rates. **Methods**: To investigate this, we have generated isogenic cell models of the known pathogenic variants and variants of uncertain significance (VUS) in CHD2 and CHD8 using a modified CRISPR/Cas9 method in HEK293 and SH-SY5Y cells. Furthermore, we have performed in-silico analysis using molecular docking and molecular dynamic simulation analysis of the missense variants in CHD2 and CHD8 proteins. **Results**: In-silico analysis has revealed that some variants (not all) are predicted to affect the binding dynamics of CHD2 and CHD8 proteins to their interacting protein partners and to the nucleosome. Preliminary overexpression western blot analysis has also indicated that missense variants in CHD2 and CHD8 affect the expression of histone 3.3 (in C2C12 and HeLa cells) and key methyl transferases such as RBBP5, KMT7, KMT1E (in SK-N-SH cells). Further functional analyses will assess the effects on chromatin organization, DNA binding dynamics, gene expression, protein stability, degradation and trafficking pathways using western blot, RT-qPCR, ELISA, cycloheximide chase assay, proteasomal/lysosomal pathway inhibitors, Co-IP, ChIP, and immunofluorescence colocalization. Additionally, differentiation and morphological effects will be studied in neuronal isogenic lines. **Conclusion**: This study will address diagnostics challenges for CHD2/8 VUS, and our CRISPR/Cas9-based models will help in understanding VUS. Finally, this study supports potential developments in the precision medicine, contributing to therapeutic innovation and improved understanding of ND etiopathology.

37. Kristoffer Panganiban; Institute of Medical Science

Supervisor: Dr. Margaret Hahn

Theme: Neuropharmacology & Drug Development

METABOLOMIC SIGNATURES DIFFERENTIATING PSYCHOSIS SPECTRUM DISORDERS FROM HEALTHY CONTROLS AND ASSOCIATION WITH WEIGHT GAIN

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Introduction: Psychosis spectrum disorders (PSDs) are a series of debilitating mental illnesses associated with intrinsic metabolic dysfunction, with the pathophysiological mechanisms of both the mental and physical symptom domains being largely unknown. Antipsychotics, the main treatment of PSDs, are known to exacerbate the metabolic problems seen in patients with PSDs. One approach to help understand these mechanisms is through metabolomics which is the study of the complete set of metabolites in the body called the metabolome. **Objective**: To investigate whether metabolomic signatures differ between patients with psychosis spectrum disorders and healthy controls and whether these signatures are associated with weight gain. **Methods**: This 12-week prospective naturalistic study used untargeted metabolomic data and included 37 minimally antipsychotic-treated PSD patients and 18 non-psychiatrically ill controls comparing differences in the baseline metabolomes of patients and controls. Nineteen patients completed the study and they were grouped based on whether they gained a clinically significant amount of weight (>7%) at endpoint when compared to baseline to identify whether metabolomic signatures could predict antipsychotic-induced weight gain. **Results:** The baseline comparison between patients with PSDs and controls showed two reduced metabolites in patients with PSDs: lysophosphatidylcholine (20:0), and carnitine (20:0) (FDR < 0.05). Fold change analysis at the 2.0x level showed that oleamide and serotonin were decreased in patients with PSDs. For patients who gained a clinically significant amount of weight (>7%), we found 5 metabolites that had an increased 2.0x fold change in patients who gained >7% weight: 3-hydroxyphenyl valeric acid, monoacylglycerol

16:0, oleamide, 2-piperidinone and bilirubin. We also found that 3 metabolites that had a decreased 2.0x fold change in patients who gained >7% weight: L-urobin, 2-acetylpyrrolidine, and glycohyodeoxycholic acid. **Conclusion**: Using metabolomics to understand the pathophysiological mechanisms that underly the mental and physical symptoms of PSDs is a promising technique. Identifying early changes in metabolomic signatures may be able to help predict which patients with PSDs are prone to antipsychotic-induced weight gain and possibly clinical/functional outcomes. However, more research is needed to help identify these potential signatures.

38. Jane Paterson; Department of Pharmacology & Toxicology

Supervisor: Dr. Chao Zheng

Theme: Neuropharmacology & Drug Development

EFFECTS OF ROCK INHIBITION IN FEMALE PS19 MICE: A PILOT PET IMAGING STUDY

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Introduction: Rho-associated protein kinase (ROCK) inhibition with Fasudil has shown therapeutic effects in AD animal models including PS19 mice. This transgenic model contains human 4R MAPT with the P301S mutation which causes tau aggregation, synaptic density loss and impaired glucose uptake. However, effects of Fasudil on synaptic density and glucose uptake have not been determined in vivo in PS19 mice. **Objective**: Determine effects of ROCK inhibition using Fasudil on synaptic density and glucose uptake in PS19 mice. **Methods**: 4-month-old female PS19 mice underwent PET imaging with the [18F]SynVesT-1 synaptic density tracer, and the [18F]FDG tracer for glucose uptake following a 3-week recovery period. Both scans included untreated mice (n=3) and mice treated with Fasudil at 30 mg/kg i.p. 4 hours before scanning (n=3). PMOD generated regional standardized uptake values (SUV), and a population-based radio-metabolite corrected one-tissue and two-tissue compartment models for [18F]SynVesT-1 from which VT was generated. SUVR was calculated for [18F]SynVesT-1 (ROI/Whole Brain) and [18F]FDG (ROI/Nucleus Accumbens), and all regions were assessed for significant changes. **Results**: Acute Fasudil treatment increased [18F]SynVesT-1 VT suggesting an increase in synaptic density. Treatment also increased [18F]FDG SUVR (ROI/Accumbens) in the midbrain, superior colliculus and inferior colliculus, and showed an increasing trend in glucose corrected [18F]FDG SUV indicating potential disease modifying effects of Fasudil in PS19 mice. **Conclusion**: ROCK inhibition using Fasudil positively affects synaptic density and glucose uptake in PS19 mice, which may indicate effects in clinical settings.

39. Daniel Phan; Faculty of Arts and Science

Supervisor: Dr. Tatyana Mollayeva

Theme: Clinical & Translational Neuroscience

DATA MANAGEMENT IN OBSERVATIONAL TRAUMATIC BRAIN INJURY RESEARCH: IMPLICATIONS FROM DATA HARMONIZATION OF SOCIAL AND CLINICAL PARAMETERS

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Introduction: Traumatic brain injury (TBI) is often to poor brain health outcomes and is a major contributor to mortality and long-term disability. Secondary analysis of social and clinical data is a critical and efficient way to maximize the potential benefit from past TBI research. The data from published observational studies exists; however, the lack of standardized data parameters is a major barrier to further use of these valuable data in its entirety. Pre-statistical harmonization of data structure, variables, and codebooks across published research would facilitate data analysis, including meta-analysis and machine learning approaches. **Objective**: We initiated a data harmonization initiative to standardize social and clinical data from TBI research. **Methods**: We conducted a systematic search for observational research on post-TBI brain health outcomes in adults that included age, sex, and injury severity on brain health outcomes. We used the PROGRESS-Plus framework, which captures social, economic, and cultural elements (e.g., place of residence, race, occupation, gender and sex, etc.) to extract social, structural, and personal variables. The variables were harmonized by collapsing analogous parameters into standardized categories through semantic matching, allowing us to collectively align structured, semi-structured, and unstructured data. **Results**: Our study included eighty-two studies that met our inclusion criteria, encompassing data on 5,447,162 participants (mean age 43, 61% male) with TBI, of which 26 (32%) included participants with mild TBI. We found substantial heterogeneity in how studies measured and reported PROGRESS-Plus and clinical data. The top three most frequently reported PROGRESS-Plus parameters, apart from age and sex/gender, were place of residence in 55 (67%), education in 40 (49%), and occupation in 35 (43%) of studies. Notably, none of the studies included information on religion. **Conclusion**: The harmonized data of 82 observational studies can potentially promote future secondary data analysis of brain health outcomes of adults with TBI, allowing for data combining from studies and provide guidance for future TBI research.

40. Hanista Premachandran; Department of Psychology

Supervisor: Dr. Maithe Arruda-Carvalho

Theme: Development & Neurodevelopmental Disorders

DEVELOPMENTAL RECRUITMENT OF MEDIAL PREFRONTAL CORTEX TO AMYGDALA PATHWAY BY FEAR LEARNING

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Introduction: The rodent medial prefrontal cortex (PFC) undergoes substantial anatomical and synaptic changes in early development. The prelimbic cortex (PL) subregion of the PFC and its connections to the basolateral amygdala (BLA) are particularly important for driving fear

expression and retrieval in adult rodents. However, fear learning is developmentally regulated, and some evidence suggests that younger rodents do not require the PFC for fear processing. **Objective**: Since there is limited research on the role of the immature PFC in fear processing, we investigated the timing of PL and PL-BLA pathway recruitment for fear conditioning. **Methods**: We first used chemogenetics to inhibit the PL and PL-BLA pathway in infancy (postnatal day (P) 15) and adolescence (P30) during fear training and tested for fear retrieval and contextual fear 24h later. **Results**: We found that while P30 mice showed impaired fear retrieval when the PL and PL-BLA pathway were inhibited during fear conditioning, P15 mice were unaffected by this manipulation, suggesting that the PL-BLA pathway is not required for auditory fear during infancy. Additionally, using a combination of optogenetics and whole-cell patch clamp electrophysiology, we found that while fear conditioning in P30 mice led to an increase in AMPA:NMDA ratios in PL-BLA synapses, P15 mice showed an absence of fear-induced synaptic plasticity in the same pathway. Lastly, we found that early life stress (ELS, maternal deprivation) can accelerate PFC recruitment for fear processing as early as P15. **Conclusion**: Overall, our results indicate that onset of the PL and PL-BLA pathway recruitment to fear encoding occurs between infancy and adolescence, and stress can alter this trajectory. Understanding the contribution of the PL-BLA pathway to early fear processing yields valuable insight into circuit maturation and the mechanisms of emotional learning at key developmental stages.

41. Charlotte Romain; Department of Cell and Systems Biology

Supervisor: Dr. Junchul Kim

Theme: Behavioral & Social Neuroscience

REWARD CONSUMPTION-MEDIATED SUPPRESSION OF THE ANTERIOR OLFACTORY NUCLEUS

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Introduction: Olfactory chemoreception is a highly conserved sensory modality vital to the perception of stimuli underlying behaviour. The anterior olfactory nucleus (AON) is a brain region within the primary olfactory cortex implicated in spatiotemporal episodic odor memory and notably sensory gating, with its suppression resulting in reduced filtering of sensory information from the olfactory bulb (OB). Previous work identified a suppression of the AON during water reward-related licking tasks. **Objective:** Here, we aimed to expand on this finding by recording in vivo peri-stimulus calcium-dependent mAON activity to further characterize this suppression. **Methods:** Freely-moving mice were presented with rewards of varying consumption mechanisms and flavours or lack thereof to investigate what type of rewards can invoke the suppression. In addition, mAON activity was recorded during a Go/No-Go behavioural task that temporally delineated water reward expectation from consumption in freely-moving water restricted mice to determine during which behavioural states the suppression occurs. **Results:** Both rewards consumed by licking or chewing elicited suppression, as did rewards with or without flavour. During the Go/No-Go task, a suppression effect was identified during the mechanical act of licking during false alarm trials as well as when licking was coupled with water consumption during successful Go trials. **Conclusion:** Altogether, these results suggest that motor information may be involved in mAON-mediated OB sensory gating and suppression of the AON likely enhances odour detection during consumption through lifting its inhibitory control over OB output neurons.

42. Angenelle Rosal; Institute of Medical Science

Supervisor: Dr. Antonio P. Strafella

Theme: Aging & Neurodegenerative Disorders

INVESTIGATING APOE4'S IMPACT ON BRAIN STRUCTURE AND ITS ASSOCIATION WITH COGNITIVE FUNCTION IN PARKINSON'S DISEASE: A STUDY FROM THE PPMI COHORT

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Introduction: Cognitive impairment is one of the most prevalent non-motor symptoms of Parkinson's Disease (PD), yet the underlying mechanisms and factors that lead to its development remains poorly understood. Apolipoprotein E4 (APOE4), a well-established genetic risk factor of Alzheimer's Disease (AD), has been found in some studies to be associated with PD-related cognitive impairment. However, its role in this non-motor symptom is still debated due to inconsistent findings. Gray matter abnormalities, specifically reductions in gray matter volume (GMV) and cortical thickness (CTh), have been observed in both subjects with PD-related cognitive impairment and APOE4 carriers independently using structural magnetic resonance imaging (MRI). However, no study has examined the impact of APOE4 on GMV and CTh in a PD cohort that may be associated with cognitive function. **Objective**: This study aimed to further clarify the role of APOE4 on cognitive function in PD by analyzing its effects on GMV and CTh in brain regions previously associated with PD-related cognitive impairment. **Methods**: 51 PD APOE4 carriers (58.78 ± 9.08 years; 16 females, 35 males) and 120 PD APOE4 non-carriers (62.99 ± 9.16 years; 48 females, 72 males) were analyzed from the Parkinson's Progression Markers Initiative (PPMI). Baseline T1-weighted MRI scans of each subject were obtained and underwent processing in FreeSurfer 7.1. ROI analyses were conducted on a priori regions previously associated with PD-related cognitive impairment, including the bilateral insula, hippocampus, superior frontal gyrus, superior temporal gyrus, dorsolateral prefrontal cortex (DLPFC), angular gyrus, and supramarginal gyrus. ANCOVAs were conducted using age, sex, disease duration, and total intercranial volume (TIV) as co-variates to examine GMV and CTh group differences. Pearson correlations and linear regression models were then used to assess relationships between regions with significant group differences and nine baseline cognitive tests. All statistical analyses were done in RStudio software. **Results**: PD APOE4 carriers had a significantly higher GMV in the left angular gyrus when compared to PD APOE4 non-carriers (p=0.011); however, this finding did not survive Bonferroni correction to account for multiple comparisons. Follow-up analyses revealed that the GMV of the left angular gyrus was correlated with Benton Judgement of Line Orientation scores (a measure of visuospatial function) in the whole PD

cohort as well as in PD APOE4 carriers and non-carriers ($p < 0.05$), but these correlations did not remain significant after controlling for co-variates. No group differences were found in CTh measures, and so no further analyses was done. **Conclusion**: The results suggests that APOE4 may not influence GMV and CTh changes in a way that impacts cognitive function in PD. Longitudinal analyses are warranted to determine whether the subtle GMV differences observed between the groups are meaningful over time in the progression of PD-related cognitive impairment.

43. Simran Sandhu; Department of Pharmacology & Toxicology

Supervisor: Dr. Meghan Chenoweth

Theme: Psychiatric Disorders

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Introduction: Migraine and anxiety are globally prevalent, heritable, disabling, and frequently co-occurring conditions that are more common in women. Research on their etiology, treatments, and sex-based disparity is limited, in part due to the underfunding of women's health research. **Objective**: Analyze the genetics of migraine and anxiety in women to explore genetic correlations, identify novel genetic risk factors, and provide support for drug design and repurposing opportunities. **Methods**: Data from genome-wide association studies (GWAS) of clinical and self-reported migraine and anxiety conducted specifically in women were used to perform multi-trait analysis of GWAS (MTAG). MTAG leverages the genetic correlation between traits to increase statistical power and identify novel risk loci not found in the original GWAS. **Results**: Genetic correlations (rg) for self reported migraine with self reported anxiety, clinically diagnosed anxiety, and clinically diagnosed migraine were 0.17, 0.07, and 0.80, respectively. MTAG analysis of self-reported migraine and self-reported anxiety yielded one novel risk locus for self-reported migraine; the lead variant, rs7276739, mapped to LINC00310, a long non-coding RNA, previously associated with coronary artery/heart disease. MTAG analysis of self-reported and clinical migraine yielded 12 novel risk loci for clinical migraine. One locus (lead SNP: rs74809038) was shared between clinical and self-reported migraine and mapped to GJA1, a gap junction gene with previous associations with heart rate. **Conclusion**: This study showcases the benefits of using MTAG for analyzing 1) comorbid heritable disorders, and 2) self-reported and clinical diagnoses of the same disorder. In each case, we identified novel risk loci not captured in the original GWASs. This work provides novel insights into the etiology of the two conditions. Next, Mendelian Randomization will be used to assess possible causality between migraine and anxiety in women

44. Can Sarica; Institute of Medical Science

Supervisor: Dr. Andres M. Lozano

Theme: Aging & Neurodegenerative Disorders

SUBTHALAMIC LOCAL FIELD POTENTIAL DYNAMICS DURING MOTOR CORTEX AND BASAL GANGLIA TRANSCRANIAL ULTRASOUND STIMULATION IN PARKINSON'S DISEASE

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Introduction: Low-intensity transcranial ultrasound stimulation (TUS) is a promising non-invasive neuromodulation method. Despite significant advancements in understanding the effects of TUS on cortical areas in animal models and healthy individuals, its impact on deep brain structures, especially in patient populations, remains largely unexplored. Herein, we examined the effects of TUS on the globus pallidus interna (GPi) and motor cortex (M1) in Parkinson's disease (PD) patients by recording local field potentials (LFPs) directly from the subthalamic nucleus (STN). **Objective**: To determine the effects of TUS on the GPi and M1 in PD patients by recording LFPs directly from STN. **Methods**: Seventeen PD patients with bilateral STN Percept PC deep brain stimulation (DBS) systems participated in this sham-controlled study. We applied theta burst (5Hz) TUS (tbTUS) for 2 minutes to each hemisphere targeting M1, GPi, and occipital cortex in separate sessions. LFPs were recorded simultaneously before, during, and at 10, 30, and 45 minutes after the sonications. During the sham condition, the procedure was performed with the stimulation intensity set to 0 watts. **Results**: Patients reported no TUS-related adverse events. Compared to sham, M1-tbTUS increased theta ($p<0.05$) and suppressed beta ($p<0.01$), while GPi-tbTUS increased beta ($p<0.01$) activity, with effects persisting ≥ 45 minutes. Occipital-tbTUS (active sham) showed no significant difference from passive sham. Movement (finger tapping) amplified M1-tbTUS effects on alpha ($p<0.05$) band. Beta-burst duration significantly decreased with M1 stimulation ($p<0.05$) but remained unchanged in the GPi group. UPDRS scores significantly improved in the M1 group ($p<0.05$). **Conclusion**: These results provide direct evidence of target engagement and specificity of TUS in cortical and deep brain structures in humans and offer promising insights into its potential as a safe, non-invasive brain stimulation technology for treating neurological disorders.

45. Ariana Seyed Makki; Institute of Medical Science

Supervisor: Dr. Karen Davis

Theme: Pain & Sensory Disorders

THETA-GAMMA PHASE-AMPLITUDE COUPLING IN THE DYNAMIC PAIN CONNECTOME IN HEALTHY INDIVIDUALS AND ABNORMALITIES IN PEOPLE WITH CHRONIC PAIN

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Introduction: How does the brain process nociceptive stimuli and contribute to chronic pain? Theta-gamma phase-amplitude coupling (PAC) could serve to gate nociceptive processing and modulation at different points of interaction within the dynamic pain connectome (DPC). **Objective**: This study investigated whether there is normally PAC of intrinsic activity within the DPC and whether it is disrupted in people with chronic pain. **Methods**: Resting-state magnetoencephalography was used to measure theta-gamma PAC in 38 healthy individuals (20 M, 18 F) and 37 individuals with chronic pain associated with ankylosing spondylitis (20 M, 17 F). The magnitude and incidence of PAC was assessed in nodes of the ascending nociceptive and descending antinociceptive pathways, default mode and salience networks. We also examined whether there were associations between PAC and each patient's chronic pain intensity, disease severity, and functional limitations. **Results**: Most or all individuals in the healthy and chronic pain groups exhibited PAC in all DPC regions tested, except the subgenual anterior cingulate cortex of the descending antinociceptive pathway (37% and 45%, respectively). Individuals with chronic pain exhibited PAC abnormalities in the right midcingulate cortex of the salience network, which also had moderate associations with disease severity and functional limitations. Compared to males, females with chronic pain showed more widespread PAC abnormalities across the DPC. **Conclusion**: This study provides novel data to implicate theta-gamma PAC as a means to shape the outcome of noxious input to the brain. These findings also point to PAC failures as a possible abnormality that could contribute to chronic pain.

46. Tianze Shi; Department of Pharmacology & Toxicology

Supervisor: Dr. Etienne Sibille

Theme : Molecular & Cellular Neuroscience

BRAIN-DERIVED NEUROTROPHIC FACTOR-INDUCED PROTEOSTASIS DEFICIT

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Introduction: Neuropeptides (NPs) 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 function. Post-mortem transcriptomic analysis on young vs. old human brains showed that expression of NPs, including brain-derived neurotrophic factor (BDNF), is disproportionately decreased during aging and in neuropsychiatric disorders. However, the molecular and cellular mechanisms underlying reduced NPs remain elusive. We hypothesized that this vulnerability may originate in the ER, where excess demand on NP synthesis causes ER stress, as in brain disorders. **Objective**: This study aims 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 and evaluated ER stress levels via immunofluorescence (IF) with ER stress markers (p-eIF2α) and behavioral outcomes. **Results:** Forced expression of preproBDNF induced ER stress (IF) and working memory deficits (Y-maze). **Conclusion**: BDNF precursor overexpression can exceed ER processing capacity, leading to ER stress-mediated proteostasis deficit and protein aggregation. Ongoing proteomic and transcriptomic studies are underway to further elucidate the underlying mechanisms.

47. Yixiong Sun; Department of Cell and Systems Biology

Supervisor: Dr. Kaori Takehara-Nishiuchi

Theme: System & Circuits Neuroscience

RIGID FUNCTIONAL CONNECTIVITY AMONG HIPPOCAMPAL CA1 NEURONS IN TGCRND8 MICE UNDERMINES THE ENCODING OF NOVEL EXPERIENCE

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Introduction: Deficits in episodic memory are a cardinal symptom of Alzheimer's disease (AD), and uncovering their physiological and circuit mechanisms is essential to connect AD molecular pathology and cognitive impairments. Transient bursts of oscillatory activity known as sharp wave ripples (SPW-R, 100-250 Hz) occur throughout the hippocampus and are necessary for the consolidation of episodic memory. Although several studies using mouse models of AD reveal abnormalities in SPW-Rs, it remains unclear how spike dynamics during SPW-Rs supporting memory consolidation is affected. **Methods**: Using in vivo electrophysiology, we recorded neuronal activity from the dorsal CA1 hippocampus of 3-5 month-old TgCRND8 (Tg) mice with AD-related amyloidosis and their healthy littermates (non-Tg). Recordings were performed during rest periods before (PRE) and after (POST) mice were subjected to an object location memory task. **Results**: We found that many CA1 excitatory cells from both Tg and non-Tg mice increased their firing rates during SPW-Rs prior to task exposure. During POST-task periods, this SPW-R modulation of firing rate was increased in a subset of non-Tg excitatory cells. In contrast, most excitatory cells from Tg mice did not show the same level of experience dependent increase. These experience-responsive cells in non-Tg mice also developed higher probability of co-firings among them but not with other excitatory cells, indicating the formation of cell assemblies encoding the experience. This specific refinement of functional coupling between experience-responsive cells was abolished in Tg mice, which could not recognize object displacement after 3 hours. **Conclusion**: Together, these results demonstrate that experience-dependent changes in spike dynamics during SPW-Rs is critical for memory consolidation, and disruption of this process is a possible mechanism behind memory deficits associated with amyloidosis.

48. Ruth Tran; Department of Psychology

Supervisor: Dr. Junchul Kim

Theme: Aging & Neurodegenerative Disorders

PROGRESSION OF OLFACTORY FUNCTION AND ALPHA-SYNUCLEINOPATHY IN PARKINSON'S DISEASE FIBRIL MODEL

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Introduction: Parkinson's disease (PD) is characterized by motor deficits which typically appear in stage 3/4 when approximately 50% of substantia nigral neurons are lost. Olfactory dysfunction occurs in 90% of patients and emerges at least 4 years before the motor symptom onset. Alpha-synuclein (a-syn) pathology accumulates in the olfactory system in the first stage of PD, particularly in the anterior olfactory nucleus (AON). The AON, a critical hub for olfactory processing, integrates bottom-up sensory input from the olfactory bulb (OB) and contextual input from the hippocampus, facilitating odour detection, discrimination and memory. **Objective:** Although hyposmia is prevalent in PD, the underlying mechanisms remain unclear. **Methods:** To address this gap, we used A53T mice injected with a-syn fibrils into the AON to model PD. Mice performed a go/no-go task to assess olfactory sensitivity, discrimination and memory. Histology was performed longitudinally to evaluate the progression of a-synucleinopathy. **Results:** Olfactory detection and discrimination function remain intact in PD mice, possibly due to sparse labelling of a-syn in the OB. Preliminary findings indicate that contextual odour memory appears to be impaired at 1 month post-injection (mpi) but recovers over time, coinciding with dense a-syn pathology in the AON at 1mpi, followed by a reduction in a-syn at 4mpi, potentially reflecting clearing mechanisms. **Conclusion:** The outcomes of the current study will enhance our understanding of olfactory deficits in PD and aid in developing a diagnostic tool for identifying PD patients at the earliest possible stage.

49. Elizabeth Waye; Institute of Medical Science

Supervisor: Dr. Tom Schweizer

Theme: Psychiatric Disorders

FUNCTIONAL CONNECTIVITY CHANGES ASSOCIATED WITH ANXIETY AND DEPRESSION FOLLOWING CONCUSSION.

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Introduction: Sports-related concussions (SRCs) are associated with elevated symptoms of anxiety and depression in the early symptomatic phase of injury. It is presently unclear to what extent emotional symptoms are associated with specific alterations in functional brain networks at early injury and how they relate to the resolution of emotional symptoms at medical clearance to return to play (RTP). **Objective**: This study aimed to investigate functional connectivity changes in recently concussed athletes vs non-concussed athletes. We used blood-oxygen-level-dependent functional magnetic resonance imaging (BOLD fMRI) to investigate whether concussion was associated with an abnormal relationship between symptoms and brain function. **Methods**: Varsity athletes were recruited from a single sports medicine clinic at the University of Toronto, including 55 concussed (mean age = 20.51 ± 2.07; 51% female) and 127 non-concussed (mean age = 20.38 ± 1.97; 51% female) that completed eyes-closed resting-state fMRI scans and the Hospital Anxiety and Depression Scale (HADS). HADS depression and anxiety sub-scores were compared between groups. Seed-based connectivity analyses then assessed the effects of concussion status, HADS score and their interaction for key brain regions implicated in depression and anxiety – identified within the subgenual anterior cingulate (sgACC) and amygdala, respectively. A subsample of 29 concussed athletes (mean age = 20.59 ± 2.18; 62% female) also returned for testing at RTP. HADS and functional connectivity change scores were compared between the groups for the same set of brain regions to assess how network-level changes evolve with symptom improvement. **Results**: During the early symptomatic phase, the concussed group reported significantly elevated symptoms of depression but not anxiety. Connectivity analysis of the sgACC found that concussed athletes had decreased connectivity to the middle cingulate cortex and increased connectivity to the posterior cingulate cortex, while HADS depression scores were correlated with decreased connectivity to the medial parietal lobe and occipital lobe for both concussed and non-concussed athletes. Analyses of the amygdala showed a distinct connectivity relationship with HADS anxiety scores for concussed athletes, with more widespread increases in connectivity. Longitudinally, athletes at RTP exhibited increased connectivity with the amygdala and the sgACC, irrespective of the change in HADS scores. Further longitudinal analysis revealed that a greater decline in HADS depression and anxiety scores was associated with decreased connectivity for the sgACC and amygdala, respectively. **Conclusion**: Our findings provide new insights into network-level changes that occur following concussion and throughout the recovery process. More specifically, symptoms of post-concussion anxiety and depression may have a distinct representation in the brain compared to uninjured athletes. These results may indicate a novel target for future post-concussion rehabilitation interventions, as well as increase our understanding of the HADS questionnaire as a potential tool for identifying individuals experiencing early onset post-concussive anxiety and depression otherwise missed by conventional symptom reporting.

50. Jiaoyang Wo; Department of Physiology

Supervisor: Dr. Paul Frankland

Theme: Cognitive Neuroscience

CD47'S REGULATION OF MEMORY PROCESSES

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Introduction: Microglia regulate synaptic connections through synaptic pruning, either eliminating or protecting synapses based on neuronal

expression of “Eat Me” or “Don’t Eat Me” signals. While “Eat Me” signals are known to promote memory forgetting by promoting synapse removal, the role of “Don’t Eat Me” signals, which protect synapses, remains largely unexplored. This study focuses on one such signal, CD47. **Objective**: We hypothesize that CD47 strengthens established engram synapses and promotes memory persistence. By selectively protecting active engram synapses from microglial pruning, CD47 may enhance the stability of engram connections and increase engram cell excitability, thereby supporting memory persistence and precision. **Methods**: We used contextual fear conditioning as the main behavioural paradigm and combined with engram tagging and manipulation techniques including TRAP2 mice and the Double Inverted Orientation (DIO) system. **Results**: We found that CD47 regulated memory persistence and precision. CD47 overexpression in engram cells promoted memory persistence by slowing fear memory extinction, inhibiting memory forgetting, and increasing memory precision at remote time point. At the cellular level, CD47 enhanced engram synaptic connectivity by increasing spine density, increased engram reactivity by facilitating engram cell activity during memory recall, and increased neuronal excitability by allocating CD47 overexpression neurons to become part of an engram supporting fear memory. **Conclusion**: This research uncovers how CD47 influences cognitive function and could lead to new understandings of microglia’s contribution to memory and cognitive functions.

51. Abigail Wolfensohn; Institute of Medical Science

Supervisor: Dr. Mojgan Hodaie

Theme: Pain & Sensory Disorders

EXPLORING GLYMPHATIC SYSTEM FUNCTION IN TRIGEMINAL NEURALGIA USING NEUROIMAGING

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Introduction: Trigeminal neuralgia (TN) is a chronic neuropathic pain disorder characterized by severe facial pain. Based on previous machine learning (ML) analysis, TN has been associated with accelerated brain aging relative to chronological age, which may predispose patients to cognitive decline and neurodegenerative disease; yet, the mechanisms underlying this phenomenon remain unclear. Emerging research has underscored the critical role of the glymphatic system (GS) in maintaining central nervous system health. The GS is a recently discovered waste clearance pathway in the brain; GS dysfunction is associated with neurodegeneration and aging. Noninvasive magnetic resonance imaging (MRI)-based techniques for assessing GS efficacy are now possible and are widely used, such as diffusion tensor imaging along the perivascular space (DTI-ALPS) and choroid plexus volume (CPV) analysis. Despite this, the relationship between the GS and chronic pain remains understudied. **Objective**: This study aims to explore GS dynamics in patients with TN. We hypothesize that TN patients will exhibit decreased GS function (i.e. lower DTI-ALPS and higher CPV) relative to healthy controls (HC), and that the degree of decreased GS function will be inversely correlated with the degree of accelerated brain aging. **Methods**: Diffusion- and T1-weighted structural MRI data was acquired from 200 surgically naive TN patients, as well as data from age- and sex-matched healthy controls acquired locally and through external data repositories. The diffusion-weighted MRI data was preprocessed to obtain diffusivity metrics that were used to compute DTI-ALPS in both cerebral hemispheres for each subject. **Results**: Preliminary results from a subsample of 50 TN and 50 HC subjects demonstrate significantly decreased DTI-ALPS indices in the TN cohort relative to HCs for both the left (1.25 ± 0.16 versus 1.45 ± 0.38, $p<0.001$, Cohen $d=0.71$) and right (1.24 ± 0.13 versus 1.43 ± 0.34, $p<0.001$, Cohen $d=0.72$) hemispheres. Additional DTI-ALPS results are pending. Furthermore, the T1-weighted MRI data will be preprocessed and segmented into cortical and subcortical regions, allowing for extraction of neuroanatomical metrics. CPV will be computed using a method based on the Gaussian Mixture Model. DTI-ALPS and CPV will be used to compare GS efficacy between TN and HC subjects. Secondary statistical and ML-based analysis will also be conducted to investigate potential relationships between GS function and variables including the duration and severity of pain, sex, and accelerated brain aging. **Conclusion**: Based on the initial DTI-ALPS analysis, our study’s findings thus far suggest a likely association between TN and worsened GS efficacy. Full results, including the CPV and brain age analysis, will provide additional clarity. Our work has the potential to provide key insights into the connection between the GS, accelerated brain aging, and chronic pain disorders like TN, elucidating the processes whereby chronic pain relates to our overall health and wellbeing. Moreover, the results of our work may help advance our knowledge of chronic pain pathophysiology and inform the development of more personalized and effective treatment strategies in the future.

52. Bozhi Wu; Department of Physiology

Supervisor: Dr. Sheena Josselyn

Theme: Behavioral & Social Neuroscience

POST-TRAINING REACTIVATION OF ENGRAM NEURONS IS IMPORTANT FOR FEAR MEMORY CONSOLIDATION

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Introduction: Memories are thought to be encoded by sparse ensembles of neurons, known as "engram" neurons, which exhibit elevated activity during memory formation. Previous studies have shown that reactivating these neurons can trigger memory retrieval, whereas their inhibition can impair recall. The lateral amygdala (LA) is a critical region for the formation of fear memories, and following a memory-encoding event, LA neurons undergo molecular and cellular changes — such as altered gene expression and protein synthesis — that support memory consolidation by strengthening synaptic connections. However, it remains unclear whether the reactivation of engram neurons immediately after learning plays a causal role in memory consolidation. **Objective**: Using both endogenous monitoring and artificial manipulation of engram neurons, we aimed to test whether their reactivation immediately post-training is necessary for consolidating auditory fear memories. **Methods**: Wild-type (WT) mice

were injected with AAVs encoding GCaMP7f into the LA and implanted with GRIN lenses for in vivo one-photon calcium imaging using the UCLA Miniscope system. To enable bidirectional optogenetic manipulation, we used the NpACY viral vector, allowing excitation with blue light and inhibition with red light. Light stimulation was delivered immediately after training to modulate the activity of the allocated engram population. Memory retrieval was assessed 24 hours later, followed by additional manipulations to further probe engram function. To label neurons activated specifically during the post-training period, we employed the scFLARE system for activity-dependent tagging. **Results**: Using calcium imaging, we observed a higher level of reactivation of putative engram neurons immediately after training. These neurons, but not non-engram neurons, also exhibited increased functional connectivity during training, post-training, and testing, suggesting coordinated activity patterns that may support memory consolidation. Then, we used optogenetics to artificially allocate the fear memory to a random subset of LA neurons and manipulated their activity immediately after training. Disrupting post-training activity — either through excitation or inhibition — impaired subsequent memory retrieval, highlighting the importance of precise post-training dynamics among engram neurons in memory consolidation. **Conclusion**: Our findings demonstrate that immediate post-training reactivation of engram neurons in the lateral amygdala is critical for the consolidation of fear memories.

53. Meng Yang; Department of Physiology

Supervisor: Dr. Zhong-Ping Feng

Theme: Neuropharmacology & Drug Development

CHANGES IN NEURAL DYNAMICS IN DEEP LAYERS OF RETROSPLENIAL CORTEX AND HIPPOCAMPUS IN NEONATAL HYPOXIC-ISCHEMIC BRAIN INJURY

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Introduction: Perinatal and neonatal hypoxic-ischemia (HI) can result in hypoxic-ischemic encephalopathy (HIE), affecting 1–3 per 1000 newborns and constituting a leading cause of neonatal mortality. Survivors often experience persistent neurodevelopmental deficits and motor impairments, including impaired motor learning, which depends on the retrosplenial cortex (RSC) and hippocampus. However, the neuronal network alterations underlying HI-induced motor learning deficits remain unclear. **Objective**: This study examined the long-term effects of neonatal HI on neuronal activity in the RSC and hippocampus using a mouse model of neonatal HI brain injury. **Methods**: Simultaneous electrophysiological recordings of neuronal firing and local field potentials were conducted in freely moving adult mice subjected to sham or HI surgery at the neonatal stage. **Results:** Following HI, a significant reduction in neurons recorded per tetrode was observed, with remaining pyramidal neurons displaying abnormal bursting and synchronized firing patterns in the ipsilateral RSC and hippocampus. Pathological spike-field synchrony was evident, with many pyramidal neurons phase-locked in the theta-to-alpha oscillatory band. Neonatal HI mice also exhibited impaired motor learning and reduced engagement of ipsilateral pyramidal neurons during behavior. **Conclusion**: This study reveals, for the first time, that disruptions in firing patterns and RSC-hippocampal communication contribute to long-term motor learning deficits following neonatal HI brain injury.

54. Meeraal Zaheer; Department of Physiology

Supervisor: Dr. Sheena Josselyn

Theme: Behavioral & Social Neuroscience

THE ROLE OF CB1 RECEPTORS ON LATERAL AMYGDALA PARVALBUMIN NEURONS DURING STRESS AND FEAR EXTINCTION

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Introduction: The interplay between stress and memory has long been recognized as a key factor in post-traumatic stress disorder (PTSD), an anxiety-based disorder characterized by intrusive memories and impaired fear memory extinction. While exposure therapy, a form of extinction training, is widely used to treat PTSD, fear memories often resurface following treatment in both patients and animal models. Previous research implicates the lateral amygdala (LA) in auditory fear memory acquisition and highlights the importance of parvalbumin (PV+) interneurons in regulating these processes. Endogenous cannabinoids (eCBs) are key regulators of stress and memory, with evidence suggesting that alterations in eCB signaling can impair the extinction of fear memories. Stress-induced changes in eCB activity are thought to decrease PV+ inhibitory activity in the LA, potentially disrupting fear extinction. **Results:** My preliminary findings suggest that cannabinoid 1 (CB1) receptors on PV+ interneurons in the LA may be pivotal players in extinction learning. This work aims to clarify how CB1 receptor activity modulates LA PV+ interneuron function in response to stress and fear extinction learning. **Conclusion**: Defining the precise role of eCB activity and PV+ interneurons is critical to develop our understanding of neural mechanisms underlying PTSD. By investigating the role of eCB signaling in regulating fear extinction, this research may inform novel therapeutic strategies for memory disorders and other stress-related disorders.

55. Sofiya Zbaranska; Department of Physiology

Supervisor: Dr. Sheena Josselyn

Theme: Behavioral & Social Neuroscience

CONTRIBUTIONS OF THE MEDIAL AMYGDALA TO SOCIAL MEMORY

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Introduction: Our ability to recognize and remember other individuals, known as social memory, is indispensable for everyday interactions. Disruptions in social memory are implicated in several neuropsychiatric disorders, such as autism spectrum disorder, schizophrenia or social anxiety. Generally, memories are thought to be stored in populations of neurons active during memory encoding and retrieval, termed engrams.

Neurons supporting social memory were identified in the hippocampal regions CA2 and ventral CA1. However, little is known about how other brain regions are involved in the social memory network. **Objective**: I propose the medial amygdala as a candidate region essential for social memory formation and retrieval. Thus, I aim to test (1) if the engram neurons in the medial amygdala are activated by specific social subjects and (2) whether their activity is necessary for social memory expression. **Methods:** Social memory will be assessed using the social novelty discrimination task where test mice are presented with a familiar and a novel mouse, and they show successful memory recall by interacting more with the novel over the familiar partner. I will induce successful and unsuccessful memory formation by injecting an oxytocin receptor antagonist or saline immediately after training. Social memory will be tested 1h or 24h later and brains will be collected for cFos quantification. Next, I will "tag" the social engram in the amygdala using genetic activity-dependent tagging tools such that neurons active during training will express a fluorescent marker. 24 hours following training, I will present the mice with either the familiar or a novel mouse. Brains will be removed, and the overlap between engram neurons tagged during training and neurons active during test will be quantified to assess engram specificity. To study the functional importance of these engram neurons, I will use an emotionally salient social memory task. For training, test mice will undergo social defeat with an aggressor mouse, and their engrams will be tagged using a chemogenetic tool, allowing these neurons to be selectively silenced during the memory test. **Results:** Our data show that disruption of oxytocin signalling following training abolishes both 1h and 24h social memory in mice. This effect is accompanied by a reduction in cFos expression (i.e., activity) in the MeA. Furthermore, we observed that the proportion of cFos+ neurons in the MeA positively scales with social memory performance tested one day after training. Next, we tagged the putative engram ensemble supporting social memory in the MeA and found that the activity of the tagged neurons exhibits higher selectivity to particular social subjects. Finally, we inhibited the activity of this putative engram ensemble during the social memory test and found that this manipulation disrupted social memory expression. **Conclusion:** Our results indicate that the medial amygdala contains engrams that play an important role in social memory.

56. Xinyang Zhang; Department of Physiology

Supervisor: Dr. Hong-Shuo Sun

Theme: Clinical & Translational Neuroscience

TRPM7 KINASE INHIBITION PROVIDES NEUROPROTECTION AND ATTENUATES NEUROINFLAMMATION IN NEONATAL HYPOXIC-ISCHEMIC BRAIN INJURY

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Introduction: Hypoxic-ischemic brain injury (HIBI) is a major cause of perinatal brain damage, contributing to significant neonatal mortality and disability, yet its therapeutics remain limited. Transient receptor potential melastatin 7 (TRPM7), a channel-kinase with both divalent cation channel activity and an atypical α-kinase function, plays a key role in ischemic and hypoxic brain damage. While its channel activity has been extensively studied, the kinase domain remains less understood in HIBI pathophysiology. **Objective**: To investigate whether TG100-115 (TG), the first documented potent inhibitor of TRPM7 kinase, provides short- and long-term neuroprotection against HIBI in vivo, and to demonstrate the potential mechanisms underlying TG's effects on HIBI. **Methods:** The HIBI model was surgically established in postnatal day 7 CD-1 mice, and brain injury was assessed histologically and morphologically. Neurobehavioral tests evaluated functional recovery. The dose response of TG was examined. Western blot, immunohistochemistry, and confocal imaging investigated the potential mechanisms of the drug. **Results**: Pre-HIBI administration of TG at three different doses significantly reduced brain infarction volume. Post-treatments up to 3 (1, 2, and 3) hours after HIBI also decreased infarction, illustrating the therapeutic time window. TG preserved the mouse brain morphology, body weight, and short-term behavioural outcomes in a 7-day observation post-HIBI. Long-term behavioural outcomes were also improved, indicating TG's long-term neuroprotection. Furthermore, TG treatments: (1) reduced HIBI-induced caspase-3 cleavage and apoptosis, preserving neuronal integrity; (2) downregulated the elevated TRPM7expression in HIBI; and (3) inhibited microglial activation and NLRP3 inflammasome-mediated neuroinflammation in HIBI. **Conclusion**: TG shows neuroprotection and anti-inflammatory effects against HIBI.

57. Sampson Zhao; Department of Pharmacology & Toxicology

Supervisor: Dr. Patricia Di Ciano

Theme: Neuropharmacology & Drug Development

ASSOCIATION OF DRIVING WITH BLOOD THC: A SYSTEMATIC REVIEW

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Introduction: Many countries rely on blood concentrations of delta-9-tetrahydrocannabinol (THC) to determine whether drivers are under the influence of cannabis. However, recent studies suggest that there is an unclear relationship between blood THC concentrations and changes in driving. **Methods**: This systematic review included peer-reviewed published studies, from inception to September 2023, investigating correlations between blood THC and driving performance in either real-world and simulated settings. The primary factors assessed were 'weaving'/lateral control, speed, car following measures (following distance and coherence), reaction time and overall driving performance.

Results: Our search identified 4,845 papers; 12 met eligibility criteria. Of the 12 studies, 10 reported no significant linear relationship between blood THC concentrations and driving measures such as weaving/lateral control (8 out of 9 studies), speed (4 out of 5), car-following tasks (2 out of 3), reaction time (1 out of 1), and overall driving performance (3 out of 3). The studies that found associations between blood THC and driving utilized complex driving scenarios. **Conclusion**: Our results suggest that the relationship of blood THC to driving is complicated and further studies are needed. Future research should investigate relationships between blood THC levels and impairment under more complex driving conditions and consider the impact of modern high-potency cannabis strains.

58. Angela Zolis; Department of Physiology

Supervisor: Dr. Evelyn Lambe

Theme: Molecular & Cellular Neuroscience

INTERACTION OF PLASTICITY PARADIGM AND SOCIAL ISOLATION IN MOUSE PREFRONTAL CORTEX

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Introduction Theta burst paradigms are increasingly applied to prefrontal cortex (PFC) in mood disorder treatments. These protocols originated in hippocampal preclinical research, where it reliably induces robust long-term potentiation (LTP). However, theta burst stimulation results in lower amplitude outcomes in the PFC and may benefit from paradigm refinement. **Objective**: Here, we developed a wide-field calcium imaging approach to observe and refine plasticity experiments in prefrontal cortical brain slices from male and female Thy1-GCaMP6f mice. **Methods**: This approach offers a novel window into the spatial spread of potentiation. In these experiments, we conduct real-time monitoring of calcium dynamics before, during, and after plasticity induction protocols, including low-frequency test pulses and theta burst stimulation aimed at eliciting LTP. By capturing both the magnitude and a spatial map of potentiation, our approach elucidates PFC plasticity dynamics. We use this method to contrast a typical theta burst paradigm used in patients with a reduced stimuli spaced paradigm. Interleaving gaps between theta burst episodes has been shown to boost LTP in other brain regions. We pursue these experiments in group-housed mice and prolonged social isolation stress littermate controls. **Results**: Both clinical and spaced paradigms elicit LTP of modest amplitude in PFC brain slices, but only the spaced theta burst protocol yields consistent area-based LTP in slices from socially isolated mice. **Conclusion**: This research indicates that a spaced approach with relatively few stimulation episodes may be effective in the prefrontal cortex.

59. Lola Zovko; Department of Pharmacology & Toxicology

Supervisor: Dr. Ali Salahpour

Theme: Neuropharmacology & Drug Development

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

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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. **Conclusion**: 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.

Oral Presentations

SESSION I

CLINICAL & TRANSLATIONAL NEUROSCIENCE

1. Regina Annirood; Institute of Medical Science

Supervisor: Dr. Robert Chen

THE CAUSAL ROLE OF THE HUMAN POSTERIOR THALAMUS IN THE CONTROL OF VISUAL ATTENTION

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Introduction: The thalamus has traditionally been considered a relay structure for transmitting information to the cortex without active involvement. However, recent animal studies have challenged this view, demonstrating that thalamic manipulations can affect executive functions. In the past, it was not feasible to causally study potential roles of the human thalamus in executive functions as traditional non-invasive brain stimulation methods could not target this structure. By using transcranial ultrasound stimulation (TUS), which allows for targeted stimulation of deep brain areas, we tested the hypothesis that the human pulvinar, a posterior thalamic nucleus, actively contributes to the control of visual attention. **Objective:** To test the hypothesis that the human pulvinar, a posterior thalamic nucleus, plays an active and causal role in visual attention control, using transcranial ultrasound stimulation (TUS). **Methods:** Fifteen healthy participants provided informed consent and completed a visual search task. In this task, participants identified a "T" character among "L" distractors on a screen, with the number of distractors varying across trials (1, 4, 8, 16, or 32). Participants pressed a key to indicate the presence or absence of the "T," with response time and accuracy recorded to assess the impact of distractor count on visual attention and search efficiency. A control task was included, targeting the globus pallidus internus (GPi), a region associated with response inhibition, using a stop signal task. In this task, participants pressed an arrow key corresponding to the direction of a white arrow displayed on the screen. In some trials, the arrow turned blue, signaling them to halt their action. The time taken to respond to the stop signal, termed the stop-signal reaction time (SSRT), served as a measure of response inhibition. We used BabelBrain, a Python-based tool, to plan optimal sonication trajectories. This ensured compensation for ultrasound loss through the skull and maintained safe acoustic intensities and thermal levels. The TUS protocol consisted of 120-second sequences of 20-millisecond ultrasound bursts delivered at 5 Hz (theta burst), repeated every 200 milliseconds, targeting either the pulvinar or GPi bilaterally. **Results:** Our results demonstrated a double dissociation of effects: TUS of the pulvinar enhanced visual attention, reflected in improved search efficiency, without affecting response inhibition. Conversely, TUS of the globus pallidus internus selectively impaired response inhibition, evidenced by longer SSRTs, while leaving visual attention unaffected. **Conclusion:** This dissociation highlights the distinct cognitive functions of the pulvinar and the globus pallidus internus, while establishing a causal link between pulvinar activity and attentional modulation. Moreover, our study demonstrates that TUS has great potential to causally investigate functions of deep brain areas that cannot be targeted by other noninvasive brain stimulation techniques.

2. Ruobing Chen; Pharmacology and Toxicology

Supervisor: Dr. Isabelle Boileau

RELATIONSHIP BETWEEN ENDOCANNABINOID METABOLISM, RESTING STATE CONNECTIVITY, AND CLINICAL OUTCOMES IN AN ALCOHOL USE DISORDER COHORT

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Introduction: Alcohol use disorder (AUD) is a chronic condition with frequent cycles of remission and relapse. One therapeutic target of interest is the endocannabinoid system (ECS) which regulates mood and stress. In particular, the enzyme fatty acid amide hydrolase (FAAH) modulates ECS tone. Prior literature demonstrated that amygdala FAAH levels were negatively related to frontoamygdala resting state connectivity. This circuit is known to be disrupted in AUD, contributing to emotional dysregulation. However, the relationship between FAAH and frontoamygdala function is unexplored in AUD. **Objective:** Examine whether resting state functional connectivity is impaired in AUD compared to healthy controls and whether lower frontoamygdala connectivity in AUD is associated with higher FAAH activity and severity of cravings, mood, and anxiety symptoms during abstinence. **Methods:** Treatment-seeking AUD (n=57, abstinent 16 ¬± 39 days) and control participants (n=29) completed a [11C]CURB positron emission tomography scan and a resting state magnetic resonance imaging scan. Amygdala FAAH levels were inferred from lambda-k3 values of [11C]CURB binding. Frontoamygdala connectivity values were represented as z-scores of resting activity correlation between amygdala and the prefrontal cortex (PFC). Group differences were assessed with analysis of variance and relationships between connectivity, FAAH, and clinical outcomes with linear regression. **Results:** Frontoamygdala connectivity was significantly lower in AUD patients relative to controls ($F(1,81)=4.030$, $p=0.048$). In AUD, there was no visibly discernible relationship between amygdala FAAH and frontoamygdala connectivity (≤=-0.023, $p=0.875$). Conversely, in controls, higher amygdala FAAH was non-significantly associated with lower connectivity (≤=-0.318, $p=0.210$). Lower connectivity marginally

predicted higher self-report negative affect (Beck Depression Inventory (≤=-0.424, p=0.074)) and alcohol obsessions/compulsions (Obsessive-Compulsive Drinking Scale (≤=-0.417, p=0.078)). **Conclusion**: Aligning with literature, AUD patients had lower frontoamygdala connectivity than controls, but the negative relationship between FAAH and connectivity was not replicated. Connectivity non-significantly predicted worse cravings, withdrawal symptoms, anxiety, and low mood. The findings indicate that the role of FAAH in the frontoamygdala circuitry may differ in AUD, reflecting disease-specific adaptations in ECS signaling. Additionally, functional brain differences are associated with the severity of clinical outcomes and should be examined as a predictor of relapse.

3. Kevan Clifford; Institute of Medical Science

Supervisor: Dr. Yuliya Nikolova

A MIDLIFE NEUROSTRUCTURAL SIGNATURE OF TRANSCRIPTOME-BASED RISK FOR DEPRESSION

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Introduction: Common variants shifting gene expression in the brain towards a more depression-like state were recently revealed to be associated with a thicker posterior cingulate cortex in a youth population. To comprehensively evaluate the mechanistic underpinnings of these effects, we require characterization of transcriptome-based risk for depression across the lifespan. **Objective:** Here, we assess outcomes of the same transcriptome-based polygenic risk score (tPRS) indexing depression-related gene expression changes on brain morphology in the large mid- to late-life UK Biobank cohort. **Methods:** tPRS was calculated using the CommonMind Consortium reference transcriptome to impute relative individual gene expression in the dorsolateral prefrontal cortex, indexing cis-eQTL SNPS of 186/566 genes weighted according to their association with MDD in a meta-analysis of case-control post-mortem transcriptome datasets. tPRS was computed in 31,384 UK Biobank participants (16,392 women, ages 46-82). Freesurfer-extracted regional surface area (SA), and cortical thickness (CT) measures were used in separate linear regression models as dependent variables with tPRS as the independent variable, controlling for demographics, 10 genetic components, and study site (FDR-corrected across 62 regions). **Results:** tPRS was associated with lower SA in the right paracentral and posterior cingulate, and left rostral anterior cingulate and paracentral regions (pFDR<=0.05). Furthermore, tPRS was associated with greater CT in the right posterior cingulate (pFDR<0.0001), replicating prior findings in youth, and in the caudal anterior cingulate (pFDR=0.031). **Conclusion:** Together with our previous work, these results suggest that a thicker posterior cingulate is likely an early-emerging and stable marker of transcriptomic vulnerability to MDD, while reduced SA in cingulate and frontotemporal regions may emerge later in life.

4. Federico Gaiti; Department of Medical Biophysics

NEURODEVELOPMENTAL HIJACKING OF OLIGODENDROCYTE LINEAGE PROGRAMS DRIVES GLIOBLASTOMA INFILTRATION

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Introduction: Glioblastoma (GBM) is a highly aggressive brain tumor with a pronounced capacity to infiltrate surrounding healthy brain tissue, a feature that severely limits the efficacy of current therapeutic approaches. While tumor cell plasticity has been implicated in this invasive behavior, the epigenetic mechanisms that enable and sustain such plasticity remain poorly understood. **Objective:** To elucidate the epigenetic and transcriptional programs underlying the invasive capacity of glioblastoma cells, with a particular focus on progenitor-like tumor cell states and their interactions with the neural microenvironment. **Methods:** We performed integrative multi-omic profiling, including single-nucleus RNA sequencing (snRNA-seq), single-nucleus ATAC-seq (snATAC-seq), and spatial transcriptomics, on GBM patient specimens. We complemented these analyses with functional perturbation assays using CRISPR/Cas9-mediated knockout of key regulatory genes (e.g., ZEB1) in patient-derived glioblastoma stem-like cells, followed by phenotypic and transcriptomic characterization. **Results:** We identified an epigenetically encoded invasive state within peritumoral progenitor-like GBM cells. These cells displayed neurodevelopmental transcriptional signatures associated with enhanced migratory capacity, synaptic activity, and NOTCH signaling. Spatial analyses revealed that these cells colocalize with neurons and exhibit features of increased neuron-tumor crosstalk. Comparative epigenomic profiling showed strong resemblance to uncommitted oligodendrocyte progenitor cells (OPCs) in the developing human brain. Functional validation confirmed that ZEB1 is a critical regulator maintaining this invasive, undifferentiated state. **Conclusion:** Our findings uncover a previously uncharacterized epigenetically regulated invasive program in glioblastoma, driven by progenitor-like cells that mimic developmental OPC states and engage in neuron-associated signaling. Targeting differentiation pathways may not only limit tumor dissemination but also impair critical interactions with the neural microenvironment. These insights provide a framework for

developing novel therapeutic strategies aimed at disrupting tumor plasticity and infiltration.

5. Barbara Gundi; Department of Physiology

Supervisor: Dr. Hong-Shuo Sun

THE ROLE OF HISTONE DEACETYLASE INHIBITOR SAHA IN NEUROPROTECTION AND CARDIOPROTECTION FOLLOWING NEONATAL HYPOXIC-ISCHEMIC BRAIN INJURY

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Introduction: Stroke is a devastating disease characterized by disrupted circulation of oxygenated blood to the brain. With the incidence of stroke in younger populations on the rise globally, hypoxic-ischemic brain injury (HIBI) becomes a major cause for neurological impairment and morbidity in neonates. HIBI has also historically introduced severe secondary injuries, like post-HI myocardial injury, creating multi-system impairments. As is seen in the case of stroke, existing treatments are proving insufficient to treat both initial and downstream pathologies, with gold standard treatments having short therapeutic windows and widespread adverse effects. As such, it is imperative that more impactful treatment options are explored. In recent years, histone deacetylase inhibitors (HDACi) have been investigated for their protective properties in hypoxic-ischemic events, with the efficacy of one already FDA-approved HDACi, suberoylanilide hydroxamic acid (SAHA), in this context remaining unknown. **Objective:** The objective of the present study is to examine the effect of histone deacetylase inhibitor SAHA in neuronal and subsequent cardiac complications following neonatal HIBI. **Methods:** Post-natal day 7 mice have been randomly assigned to receive a 50 µL single intraperitoneal injection of either SAHA or Vehicle of SAHA treatment 30 minutes prior to or following ischemic surgery. 24 hours post-surgery, tissue was collected for histological assessment using TTC staining. Nissl staining and whole-brain morphology will be examined 7- and 14-days post-surgery, respectively. Short-term behavioural assessments were carried out on days 1-, 3- and 7-days post-surgery, including grip test, righting reflex, geotaxis and cliff avoidance, to evaluate the severity of motor, behavioural, and neurodevelopmental deficits. Long-term assessments, including rotarod, novel object recognition, and one-trial passive avoidance will be carried out at 21 days post-surgery. Myocardial function will be evaluated using echocardiography 24 hours post-surgery and histology will be examined using TTC staining. Finally, the respective mechanisms will be evaluated using Western Blot and qPCR. **Results:** TTC staining of vehicle and SAHA 25 mg/kg groups treated according to pre-30min-treatment paradigm revealed a significant reduction in corrected infarct volume of nearly 50%. Mice that received SAHA 25mg/kg post-30min-treatment also showed a significant reduction in corrected infarct volume. Additionally, SAHA pre-treated animals demonstrated improved performance on geotaxis at day 3 post-HI and cliff avoidance behavioural tasks at all time points, as well as improved righting reflex on day 1 and grip test on all days, relative to the Vehicle group. Post-treatment behavioural testing yielded similar results. Assessments pertaining to cardiac function and mechanisms of action are underway. **Conclusion:** Ultimately, SAHA pre-treatment has been shown to improve neuronal damage and accompanying behavioural deficits following neonatal HIBI, introducing a new potential therapeutic option for HIBI.

6. Kathrin Mertel; Department of Music

Supervisor: Dr. Michael Thaut

CAN MUSIC TRAINING ENHANCE/AFFECT WORKING MEMORY AND SPEECH-IN-NOISE PERCEPTION IN COCHLEAR IMPLANT USERS? A RANDOMIZED CONTROLLED STUDY OF EEG MEASURES OF IMPROVEMENT

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Introduction: A cochlear implant (CI) enables postlingually deafened individuals to understand speech; however, due to technical restrictions, users face significant limitations in noisy conditions. Music training has been shown to augment shared auditory and cognitive neural networks for processing speech and music and to improve auditory-motor coupling, which benefits speech perception in noisy environments. These findings present promising prerequisites for multi-modal neurologic music training (NMT®) to enhance speech-in-noise (SIN) perception in adult CI users. Additionally, a better understanding of the neurophysiological correlates during working memory (WM) and SIN tasks following multi-modal music training may assist clinicians in optimizing rehabilitation strategies. **Objective:** This study aims to investigate the effects of a 4-week multi-modal NMT® training program on WM and SIN performance in adult postlingually deafened CI recipients and to explore corresponding changes in neural activity, particularly alpha oscillations in prefrontal areas. **Methods:** Eighty-one postlingually deafened adult CI recipients will participate in a 4-week multi-modal NMT® training program targeting pitch, rhythm, and timbre conditions. Behavioral outcomes will be assessed through pre- and post-tests, and neurophysiological data will be collected using a novel EEG approach that measures alpha oscillation modulations during the sentence-final-word-identification-and-recall test (SWIR-EEG). **Results:** Preliminary results from 27 participants undergoing short-term multi-modal music training indicate a mild improvement in speech-in-noise (SPiN) understanding, with no observed effect on working memory. No differences have been found between the different training conditions. Neurophysiological analysis is ongoing to clarify the relationship between cognitive function and SPiN performance beyond CI limitations. **Conclusion:** Short-term multi-modal NMT® has shown a slight enhancement of SPiN perception in adult CI users so far, although effects on WM have not yet been observed. These preliminary results, based on a small and heterogeneous sample, suggest promising trends. Ongoing neurophysiological analysis is expected to further clarify the potential for targeted music-based interventions to improve SPiN performance and enhance quality of life for postlingually deafened adult CI recipients.

7. Elina Nezon; Rehabilitation Sciences Institute

Supervisor: Dr. Kristin Musselman

ENHANCING KNOWLEDGE, CONFIDENCE, AND USE OF FUNCTIONAL ELECTRICAL STIMULATION AMONG THERAPISTS: AN IMPLEMENTATION INTERVENTION IN CEREBRAL PALSY REHABILITATION

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Introduction: Functional Electrical Stimulation (FES) is an evidence-based therapeutic tool that may be used in pediatric neurorehabilitation. However, Canadian physical and occupational therapists (PTs, OTs) do not commonly use FES due to a lack of knowledge about how to apply it. This highlights the need for improved education and resources to support its application. **Objective:** To evaluate the impact of an implementation intervention aimed at enhancing PTs'and OTs' knowledge, confidence, and use of FES. **Methods:** Seventeen PTs (16 female, 1 male) and one female OT (mean age 30.6 ¬± 6.9 years) were recruited from 5 pediatric rehabilitation centers in Ontario (3 private sector, 2 public) through convenience sampling. To be eligible, participants reported a caseload of at least 20% of clients with cerebral palsy (CP) in the past year, no formal education in FES, and infrequent or no use of FES (i.e. <20% of treatment sessions). A pre-post study design was used. The implementation intervention followed strategies from the Expert Recommendations for Implementing Change. It included a six-week online course with weekly pre-recorded lectures, interactive activities, group mentoring, a reflective assignment, and the provision of an FES device to keep. Assessments, including an FES knowledge quiz, an FES Confidence Questionnaire, a survey of FES use, and an adapted version of the Technology Assistance Model 2 (TAM2) Questionnaire, were administered pre- and post-intervention. Index scoring transformed Likert scale responses into numerical values for scoring the survey of FES use and TAM2 Questionnaire. Pre- and post-scores were compared with paired t-tests or Wilcoxon signed-rank tests, as appropriate, with alpha set to 0.05. **Results:** Statistically significant increases were seen in participants' knowledge of FES ($p<0.001$), confidence in applying FES ($p<0.001$), FES use ($p=0.023$) and FES results demonstrability ($p=0.012$), a component of the TAM2. There were no significant changes in the other TAM2 components, including perceived ease of use and usefulness, subjective norm, voluntariness, image, output quality, job relevance, intention to use and proposed facilitating conditions ($p=0.11$-0.94). **Conclusion:** Participants experienced significant improvements in their FES knowledge, confidence in applying FES, and FES results demonstrability. Other components of the TAM2 did not change, possibly because FES acceptance was already high among the participating PTs and OTs. By demonstrating the effectiveness of a structured educational intervention, this study may bridge the knowledge-practice gap as well as improve patient outcomes, as increased use of FES in therapy could support functional recovery for individuals with CP. This study advocates for accessible resources for therapists on FES implementation and promotes better access to FES care, which may reduce disparities in care for people with CP.

8. Yutong Sun; Department of Medical Biophysics

Supervisor: Dr. J. Jean Chen

THE HEMODYNAMIC INFLUENCE ON DIFFUSION MRI AT MULTIPLE B-VALUES IN THE HEALTHY HUMAN CEREBRAL WHITE MATTER

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Introduction: Diffusion magnetic resonance imaging (dMRI) has been widely adopted to study brain structural integrity especially in the white matter (WM) by assessing the distribution of water molecules in the brain tissue. However, dMRI, by definition, is sensitive to all types of water molecule diffusion regardless of the origin, meaning that the unmodeled contribution from cerebral blood flow (CBF) potentially biases the dMRI measurements. This is especially of concern in the grey matter (GM), where CBF is higher, but has never been systematically assessed in the human white matter (WM) either. Although the dMRI image can be made less sensitive to fast flows by increasing the diffusion weighting (b values), previous research in rat models showed that dMRI measures such as mean diffusivity (MD) can differ by various hemodynamic states even using medium to high b values (1000-2000s/mm2). **Objective:** This work aims to characterize the role of perfusion in diffusion imaging in the human brain across multiple b values using a hypercapnia experiment, and to compare it to predictions based on simulations. **Methods:** Hypercapnia was used as a vasodilatory stimulus to induce temporary hemodynamic changes in the subject by inhaling 4% CO24 in a block-design protocol: 4min-off, 6 min-on, 2 min-off. dMRI data was collected on the subject under both the baseline and hypercapnic conditions using a Siemens Prisma 3T scanner, TR=3.1s, TE=0.064s, 1.5mm isotropic resolution, 6, 50, and 50 directions on b=250, 1000, and 2000s/mm2 respectively. Pseudo-continuous arterial spin labeling (pCASL) data was collected with TR=5.2s, TE=0.013s, labeling duration of 0.7 s and post-labelling delay=1.5s. pCASL images were preprocessed with slice-timing correction, motion correction, and outlier removal, followed by cerebral blood flow (CBF) quantification using FSL's oxford_asl5. dMRI images were corrected for eddy currents and susceptibility distortions using FSL's eddy and topup and then fitted into the diffusion tensor imaging (DTI) model to calculate the MD6. The hypercapnia-driven difference in MD between two gas conditions was calculated in percentage voxelwise in the WM. The effect of CBF change on MD at each b value was then simulated using an in-house MATLAB script, which incorporated 3 aspects of a hypercapnic challenge: (1) CBF-induced pseudo-diffusion and cerebral spinal fluid (CSF) volume change (assuming diffusivity of free-water, no CSF flow); (2) Blood oxygenation change, assuming no metabolic alterations; (3) Cerebral blood volume (CBV) change, causing a reciprocal CSF volume fraction change; SNR=10, 5,000 iterations. **Results:** CBF was found to partially increase with hypercapnia in the GM and partially decrease in the WM. Likewise, MD was found to be higher at hypercapnia in certain regions and lower

in other regions. As predicted by the simulation results, CO2 effect on MD was most pronounced at b=250/mm2, but also persists despite increasing diffusion weighting at b=1000 and 2000 s/mm2. A simulated CBF increase by 40% led to an overestimation of MD when the baseline CBV was higher than 8%, with the level decreasing from b=1000s/mm2 to b=2000s/mm2, while a simulated decrease in CBF by 40% also led to an overestimation of MD when the baseline CBV was higher than 12%, with the level decreasing with b values. The effect of CO2 was also found to be dependent on the depth of brain tissue, with the magnitude of MD change increasing from superficial to deep WM. **Conclusion:** Our work showed that hypercapnia impacts WM MD in a region- and b-value-dependent manner. At lower diffusion weighting (b=250s/mm2), the larger MD variations might indicate increased sensitivity to perfusion-related water motion. The b=1000s/mm2 and b=2000s/mm2 shells were less affected by CO2, but the hemodynamic influence persists in these medium to high diffusion-weighted images, contrary to conventional expectations. Although the MD bias decreased with increasing b value, as predicted by our simulations, this unmodeled hemodynamic effect may become an obstacle when interpreting dMRI metrics regarding microstructural components. Also contrary to expectations, CBF decreased in large swathes of WM regions during hypercapnia, in contrast to the expected increase. This is consistent with previous observations in WM pathologies, and puts into question whether the changes in MD are mainly due to CBF changes. The observed variability in both MD and CBF changes across WM highlights the complexity of the physiological response to elevated CO2. The simulated predictions demonstrate the dependence of MD estimation biases on the magnitude of CBF changes. Future work should explore the driving factors for the bidirectional CBF and MD changes.

SESSION II

INTEGRATIVE SOCIAL, BEHAVIORAL, AND COMPUTATIONAL NEUROSCIENCE

9. Mryam Ali; Department of Psychology

Supervisor: Dr. Benjamin Dunkley

SYMPTOM-DRIVEN SUBTYPES OF PTSD EXHIBIT DISTINCT NEURAL OSCILLATORY SIGNATURES REVEALED WITH MAGNETOENCEPHALOGRAPHY (MEG)

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Introduction: Posttraumatic Stress Disorder (PTSD) has historically been classified as a fear-based disorder but is better understood as a neurophysiological stress injury that disrupts memory processing. Trauma-related changes in brain function manifest as abnormalities in slow (delta, 1-4 Hz) and fast (gamma, +30 Hz) neural oscillations. However, traditional case-control studies obscure PTSD heterogeneity, masking distinct neurophysiological subtypes. This study addresses this gap by using data-driven clustering of PTSD symptoms to uncover specific neural phenotypes. **Objective:** This study aims to identify neurophysiological subtypes of PTSD by examining symptom-driven clustering and corresponding neural signatures, moving beyond traditional case-control approaches. **Methods:** A total of 111 Canadian Armed Forces (CAF) and Veteran participants (57 PTSD, 54 trauma-exposed controls) underwent resting-state MEG recordings. Group contrasts, controlling for anxiety, depression, and concussion history, identified PTSD-specific neural abnormalities. Hierarchal clustering of PTSD Checklist-Military Version (PCL-M) subscores (re-experiencing, avoidance, hyperarousal) classified participants into symptom-driven subgroups. Neural oscillatory activity was compared across subtypes. **Results:** Group contrasts revealed significant differences in delta and gamma activity between PTSD and trauma-exposed controls, indicating widespread neural dysfunction. Clustering identified three PTSD subtypes, with beta activity (15-25 Hz) distinguishing them: hyperarousal-dominant subtypes exhibited elevated beta, reflecting emotional dysregulation, while re-re-experiencing/avoidance subtypes showed suppressed beta, suggesting impaired cognitive control and inhibitory dysfunction. **Conclusion:** These findings challenge the notion of PTSD as a unitary disorder, instead highlighting distinct neurophysiological subtypes. Beta activity emerged as a key marker of symptom-specific neural dysfunction, providing a foundation for personalized treatment strategies targeting distinct neural processes to improve clinical outcomes.

10. Liv Ansley-Engel; Department of Psychology

Supervisor: Dr. Robert Rozeske

CONTEXT FEAR DISCRIMINATION LEARNING MODULATES DOPAMINE SIGNALING IN THE MEDIAL PREFRONTAL CORTEX

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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. The medial prefrontal cortex (mPFC) is a key structure for 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 guides adaptive actions. **Objective:** To further characterize the role of the mPFC during context threat uncertainty, we developed an apparatus to "teleport" mice between contexts to measure fear discrimination. **Methods:** We expressed the biosensor GRABDA in the mPFC to monitor dopamine signaling with fiber photometry during the teleportation task. **Results:** We observed that stronger conditioning protocols produced prolonged dopamine transients. During the test day, mice discriminated threatening from neutral contexts and the "teleportations" were accompanied by increased dopamine signaling. Moreover, strong conditioning produced the greatest mPFC dopamine during context "teleportations". Males and females discriminated similarly, but differences in dopamine dynamics emerged. Optogenetic inhibition during context transitions is required to assess the necessity of mPFC dopamine in context fear discrimination. These results suggest that prefrontal dopamine dynamics are altered during context fear memory encoding and retrieval. **Conclusion:** Together our findings indicate prefrontal dopamine may be a target for therapeutics designed to reduce fear generalization which could benefit those with anxiety disorders.

11. Madison Fedele; Cell and Systems Biology

Supervisor: Dr. Laura Corbit

EXAMINING MICROGLIAL ACTIVATION IN THE BRAIN OF RAT MODELS DURING AN OBESOGENIC DIET

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Introduction: Obesity has been associated with impairments in behavioural flexibility, including a bias toward habitual over goal-directed actions. Neuroinflammation within the striatum, particularly driven by microglial activation, has been proposed as a key mechanism linking high-fat diet exposure to these behavioural deficits. However, the specific molecular pathways through which microglia modulate action control remain unclear. One candidate mechanism involves purinergic signalling, where extracellular ATP released during metabolic stress activates microglial P2X4 receptors, potentially altering plasticity in the dorsal medial striatum (DMS), a region critical for goal-directed behaviour. **Objective:** This study aimed to determine whether microglial purinergic signalling in the DMS is sufficient to bias behavioural control toward habit formation, mimicking the effects of an obesogenic diet. **Methods:** Rats were trained to lever press for food pellets under random ratio schedules designed to promote goal-directed behaviour. After reaching training criteria, rats received bilateral infusions of ATP or saline directly into the DMS immediately before outcome devaluation testing. Outcome devaluation was achieved by sensory-specific satiety, and lever-press behaviour was measured in extinction to assess sensitivity to changes in outcome value. **Results:** ATP-infused rats showed insensitivity to outcome devaluation, indicating a shift toward habitual responding. In contrast, saline-infused controls maintained goal-directed behaviour, reducing lever pressing when the outcome was devalued. This pilot data suggests that ATP-mediated purinergic signalling in the DMS disrupts goal-directed control. **Conclusion**: These findings indicate that microglial purinergic signalling in the DMS plays a critical role in modulating behavioural flexibility. Specifically, ATP-driven activation promotes habitual behaviour, potentially explaining how obesogenic diets impair goal-directed control via neuroinflammatory pathways. Future work will examine purinergic signalling effects in the dorsolateral striatum (DLS) to explore its role in habitual behaviour.

12. Talia Fiaani; Institute of Medical Science

Supervisor: Dr. Aylin Reid

TARGETING INTRACELLULAR PROTEIN DEGRADATION SYSTEMS AS A THERAPEUTIC INTERVENTION FOR CDKL5 DEFICIENCY DISORDER

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Introduction: The genetic condition Cyclin-dependant kinase-like 5 (CDKL5) deficiency disorder (CDD) is an X-linked epileptic encephalopathy and neurodevelopmental disorder characterized by early onset-seizures, developmental delays, and impairments in motor, cognitive and autonomic functions. CDKL5's kinase activity is essential for phosphorylating proteins regulating neuronal structure and synaptic transmission. Our lab has focussed on EB2 and MAP1S, two of the main substrates for CDKL5 that are left unphosphorylated in CDD contributing to the microtubule and cytoskeleton dysfunction central to the pathogenesis of CDD. The protein CDKL2 has shown to have compensatory action to these same targets, though it is kept at low and inefficient levels due to a high sensitivity to degradation by proteosome systems. **Objective:** We hypothesize that CDKL2 upregulation through proteosome and lysosome inhibitors will improve neuron circuit function and reverse the increased seizure sensitivity found in CDKL5 KO and patient specific CDKL5 mutation mice through restoration of phosphorylated EB2 and MAP1S. We aim to test this hypothesis through the treatment and observation of both mouse models with FDA approved drugs. **Methods:** 1) Characterize seizure sensitivity and behavioural differences between wild type and two CDKL5 mouse models , a patient specific mutation and a CDKL5 KO mutation. 2) Treat mice with FDA approved proteosome and lysosome inhibitors Ixasomib and Chloroquine and observe changes to the phenotypes. 3) Examine differential protein expression, specifically EB2, MAP1S and CDKL2 to verify mechanism of action. **Results:** 1) CDKL5 mutant mice have reduced anxiety-like behaviour, hyperexcitability, and reduced baseline levels of EB2 and MAP1S. 2) Both Ixasomib and Chloroquine restored the anxiety-like behaviour and deficits in EB2 and MAP1S, and increased CDKL2 protein levels. **Conclusion:** Proteosome and Lysosome inhibitors have shown promising results in improving deficits seen in CDD mouse models. Our lab has not investigated the seizure susceptibility phenotype; however, this will be important to understand the complete therapeutic effect of these FDA approved drugs.

13. Annelies Hoorn; Department of Physiology, SickKids

Supervisor: Dr. Sheena Josselyn

TEMPORAL DYNAMICS OF NEURONAL EXCITABILITY IN THE LATERAL AMYGDALA MEDIATES ALLOCATION TO AN ENGRAM SUPPORTING CONDITIONED FEAR MEMORY

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Canada; 4 Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada; 5 Boston Children Hospital, Boston, MA, United States.

Introduction: Memories are encoded by ensembles of neurons (engrams) that are active during learning. Within a given brain region, eligible neurons compete for allocation to an engram and neurons with increased excitability at the time of training are likely to be allocated to the engram. Previous findings show that neurons with increased excitability during training also have increased excitability for ~6h. **Objective:** Here, we examined the temporal dynamics of neuronal excitability important for memory allocation. We focused on the lateral amygdala (LA) and cued fear memory. **Methods:** To examine the functional role of this increased excitability on memory allocation, we artificially increased excitability in a small subset of LA neurons before fear conditioning, biasing engram allocation up to 9 hours before training. Second, we wanted to investigate which genes are involved in optogenetic allocation. We investigated genetic changes induced by optogenetic excitation using spatially resolved gene expression (MERFISH). Third, we examined endogenous excitability, using calcium imaging in freely moving mice, allowing to image the activity of neurons over time. **Results:** We found that the most excitable neurons during learning where also significantly more excitable up to ~6 hours prior to learning, when compared to the less excitable neurons. To understand the functional role of these endogenously active neurons and memory allocation, we used a calcium based activity dependent-tagging system (scFLARE). We found that during the test, silencing the neurons that were more excitable 1 hour, but not 24 hours prior to learning, leads to attenuated memory expression. **Conclusion:** Together, these findings highlight the temporal specificity of excitability in the LA and its pivotal role in selecting which neurons become part of a memory engram.

14. Zeenat Ladak, Applied Psychology & Human Development

Supervisor: Dr. Richard Volpe

EXPLORING PATIENT EXPERIENCES OF PRENATAL HEALTHCARE IN ONTARIO: AN EQUITY-ORIENTED QUALITATIVE STUDY

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Introduction: The extent to which prenatal care is equity-oriented significantly influences patient satisfaction, care-seeking decisions, and health outcomes for both parent and newborn. Health inequities shape care experiences, disproportionately affecting marginalized populations (e.g., individuals with low incomes, rural residents, racial minorities). **Objective:** This study explores prenatal patients' care experiences and examines the impact of health inequities across Ontario. **Methods:** This patient/partner-oriented, cross-sectional, explanatory mixed-methods study was guided by Cochrane's PROGRESS-Plus equity framework. Purposeful, maximum variation sampling recruited Ontarians who had been pregnant or experienced pregnancy loss within the last 12 months. Participants completed a 5-minute demographic and pregnancy characteristics survey, followed by a 1-hour semi-structured interview on their prenatal care experiences and equity impacts. Analysis included descriptive statistics, inductive coding, and deductive coding. **Results:** This study included 18 participants, half identifying as racial minorities. Most interacted with a primary care physician during pregnancy (n=16), half engaged with an obstetrician or nurse, and eight with a midwife. Two themes emerged: Variations in Access to Care, with experiences ranging from powerlessness to continuity of care challenges, influenced by geographical and financial barriers; and Variations in Accommodations for Preferred Care, encompassing empathetic practitioners, validation of concerns, and power dynamics, influences by discrimination and advocacy for personalized support. Ultimately, these themes impacted maternal mental health during pregnancy by increasing stress that was perceived to impact their health during pregnancy and newborn and child behaviour following birth. **Conclusion:** Findings can inform healthcare professionals and policymakers on prenatal patients' expectations for care delivery (e.g., trust-building) and equity-related factors (e.g., geographic access), offering potential areas of focus to improve the pregnancy care experience.

15. Jiya Shah; Institute of Medical Science

Supervisor: Dr. Erin Dickie

ASSOCIATIONS BETWEEN DEVELOPMENTAL BRAINAGE AND PSYCHOSIS SPECTRUM SYMPTOMS (PSS): PRELIMINARY RESULTS FROM THE TAY-CAMH COHORT STUDY

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Introduction: Deviations from normative neurodevelopment have been associated with the risk of developing mental illness. **Objective:** Here, we investigated the relationship between brain-age-gap-estimation (brainAGE) and psychosis spectrum symptoms (PSS) in youth seeking mental health care. Additionally, we determined whether an association between brainAGE and PSS varied between cortical networks using the Network-brainAGE calculator. **Methods:** MRI data collected as of Jan 1 2024, as part of the ongoing Toronto Adolescent and Youth (TAY) CAMH Cohort Study (n=418; 11-24y, M=144, F=274) were analyzed. 51.19% met criteria for PSS using the PRIME Screen-Revised. Morphometric features (Schaefer 400 and 1000 parcellation) from baseline structural scans were used to calculate sex-specific whole brain developmental brainAGE and Network-brainAGE. BrainAGE was calculated as the difference between the predicted brain-age and chronological age. **Results**: The brainAGE model-predicted age was highly correlated with chronological age (r=0.84). Higher adjusted (corrected for biases in the model) brainAGE was associated with the presence of PSS (d=-0.26, t=2.97, $p<0.05$). Significant associations were found for executive control and dorsal attention Network-brainAGE (d=-0.26; d=-0.27 respectively, $p<0.05$ Bonferroni corrected). **Conclusion:** The strong correlation between model-predicted age and

chronological age demonstrates the feasibility of using developmental brainAGE metrics in youth accessing mental health services. Previous literature has shown accelerated brain aging in schizophrenia. These preliminary results suggest that youth with PSS may feature morphological features aligned with those found in individuals with schizophrenia spectrum diagnoses.

16. Rossi Tomin; Faculty of Dentistry

Supervisor: Dr. Massieh Moayedi

CORRELATIONS AMONG ENDOGENOUS PAIN MODULATION MECHANISMS

Tomin R[1]; Gao W[5]; Khalil O[1]; Sexton C[1]; Murray K[10]; Khan J[6]; Atlas LY[7,8,9]; Finn DP[10,11,12]; Moayedi M[1,2,3,4]

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Introduction: Several paradigms produce profound analgesia, but whether they engage the same systems remains unclear. Placebo analgesia (PA) arises from psychosocial factors and involves the opioidergic and endocannabinoidergic systems (OP and eCB). Offset analgesia (OA) is a contrast modulation paradigm with unknown mechanisms, but it is not OP-related. Conditioned pain modulation (CPM) relies on modulatory circuits activated by a conditioning noxious stimulus and is primarily OP-driven. Additionally, recent evidence highlights sex differences in pain modulatory circuitry and pharmacology. **Objective:** This study aims to determine whether analgesia from PA, OA, and CPM is associated, suggesting shared neurobiology. We hypothesize some overlap between CPM and PA, but not OA, and explore sex-specific effects. **Methods:** Forty-nine healthy participants (24 female) underwent calibration and a PA paradigm with classical conditioning and placebo/control conditions. They then completed an OA paradigm, with a noxious stimulus at 46C (T1), raised to 48C (T2), and returned to 46C. Finally, they underwent a CPM paradigm, using a water bath as a conditioning stimulus and pressure pain thresholds as a test stimulus. Pain reduction ratings across paradigms were correlated using appropriate tests within sexes and at the group level ($p<0.05$). **Results:** No significant correlations were found across paradigms when analyzing the entire population. Additionally, no significant sex differences emerged in pain modulation patterns. **Conclusion:** The results indicate that PA, OA, and CPM likely operate through distinct, independent mechanisms, with no clear overlap in their modulatory pathways. These findings suggest that CPM may not be exclusively OP-driven, and that other neurobiological mechanisms may contribute to its effects.

SESSION III

MOLECULAR NEUROSCIENCE & NEURODEGENERATIVE DISORDERS

17. Ilakkiah Chandran; Institute of Medical Science

Supervisor: Dr. Danielle Andrade

A GLOBAL PERSPECTIVE ON TRANSITIONING FROM PEDIATRIC TO ADULT CARE IN EPILEPSY

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Introduction: Globally, every year, approximately 1.1 million youth with epilepsy move from the pediatric healthcare system (PHS) to the adult healthcare system (AHS). **Objective:** The International League Against Epilepsy Transition Task Force (ILAE-TTF), set out to evaluated the global state of transition (or transfers) of epilepsy patients. This movement of patients to the AHS is often a simple handover process that occurs during a single event, i.e. a transfer of care. Simple transfers are often initiated solely based on the patient's age and can be associated with several obstacles that may interrupt the delivery of care to these patients. This may lead patients, caregivers, and practitioners to perceive this period in the patient's healthcare journey as uncertain and challenging. A planned transition involving a multidisciplinary team that addresses patients' needs has shown to preserve their quality of life and well-being. Despite recognizing the importance of effective transition programs, there is a lack of focused investigation into the current state of transition programs around the globe. **Methods:** A questionnaire validated by the ILAE-TTF was distributed through the ILAE Chapters. Descriptive analyses, Fischer's Exact Tests, and logistic regression models were used. **Results:** 316 participants from 59 countries completed the study, (54.4%) were adult neurologists (AN), the remaining were child neurologists (CN). There was a disparity between respondents from upper- and lower-income country (294 vs. 17. Five did not disclose their country), so we used

Global North (GN) and Global South (GS) classifications (111 vs.201, respectively). 59% of respondents described not having an epilepsy transition program in their workplace, country or not knowing whether transition programs existed in their country. This was worse among neurologists from the GS (OR = 0.168, p <0.001). Practitioners from the GS were more likely to recommend delaying the transfer to 18 years or more for adolescents with developmental disorders, autism, ketogenic diet, or neuromodulation. Half of the respondents believed pediatric teams should continue follow-up post-transfer. Educational gaps for patients and caregivers were reported in the areas of vocational and employment opportunities, schooling options, sexuality, contraception, and pregnancy, and driving. There was also ambiguity in role responsibility between pediatric and adult neurologists. Barriers to transition programs included: lack of multidisciplinary teams, adapted clinical settings, financial support, and education/training on transition, and lack of adult neurologists knowledgeable in childhood-onset epilepsies. Recommendations for improve transition include: a) integration of transition training in neurology curricula; b) creation of dedicated clinical structures and care networks for adolescents and young adults; c) joint consultations between pediatric and adult neurologists; and the strongest consensus on d) implementation of national guidelines on transition. **Conclusion:** These findings highlight the universal recognition of the importance of holistic care for adolescents with epilepsy, while also underscoring how regional and resource-related differences, as well as fragmented provider roles shape healthcare priorities and patient experiences during transition.

18. Dipa Chatterjee; Department of Pharmacology

Supervisor: Dr. Martin Beaulieu

PREFRONTAL FMR1 AUTOSOMAL HOMOLOG 1 (FXR1) MEDIATES RESILIENCY TO STRESS

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Introduction: Mechanisms responsible for maintaining allostasis under chronic stress are key regulators of mental stability. Dysregulated allostasis leads to the development of many mental disorders associated with depression/anxiety-related symptoms. **Objective:** Interestingly, the RNA-binding protein FXR1 (FMR1 autosomal homolog 1) has been associated with various disorders (insomnia, schizophrenia, bipolar disorder) and modulating synaptic homeostasis. However, direct effects of prolonged environmental stress on FXR1 remain unknown. **Methods:** Here we characterized the effects of chronic stress on FXR1 (and vice-versa) by subjecting C57BL/6J mice to chronic restraint stress (CRS: 1h, 2-times/day, for 5 weeks). Subsequently, FXR1 overexpression or knockout (via CRISPR) viruses were injected into the prefrontal cortex (PFC) bilaterally, followed by CRS. Various behavioural and molecular/cellular measurements were taken. **Results:** CRS reduced FXR1 levels in the PFC without changing its X-linked homolog FMRP. Additionally, exposure to BDNF increased FXR1 levels, while Corticosterone decreased FXR1. Overexpression of FXR1 resulted in decreased anxiety-like behaviours at baseline and rescued apathy/anhedonia/anxiety-like behaviours after chronic stress exposure, while FXR1 knockout increased anxiety-like behaviours at baseline. **Conclusion:** Together, our results suggest chronic stress reduces FXR1 levels in the PFC, and overexpressing FXR1 can increase resiliency. This highlights an integrative mechanism involving FXR1 in disrupted stress regulation and homeostasis, while highlighting FXR1 rescue as a viable avenue for therapy.

19. Bianca Hill; Department of Immunology

Supervisor: Dr. Veronique Miron

MONOCYTES REDUCE THE EFFICIENCY OF CENTRAL NERVOUS SYSTEM REMYELINATION

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Introduction: MS is a neurodegenerative disease resulting from damage to the CNS, termed demyelination. The efficiency of the reinstatement of myelin, known as remyelination, decreases with MS progression, leading to axon loss and dysfunction. The differentiation of oligodendrocyte progenitor cells (OPCs) is altered in MS, and CNS myeloid cells are promising candidates for the regulation of remyelination and OPC behaviour as they are required for OPC responses during remyelination and influence oligodendrocyte heterogeneity, yet are dysregulated in MS. CNS myeloid cells encompass resident populations, such as microglia, and infiltrating blood-monocyte derived populations, with less being known about the latter in the context of remyelination despite the fact that infiltrating immune cell populations can comprise up to 60% of myeloid cells in MS lesions. **Objective:** To determine the role of infiltrating monocyte myeloid populations in regulating remyelination efficiency in transgenic mice that lack circulating classical "inflammatory" monocytes (CCR2-/-), or mice that have fluorescently labelled inflammatory monocytes (CCR2RFP/+). **Methods:** We induce focal demyelinating lesions in the white matter tract, corpus callosum, and assess remyelination efficiency, glial cell activity, and monocyte responses using bulk RNA sequencing, immunofluorescence, and flow cytometry. **Results**: Our lab has discovered that monocytes are present in remyelinating lesions and that inhibiting classical monocyte activity enhances remyelination efficiency through immunofluorescence staining of myelin basic protein (MBP) in Ccr2-/- mice compared to wildtype controls. We have also found that these classical monocytes do not mature into differentiated macrophages, as immunofluorescence staining showed that >90% of

RFP+ cells were negative for the macrophage marker, Iba1, at 21 days post lesion (dpl) when remyelination is complete. Flow cytometry of lesioned CCR2-/- mice showed that the absence of classical monocytes increases the recruitment of another monocyte subset, termed "non-classical" that is often implicated in tissue repair. Additionally, RNA sequencing of CD45hiCD11b+ cells in Ccr2-/- lesions showed increases expression of genes associated with dendritic cells (DCs), which are absent in the wildtype counterparts with poor remyelination efficiency. Additionally, the absence of inflammatory monocytes alters oligodendrocyte heterogeneity, which is shown in immunofluorescence staining of Ccr2-/- mice compared to wildtypes for oligodendrocyte markers, such as Olig2 and Serpina3n. **Conclusion**: These findings indicate that infiltrating myeloid populations alter the cellular heterogeneity within the CNS during remyelination which leads to poor remyelination efficiency. Our discovery that infiltrating blood-monocyte derived myeloid cells impact remyelination through their interaction with other glial and immune cell populations highlights the importance of elucidating the cellular dynamics of these infiltrating immune cells in the context of remyelination. These results show the potential of a new cellular target for remyelination therapeutics, highlighting the non-redundant role of infiltrating immune cells to the glial cell compartment of the CNS.

20. Ahmad Israwi; Department of Cell & Systems Biology

Supervisor: Dr. Joanne Nash

NEURONAL EXCITATION AND SYNAPTIC PLASTICITY REQUIRE TRPV4 ACTIVATION IN PRIMARY HIPPOCAMPAL CULTURED NEURONS

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Introduction: Transient receptor potential vanilloid (TRPV4) is a polymodal bivalent cation channel, sensitive to physiological temperatures (34-41C), mechanical stretch, as well as endogenous ligands including arachidonic acid (AA) derivatives, 5,6, epoxyeicosatrienoic acid (EET) and anandamide. TRPV4 is highly expressed in the hippocampus and is localized to the plasma membrane, endoplasmic reticulum (ER), and mitochondria. **Objective:** Previous studies have shown that TRPV4 regulates neuronal excitability at physiological temperatures and mediates calcium release from ER stores. However, little is known of its role in synaptic plasticity and transmission. **Methods:** Chemical-LTP (cLTP) (90mM KCl, 3x1s) was induced in primary hippocampal neurons, significantly increasing post-synaptic expression of GluA1 (146.3±15.9%) and TRPV4 (157±38.9), as well as mitochondria and TRPV4+ve mitochondria. **Results:** These increases were blocked following exposure to TRPV4 antagonists RN9893 (3μM) and RN1734 (10μM), suggesting a role for TRPV4 in mediating cLTP induced synaptic plasticity. In primary hippocampal cells virally transduced with SynGCaMP6f, TRPV4 antagonists also displayed a dose dependent blockade of spontaneous firing frequency (-99.15±0.15%) and amplitude (-87.01±2.25%) and slowed the decay of KCl-induced calcium release (-64.8±2.3%). **Conclusion:** These studies suggest that TRPV4 is necessary for calcium signalling and cLTP and likely exerts these roles through regulating calcium dynamics. Studies are currently underway to delineate the role of TRPV4 in other forms of hippocampal synaptic plasticity using electrophysiology.

21. Shinwon Kang; Department of Physiology

Supervisor: Dr. Graham Collingridge

PARALOG-SPECIFIC ROLES OF GSK-3 IN SYNAPTIC PLASTICITY: DIVERGENT SUBCELLULAR LOCALIZATION AND SUBSTRATE REGULATION

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Introduction: Glycogen synthase kinase-3 (GSK-3) is a serine/threonine kinase that regulates diverse cellular processes. In the brain, GSK-3 plays a pivotal role in synaptic plasticity - the process by which synaptic connections are strengthened (long-term potentiation; LTP) or weakened (long-term depression; LTD) - which is fundamental mechanisms for learning and memory process. Pathological hyperactivity of GSK-3 has been implicated in neurodegenerative disorders such as Alzheimer's disease, prompting the development of pharmacological inhibitors. However, clinical usage GSK-3 inhibitors have been limited by safety and efficacy issue. GSK-3 exists as two paralogs: GSK-3α and GSK-3β. While distinct functions have been suggested for each paralog, their specific roles are unclear, which may offer key insights necessary for targeted drug design. Especially, their roles in mechanistically distinct forms of synaptic plasticity and in subcellular region–specific functions in the adult brain remain largely unexplored. **Objective:** To define the paralog-specific contributions of GSK-3α and GSK-3β to adult hippocampal synaptic plasticity and identify the subcellular distribution and substrate preference that underlie their distinct roles. **Methods:** Conditional knockout (cKO) mice lacking either GSK-3α or GSK-3β in excitatory neurons were generated using a CamKIIα-Cre driver, which is expressed postnatally. Paralog-selective inhibitors (BRD0705 for GSK-3α; BRD3731 for GSK-3β) were used in parallel to systematically inhibit GSK-3 in the wild-type mouse. Synaptic plasticity was assessed in acute hippocampal slices by extracellular field recordings at the CA3–CA1 Schaffer collateral pathway. Mechanistically distinct forms of synaptic plasticity were induced: NMDA receptor-dependent LTD and mGluR-dependent LTD for synaptic depression, and either compressed theta-burst stimulation (cTBS) or spaced theta-burst stimulation (sTBS) for long-term potentiation (LTP). Subcellular localization of GSK-3 paralogs was examined in wild-type hippocampal tissue using subcellular fractionation, complemented by AI-based predictive modeling (ProtGPS). Phosphorylation of Tau and GluA1 was measured in synaptoneurosome by immunoblotting. Both male and female mice were used in approximately equal numbers for all experiments to minimize sex bias. **Results:** The involvement of GSK-3 in adult

hippocampal synaptic plasticity was found to be both mechanism- and protein synthesis-dependent. Both GSK-3α and GSK-3β were required for the induction of metabotropic glutamate receptor-dependent long-term depression (mGluR-LTD), a form of synaptic weakening that relies on translational mechanisms. In contrast, NMDA receptor-mediated LTD was unaffected by deletion of either paralog, indicating a selective involvement of GSK-3 in specific forms of synaptic depression. Pharmacological inhibition of GSK-3α in wild-type mice selectively enhanced late-phase long-term potentiation (L-LTP or LTP2), which was induced by sTBS protocol and is dependent on protein synthesis. This finding suggests a mechanism-specific role for GSK-3α in limiting LTP in the adult hippocampus. Biochemical and AI-based analyses revealed distinct subcellular localizations: GSK-3β was predominantly enriched at synaptic and nuclear compartments, with reduced presence in the cytoplasm, whereas GSK-3α was primarily cytoplasmic, exhibiting significantly lower synaptic enrichment. Also, the substrate phosphorylation profiles were differed in regulating Tau and GluA1 in synaptic compartment. Specifically, GSK-3β preferentially phosphorylated Tau at Ser396 - a phosphorylation site linked to Alzheimer's disease pathology- while GSK-3α knockout resulted in increased phosphorylation of GluA1 at Ser845, a critical step in AMPA receptor trafficking and stabilizing at post-synaptic density during LTP. **Conclusion:** This study identified distinct yet overlapping roles for GSK-3α and GSK-3β in regulating adult hippocampal synaptic plasticity, mediated through differential subcellular localization and selective substrate targeting. Despite the high kinase domain homology between the two paralogs, their unique neuronal compartmentalization raises important questions regarding the mechanisms that drive differential subcellular distribution and how disruptions in localization might underpin synaptic pathologies.

22. Amy Munkyeong Kwon; Faculty of Music

Supervisor: Dr. Michael Thaut

CERVICAL DYSTONIA RELATED DISORDER SYMPTOMS AND ITS SYMPTOM MANAGEMENT WITH NEUROLOGIC

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Introduction: Cervical dystonia (CD) is a focal movement disorder with an unknown cause. CD is characterized by involuntary and prolonged muscle contractions leading to abnormal postures, pain, and psychosocial distress. Current treatments such as botulinum toxin (BTX) injections, oral medications, and surgical interventions is invasive, shows undesirable side effects, and have been reported inefficacy in addressing the issue. There is a demand in this population for non-invasive, complementary therapies that address both physical and emotional symptoms. **Objective:** This study aims to investigate the effectiveness of Neurologic Music Therapy (NMT) in managing symptoms related to CD (pain, tension and mood), with a goal of focusing on three different approaches : relaxation, strengthening, and a combination of both. **Methods**: A metronome was utilized by the therapists to facilitate the timing, coordination, and regulation of body movements. Musical instruments such as a piano and flute were used during musical play throughout the session. Singing was also used to facilitate many interventions, encouraging vocalization and breath control. Some individuals were equipped with some exercising weights to use during the gait exercises, like RAS. The sessions were conducted virtually with each therapist equipped with reliable working wifi, computers and functioning cameras to ensure clear audiovisual communication. Additionally, lotion was recommended to be used during the warm-up phase, allowing participants to gently massage affected areas and prepare their muscles for movement-based activities. Participants were also encouraged to keep water bottles nearby during the sessions. The NMT sessions consist of three different approaches to interventions. Each week, the group focused on a different approach. This continued throughout the course of the 12 sessions. The three methods were used within the 12 weeks in a random order to eliminate the possibility of further bias. The first type of session focused on strengthening. Then, the following week focused on relaxation. The third week‚Äôs session included the combination of both strengthening and relaxation interventions. For the strengthening sessions, after a brief (~3 minutes of massage) to warm up the physical body movement, the first NMT technique used was Voice Intonation Therapy (VIT), which focuses on strengthening the vocal cords and the throat. The second technique, Oral Motor and Respiratory Exercises (OMREX), focuses on deeper breaths and accentuating more intense oral motor movements. Lastly, strengthening Patterned Sensory Enhancement (PSE) will focus on strengthening activities like punching, kicking, etc. at a faster tempo (BPM = 100+). During the relaxation exercises, a contrasting approach will be used. For the relaxation sessions, most of the interventions will include massaging and slow, low impact exercises as well as vocal strengthening/relaxation techniques. This incorporates the combination of neurologic music therapy techniques of Oral Motor and Respiratory Exercises (OMREX), and slower tempo (BPM ~50) Patterned Sensory Enhancement (PSE). The PSE focused on slow, small movements accompanied by activities known to reduce heart rate, such as massaging, deep breathing, and slow stretching to promote relaxation. During the relaxation methods, approximately 7 minutes will be dedicated to massage, often accompanied by slow and calm music. **Results:** This research indicate that relaxation-focused interventions (e.g., music listening, stretching) can drastically reduce pain and positively improve mood. A combination of both strategies yielded the most stable symptom relief in preliminary studies, though research specifically targeting NMT and CD remains limited. **Conclusion:** Through this research, NMT shows promising and positive signs of providing safe and non-invasive approach to managing CD related symptoms. Specifically, relaxation focused intervention sessions provide more positive and dramatic changes. Combination approach provide less dramatic but a more consistent positive changes. While more direct and larger scale research is needed to further validate this statement, integrating NMT into multidisciplinary care may enhance both physical and psychosocial outcomes for individuals with cervical dystonia.

23. Jonathan Monteiro; Department of Immunology

Supervisor: Dr. Veronique Miron

MICROGLIA PREVENT SPONTANEOUS RECURRENT CENTRAL NERVOUS SYSTEM DEMYELINATION

Hill BM[1,2,3]; Holloway RK[1,2,3]; Forbes LH[4,5]; Davies CL[5]; Monteiro J[1,2,3]; Brown C[4,5]; Rose J[4,5]; Fudge N[6]; Plant P[1]; Mahmood A[4,5]; Brand-Arzamendi K[1,2]; Kent SA[4,5]; Molina-Gonzalez I[4,5]; Gyoneva S[7]; Ransohoff RM[7-8]; Wipke B[7,9]; Priller J[4,10,11,12]; Schneider R[1,2]; Moore CS[6]; Miron VE[1,2,3,4,5]

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University of Cincinnati, Cincinnati, Ohio, USA; 5 Neuroimmunology Research Group, Netherlands Institute for Neuroscience, Amsterdam, The Netherlands; 6 UK Dementia Research Institute, University of Edinburgh, Edinburgh, United Kingdom; 7 Montreal Neurological Institute, McGill University, Montreal, Quebec, Canada

Introduction: Multiple sclerosis (MS) is a neurodegenerative disease caused by loss of myelin, termed demyelination, and myelin-forming oligodendrocytes in the central nervous system (CNS). While originally thought to be mediated by peripheral immune cells, therapeutics targeting these immune cells do not slow progression, suggesting other mechanisms at play. Microglia play a role, as they downregulate homeostatic genes early in disease, suggesting a loss of function. Microglia are also dysregulated at sites of early myelin damage that have no immune infiltration, suggesting a microglial role in disease initiation. However, the mechanisms by which microglia prevent oligodendrocyte dysfunction and demyelination are unknown. **Objective:** Determine mechanisms that mediate demyelination in the absence of microglia homeostatic functions. **Methods:** We model loss of microglia function using Csf1r-FIREΔ/Δ mice, which lack microglia from development, but develop myelin normally. We use single cell RNA sequencing, electron microscopy, and immunofluorescence to understand associated mechanisms in mouse and human tissue. **Results:** We find that absence of microglia alone is sufficient to mimic myelin dynamics observed in MS. We observed focal white matter demyelination in Csf1r-FIREΔ/Δ mice at 6 months, followed by myelin repair, and a recurrent demyelination at 12 months that persisted. Demyelination was preceded by the emergence of a dysfunctional Serpina3n+ oligodendrocyte population and was concurrent with the upregulation of ferroptosis markers; staining for the homologous population in human MS brains revealed an increase in demyelinating lesions. In the absence of microglia, TGFβ signaling was reduced in oligodendrocytes, and conditional knockout of TGFβ1 from microglia mirrored age-dependent demyelination and ferroptosis seen in the absence of microglia. scRNAseq revealed STAT3 as a regulator of oligodendrocytes during demyelination, and inhibition of STAT3 prevented demyelination and oligodendrocyte ferroptosis. **Conclusion:** Loss of microglia homeostatic TGFβ1 production is sufficient to induce a pattern of myelin damage that mimic MS. Demyelination was associated with a Serpina3n+ oligodendrocyte population in both mouse and human tissue, and we uncover STAT3 as a new therapeutic target to prevent loss of these dysfunctional oligodendrocytes in MS.

24. Ishnoor Singh; Department of Physiology

Supervisor: Dr. Mike Wheeler

CONNECTING SPECIFIC CENTRAL GLP-1 RECEPTORS FUNCTIONALLY WITH GLUCOSE HOMEOSTASIS AND ENERGY BALANCE

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Introduction: The central nervous system regulates metabolism, maintaining energy and glucose homeostasis. Glucagon-like peptide 1 (GLP-1), encoded by the proglucagon (Gcg) gene, is a key neuropeptide produced by NTS neurons, modulating appetite and feeding behavior. While GLP-1's systemic roles are known, its central mechanisms, particularly in feeding and glucose control, remain unclear. Arcuate nucleus of the hypothalamus (ARC), a critical hypothalamic region, receives dense Gcg projections, suggesting GLP-1 signaling in the ARC may regulate energy and glucose balance. This study focuses on investigating the specific role of GLP-1 signaling in the ARC, aiming to elucidate its effects on energy and glucose homeostasis.
Objectives: Examine the effects of ARC GLP-1R neuronal activation/inhibition on feeding and to determine their role in glucose homeostasis, insulin signaling, and secretion. **Methods:** Chemogenetic activation/inhibition of ARC GLP-1R neurons was achieved via Cre-dependent DREADDs in GLP-1R-Cre mice. Food intake, glucose tolerance, and insulin secretion were assessed following ligand administration. **Results:** Activation suppressed food intake, while inhibition increased it, confirming an anorexigenic role. Inhibition also led to glucose intolerance and impaired insulin signaling. Surprisingly, activation enhanced insulin secretion without altering blood glucose. **Conclusions:** ARC GLP-1R neurons regulate appetite and glucose homeostasis. While acute activation boosts insulin secretion, chronic effects on glucose regulation require further study.

SESSION IV

PAIN, SENSATION, AND NEURAL CIRCUITS

25. Irina Alymova; Cell and Systems Biology

Supervisor: Dr. John Peever

A DOPAMINE-HISTAMINE CIRCUIT CONTROLS AROUSAL

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Introduction: Dopaminergic agents, such as modafinil, are commonly prescribed to patients struggling with daytime sleepiness, highlighting dopamine's key role in wakefulness regulation. Despite the widespread use of these agents, the specific dopaminergic circuits involved in wakefulness control remain understudied. Prior work in our lab revealed that dopamine neurons in the A11 hypothalamic nucleus control wakefulness. It contains the highest proportion of wake-on dopamine cells compared to other dopaminergic nuclei, and activation of these cells promotes arousal. However, how A11 cells communicate with their downstream targets to promote wakefulness remains unknown. **Objective:** Here, we hypothesize that the A11 neurons modulate wakefulness through interactions with the histamine neurons of the tuberomammillary nucleus (TMN), a well-established wake-promoting region. **Methods:** Using a genetically encoded dopamine sensor (i.e., GRAB DA), we found that dopamine release onto the TMN is highest during wakefulness and lowest during sleep (n =7). **Results:** Additionally, we found that optogenetic activation of the A11 axonal projections in the TMN prolonged periods of wakefulness by 67% compared to their own baseline recordings (paired t-test, $p < 0.05$, n = 7) or control groups (unpaired t-test, $p < 0.05$, n = 5). Through cfos staining, we found that manipulation of these dopaminergic projections increases the activity of histamine cells in the TMN (n = 4). **Conclusion:** These results suggest that A11 dopamine projections to the TMN modulate wakefulness, primarily by lengthening wakefulness episodes. By identifying the underlying mechanisms of this circuit, future work

might help develop more effective and region-specific pharmacological treatments for sleep disorders, such as insomnia.

26. Matthew Cormie; Faculty of Dentistry

Supervisor: Dr. Massieh Moayedi

DOES THE THERMAL GRILL DRIVE PERIPHERAL OR CENTRAL SENSITIZATION? IMPLICATIONS FOR UNDERLYING MECHANISMS.

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Introduction: It remains unknown if paradoxical pain from the thermal grill illusion (TGI) results from the activation of peripheral nociceptors, or if the inputs are integrated in the central nervous system. Should peripheral nociceptors be activated, we would expect primary hyperalgesia. If integration occurs in the spinal cord, secondary hyperalgesia will occur. If wide dynamic range neurons are involved, we would expect brush allodynia to occur. Finally, if integration occurs in supraspinal regions, there would be no sensitization. **Objective:** We aim to determine whether the thermal grill (TG) elicits peripheral and/or central sensitization. We hypothesize that phasic TG will elicit secondary, but not primary hyperalgesia. We are agnostic on whether the TG will elicit brush allodynia. **Methods:** Fifty-two participants (26 females) received a phasic thermal grill (phTG) paradigm with individually calibrated thermal grill stimulation (non-painful and between 5-42C): 8 repetitions, 40s stimulation, 20s inter-stimulus interval. Participants rated pain intensity and stimulus unpleasantness. We measured brush allodynia and primary hyperalgesia pre- and post-phTG within the area of stimulation. Secondary hyperalgesia was calculated as the area of heightened sensitivity to mechanical pinpricks around the phTG stimulation site. **Results:** No participants developed brush allodynia ($p>0.05$). The TG led to primary hyperalgesia ($p=0.0002$) and secondary hyperalgesia ($p=2.42x10-18$), however within a subsample of participants receiving thermal stimuli within the innocuous range (19-41C; N=7). **Conclusion:** TGI induces secondary hyperalgesia, indicating integration on second-order nociceptors. The TGI also induced primary hyperalgesia, but only when component temperatures were within the mild noxious range, indicating a potential integration with peripheral nociceptors. TGI did not elicit brush allodynia, eliminating the contribution of wide dynamic range neurons. This study is the first to use altered states to determine the mechanisms of the TGI. These findings provide novel mechanistic understanding of the TGI, and thermal nociceptive integration.

27. Omar Khalil, Faculty of Dentistry

Supervisor: Dr. Massieh Moayedi

EXPLORING AVOIDANCE AND APPROACH LEARNING IN UNCERTAIN ENVIRONMENTS: A COMPUTATIONAL STUDY OF PAIN AND REWARD LEARNING

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Introduction: Decision-making in uncertain environments requires individuals to adjust behaviour based on outcomes, a process guided by reinforcement learning. While previous studies have explored appetitive and aversive learning, few have done so in uncertain contexts, often relying on reinforcement learning models with fixed learning rates. We use the Hierarchical Gaussian Filter (HGF) to model adaptive learning and compare appetitive, aversive, and interactive learning behaviours. **Objective:** To examine how adaptive learning varies across pain, reward, and combined motivational contexts, and how these differences relate to sex and pain-related psychological traits. **Methods:** A total of 128 participants (67F) completed a probabilistic reinforcement learning task, assigned to one of three groups: reward-learning (monetary gain), pain-avoidance learning (thermal pain), or approach-avoidance learning (reward and pain outcomes). We modelled learning using a mean-reverting HGF and analyzed group- and sex-level differences. Additionally, we examined associations between learning parameters and psychological traits [BAS-Drive, Fear of Pain (FPQ), Pain Catastrophizing Scale (PCS)]. **Results:** A significant difference in omega 2 (ω2), a proxy for vigilance, was observed between groups, with pain-avoidance showing higher ω2 ($p=0.042$). A sex difference in ω2 suggested that this group effect was driven by males ($p=0.018$). No significant associations emerged between ω2 and psychological traits in the reward-learning and approach-avoidance groups, but ω2 was significantly positively correlated with FPQ in the pain-avoidance group ($p=0.01$). **Conclusion:** Our findings suggest that the presence of pain alone leads to the highest vigilance, possibly driven by males, while the presence of monetary rewards may shift value and attention away from pain, reducing vigilance. Within the pain-avoidance group, a positive correlation between FPQ and ω2 suggests that fear of pain may underlie increased vigilance.

28. Faraz Moghbel; Department of Physiology

Supervisor: Dr. Etay Hay

DERIVING CONNECTIVITY FROM SPIKING ACTIVITY IN DETAILED MODELS OF LARGE-SCALE CORTICAL MICROCIRCUITS

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Introduction: Inferring detailed cortical microcircuit connectivity is essential for uncovering how information is processed in the brain. A common method in vivo uses short-lag spike cross-correlations to

derive putative monosynaptic connections, but inactive neurons and correlated firing can hinder the derivation accuracy. **Objective:** Previous computational studies that developed methods to derive connectivity from cross-correlations employed simplified or small network models and thus did not address the above key confounds of physiological large-scale networks. **Methods:** We tested connectivity derivation using simulated ground-truth spiking from detailed models of human cortical microcircuits in different layers and between key neuron types. **Results:** While derivation accuracy was high for cortical layer 5 microcircuits, we showed that low firing and inactive neurons in layer 2/3 microcircuits resulted in poor performance. We then showed that general activation paradigms for layer 2/3 microcircuits led to only a moderate improvement in derivation performance, due to a trade-off between reducing the proportion of inactive neurons and increasing correlated overactive neurons. We further improved the connection derivation performance using a more refined activation paradigm leading to jittered moderate spiking, which decreased inactive neurons without incurring unwanted correlations. **Conclusion:** Our results address key physiological challenges and provide methods to improve performance in deriving connections from spiking activity in large-scale neuronal microcircuits.

29. Pedram Moouseli; Faculty of Dentistry

Supervisors: Dr. Iacopo Cioffi; Dr. Massieh Moayedi

PREDICTIVE MODELS OF EXPERIMENTALLY INDUCED FACIAL PAIN BASED ON QUANTITATIVE SENSORY TESTING, BEHAVIORAL, AND PSYCHOLOGICAL FACTORS IN INDIVIDUALS WITH PAINFUL TEMPOROMANDIBULAR DISORDERS AND PAIN-FREE CONTROLS

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Introduction: Pain in the chewing muscles is a hallmark symptom of myogenic temporomandibular disorders (TMD). While quantitative sensory testing (QST) and psychological questionnaires provide insights into these domains, whether they can be used to predict the intensity of evoked facial pain in TMD remains unknown. **Objective:** This study aimed to develop predictive models of facial pain evoked by a standardized repetitive tooth clenching task, based on QST measures, behavioral and psychological measures, and to compare their utility in predicting evoked jaw muscle pain between individuals with painful TMD and pain-free controls. **Methods:** We included 46 TMD patients (33F, 27.3¬±6.5 years) and 56 pain-free controls (28F, 26.2±5.85 years). Participants performed a tooth clenching task consisting of 15 repetitions of 30-second clenching at 20-30% of their maximum voluntary contraction (MVC), followed by clenching at MVC until failure. Post-MVC pain intensity in the right masseter muscle was the prediction target. QST measures included thermal detection and pain thresholds, mechanical temporal summation, and pressure pain thresholds (PPT) on the area over the masseter and temporalis muscles before and after the clenching task. Behavioral and psychological factors were assessed using self-report questionnaires, including the Oral Behaviour Checklist (OBC), the State-Trait Anxiety Inventory, the Somatosensory Amplification Scale, the Beck's Depression Inventory, and the Pain Catastrophizing Scale. Partial Least Squares (PLS) regression models with 10-fold cross-validation were employed, with separate models trained for controls and patients with TMD, and using only QST measures, only psychological factors, or a combined set of both. **Results:** The combined model (QST + behavioral and psychological factors) successfully predicted post-MVC pain in the TMD group (r=0.33, p=0.027) and controls (r=0.36, p=0.007). Models based solely on QST measurements predicted pain only in controls (r=0.38, p=0.005), with temporal summation and PPT being the most significant predictors, but not in the TMD group (r=0.13, p=0.3722). In contrast, models relying solely on questionnaires predicted pain exclusively in the TMD group (r=0.38, p=0.007), with state anxiety and OBC showing the strongest contributions, but not in the control group (r=-0.02, p=0.89). Similar effects were observed for the left masseter pain. **Conclusion:** These findings demonstrate a differential contribution of behavioral, psychological, and somatosensory factors to evoked facial pain in TMD and in pain-free individuals. In TMD, behavioral and psychological factors are key predictors; whereas, in pain-free individuals somatosensory sensitivity has more predictive ability. Our data support the central role of behavioral and psychological factors in the pathophysiology of muscle pain in TMD.

30. Huseyin Taskin; Institute of Medical Science

Supervisor: Dr. Robert Chen

TRANSCRANIAL ULTRASOUND MODULATION OF CEREBELLAR INHIBITION

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Introduction: The cerebellum inhibits the primary motor cortex (M1), a key mechanism for motor learning and precision. This inhibition is typically measured non-invasively using a transcranial magnetic stimulation (TMS) protocol, where a TMS pulse to M1 elicits motor-evoked potentials (MEP) in hand muscles, and a preceding cerebellar pulse reduces MEP amplitude. While cerebellar lobules V and VIII are thought to be involved in this inhibition, TMS lacks the focality to isolate their individual contributions, as it activates a large portion of the cerebellar cortex. Transcranial ultrasound stimulation (TUS), a novel neuromodulation technique that uses ultrasound waves to modulate neuronal activity, offers deeper and more focal stimulation than TMS, making it a promising tool for cerebellar functional mapping. **Objective:** This preliminary study assessed whether TUS can modulate M1 excitability via cerebellar stimulation. We hypothesized that TUS targeting lobules V and VIII would decrease M1 excitability, whereas TUS targeting the dentate nucleus, a primary cerebellar output region with excitatory projections to the cortex, would increase M1 excitability. **Methods:** The M1 hand region was identified with TMS, and baseline MEP amplitude was recorded by averaging responses from 20 pulses. TUS (PRF = 1000Hz, duty cycle = 10%) was applied to lobules V, VIII, and the dentate nucleus for 0.5 s, with TMS pulse delivered to M1 0.45 s into ultrasound stimulation. Each cerebellar site was stimulated 20 times with 5-second intervals. Sham conditions included (1) TUS applied to V1, (2) zero-watt TUS, and (3) TUS with the transducer flipped away from the head. **Results:** Ultrasound sonication of lobule V and VIII resulted in inhibition of M1 excitability on average, while

dentate sonication showed excitation. However, dentate excitation was present only in three subjects, while the remaining two exhibited inhibition. The reason for this inconsistency could be due to inadvertent modulation of inhibitory white matter pathways entering the dentate in these subjects. The sham conditions yielded values similar to baseline. **Conclusion:** These preliminary findings demonstrate that both lobule V and VIII contribute to cerebellar inhibition of M1. Additionally, the results show the potential of TUS for selective stimulation of cerebellar lobules. The main study will refine targeting and investigate variability in dentate responses.

31. Ryan Yip; Department of Cell and Systems Biology

Supervisor: Dr. Ina Anreiter

M6A MODIFICATION REGULATES SEX-SPECIFIC CHAPERONE EXPRESSION IN THE DROSOPHILA BRAIN

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Introduction: N6-methyladenosine (m6A) is one of the most well-studied post-transcriptional modifications in eukaryotic mRNA, regulating various stress responses. In the brain, stress responses are crucial to maintain neuronal and cognitive function short and long-term. Thus, understanding how m6A facilitates cellular homeostasis in the brain in response to stress may provide valuable insights to stress-induced neurodegenerative phenotypes. **Objective:** Here we investigate the role of m6A in regulating the response of heat stress in fly brain. Materials and **Methods:** Through immunoblotting and survival assays; **Results:** We show that m6A levels in the brain increase upon heat stress; and there is a sex-specific chaperone expression patterns as well as to functionally link these to METTL3, the core enzyme that deposits m6A. **Conclusion:** METTL3 knockout female mutants have increased levels of Hsp70 expression in the brain and higher resilience to heat stress. Interestingly, Hsp90 showed delayed response in METTL3 KO females but not in males upon heat shock, demonstrating sex-specific response. Overall, our data suggest m6A modification in Drosophila regulates stress response in the brain in a sex-specific manner.

32. Luka Zigomanis; Insitute of Biomedical Engineering

Supervisor: Dr. Kei Masani

SPECTRAL-TEMPORAL CORTICAL CONTRIBUTIONS TO POSTURAL SWAY CONTROL

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Introduction: The role of supraspinal drive in postural control remains a key area of interest for both researchers and clinicians. While vestibular and reticulospinal pathways are known to contribute significantly to posture maintenance, the corticospinal pathway is also thought to play a crucial role in modulating muscle activation to preserve balance. Understanding the motor cortex's contribution to this process provides insight into the mechanisms of postural control. **Objective:** We aim to investigate the spectral-temporal motifs of cortical contributions to the control of standing posture. **Methods:** Electroencephalography (EEG) and electromyography (EMG) was recorded under various standing conditions, contrasting natural postural sway to voluntary sway. During quiet standing, the whole-body center of mass (COM) exhibits small fluctuations. Based on the inverted pendulum model, postural sway was defined by the velocity zero-crossings, referred to as a "unit sway". Spectral-temporal patterns of cortical EEG and shank EMG signals were quantified through ensemble averages over a unit sway. Corticomuscular connectivity was analyzed using both corticomuscular coherence (CMC) and temporal-dependent phase-amplitude relationships to assess linear and non-linear interactions between EEG and EMG signals. **Results:** Spectral-temporal analysis revealed that phasic beta-band activity aligns with key fluctuations in COM velocity in the anterior-posterior direction. Voluntary sway responses are comparatively driven by continuous cortical beta-band activity irrespective of the phase of the unit sway. While weak beta-band CMC was observed between the plantar flexors and the motor cortex, strong phase-amplitude coupling between cortical and muscular activity indicated prominent non-linear corticospinal contributions to standing posture. **Conclusion:** We have shown that distinct spectral-temporal cortical beta-band activity is aligned with key postural sway perturbations, driving non-linear spectral connectivity with the plantar flexors muscles. Contributions to the understanding of the neural mechanisms of postural control will support the design of effective therapies to help neurologically injured patients restore their upright balance.

SESSION V

PSYCHIATRIC DISORDERS

33. Katharina Göke; Institute of Medical Science

Supervisor: Dr. Daniel Blumberger

THE EFFECTS OF RTMS ON SELF-REPORTED QUALITY OF LIFE IN YOUNGER AND OLDER ADULTS WITH MAJOR DEPRESSIVE DISORDER

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Introduction: Repetitive transcranial magnetic stimulation (rTMS) is a well-established intervention for treatment-resistant depression. However, its effects on patient-reported outcomes such as quality of life (QoL) have not been fully characterized, especially among older adults.

Objective: This study compares the effect of rTMS on QoL in younger (<60 years) vs older (>60 years) adults with depression. **Methods:** We analyzed data from 531 participants with depression (ages 18-89) from two randomized clinical trials (THREE-D and FOUR-D). All participants received either unilateral or bilateral rTMS or theta burst stimulation. QoL was assessed using the Quality of Life Enjoyment and Satisfaction Questionnaire, Short Form at baseline, end of treatment, and 12-week follow-up and compared between younger adults (age < 60; n=360) and older adults (age > 60, n=171). Clinical relevance of changes was evaluated through effect sizes, using a predefined threshold of 12 points for a minimal clinically important difference, and comparisons with community norms. **Results:** After rTMS treatment, both younger and older adults experienced statistically significant improvements in QoL, with medium to large effect sizes. The effect was sustained over 12 weeks of follow-up. At baseline, 0.8% of younger and 2.8% of older adults reported normal QoL, which significantly increased to 19.7% and 19.4%, respectively, by the end of treatment, and 23.6% and 26.8% at the 12-week follow-up. **Conclusions:** rTMS yielded acute and sustained clinically meaningful improvements in QoL, with similar effects among younger and older adults with depression. The magnitude of improvement was comparable to, or exceeded, that reported in antidepressant trials.

34. Danica Johnson; Insitute of Medical Science

Supervisor: Dr. Joshua Rosenblat

ASSESSING COGNITIVE OUTCOMES IN TREATMENT-RESISTANT DEPRESSION FOLLOWING PSILOCYBIN-ASSISTED PSYCHOTHERAPY

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Introduction: Cognitive deficits within treatment-resistant depression (TRD) often do not improve with conventional antidepressants. Psilocybin-assisted psychotherapy (PAP) has shown promise as a novel intervention for TRD; however, few studies have assessed its effects on cognition. **Objective:** To evaluate the short-term effects of psilocybin-assisted psychotherapy on cognitive functioning in individuals with treatment-resistant depression and to determine whether cognitive changes are independent of mood improvements. **Methods:** In this post-hoc analysis of a pilot PAP trial (NCT05029466), we assessed cognitive outcomes (Digit Symbol Substitution Test [DSST], Trail Making Tests A and B [TMT-A/-B]) in TRD patients randomized to a PAP treatment arm (n = 12; 25 mg psilocybin plus psychotherapy) or a delayed-treatment waitlist control arm (n = 14). We analyzed within- and between-group changes with paired and independent t-tests or Wilcoxon and Mann-Whitney U tests and conducted a mediation analysis to examine whether depressive symptom changes (Montgomery-√Ösberg Depression Rating Scale scores) mediated cognitive outcomes. **Results:** After two weeks, we observed significant within-group improvements in the treatment arm on the TMT-A (mean difference= -8.67, p < .001, d = 1.29) and TMT-B (median difference = -13.50, z = -2.554, p = .011), but no significant changes in the waitlist arm for any cognitive outcomes. Between-group comparisons showed that TMT-B improvements in the treatment arm significantly exceeded those of the waitlist arm (U = 37.00, p = .016), while TMT-A improvements did not differ significantly between arms (p = .133). Our mediation analysis revealed depressive symptom reductions did not significantly mediate TMT-B performance gains (b = 0.81, 95% CI [-6.57, 16.62]). **Conclusion:** These preliminary findings suggest that PAP may have mood-independent pro-cognitive effects in TRD patients, warranting further research with larger samples.

35. Shannen Kyte; Institute of Medical Science

Supervisor: Dr. Philip Gerretsen

THE NEURAL CORRELATES OF IMPAIRED ILLNESS AWARENESS IN ADDICTION: FMRI ANALYSIS OF THE COGNITIVE DYSFUNCTION IN ADDICTIONS (CDIA) STUDY

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Introduction: Impaired illness awareness (IIA) or insight into illness occurs in up to 93% individuals with substance use disorders (SUDs) depending on the stage of illness and is a significant barrier to seeking and adhering to treatment. IIA is suggested to arise from frontoparietal brain network dysfunction. Limited studies have investigated the neural correlates of IIA in SUDs. **Objective:** Therefore, the aim of this study was to examine the brain regions implicated in IIA in SUDs. **Methods:** This study included 21 participants with SUDs. Illness awareness was assessed using the Alcohol Use Awareness and Insight Scale (AAS) or Substance Use Awareness and Insight Scale (SAS) depending on the participant's primary substance of use. Each participant completed an MRI scan that involves an individually tailored fMRI task paradigm, which consists of a bank of brief stimuli, consisting of yes/no questions/statements derived from the core domains of IIA: (1) illness awareness, (2) symptom attribution, and (3) awareness of need for treatment; and (4) control stimuli. Participants will be grouped into impaired versus intact IIA. Task-based fMRI analyses consisting of: (1) regression analysis with AAS and SAS average scores as the variable of interest, and a (2) group comparison between intact and impaired IIA are being completed. **Results:** It was found that higher alcohol and cannabis use severity was associated with greater awareness of alcohol and cannabis addiction, respectively. Among individuals with cannabis addiction, illness awareness was also positively associated with anxiety levels. Additionally, scores derived from the fMRI task

paradigm were strongly correlated with pre-scan AAS and SAS scores. We expect to see that impaired IIA in SUD is related to frontoparietal cerebral activity as observed in other neuropsychiatric conditions. **Conclusion:** The identification of neural biomarkers associated with IIA in SUDs can serve as potential therapeutic targets for novel interventions, such as non-invasive brain stimulation, to improve IIA in SUDs, which may facilitate treatment adherence and other clinical outcomes of SUDs.

36. Kateryna Maksyutynska; Institute of Medical Science

Supervisor: Dr. Mahavir Agarwal

CAN IMPROVEMENTS IN METABOLIC HEALTH IMPACT COGNITIVE OUTCOMES IN INDIVIDUALS WITH MOOD DISORDERS? REAL-WORLD DATA FROM A JOINT MENTAL HEALTH & METABOLISM CLINIC

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Introduction: Individuals with mood disorders experience significant cardiometabolic burden, such as higher rates of type 2 diabetes and obesity, which is negatively associated with illness severity and quality of life. Early evidence of the use of metabolic pharmacological therapies has shown promise in improving multifaceted symptom domains. As a result, metabolic pathways have become novel targets for addressing chronic illness due to the growing incidence of treatment resistance and limited treatment options for cognitive decline in this patient population. **Objective:** This study utilizes real-world data from a Mental Health and Metabolic Clinic to explore the association between weight loss and cognition in patients with mood disorders treated for metabolic dysfunction. **Methods:** A retrospective chart review was conducted of all patients diagnosed with a mood disorder and enrolled in the Mental Health and Metabolism Clinic at the Centre for Addiction and Mental Health (CAMH) in Toronto, Canada, between January 2018 and November 2024 (REB #181-2024). Data was collected from the Brief Cognitive Assessment Tool (BCAT), a cognitive battery comprised of four instruments evaluating working memory, verbal fluency, and processing speed, completed as part of the clinic's standardized assessment. Weight and other metabolic data were collected from the day of cognitive assessment completion. A Spearman's Rank correlation analysis was performed to assess the association between changes in cognitive and metabolic parameters. **Results:** Seventy-five patients with mood disorders (mean age: 35.6 ± 12.6 years; 24.0% male) completed the BCAT and were included in analyses. The primary mood disorder diagnoses of the included sample were bipolar disorder (58.7% BD-I; 13.3% BD-II; 5.3% BD-NOS) and major depressive disorder (22.7%). Patients were treated with a lifestyle only (10.7%), add-on metformin (65.3%), topiramate (8.0%), semaglutide (13.3%), or semaglutide + metformin (2.7%) intervention at baseline. From this group, 53 (70.7%) of patients experienced an average weight loss of 7.2 ± 7.2 kg over 37.4 ± 20.2 weeks between cognitive assessments. A significant positive correlation was identified between weight loss and verbal fluency (Spearman's =0.318; p=0.020), with greater weight loss associated with improved cognitive performance. No significant correlation was found between changes in weight and global cognition, working memory, or processing speed. **Conclusion:** This study highlights the close association between metabolic and cognitive outcomes, and emphasizes the importance of metabolic monitoring in the context of severe mental illness. Future research must work to identify the underlying mechanisms of this interaction and reproduce findings in randomized controlled trials.

37. Ayesha Rashidi; Institute of Medical Science

Supervisor: Dr. Stephanie Ameis

UNDERSTANDING THE DIMENSIONS OF SOCIAL COGNITION IN AUTISM SPECTRUM AND SCHIZOPHRENIA SPECTRUM DISORDERS

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Introduction: Individuals with autism spectrum disorder (ASD) and schizophrenia spectrum disorders (SSDs) exhibit overlapping impacts on social cognition relative to typically developing controls (TDCs), contributing to significant impairments in psychosocial functioning and quality of life. Despite being recognized as a transdiagnostic clinical construct according to the NIMH's Research Domain Criteria framework, a unified dimensional model of social cognition that accurately reflects its latent structure across diagnostic boundaries remains elusive. **Objective:** Examine the factor structure of social cognition to clarify the underlying architecture, as it reveals the scope, dimensionality, and interrelationships of its components. **Methods:** Participants (total N=584; ASD N=100, SSDs N=275, TDCs N=209; aged 16-55 years; 61% male) completed social cognitive (ranging from emotion recognition to complex mental state inference), clinical, functional, and neurocognitive measures. Structural equation modeling was used to test social cognitive models, measurement invariance across groups, and relationships with outcome measures. **Results:** Confirmatory factor analysis revealed a two-factor model with lower-level simulation and higher-level mentalizing fit the social cognitive data well across participants (œá2=24.49, df=13, P=0.027, CFI=0.989, TLI=0.983, RMSEA=0.040, SRMR=0.022) and showed adequate measurement invariance across ASD, SSDs, and TDC groups. Both clinical groups showed lower simulation and mentalizing scores than TDCs ($p<0.01$), with SSDs significantly lower than ASD ($p<0.001$). **Conclusion:** Preliminary results reveal a common structure of social cognition consisting of distinct lower-level (simulation) and higher-level (mentalizing) processes. This two-factor model was consistent across ASD, SSDs, and TDCs, suggesting that social cognition can be meaningfully characterized by these dimensions regardless of diagnostic category.

38. Alexandra Sas; Temerty Faculty of Medicine

Supervisor: Dr. Victor Tang

FEASIBILITY, IMPLEMENTATION, AND REAL-WORLD EFFECTIVENESS OF REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION FOR TOBACCO SMOKING CESSATION

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Introduction: Repetitive transcranial magnetic stimulation (rTMS) is a novel and non-invasive smoking cessation treatment. This excitatory stimulation is offered at 10 Hz for 18 sessions over 6 weeks with the first 3 weeks as daily sessions and the last 3 weeks as weekly sessions. **Objective:** The studies that led to rTMS approval excluded patients with mental illness therefore it is unclear whether this intervention would be equally feasible and acceptable in real-world settings that include such patients. **Methods:** We evaluated the feasibility and acceptability of rTMS for smoking cessation by surveying and interviewing patients recruited from a nicotine clinic in a tertiary psychiatric hospital. A subset of 11 consented and were eligible to enroll in the treatment and we hypothesized that at least 70% of those would complete treatment. **Results:** Of the 74 survey participants, 47.3% reported having a psychiatric condition, with depression and anxiety being most prevalent. The Acceptability of Intervention Measure showed that 81.8% of participants agreed that the treatment was appealing and 68.9% found the time commitment acceptable. The maximum time participants were willing to travel for this intervention was 45 (± 26) minutes, but 47.3% reported that travel costs were likely unaffordable. Thematic analysis of 27 interviews showed that participants' dissatisfaction with available treatments, the potential for mental health improvement, the desire for in-person care, and trust in the healthcare institution were motivators to pursue rTMS. Conversely, time commitment and transportation unaffordability were barriers for pursuing rTMS. Out of 11 patients who enrolled in treatment, 7 completed treatment (63.6%), 1 dropped during treatment, and 3 dropped before treatment. One person reached abstinence by the end-of-treatment. **Conclusion:** There was high interest among smoking cessation patients in rTMS, but the travel commitment was a common access barrier. Most of the patients who started rTMS completed the full regimen. Many real-world smokers present with comorbid psychiatric conditions therefore researching implementation facilitators and barriers is necessary to inform the integration of rTMS before it is more widely adopted into routine clinical care.

39. Earvin Tio; Institute of Medical Science

Supervisor: Dr. Daniel Felsky

UNDERSTANDING THE BIOPSYCHOSOCIAL MECHANISMS OF RISK FOR SUICIDE USING MACHINE LEARNING AND A RESILIENCE FRAMEWORK

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Introduction: Traditional approaches to modelling suicide risk often analyze individuals with psychiatric history separately from healthy controls. This paradigm ignores the phenomenon of resilience in the face of psychiatric adversity, and conversely, acute or unexplained suicidality. **Objective:** We aim to develop a two-stage resilience model of suicide in a large population-based cohort using machine learning to identify modifiable factors which may protect against suicide despite a high burden of non-modifiable risk factors and psychiatric symptoms. **Methods:** First, we trained a random forest classifier on 145 unmodifiable and psychiatric risk factors for suicide (e.g., traumatic and adverse life events, depressive symptoms, and psychosocial factors) to predict self-reported lifetime suicide attempt in the UK Biobank (N=10,878; mean age=52, SD=7.5 years; 67% female; 53% attempted). Then, we fit a second model on the prediction errors of the first model (a residual measure of "suicide resilience") using extreme gradient boosting, trained on a new set of 202 research-based and modifiable factors (e.g., blood biomarkers, cognitive function, early life factors, health and medical history, lifestyle and environment, physical measures, sociodemographics, and genetic risk scores). Post-hoc shapely additive explanations were calculated to determine feature importance for each participant. **Results:** Our first-stage model of suicide attempt achieved an AUC of 0.94 and the second-stage model further explained 17% of variance in the prior prediction errors. Age at recruitment, age at first sexual intercourse, and years of education were identified as top features predicting suicide resilience (i.e., individuals with no self-reported lifetime suicide attempt despite a high-risk profile of known risk factors). **Conclusion:** The suicide resilience framework presented here allows for a better understanding of how modifiable factors may mitigate risk of suicide despite the presence of known, unmodifiable risk factors. Identifying novel biopsychosocial correlates of suicide resilience can inform future research by uncovering putative interventional targets for suicide prevention.

40. Yutong Wang; Department of Pharmacology & Toxicology

Supervisor: Dr. Thomas Prevot

CHRONIC STRESS EXPOSURE IN MICE INDUCES SOMATOSTATIN NEURON VULNERABILITY ASSOCIATED WITH ALTERED MRNA AND MIRNA EXPRESSION RELATED TO PROTEIN PROCESSING REGULATION

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Introduction: Chronic stress is a leading risk factor to developing major depressive disorders (MDD). Clinical and preclinical studies showed a deficit in aminobutyric acid (GABA) levels and signaling dysfunction, particularly due to dysfunction of the somatostatin-positive (SST+) GABAergic neurons. SST+ cells vulnerability to stress seems linked to endoplasmic reticulum stress, and we hypothesize that dysregulations of ER-related genes in a mouse model of chronic stress are linked to symptoms severity. **Objective:** To investigate how ER stress-related genes and miRNAs may contribute to the mechanisms

leading to SST+ interneuron vulnerability under chronic stress. **Methods:** Leveraging the available dataset from a RNA-seq study from a mouse model of chronic stress, we used bioinformatics analysis to identify key molecular biomarkers in SST+ interneurons. Differentially expressed genes (DEGs) were identified for both mRNA and miRNA, followed by Gene Oncology (GO) functional enrichment analysis using DAVID. A protein-protein interaction (PPI) network was constructed using the STRING database and visualized in Cytoscape. Five essential gene modules were identified using MCODE tool. **Results:** A total of 934 differentially expressed genes (DEGs)were identified(768 upregulated, and 166 downregulated). Among the top five hub genes highlighted, HSPA5, and EIF2S1, were functionally associated with ER lumen and misfolded protein binding. Regarding miRNA analysis results, five up-regulated miRNAs (MI0005520, MI0014097, MI0014096, MI0000625, MI0003518) were identified among 1177 miRNA. Furthermore, spearman correlation analysis between gene expression and behavioral performance revealed significant associations between central genes and z-scored cognitive performance, reinforcing the role of SST+ interneuron dysregulation in stress-induced cognitive impairment. **Conclusion:** These findings suggest that ER dysfunction may contribute to SST+ interneuron vulnerability to chronic stress, ultimately affecting cognitive function in stress-related depression.

41. Jerry Li; Institute of Medical Science

Supervisor: Dr. Mojgan Hodaie

DECIPHERING NEURAL SIGNATURES OF PAIN IN TRIGEMINAL NEURALGIA WITH MACHINE LEARNING AND STRUCTURAL BRAIN IMAGING

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Introduction: Trigeminal neuralgia (TN) is a surgically treatable neuropathic pain condition that causes debilitating facial pain. Conventional imaging of TN brains is unable to identify biomarkers that characterize and predict surgical response. However, the definition of these biomarkers is important and clinically relevant in identifying potentially reversible pain signatures associated with TN. We have previously identified brain signatures associated with TN in a cross-sectional manner. In this study, we explore changes in subcortical structures along a timeline of surgical recovery, using machine learning (ML). We hypothesized that these structures comprise a pain signature that is predictive of TN and has the ability to normalize following surgical pain relief. **Objective:** To identify a pain signature associated with TN and investigate whether it normalizes following pain-relieving surgery. **Methods:** Structural brain magnetic resonance imaging (MRI) scans were obtained before and after 117 TN patients underwent pain-relieving surgery. Each patient was age- and sex-matched with unique, healthy, pain-free controls from 4 external databases. Every TN patient was considered a surgical responder, having had at least 75% reduction in pain following surgery. TN scans were obtained within 6 months pre- and between 6-10 months post-surgery. FreeSurfer 7.0 was used to process images into subcortical volumes. An ensemble of 10 optimized support vector classifiers (SVC) was assembled after training 1000 SVC models to differentiate between 834 HC and 117 pre-surgery TN responders, oversampled to 834 to match the number of HC subjects. Each SVC underwent parsimonious backward sequential feature selection followed by grid search for hyperparameter tuning, using nested, stratified 10-fold cross-validation. The ensemble was externally validated on 100 local HC to demonstrate its generalizability. Shapley additive explanation values, principal component analysis, and uniform manifold approximation and projection were used to interpret ensemble predictions for improved explainability. **Results:**
Before surgery, the ensemble correctly classified 116/117 TN responders and 115/117 healthy subjects (99% accuracy; ROC-AUC = 0.998). After surgery, a significant number of TN responders were reclassified as HC ($q < 0.001$). 29 responders were now classified as healthy (ROC-AUC = 0.981), reflecting that a substantial proportion of surgical responders underwent normalization, or now had structural motifs highly similar to healthy brains after pain relief. Comparing ensemble prediction probabilities revealed that the brains of 96/117 TN responders (82%) shifted towards a healthier phenotype. Predictions were highly influenced by cognitive regions. The most impactful feature in the ensemble was the left accumbens area, with larger volumes pushing predictions towards TN. Decomposition of data revealed that normalization in brain volumes after pain-relieving surgery was likely non-linear in nature. **Conclusion:** Our longitudinal study identifies a novel, reversible pain signature unique to TN. We illustrated that brain structure alone is enough for ML to distinguish between TN and being pain-free, and that recovery from neuropathic pain may be detectable within a year of pain-relieving surgical intervention. These findings provide a foundation for mechanistic studies of subcortical regions in TN, many of which are related to cognition, and support the potential for ML to augment clinicians.

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