2023 VAST Summer Student Symposium

August 17, 2023, 12pm – 3pm MST, 2pm – 5pm EST

Keynote Presentation:

2:00-2:05 pm – Welcome

2:05-2:25 pm – Using in-vivo neuroimaging biomarkers to study the intersection of Alzheimer's disease with cerebral small vessel disease
Julie Ottoy
Sunnybrook Research Institute / University of Toronto

Student Presentations from VAST Summer Scholars:

2:30-2:40 pm – In vivo injections in mice of antibodies targeting the Vascular Endothelial Growth Factor Receptor 2 (VEGFR2)
Philippe Rousseau*, Louise Reveret, Hélène Girouard, Frédéric Calon*
Laval University

2:40-2:50 pm – VAST experience-integrated research placement: Recreation therapy and VCI
Bryn Florence*, Erin Mazerolle*
St. Francis Xavier University

2:50-2:55 pm – Establishing how age, sex, and lipid metabolism in Alzheimer's Disease (AD) intersect to elicit vascular impairment *in vivo* (recorded)
Kristin Bessai*, Erin Mazerolle, Steffany Bennett*
University of Ottawa

2:55-3:05 pm – Sex-specific lipidomic determinants of vulnerability and resistance to dementia
Sandra Bojic*, Miroslava Cuperlovic-Culf, Eric Smith, Steffany Bennett*
University of Ottawa

3:05-3:15 pm – Influence of vascular health on cognition assessed in older adults with attention-deficit/hyperactivity disorder
Hayley Huston*, Sara Becker, Eric Smith, Brandy Callahan*
University of Calgary

3:15-3:20 pm – Rich-club behavior and analyses in the human brain connectome as novel early biomarkers of cognitive decline (recorded)
George Tadros*, Jen Guo, Noaah Reaume, Connor McDougall, Emma Towlson, and Philip Barber*
University of Calgary

3:20-3:30 pm – Neuroimaging markers of small vessel disease in adults with moderate-great complexity congenital heart disease
Preet Gandhi*, V. Dizonno, S. Mangat, B. Marginean, R. Bates, N. Ratnaweera, J. Andrade, M.K. Heran, K. LeComte, J. Smith, J. Grewal, T.S Field*
University of British Columbia

Workshop on Impact Assessment:

3:30-5:00 pm – Impact Assessment: The key to sharing the story of your research with anyone
Ty McKinney
Branch Out Neurological Foundation

Abstracts:

In vivo injections in mice of antibodies targeting the Vascular Endothelial Growth Factor Receptor 2 (VEGFR2)

Philippe Rousseau, Louise Reveret, Hélène Girouard, Frédéric Calon

The blood-brain barrier (BBB) is a selective barrier between the blood and the brain, allowing cerebral blood vessels to regulate molecule and ion movement while protecting the brain from toxic peripheral molecules. Interestingly, it is estimated that only 2% of molecules can cross the BBB. Vascular endothelial growth factor receptor 2 (VEGFR2) is an important receptor expressed in the blood vessels of many organs, including the brain, and plays a key role in angiogenesis. Previous results in the laboratory showed that this receptor can be internalized in vitro in endothelial cells. Our hypothesis is that VEGFR2 can also be internalized in vivo in the murine brain microvessels and could potentially serve as delivery vectors through the BBB. After I.V injections in balb/c mice of fluorescent antibodies targeting VEGFR2, we showed that VEGFR2 was internalized in the microvessels of the brain. Our preliminary results also indicated that VEGFR2 did not colocalize with lysosome marker. Further work is needed to determine if VEGFR2 could be trapped in endosomes. Two different antibody clones targeting VEGFR2 were tested and gave comparable results. These encouraging first results demonstrate that VEGFR2 can be internalized in brain endothelial cells in vivo in the mouse and is thus a potential candidate to target the BBB.

VAST experience-integrated research placement: Recreation therapy and VCI

Bryn Florence and Erin L. Mazerolle

Experience-integrated research was developed by VAST to introduce junior undergraduate students to VCI and the research process. Rather than complete a research project, I worked in recreation therapy at a local nursing home and gained hands-on experience with people who have dementia, stroke, and VCI. I also worked with a faculty mentor to link my experiences at the nursing home to research, as well as the development of a chapter on VCI for an open educational resource. Throughout the summer, I worked on building and maintaining VAST's emerging relationship with the nursing home. Ultimately, such relationships will help us develop research questions, practices, and processes that are more relevant to the populations we study. In the future, I hope to complete an honours project related to VCI, and am actively pursuing a new partnership with Arts Health Antigonish, a local not-for-profit community organization whose mandate is to foster creative expression for community health and well-being.

Establishing how age, sex, and lipid metabolism in Alzheimer's Disease (AD) intersect to elicit vascular impairment *in vivo*

Kristin Bessai, Erin Mazerolle, Steffany Bennett

Background: Alzheimer's disease (AD) has a complex and multifaceted pathophysiology, with vascular factors such as cerebral amyloid angiopathy emerging as contributing components of cognitive impairment. In vivo, N5 TgCRND8 mice have shown a sexual dimorphism in cognitive impairment and mortality rate. A subset of these mice have a higher mortality rate from strokes due to vascular amyloidosis. Understanding the roles of age, sex, and lipid metabolism may help explain this dimorphism.

Methodology: TgCRND8 mice (n=5/sex /genotype) were followed longitudinally from 1-6 months of age with monthly plasma collection from the saphenous vein and cognitive assessment via nest-building. Circulating lipid abundances in all plasma samples will be quantified via liquid chromatography tandem

mass spectrometry. At each monthly endpoint (1-6 months), cerebral amyloid angiopathy will be visualized using immunofluorescence and vascular amyloid beta will be quantified via ELISA.

Results: It is anticipated that the above data will: (i) identify animals with vascular amyloidosis regardless of phenotype; (ii) establish the extent of vascular amyloidosis present within these animals and (iii) determine whether animals with vascular amyloidosis and cerebral vessel disease can be retrospectively predicted by their circulating lipidome.

Significance & Impact: Investigating how these factors converge to influence cerebrovascular dysfunction and cognitive decline and may encourage the discovery of new predictive or diagnostic biomarkers. Furthermore, investigating their complex interaction is crucial in identifying the driving mechanisms of sexual dimorphism seen in AD pathology in vivo.

Sex-specific lipidomic determinants of vulnerability and resistance to dementia

Sandra Bojic, Miroslava Cuperlovic-Culf, Eric Smith, Steffany Bennett

Background: Vascular cognitive impairment (VCI), Alzheimer's disease (AD), Dementia with Lewy Bodies (DLB), Parkinson's Disease with Dementia (PDD), Parkinson's Disease (PD), and mild cognitive impairment (MCI) are major causes of progressive cognitive decline and dementia. There exist sex-specific differences in risk factors, symptom presentation, and disease progression. While aberrant lipid metabolism is linked to the development and progression of these disorders, the underlying mechanisms responsible for cognitive decline remain unclear. Understanding the interplay between lipids and these cognitive disorders can lead to poten8al therapeu8c strategies involving sex-specific modulation of lipid metabolic pathways.

Methodology: This study employed a targeted lipidomics approach to profile and quantify sphingolipids and glycerophosphocholines and investigate potential sex-based differences. Lipids were extracted using a modified Bligh and Dyer protocol. Profiling was performed by liquid chromatography-electrospray ionization-tandem mass spectrometry (LC-ESI-MS/MS).

Results: We identified 176 lipids (63 sphingolipids and 113 glycerophospholipids) in the plasma of 256 subjects, comprising controls and patients with cognitive disorders. We expect to find several lipid species that differ by sex and disease state.

Significance & Impact: This study highlights the intricate relationship between lipid metabolism, dementia, and sex and holds the potential to extend our existing knowledge of the relationship between the lipidome and cognitive decline. Exploring sex-specific differences may reveal useful biomarkers and lead to a more comprehensive understanding of these disease processes.

Influence of vascular health on cognition assessed in older adults with attention-deficit/hyperactivity disorder

Hayley Huston, Sara Becker, Eric E. Smith, Brandy L. Callahan

Background: Individuals with attention-deficit/hyperactivity disorder (ADHD) frequently engage in behaviours detrimental to their vascular health (e.g., smoking), which can lead to the accumulation of vascular risk factors (VRFs; e.g., hypertension). These behaviours can inflict strain on the vascular system by decreasing the brain's blood supply. Evidence suggests that adults with ADHD are at greater risk than their peers to experience later-life cognitive decline, since cognitive health depends heavily on effective blood flow to the brain. This study aims to examine the relationship between cognition and self-reported VRFs in individuals with ADHD.

Methods: We are recruiting 110 older adults with ADHD. Participants will undergo a comprehensive assessment of memory, processing speed, and executive functioning. Through a questionnaire, participants will report whether they have any of the following VRFS: hypertension, hyperlipidemia,

obesity or diabetes. The relationship between VRF's and cognition will be assessed through using linear regression, controlling for age and gender.

Results: Given the vulnerability of vascular health in adults with ADHD, and that effective cognitive performance depends on vascular health and cognition, we expect individuals who self-report more VRFs will perform worse on cognitive tasks compared to those who report fewer VRFs. We expect to have data collected on 12 participants by the end of August; these findings will be discussed at the symposium.

Significance: This project will provide novel insight into how vascular mechanisms influence cognitive performance in individuals with ADHD. By clarifying this connection, cognitive decline in older individuals may be mitigated and disease-related costs may be reduced.

Rich-club behavior and analyses in the human brain connectome as novel early biomarkers of cognitive decline

George S. Tadros, Jen Guo, Noaah Reaume, Connor C. McDougall, Emma K. Towlson, and Philip A. Barber.

Background: Transient ischemic attack (TIA) patients have an increased risk of early dementia, representing an ideal population to investigate preclinical dementia. Rich club is a phenomenon where highly connected nodes form a "rich club" amongst themselves, thus playing an important role in global communication. The rich club has been shown to experience disruptions in established dementia such as Alzheimer's disease and small vessel disease, suggesting its sensitivity to WM connectivity changes in various clinical manifestations of dementia. In this study we thus aim to determine whether the prominence of the rich club effect differs between the TIA and controls across time, as well as its association with cognition.

Methods: TIA (n=36) and non-TIA controls (n=35) underwent DTI imaging at baseline, 1-year, 3-year, and 5-year post-TIA or recruitment. Whole-brain tractography utilizing constrained spherical deconvolution (CSD) was performed to construct whole-brain connectomes for both groups at all available timepoints. The maximum normalized rich club coefficient (Φmax) was used as an indicator of the prominence of the rich club effect.

Results: The prominence of the rich club effect was not significantly different between TIA and non-TIA controls at baseline or 1-year follow-up ($p>0.05$). However, TIA patients showed a significantly less prominent rich club effect at 3-year and 5-year compared to controls ($p=0.030$ and 0.029, respectively). Linear mixed effect models showed no association between changes in rich club prominence and changes in cognition ($p>0.05$ for all domains investigated).

Significance & Impact: The decrease in rich club prominence seen in TIA patients relative to controls may be a novel biomarker for future cognitive decline. This potential biomarker might play an important role in early detection of dementia, and patient selection for future vascular risk reduction trials or trials of novel dementia therapeutics.

Neuroimaging markers of small vessel disease in adults with moderate-great complexity congenital heart disease

P. Gandhi, V. Dizonno, S. Mangat, B. Marginean, R. Bates, N. Ratnaweera, J. Andrade, M.K. Heran, K. LeComte, J. Smith, J. Grewal, T.S Field

Background: Neuroimaging studies of adults with congenital heart disease (ACHD) with critical heart lesions have demonstrated markers associated with cerebral small vessel disease (SVD), including white matter hyperintensities (WMH) and microbleeds (CMB), but the burden of these findings in the broader ACHD population is not well characterized.

Methodology: This cross-sectional project is part of an ongoing longitudinal study examining neuroimaging and cognition in ACHD with moderate-severity complexity cardiac lesions. We qualitatively assessed current participants' (n=81) baseline MRIs for markers of SVD (WMH, CMB, lacunes). We derived the modified SVD (mSVD) score, a validated summary score with a maximum of 3 points, where 1 point each is awarded for moderate-severe WMH, >1 CMB, and >1 lacune.

Results: Mean age was 35.5 (SD 10.5); 43% female. Moderate-complexity lesions comprised 78%; 22% severe. There was an overall low burden of conventional vascular risk factors. Over one-quarter (28%) had a history of arrhythmia; half (49%) had a history of cardiac surgery with bypass. Overall, burden of SVD markers was higher than expected for age compared to the general population, with 79% having an SVD score of >1. Burden of SVD was numerically greater in the severe group (94% with an SVD score of ≥1 vs. 75%).

Significance & Impact: Markers of SVD are common in moderate-severe ACHD. Whether they are associated with vascular risk factors or cognitive performance, or confer risk of future vascular events in this population, is under investigation. Ongoing work will examine the nature of these relations.