



2021 INTERNATIONAL SYMPOSIUM

# Promoting Healthy Brain Aging and Preventing Dementia

## RESEARCH AND TRANSLATION

Virtual Event | May 18-19, 2021



Campus Alberta  
**Neuroscience**

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[albertaneuro.ca/education/#HBAD](http://albertaneuro.ca/education/#HBAD)

**On behalf of the Conference Organizing Committee and Campus Alberta Neuroscience, welcome to the third international conference on Promoting Healthy Brain Aging and Preventing Dementia: Research and Translation.**

Dementia is a global, national, and local issue. In Canada, approximately 15% of people 65 and older are living with dementia, and the combined direct and indirect costs are a staggering \$33 billion per year. The solutions to the problems presented by dementia will also be found globally, nationally, and locally. The Alberta Healthy Brain Aging and Dementia (HBAD) community – led by a committee of dementia researchers from the Universities of Alberta, Calgary, and Lethbridge – is a research team that brings together Alberta researchers and clinicians along the entire spectrum of dementia research, from basic to translational sciences. Brought together and facilitated by Campus Alberta Neuroscience, the HBAD team aims to transform the dementia research and translation landscape by understanding and enhancing healthy brain aging while delaying or preventing dementia.

The overarching goal of HBAD is to accelerate diagnostic advancements, improve cognitive health and reduce the overall burden of dementia. To this end, HBAD is reaching out to the national and international research community in aging and dementia to form collaborative partnerships as part of the global battle against dementia.

The Alberta HBAD community is proud to host its first virtual dementia symposium. We sincerely hope you find this conference to be a unique and valuable learning experience. We look forward to the opportunity to connect with the international community to determine how we can all work together to improve outcomes for those with dementia

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## SCIENTIFIC PROGRAM COMMITTEE

**Roger A. Dixon**  
University of Alberta

**Robert Sutherland**  
University of Lethbridge

**Marc Poulin**  
University of Calgary

**David Westaway**  
University of Alberta

**Eric E. Smith**  
University of Calgary

# AGENDA DAY 1

Tuesday, May 18

OPEN MAY 17-ON  
FOR VIEWING

## Oral Abstract Presentations

12:30 – 12:45 PM

### Opening Remarks

George Andrews of Alzheimer Society of Alberta and Northwest Territories and Jennifer Dotchin of Campus Alberta Neuroscience

12:45 – 2:00 PM

## SESSION 1: Applied Science and Intervention for Brain Health and Dementia

Sponsored by Alzheimer Society of Alberta and Northwest Territories (ASANT)

Moderated by: Marc Poulin, University of Calgary – Calgary, Canada

12:45 PM

Generation 100; The Long-term Effect of High-intensity Interval Training on Morbidity and Mortality in Older Adults

Dorthe Stensvold, Norwegian University of Science and Technology – Trondheim, Norway

1:00 PM

Sleep in the Aging Brain: Associations with Alzheimer's Disease Pathophysiology and Memory Impairment

Bryce Anthony Mander, University of California, Irvine – Irvine, United States of America

1:15 PM

Physical Activity in Dementia Risk Reduction: Where Do We Go From Here?

Laura Middleton, University of Waterloo – Waterloo, Canada

1:30 PM

Multidomain Interventions for Risk Reduction and Prevention of Dementia: From FINGER to World-Wide FINGERS

Miia Kivipelto, Karolinska Institutet – Stockholm, Sweden

1:45 PM

Question and Answer

2:00 – 2:45 PM

## Networking Break & Oral Abstract Presentations

2:45 – 4:00 PM

## SESSION 2: COVID-19 Effects on the Brain: Direct, Indirect, and Persisting Consequences

Moderated by: Eric E. Smith, University of Calgary – Calgary, Canada

2:45 PM

Seeing Through Brain Fog: Disentangling the Cognitive, Physical, and Mental Health Sequelae of COVID-19

Adrian M. Owen, Western University – London, Canada

3:00 PM

Canadian Longitudinal Study on Aging (CLSA) COVID-19 Brain Study: Rationale and Study Design

Teresa Liu-Ambrose, University of British Columbia – Vancouver, Canada

3:15 PM

Evaluating the Impact of COVID on People Living with Dementia in Alberta

Dallas Seitz, University of Calgary – Calgary, Canada

3:30 PM

The Impact of COVID on Stroke (Incidence, Care, and Outcomes)

Richard H. Swartz, Sunnybrook HSC, University of Toronto – Toronto, Canada

3:45 PM

Question and Answer

4:00 – 5:00 PM

## KEYNOTE 1: Will Promoting Brain Health Also Prevent Dementia?

Kaarin Anstey, University of New South Wales – Sydney, Australia

Moderated by: Marc Poulin, University of Calgary – Calgary, Canada

# AGENDA DAY 2

Wednesday, May 19

9:00 – 10:15 AM

## SESSION 3: Integrating Big Data, Neuroinformatics, and Precision Health Approaches

Moderated by: Roger A. Dixon, University of Alberta – Edmonton, Canada

9:00 AM **Integrating Machine Learning, Omics Analyses and Neurodegeneration**  
David Wishart, University of Alberta – Edmonton, Canada

9:15 PM **A Roadmap From Heterogeneity to Subtypes of Alzheimer's Disease and Related Disorders**  
AmanPreet Badhwar, CRIUGM, Université de Montréal – Montréal, Canada

9:30 AM **Multi-modal Biomarkers and Integrative Neuroinformatic Tools for Personalizing Treatments in Neurodegeneration**  
Yasser Iturria-Medina, McGill University – Montréal, Canada

9:45 AM **Combining Epidemiological and Precision Health Approaches to Understand Sex Differences in Alzheimer's Disease**  
Michelle M. Mielke, Mayo Clinic – Rochester, United States of America

10:00 AM **Question and Answer**

10:15 – 11:00 AM **Networking Break & Oral Abstract Presentations**

11:00 – 12:15 PM

## SESSION 4: Challenges of Animal Models and Clarifying the Science Surrounding the Amyloid Hypothesis

Moderated by: David Westaway, University of Alberta – Edmonton, Canada

11:00 AM **Novel Mouse Models of Late-onset Alzheimer's Disease**  
Michael Sasner, The Jackson Lab – Bar Harbor, United States of America

11:15 AM **The Role of Hormones in Alzheimer's Disease**  
Fernanda De Felice, Queen's University – Kingston, Canada

11:30 AM **Intersecting Etiologies of Alzheimer's Disease and Prion Diseases Present Therapeutic Opportunity**  
Gerold Schmitt-Ulms, University of Toronto – Toronto, Canada

11:45 AM **Dissecting the Individual Roles of CD33 Isoforms Connected to Alzheimer's Disease Susceptibility**  
Matthew Macauley, University of Alberta – Edmonton, Canada

12:00 PM **Question and Answer**

12:15 – 1:15 PM

## KEYNOTE 2: Human Genetics Implicates Microglial Function in Alzheimer's Disease Risk

Alison Goate, Icahn School of Medicine at Mount Sinai – New York, United States of America

Moderated by: David Westaway, University of Alberta – Edmonton, Canada

1:15 – 2:00 PM **Closing Panel**

Moderated by: Robert Sutherland, University of Lethbridge – Lethbridge, Canada

Closing Panel: Alison Goate, Bryce A. Mander, David Hogan and David Westaway

2:00 – 2:15 PM

**Presentation Awards and Closing Remarks**

*Sponsored in part by the Canadian Institutes of Health Research, Institute of Aging (CIHR IA)*

# Abstract Oral Presentations

Theme 1: Applied Sciences and Interventions for Brain Health and Dementia

## ABSTRACT #1:

### Novel peptide aptamers as potential therapeutic candidates for the treatment of Alzheimer's disease

Tahir Ali (1, 2), Antonia N. Klein (1, 3), Alex Vu (1, 2), and Sabine Gilch (1, 2)

1- Calgary Prion Research Unit, Department of Comparative Biology & Experimental Medicine, Faculty of Veterinary Medicine, University of Calgary, Calgary, Alberta, Canada

2- Hotchkiss Brain Institute, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada

**Introduction:** Alzheimer's disease (AD) is a progressive age-associated neurodegenerative disease and major cause of dementia. AD represents a global health problem that has affected more than 50 million people worldwide. There is currently no treatment available for AD. Amyloid beta oligomers (A $\beta$ O) are primary neurotoxic species in AD pathogenesis. The interaction of A $\beta$ O with the cellular prion protein (PrPC) subsequently mediate AD pathologies. The interference with A $\beta$ O-PrPC interaction is a valuable strategy for developing therapeutics for AD. Previously, we developed peptide aptamers (PAs) binding to the PrPC, partially covering the binding site of A $\beta$ O. In this study, we aimed to investigate the PAs therapeutic effects in in vitro and in vivo AD models.

**Methods:** PAs and the thioredoxin A (trxA) control were expressed in *E. coli* and purified by Ni<sup>2+</sup>-affinity chromatography. Mouse neuroblastoma N2a cells (overexpressing mouse PrP) were treated with A $\beta$  (1  $\mu$ M) and PAs or the trxA scaffold as a control (10  $\mu$ g/ml), and after 24 hr an MTT assay was performed. Following these in vitro experiments, we performed in vivo experiments using transgenic 5xFAD mice. The 5xFAD mice were treated with PAs at a 14.4  $\mu$ g/day dosage for 6 weeks by intracerebroventricularly using Alzet® osmotic pumps. After completion of treatment, fear conditioning test (FCT) was performed for consolidated memory functions. Following behavioral tests, we processed brain homogenates of PA-treated and control 5xFAD mice for biochemical analysis of basic AD pathologies.

**Results:** The MTT results indicated that PA treatment significantly reduced A $\beta$ O-induced toxicity. In the FCT, we observed that PA treatment increased the freezing percentage and indicate that PAs significantly improved consolidated memory functions of 5xFAD mice as compared to the non-treated 5xFAD mice. We also found that PA treatment reduced A $\beta$  dodecamer and dimer forms. Additionally, PAs reduced levels of phosphorylated c-Jun N-terminal kinase and glial fibrillary acidic protein, a marker of neuroinflammation.

**Conclusion:** Overall, PA treatment reduces toxicity of A $\beta$ O in neuronal cells and rescued A $\beta$  pathology, neuroinflammatory signaling and improved memory functions in the 5xFAD mouse model of AD. In summary, our results demonstrate that PAs would be valuable potential therapeutics to treat AD.

# Abstract Oral Presentations

Theme 1: Applied Sciences and Interventions for Brain Health and Dementia

## ABSTRACT #2:

### Identification of Novel Metabolomic Biomarkers in Alzheimer's Disease

**Mirela Ambeskovic (1), Giselle Tiede (1), Tanzi Hoover (1), Jeffrey T Joseph (2), Tony Montina (3), and Gerlinde A.S. Metz (1)**

1- Department of Neuroscience, University of Lethbridge, Lethbridge, Alberta, Canada

2- Department of Pathology & Laboratory Medicine, University of Calgary, Calgary, Alberta, Canada

3- Department of Chemistry and Biochemistry, University of Lethbridge, Lethbridge, Alberta, Canada

**Introduction:** Alzheimer's disease (AD) is the most common neurodegenerative diseases and leads to emotional dysregulation and memory and speech deficits. However, the mechanisms contributing to AD-related pathology are still poorly understood. Metabolomics, a systematic study of chemical metabolites found in tissues as the result of cellular activity, may provide a novel method for identifying these mechanisms and discover novel predictive, diagnostic, and therapeutic targets. Using an untargeted metabolomics approach, we investigated 1) metabolomic profiles of non-AD vs AD human brain tissue, and 2) alterations of the brain tissue metabolome for regions with common and uncommon AD related pathology.

**Methods:** Post-mortem brain tissues (Brodmann area BA17, BA22 and BA40) were retrieved from the Calgary Brain Bank from categorized non-AD and AD patients. Tissues were processed and analyzed using proton nuclear magnetic resonance ( $^1\text{H}$  NMR) spectroscopy. Both univariate analysis and a multivariate machine learning approach involving permutation testing were used to determine metabolite signatures across brain regions. The complete list of altered metabolites was then used for the pathway topology analysis.

**Results:** We identified distinct metabolomic profiles associated with AD. All three brain regions showed metabolomic changes, with the most metabolites altered in the posterior temporal gyrus (BA22) and the least in the primary visual cortex (BA17). Consistently across all regions, valine, isoleucine, phenylalanine and tyrosine were downregulated while GABA was upregulated. Pathway topology analysis revealed that these metabolites are involved in aminoacyl-tRNA biosynthesis, valine, leucine and isoleucine biosynthesis and phenylalanine metabolism pathways. Interestingly, BA22 and BA40 both showed altered levels of glutamate and potential alterations in the alanine aspartate and glutamate metabolism pathway, but not BA17.

**Conclusions:** AD leads to distinct metabolomic signatures. These signatures include potential alterations in brain region-common metabolic pathways involved in protein biosynthesis, energy metabolism, and catecholamine biosynthesis, and brain region-specific metabolomic pathways involved in neurotransmission which may be involved long-term neurodegenerative changes. Identification of region-specific and region-common metabolic pathways involved in AD will aid in developing early diagnostic biomarkers and significantly advance the development of personalized medicine approaches.

# Abstract Oral Presentations

Theme 1: Applied Sciences and Interventions for Brain Health and Dementia

## ABSTRACT #3:

### Stability optimization of a rationally designed, structure-based vaccine candidate targeting prion diseases

**Andrew Fang, Xinli Tang, Xinyi Huang, and Holger Wille**

Centre for Prions and Protein Folding Diseases & Department of Biochemistry, University of Alberta, Edmonton, Alberta, Canada

**Introduction:** The misfolding of cellular prion protein (PrP<sup>C</sup>) into the infectious isoform (PrP<sup>Sc</sup>) causes transmissible spongiform encephalopathies (TSEs). The lack of a prophylactic or therapeutic vaccine means uncontrolled spread and an invariably fatal outcome for the host. We have developed a vaccine candidate that shows efficacy when tested in vivo (mice). We were also able to create PrP<sup>Sc</sup>-specific monoclonal antibodies derived from the vaccine. However, protein stability issues prevented us from further testing. By solving these stability issues, we hope to use other in vivo prion models and further test the efficacy of our vaccine.

**Methods:** A vaccine candidate was previously constructed, expressed, purified and refolded, and showed efficacy when given to a transgenic (Tg) mouse model of Gerstmann-Sträussler-Scheinker disease (GSS). Sodium dodecyl sulphate–polyacrylamide gel electrophoresis (SDS-PAGE) and negative staining electron microscopy was used to confirm the purity and refolding of purified products, respectively. Enzyme-linked immunosorbent assays (ELISAs) combined with our monoclonal antibody were used to confirm the presence of a non-linear epitope, indicative of proper vaccine folding. Protein were lyophilized for a minimum of 48 hours.

**Results:** One of our vaccine candidates was able to keep our mice disease free (>250 days) when compared to unimmunized mice, and PrP<sup>Sc</sup>-specific monoclonal antibodies have also been identified and created. Using one of these monoclonal antibodies with an ELISA, we were able to see that prolonged storage of our vaccine candidate resulted in protein denaturation. We found that under low salt conditions, our vaccine was unstable, but could be partially remedied via higher salt concentrations. Lyophilization of our vaccine candidate was also able to prevent protein denaturation. Both are potential methods to reduce denaturation and keep our vaccine candidate properly folded.

**Conclusions:** Our vaccine candidate showed stability issues due to low salt conditions, and can be remedied via lyophilization. Resolving these issues allows us to further test and improve our vaccine candidate.

# Abstract Oral Presentations

Theme 1: Applied Sciences and Interventions for Brain Health and Dementia

## ABSTRACT #4:

### Vaccine adjuvants affect the efficacy of a prion vaccine in a Gerstmann–Sträussler–Scheinker disease mouse model

**Madeleine Fleming (1, 2), Andrew Fang (1, 2), Brian Tancowny (1, 2), and Holger Wille (1, 2, 3)**

1- Department of Biochemistry, University of Alberta, Edmonton, Alberta, Canada

2- Centre for Prions and Protein Folding Diseases, University of Alberta, Edmonton, Alberta, Canada

3- Neuroscience and Mental Health Institute, University of Alberta, Edmonton, Alberta, Canada

**Introduction:** Prion diseases are fatal neurodegenerative diseases caused by the misfolding of the cellular prion protein to its infectious form. Gerstmann–Sträussler–Scheinker disease (GSS) is a rare, genetic and fatal prion disease in humans that is characterized by dementia and ataxia. The TgP101L mouse line carries a GSS mutation and recapitulates the human disease. A protein, previously constructed in the Wille lab, has shown potential as a structure-based prion vaccine. This protein mimics the proposed 4-rung  $\beta$ -solenoid structure modified from an innocuous fungal protein, HET-s. This antigen has shown promising results in preventing disease onset in TgP101L mice when co-administered with Freund's adjuvant. Adjuvants are compounds added to a vaccine that potentiate its immune response, leading to greater antibody production and longer lasting immunity. Freund's adjuvant is a potent and non-specific immunopotentiator that is too toxic for human use. Therefore, this vaccine trial aims to replace Freund's adjuvant with a safer but equally effective adjuvant. Aluminum hydroxide (alum), when used as an adjuvant, stimulates a Th2 immune response and has been commonly used in vaccines for nearly a century. Another experimental adjuvant, QS21, stimulates a Th1 immune response.

**Methods:** In this study, alum and QS21 adjuvants were compared by immunizing TgP101L mice on a prime-boost schedule with the antigen and either adjuvant (10 mice per group). We then measured the antibody titre in the serum following each immunization using an ELISA and observed symptom onset and progression relative to non-immunized mice.

**Results:** Our results illustrate that alum leads to higher antibody production than both Freund's and QS21. The mice immunized with the prion vaccine and either alum or QS21 have a significant delay in GSS symptom onset and an increased survival rate relative to unimmunized TgP101L mice.

**Conclusions:** Our results indicate that alum can safely be co-administered with the antigen to potentiate an immune response that considerably delays the onset of prion disease in transgenic mice. Therefore, we can use alum to further optimize our prion vaccine with the intention of future clinical use.



# Abstract Oral Presentations

Theme 1: Applied Sciences and Interventions for Brain Health and Dementia

## ABSTRACT #5:

### Rationally designed, structure-based vaccines candidates targeting $\alpha$ -synucleinopathies

**José M. Flores-Fernández (1, 2), Aishwarya Sriraman (1, 2), YongLiang Wang (1, 2), Enrique Chimal-Juárez (1, 2), Xiongyao Wang (1, 2), Brian Tancowny (1, 2), Xinli Tang (1, 2), and Holger Wille (1, 2, 3)**

1- Centre for Prions and Protein Folding Diseases, University of Alberta, Edmonton, Alberta, Canada

2- Department of Biochemistry, University of Alberta, Edmonton, Alberta, Canada

3- Neuroscience and Mental Health Institute, University of Alberta, Edmonton, Alberta, Canada

**Introduction:** Parkinson's disease is mainly caused by the misfolding of the  $\alpha$ -synuclein protein. This protein adopts a beta-sheet rich conformation and aggregates into amyloid fibrils that are found in the brain of  $\alpha$ -synucleinopathies' patients (i.e. Parkinson's Disease, Lewy Body Dementia, and Multi System Atrophy). Up to now any attempts to develop vaccines for these diseases have used the protein and peptides in its linear form without any control of its tertiary and quaternary structure, which resulted in failure to achieve protection. Here, we present a new approach to design structure-based vaccine candidates using structurally defined antigens that result in disease-specific immune responses.

**Methods:** The fungal prion protein Het-s natively adopts a beta-sheet rich conformation and was engineered as a vaccine to express antigenic determinants in a structurally controlled manner. These vaccines were expressed as recombinant proteins in *E. coli*, purified, and refolded. All candidates were then analyzed by negative stain electron microscopy for their proper folding and only those constructs that mimicked the amyloid fibril structure were injected into mice. Antisera collected and tested by ELISA to determine their specificity.

**Results:** After the purification and refolding of the engineered proteins, several vaccine candidates showed the expected self-assembly into amyloid fibrils by negative stain electron microscopy. Just the self-assembled constructs were used to immunize FVB/NJ mice. Antisera collected from vaccine candidates  $\alpha$ -synC3,  $\alpha$ -synC6,  $\alpha$ -synC8, and  $\alpha$ -synC9 elicited specific immune responses when they were tested against brain homogenates from patients who died from  $\alpha$ -synucleinopathies. Brain homogenates from non-neurologic patients were used as controls.

**Conclusions:** The immune specific responses against disease-relevant samples showed that rationally designed, structure-based vaccines targeting misfolded  $\alpha$ -synuclein are feasible and may result in a prophylactic vaccine against Parkinson's Disease, Lewy Body Dementia, or Multi System Atrophy.

# Abstract Oral Presentations

Theme 1: Applied Sciences and Interventions for Brain Health and Dementia

## ABSTRACT #6:

### Noise damage accelerates auditory aging and tinnitus: a Canadian population-based study

Zahra Jafari (1), Thomas Copps (2), Glenn Hole (2), Bryan E. Kolb (1), and Majid H. Mohajerani (1)

1- Department of Neuroscience, Canadian Centre for Behavioural Neuroscience, University of Lethbridge, Lethbridge, Alberta, Canada

2- Audiology First, Lethbridge, Alberta, Canada

**Introduction:** Age-related hearing loss (ARHL/presbycusis) is the third most challenging disability in older adults after hypertension and arthritis, and is prevalent in nearly two-thirds of adults aged 70 years and older in the US (Lin et al., 2011). Noise is a known modifiable risk factor of ARHL, which can drive adverse auditory and non-auditory effects. Few large-scale studies, however, have shown how chronic noise exposure (CNE) impacts the progression of auditory aging and tinnitus during the lifespan.

**Methods:** This retrospective cohort study was conducted in Lethbridge, the third-largest city in the province of Alberta. Data of 928 individuals tested between 2015-2019, aged 30-100 years without (n=497) or with (n=431) the experience of CNE were compared in their hearing assessments (tonal and speech audiometry) and tinnitus. We were able to perform this research in Lethbridge because of known industries and vast agricultural lands in southern AB, which allowed us to collect the appropriate sample size in all age decades. In order to only investigate the effect of CNE on ARHL and tinnitus, individuals with other risk factors of hearing loss were excluded from the study. Multivariate analysis of variance and non-parametric tests (Mann-Whitney-U/Kruskal-Wallis tests) were applied for statistical analysis.

**Results:** Our findings demonstrate the significant impact of noise damage on a greater ARHL per age decades (7-17dB,  $\leq 0.001$ ), the acceleration of a significant ARHL at least by 2 decades, and the loss of speech recognition ability (85.0% vs. 80.0%,  $\leq 0.001$ ). There was an increased tinnitus prevalence per age decade with the highest rate in the sixth decade in both groups, as well as an elevated prevalence of both constant (28.10% vs. 8.85%,  $\leq 0.001$ ) and intermittent (19.1% vs. 11.3%,  $\leq 0.001$ ) tinnitus in the CNE group than the control group.

**Conclusions:** Our findings indicate how exposure to chronic occupational noise adds to the ARHL severity and tinnitus prevalence, as well as suggests the critical decades for hearing assessment and rehabilitation. The findings should be further noticed by health policy-makers in light of the association between midlife hearing loss/tinnitus and accelerated development of cognitive decline and dementia.

# Abstract Oral Presentations

Theme 1: Applied Sciences and Interventions for Brain Health and Dementia

## ABSTRACT #7:

### Enhancing the potassium chloride cotransporter KCC2 improves performance in a spatial navigation task in transgenic mice expressing Alzheimer's disease-related mutations

**Brendan B. McAllister (1), Iason Keramidis (2), Jogender Mehla (1, 3), Phil Degagne (1), Antoine G. Godin (2), Yves De Koninck (2), and Majid H. Mohajerani (1)**

1- Canadian Centre for Behavioural Neuroscience, University of Lethbridge, Lethbridge, Alberta, Canada

2- CERVO Brain Research Center, Laval University, Québec City, Québec, Canada

3- Dept. of Neurosurgery, Washington University School of Medicine, St. Louis, Missouri, United States

**Introduction:** Cortical hyperactivity has been noted early in Alzheimer's disease (AD), both in patients and mouse models. One possible cause is disrupted inhibitory GABAergic signaling, which can result from impaired chloride homeostasis. The potassium-chloride cotransporter 2 (KCC2) is critical for keeping the intracellular chloride concentration low, maintaining the efficacy of GABAergic signaling. Notably, it has been reported that KCC2 is decreased in sporadic AD patients' brains. We hypothesize that KCC2 hypofunction is a primary cause of neuronal hyperactivity in AD, which contributes to disease progression and induces cognitive impairments. We are evaluating whether CLP290, a KCC2 enhancing drug, can rescue KCC2 levels, reduce network abnormalities, and reverse cognitive impairments in a mouse model of AD.

**Methods:** The aggressive amyloidogenic 5xFAD transgenic line was used. KCC2 levels were assessed by immunofluorescence analysis of layer II/III pyramidal neurons in 4 and 6-month-old mice (control: n = 9, n = 14; 5xFAD: n = 13, n = 12, respectively). To assess whether short-term KCC2 enhancement improves cognitive performance, 6-month-old 5xFAD mice were treated daily with CLP290 while they underwent a battery of behavioural tests (vehicle: n = 15; CLP290: n = 15), including the Morris water task. Brains were then collected to examine KCC2 levels (vehicle: n = 10; CLP290: n = 10). Finally, the effect of acute CLP290 treatment on cortical oscillatory activity was assessed by recording local field potentials in freely moving 5xFAD mice (n = 7).

**Results:** Global KCC2 protein levels were lower in 4-month-old 5xFAD mice compared to non-transgenic littermates ( $p < .001$ ), and membrane protein levels were decreased at both 4 and 6 months of age ( $p = .004$  and  $p = .015$ , respectively). Short-term CLP290 treatment increased KCC2 expression ( $p = .009$ ) and improved performance in the Morris water task probe trial ( $p = .044$ ). Acute CLP290 treatment tended to decrease gamma oscillation power in the barrel cortex, though not significantly so ( $p = .069$ ).

**Conclusions:** KCC2 is a promising target for preventing hyperactivity and cognitive impairments in AD. Additional experiments are required to determine whether long-term CLP290 treatment can slow disease progression in mouse models.

# Abstract Oral Presentations

Theme 1: Applied Sciences and Interventions for Brain Health and Dementia

## ABSTRACT #8:

### Quantitative Susceptibility Maps of Iron Deposition in Pre-Dementia Transient Ischemic Attack Patients

**Brooklyn McDougall, Meaghan Reid, MSc, Connor McDougall, MSc, Hongfu Sun, PhD, Noah Reaume, Rani Gupta Sah, PhD, Shelagh Coutts, MD, Christopher D. d’Esterre, PhD, Philip A. Barber, MD**

University of Calgary, Calgary, Alberta, Canada

**Introduction:** Patients with Transient Ischemic Attack (TIA) have increased risk of dementia. Magnetic Resonance Imaging (MRI) modality Quantitative Susceptibility Maps (QSMs) measure iron deposition which has shown to be associated with neurodegeneration, and therefore might be a useful tool for assessing cognitive decline in TIA patients without dementia.

**Methods:** Sixty-nine (N=69) TIA patients and forty-six (N=46) age- and intellectual-matched healthy controls were recruited from the PREVENT study. Neuropsychological assessments and MRI scans were performed within 10 days of incident event and were repeated at 1 year. Susceptibility values were extracted from subcortical regions on the QSM. Two-way two-sample t-tests were used to compare TIA and control groups and linear regression was used to analyze the relationship between the predictor values – QSM iron susceptibility – and the outcome values – cognition.

**Results:** TIA patients were  $67.7 \pm 9.5$  years old and had a premorbid intellect of  $108.3 \pm 9.4$  whereas control participants were  $65.4 \pm 8.5$  years old and had a premorbid intellect of  $109.5 \pm 8.1$ . There was no significant difference between the two groups for age ( $p=0.180$ ) or premorbid intellect ( $p=0.468$ ). TIA patients had a median MMSE score of 30.0 (28.0-30.0), whereas control participants had a median score of 30.0 (29.0-30.0) ( $p=0.030$ ). At baseline, TIA patients performed significantly worse in BVMT Total ( $p=0.03$ ), BVMT Delayed ( $p=0.03$ ), TMT A ( $p=0.003$ ), TMT B ( $p=0.011$ ), and WAIS-IV DS Coding ( $p<0.001$ ). TIA patients had significantly higher QSM values than the control group within the caudate ( $p=0.025$ ) at baseline. Further, TIA patients had significantly larger iron deposits (characterized by extreme susceptibility values) within the caudate (28% of region) compared to controls (21%) ( $p=0.04$ ) at baseline. Caudate iron deposits in TIA patients also increased 1.37% over one year, compared to the control group, 1.07%. Other subcortical regions did not significantly differ between the groups at baseline or 1-year follow-up. There was no correlation between susceptibility and cognition at baseline.

**Conclusions:** QSM iron susceptibility values within the caudate are promising biomarkers to utilize when assessing pre-dementia patients, such as TIA patients. The PREVENT study will further explore the relationship with iron, brain atrophy and cognition over a longer period of follow-up.

# Abstract Oral Presentations

Theme 1: Applied Sciences and Interventions for Brain Health and Dementia

## ABSTRACT #9:

### Machine Learning Analyses to Identify Predictors of Incident Dementia in Parkinson's Disease

**G. Peggy McFall (1, 2), Linzy Bohn (1), Myrlene Gee (3), Shannon M. Drouin (1), Wei Han (4), Liang Li (4), Richard Camicioli (2,3), and Roger A. Dixon (1, 2)**

1- Department of Psychology, University of Alberta, Edmonton, Alberta, Canada

2- Neuroscience and Mental Health Institute, University of Alberta, Edmonton, Alberta, Canada

3- Department of Medicine (Neurology), University of Alberta, Edmonton, Alberta, Canada

4- Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada

**Introduction:** Parkinson's Disease (PD), a complex multisystem movement disorder, is characterized by pathological degeneration of nigrostriatal dopaminergic neurons and the presence of Lewy body deposition leading to motor dysfunction. A potential non-motor symptom of PD is cognitive decline that can lead to dementia (PDD). Accumulating research has identified multiple candidate risk factors for subsequent PDD. We applied machine learning technology to a battery of baseline dementia risk factors in order to identify the best predictors of later PDD in a sample of initially non-demented persons with PD.

**Method:** Participants at baseline were 48 non-demented PD patients (M age = 71.5; 44% female). At 36-month follow-up, 14 were clinically diagnosed with PDD. We used Python (3.7) and random forest classification to simultaneously examine 42 risk factors in order to determine the best set of predictors for discriminating PD patients with incipient dementia (PDID) from those continuing as non-demented (PDND). The predictor pool represented multiple dementia risk modalities: demographic, lifestyle, cardiovascular, cognitive, genetic, imaging, metabolite, mobility, functional, sensory, and psychological.

**Results:** Thirteen predictors provide more than 60% of the model's interpretation (AUC = .82, 90% Accuracy). PDID was predicted by: metabolite biomarker panel (lower levels of decreased risk PDID panel), cognitive (poorer performance on three executive-speed tasks), mobility (greater number of steps, worse balance), higher levels of a brief PDD risk scale, imaging (larger third ventricle volume), functional (poorer finger dexterity), demographic (older age), lifestyle (lower level of daily independence), and cardiovascular (more drop in systolic and diastolic blood pressure).

**Conclusions:** Not all persons with PD develop dementia and there is no established protocol for detecting elevated post-diagnosis PDD risk. In this study, a set of dementia risk factors from seven modalities discriminated PDID from PDND three years prior to dementia diagnosis. An accurate multi-modal PDD risk assessment may be possible.

# Abstract Oral Presentations

Theme 1: Applied Sciences and Interventions for Brain Health and Dementia

## ABSTRACT #10:

### A humanized, PrPSc-specific nanobody for passive immunotherapy against sporadic prion diseases

Vineet Rathod (1, 2), Jose Miguel Flores-Fernandez (1, 2), Jessica Cashion (1, 2), and Holger Wille (1, 2, 3)

1- Department of Biochemistry, University of Alberta, Edmonton, Alberta, Canada

2- Centre for Prions and Protein Folding Diseases, University of Alberta, Edmonton, Alberta, Canada

3- Neuroscience and Mental Health Institute, University of Alberta, Edmonton, Alberta, Canada

**Introduction:** Creutzfeldt-Jakob disease (CJD) belongs to a group of inexorably progressive and fatal dementias with an incidence of 1-1.5 cases per million people per year. Sporadic CJD (sCJD) is the most common form (~85%) and patients exhibits rapid deterioration of cognitive function, with death occurring within 12 months of onset. Currently, there is no effective therapy other than palliation. The crucial event in the pathogenesis of prion disease is the conversion of the cellular prion protein (PrPC) into an abnormally folded and infectious form (PrPSc).

**Methods:** On-going experiments in the Wille lab targeting PrPSc via active immunotherapy resulted in a rationally designed, structure-based vaccine that elicited an immune response specific for the disease-causing conformer only. The immune response to this vaccine candidate allowed the generation of a PrPSc-specific monoclonal antibody, which we engineered into a humanized, recombinant nanobody that will be tested as a potential passive immunotherapy against sCJD. In addition to a conventional recombinant nanobody, we also engineered a single domain antibody fragment (nanobody) that is linked to a variable heavy chain of the mouse mAb8D3 for better delivery across the blood-brain barrier (BBB) via receptor-mediated transcytosis.

**Results:** We determined that the nanobody is selective for the infectious prion conformer only and binds pivotal surface residues of PrPSc. I was able to successfully clone a recombinant humanized PrPSc nanobody and bispecific therapeutic nanobody. These clones have been expressed in *E. coli*, purified and tested for their ability to bind Vacc14R1 and native PrPSc, which served as quality control measures.

**Conclusions:** To test the efficacy of the engineered nanobody, we will use a human transgenic mouse model, which will be intracerebrally challenged with prions. The therapeutic nanobody will be tested after the mice were challenged with prions and towards the end of the incubation period (clinical signs developed) to see if beneficial effects on the survival of the animals can be achieved. The recombinant, humanized nanobody should be able to avoid neurotoxicity and immunogenicity and due to its monovalent nature and allow for better penetration into the brain.

# Abstract Oral Presentations

Theme 1: Applied Sciences and Interventions for Brain Health and Dementia

## ABSTRACT #11:

### Train your Brain: Validating at-home cognitive training in light of the COVID-19 pandemic

**Taylor Snowden (1), Hannah Reid (1), Jocelyn Faubert (2), and Brian Christie (1, 3, 4)**

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3- Island Medical Program, University of British Columbia, Victoria, British Columbia, Canada

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**Introduction:** With improvements in health care and living conditions, the average age of our population has increased steadily. Though it is not currently known which seemingly healthy individuals will progress into dementia, this divergence likely occurs in midlife. Researchers hypothesize that non-pharmacological interventions should be targeted to individuals before symptom onset for the greatest efficacy. Three-dimensional multiple object tracking (3D-MOT) is a type of cognitive training that offers cognitive benefits to a wide range of individuals including healthy older adults, older adults with subjective memory decline, and adults with histories of mild traumatic brain injuries. 3D-MOT is most typically conducted with active 3D technology in standardized research labs; however, the COVID-19 global pandemic challenged the typical research process. Using a modified system, designed for smaller screens and anaglyph 3D, we sought to understand if 3D-MOT could be conducted from the comfort of one's home on their personal computer and lead to the same benefits observed as the in-lab version.

**Methods:** 20 adults (10 female, mean age = 68.3 years, range = 57-83 years) were recruited for participation in the at-home training (AHT) group. 20 participants who had previously completed in-lab 3D-MOT, matched for age and sex, were used as a control (CON) group. Cognitive status was assessed using the Mini-Mental State Examination (MMSE), and all participants were deemed cognitively healthy (MMSE > 26). AHT participants were loaned the necessary equipment (e.g. 3D-glasses, computer equipment), and engaged in 10 training sessions over five weeks (2x per week). Individual session scores and projected learning rates were assessed between groups.

**Results:** There were no demographic differences between groups (age, sex, MMSE score). No differences in session scores ( $p > 0.05$ ), or learning rates ( $p > 0.05$ ) between groups were observed, and both groups demonstrated large improvements in the task over time ( $p < 0.001$ ).

**Conclusions:** From these results, we can conclude that 3D-MOT is a promising, and accessible type of cognitive training that can be conducted with cognitively healthy adults from home. Our lab will continue this research by expanding to other groups who may benefit from cognitive training.

# Abstract Oral Presentations

Theme 3: Integrating Big Data, Neuroinformatics, and Precision Health Approaches

## ABSTRACT #12:

### Data-driven analyses of longitudinal hippocampal imaging trajectories: Discrimination and biomarker prediction of change classes and clinical outcomes

**Shannon M. Drouin (1), G. Peggy McFall (1, 2), Oliver Potvin (3), Pierre Bellec (4, 5), Mario Masellis (6, 7), Simon Duchesne (3, 8), and Roger A. Dixon (1, 2)**

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8- Radiology Department, Université Laval, Québec City, Québec, Canada

**Introduction:** Hippocampal atrophy is a well-known neuronal injury biomarker of exacerbated memory decline and clinical aging outcomes, such as Mild Cognitive Impairment and Alzheimer's disease (AD). However, among cognitively normal (CN) aging adults, substantial differences in hippocampal trajectory patterns and associated brain aging and AD biomarkers can be observed.

**Methods:** We used baseline biomarker and longitudinal MRI (volumetric) Alzheimer's disease Neuroimaging Initiative (ADNI) data (6 waves, M age = 75 years, 59.8-94.6 age band) from CN adults (n = 351). First, we applied latent class growth analyses to identify trajectory classes for the left (LHC) and right (RHC) trajectory distributions. Second, using random forest analyses, we tested 38 multi-modal AD-related biomarkers for their relative importance in discriminating lower classes (with potential elevated risk of pathological changes) versus higher classes (with potential reduced or delayed risk of morphometric shrinkage) trajectory classes. Third, we incorporated the new trajectory class variables in prediction models of last-wave diagnosis (AD vs CN).

**Results:** First, three LHC and RHC trajectory classes were identified. Second, the highest LHC and RHC trajectory classes were predicted by female sex, lower education and higher plasma A $\beta$ 1-42. The LHC highest class was also predicted by higher plasma tau and A $\beta$ 1-40, lower geriatric depression scores, and higher BMI. Third, AD diagnosis was predicted by lowest trajectory class membership, higher CSF t-tau, and lower CSF A $\beta$ 1-42.

**Conclusions:** We applied three phases of data-driven analyses to individualized LHC and RHC 35-year trajectory distributions. Our data-driven trajectory analyses detected three comparable latent classes underlying the heterogeneity of both LHC and RHC aging changes. Although the dynamic and structural patterns of LHC and RHC trajectories were similar, machine learning models revealed that LHC was deeply discriminated by AD biomarkers. The inclusion of novel trajectory class variables showed that asymptomatic atrophy powerfully predicted AD diagnosis. Integrating data-driven trajectory and biomarker approaches elucidated the dynamics of pre-AD brain changes.



# Abstract Oral Presentations

Theme 3: Integrating Big Data, Neuroinformatics, and Precision Health Approaches

## ABSTRACT #13:

### **Bridging Integrator 1 (BIN1, rs6733839) and sex are moderators of vascular health predictions of memory aging trajectories**

**Mackenzie Heal (1), G. Peggy McFall (2), David Vergote (3), and Roger A. Dixon (1, 2)**

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3- Campus Saint-Jean, University of Alberta, Edmonton, Alberta, Canada

**Introduction:** After the well-known Apolipoprotein E (APOE), Bridging Integrator 1 (BIN1) is among the most promising risk loci for sporadic Alzheimer's disease (AD), potentially operating through the tau pathology pathway (e.g., increased tangle burden). Early candidate gene studies on its association with cognitive impairment are accumulating moderate supportive evidence, but little is known about its effect on long-term cognitive trajectories, or interactions with other AD biomarkers. This study incorporates the BIN1 risk loci into an established research platform of the Victoria Longitudinal Study (VLS) genetic database. Specifically, we examine BIN1 risk and its moderating role with vascular health (pulse pressure) and sex in predictions of differential 40-year memory trajectories.

**Methods:** After applying exclusionary criteria, the subsample included n=623 participants (Wave 1 M age=70.1; 66.8% female; M education=15.3 years), with the trajectory distribution spanning a 40-year band (ages 53-97). All analyses were conducted in Mplus 8.5. We established a 4-indicator latent variable of episodic memory using confirmatory factor analyses and standard fit indices. Initial analyses compared the standard series of four unconditional growth models. The main analyses were conducted in two phases to investigate moderation of the expected pulse pressure effect on memory change by (a) genetic risk and (b) further stratified by sex.

**Results:** Initial analyses showed that both memory level (intercept) and decline (slope) were modelled as free to vary across individuals. For the first moderation analysis, lower pulse pressure was associated with higher level and shallower decline in memory, but selectively for persons with lower BIN1-related AD risk. Within the higher genetic risk strata (TT genotype), vascular health did not significantly predict memory level or decline. For the second moderation analysis, when further stratified by sex, the lower BIN1 risk moderation of (better) vascular health and (shallower) memory decline was selective for females.

**Conclusion:** These preliminary results parallel the previous platform study (with APOE) in that BIN1 and sex sequentially moderated the vascular health association with memory decline in asymptomatic aging. This multi-modal biomarker interaction approach, disaggregated by sex, can be an effective method for enhancing precision AD risk assessment.

# Abstract Oral Presentations

Theme 3: Integrating Big Data, Neuroinformatics, and Precision Health Approaches

## ABSTRACT #14:

### In Silico Model of Neurodegeneration using Deep Convolutional Neural Networks

**Jasmine A. Moore, Anup Tuladhar, Zahinoor Ismail, and Nils D. Forkert**

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**Introduction:** Despite current research already investigating the possibility of using deep learning networks as models of the human brain, the potential of using these networks to model neurodegenerative diseases remains largely understudied. In this work, we present a feasibility study to model neural disease in silico with deep convolutional neural networks (DCNNs).

**Methods:** Axonal injury was simulated using a VGG19 DCNN, which is one of the best approximations of mammalian neuronal activation data. The DCNN was trained to perform visual object recognition on the Imagenette database, comprised of 13,394 naturalistic images categorized into ten classes. Simulated axonal injury was inflicted on the trained baseline DCNN by randomly setting  $x\%$  of the weights connecting nodes in the model to zero, effectively severing connections between neurons in the model. The weights that were injured was randomly selected and the model performance analyzed 25 times. The model was progressively injured in 1% increments of damaged connections. Saliency maps, which are tools for visualizing a DCNN's regions of focus, were generated using the uninjured and injured networks for test set images to further investigate loss of visual cognition.

**Results:** As injury accumulated in the DCNN, cognitive function in the network progressively decreased. Visual analysis of saliency maps revealed that attention of the uninjured models was correctly focused on sections of the test images that were relevant for the correct classification. As damage increased, model focus shifted away from the main objects in the images. This shift in attention was reflected in the increase in the mean squared error and decrease in the structural similarity index measure between the saliency maps of the uninjured and injured models, as a function of injury.

**Conclusions:** The results of this study show that DCNNs can be used for modeling cognitive deficits that accompany neurodegenerative diseases such as dementia. Results from this study suggest that DCNN models become more cognitively impaired regarding object recognition and correct attention focus with greater injury. This relationship is analogous to cognitive decline seen in patients affected by neurodegenerative diseases, who experience a loss of object recognition capabilities.

# Abstract Oral Presentations

Theme 3: Integrating Big Data, Neuroinformatics, and Precision Health Approaches

## ABSTRACT #15:

**To create a better verifiability of machine learning networks, an explainable machine learning approach is applied to a network classifying Alzheimer subjects versus healthy subjects.**

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2- Seaman Family MR Research Centre, Foothills Medical Centre, Calgary, Alberta, Canada

3- Radiology and Clinical Neurosciences, Hotchkiss Brain Institute, University of Calgary, Calgary, Alberta, Canada

**Introduction:** Alzheimer's disease (AD) diagnosis is performed through clinical assessment of neurological status. Magnetic resonance (MR) imaging also plays a significant role in assessing brain health. With the increasing amount of accessible MR data, deep learning models have become an important tool for brain analysis. Nevertheless, the decision-making process of these models remains a "black box" to the user. To foster trust and procedural verification, explainable deep-learning methods are needed to interrogate function of the "black box". Here, we demonstrate the use of layer-wise relevance propagation (LRP) applied to a simple AD - no AD deep learning classification model.

**Methods:** A total of 935 T1-weighted volumes from the ADNI (AD Neuroimaging Initiative) dataset were skull stripped and split into two groups: 613 healthy subjects and 322 AD patients. These labelled data were evenly divided into 565 individuals for training, 181 for validation, and 189 for testing. A convolutional neural network was trained to classify healthy subjects from AD patients. LRP was then applied to our model to produce subject-specific heatmaps. Each heatmap highlighted the relevant voxels which were important for the decision-making process (voxels that both support and did not support the classification).

**Results:** Our deep learning network achieved a classification accuracy rate of 83.9 %. The LRP heatmaps highlighted a number of brain regions that were important to the model decision. Heatmaps were subject-specific but common areas were found to drive the decision-making process including: pixels around the ventricles and deep brain structures. In addition, the model assessed brain atrophy in making decisions.

**Conclusions:** T1-weighted images are suitable to train a convolution neural network for AD classification. LRP-derived heatmaps can increase transparency of deep learning models and so facilitate model verifiability. LRP allows for a patient-specific analysis of the general model. Further quantitative analysis of the heatmaps are needed to generalize the outcome in our AD classification task, so that, potentially, new regions associated with AD classification can be identified.

# Abstract Oral Presentations

Theme 3: Integrating Big Data, Neuroinformatics, and Precision Health Approaches

## ABSTRACT #16:

### The Metabolomic Profile of Alzheimer's Disease in Hippocampal Brain Tissue

**Giselle Tiede (1, 2, 3), Tanzi Hoover (1, 2), Mirela Ambeskovic (1, 2), Spencer Trombley (1, 2, 3), Jeffrey T. Joseph (4), Tony Montina (3, 5), and Gerlinde A.S. Metz (1, 2, 3)**

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4- Hotchkiss Brain Institute, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada

5- Department of Chemistry and Biochemistry, University of Lethbridge, Lethbridge, Alberta, Canada

**Introduction:** To date, Alzheimer's Disease (AD) can only be accurately diagnosed post-mortem by observing characteristic morphological traits in the brain, including amyloid plaques and neurofibrillary tangles. Besides, most patients do not present clinical symptoms typical of the deterioration of mental state associated with AD until further in the disease's progression, thus making early detection nearly impossible. Accurate early diagnosis methods would allow for more specialized care geared towards AD and more effective personalized and preventative treatments. This metabolomics-based study of AD aimed to identify cellular changes that can potentially be used in early AD diagnosis. Metabolomics is the quantification and identification of the metabolome present in cells, tissue, and biofluids. The metabolome is a representation of all small downstream molecules produced by various cellular activities. A better understanding of changes in the brain's metabolome will result in a more precise idea of what AD biomarkers may be detected elsewhere in the body.

**Methods:** Nuclear magnetic resonance (NMR) spectroscopy is an ideal tool for quantifying and comparing the metabolomic profiles of tissues associated with AD. In this study, we investigated the hippocampus's metabolomic profile—a brain region that is essential for memory. Brain tissues were obtained from the Calgary Brain Bank and categorized as either AD (n=11) or control (n=11). Using univariate, multivariate, and machine learning analysis, we identified 47 specific metabolites that could accurately classify AD versus non-diseased tissue.

**Results and Conclusions:** Forty-two metabolites were identified. These key biomarkers within this region include L-selenomethionine, L-cystathionine, and L-leucine. Biochemical pathways that are potentially affected by AD are: aminoacyl-tRNA biosynthesis, valine, leucine, and isoleucine biosynthesis, and alanine, aspartate and glutamate metabolism. These results provide new insight into the mechanistic changes that may underly AD pathology, confirm our current understanding, and provides targets for future studies of downstream and accessible biomarkers, such as biofluids.

# Abstract Oral Presentations

Theme 4: Challenges of Animal Models and Clarifying the Science  
Surrounding the Amyloid Hypothesis

## ABSTRACT #17:

### Spatial encoding of a linear environment by hippocampal CA1 neurons in APP knock-in mice expressing Alzheimer's disease-related mutations

**Samsoon Inayat, Brendan McAllister, Jianjun Sun, Bruce L. McNaughton, Robert J. Sutherland, and Majid H. Mohajerani**

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**Introduction:** Impaired spatial navigation is a hallmark symptom of Alzheimer's disease (AD), and brain regions critical for navigation, such as the hippocampus, are affected early in AD. Experiments on transgenic AD mouse models have demonstrated that spatial representations formed by hippocampal place cells degrade with disease progression. However, only limited work has examined place cell function in newer knock-in AD models, which avoid some limitations of transgenic models. The present study was conducted to assess hippocampal spatial encoding in APP knock-in mice.

**Methods:** We crossed the aggressive amyloidogenic APPNL-G-F knock-in strain with the Thy1-GCaMP6s strain that expresses a calcium sensor in neurons. The resulting mice (abbreviated APP) were compared to Thy1-GCaMP6s controls. The Morris water task was used to assess spatial navigation ability in freely moving mice (control:  $n = 11$ ; APP:  $n = 12$ ). Two-photon calcium imaging was used to assess spatial encoding of a linear environment by cells in the hippocampal CA1 region (control:  $n = 8$ ; APP:  $n = 6$ ). During imaging, head-restrained mice performed an air-puff induced running task on a non-motorized treadmill belt. Approximately 12-month-old mice were used for imaging.

**Results:** APP mice showed navigation deficits in the Morris water task at 12 and 18 months of age ( $p = .002$  and  $p < .001$ , respectively). However, spatial encoding of the linear treadmill environment remained intact in APP mice. Spatially-tuned cells (i.e., cells that fired at a particular location on the belt) did not differ in percentage between APP and control mice, nor did the properties of these cells, including firing field widths and strength of modulation by spatial position. These results were consistent regardless of whether the mice ran on a blank belt, relying primarily on self-motion information to track distance, or on a belt with sensory cues.

**Conclusions:** Our results suggest that amyloid-beta pathology in APP knock-in mice does not affect CA1 hippocampal spatial encoding of a linear environment. This is consistent with the idea that impaired place cell function in transgenic AD models is an artifact of physiologically unrealistic APP overexpression.

# Abstract Oral Presentations

Theme 4: Challenges of Animal Models and Clarifying the Science  
Surrounding the Amyloid Hypothesis

## ABSTRACT #18:

### Advanced Photophysical Properties of Amyloid Probes BSB and MCAAD-3 for Sensitive Detection of Protein Misfolding across Different Cases of Alzheimer's Disease

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**Introduction:** Neurodegenerative diseases such as Alzheimer's disease (AD) are characterized by the presence of misfolded protein aggregates enriched in beta-sheet structures. Small organic fluorophores such as Congo Red can be used for visualization of these deposits in histological samples. Here we explore the potential of two amyloid dyes, (trans,trans)-1-Bromo-2,5-bis-(3-hydroxycarbonyl-4-hydroxy)styrylbenzene (BSB) and MCAAD-3, used in combination, along with advanced spectral imaging and analysis tools for the sensitive detection of misfolded protein pathology in 5xFAD mouse and human AD samples. This new approach outperforms single-probe or immunohistochemical labeling, revealing unexpected and highly informative nanostructural heterogeneities in such deposits, that are undetectable by conventional means.

**Methods and Results:** Using 5xFAD mouse and human AD brain sections, we examined the effect of prolonged incubation of BSB and MCAAD-3 at sub-micromolar concentrations on emission spectra of these dyes bound to protein deposits. Imaging the samples on a spectral confocal microscope, coupled with advanced spectral analysis tools, allowed us to detect and quantify the subtle spectral shifts across different types of protein deposits. Emission signatures of either probe used in the study varied depending on the organization of beta sheets in the amyloid fibrils. In addition to this conformational sensitivity of BSB and MCAAD-3, simultaneous staining of the samples with both dyes also revealed different affinities of these dyes to protein aggregates. Both phenomena contributed to the richness of spectral information that was analyzed in a quantitative manner using custom-written analysis algorithms. As a result, the amyloid plaques composed predominantly of misfolded amyloid beta peptide, neurofibrillary tangles made of hyperphosphorylated tau protein, and vascular amyloid, exhibited unique spectral signatures. Our staining, imaging, and analysis paradigm allowed for sensitivity and differentiation of protein misfolding pathology that complemented conventional methods.

**Conclusions:** Our findings show how complex interactions of different small organic amyloid dyes in dual-probe staining paradigms can be harnessed to interrogate subtle changes in protein misfolding pathology that have not been possible to detect using conventional methods. The results of our study have great potential to improve our ability to detect, identify structural differences in deposits of, and to better understand the pathophysiology of various neurodegenerative diseases.

# Abstract Oral Presentations

Theme 5: Other (this includes research that is relevant to healthy brain aging and dementia but does not fit in the other theme categories)

## ABSTRACT #19:

### Impaired cerebrovascular reactivity is a core feature of cerebral amyloid angiopathy

**Andrew E. Beaudin (1, 2), Cheryl R. McCreary (1, 2, 3, 4), Erin L. Mazerolle (2, 3, 5), Myrlene Gee (6), Breni Sharma (1, 2), Arsenije Subotic (1, 2), Angela Zwiers (1), Emily Cox (1), Krista Nelles (6), Anna Charlton (1), Richard Frayne (1, 2, 3, 4), Zahinoor Ismail (1, 2, 7, 8), Christian Beaulieu (9), Glen C. Jickling (6), Richard Camicioli (6, 10), G. Bruce Pike (1, 2, 3, 4), and Eric E. Smith (1, 2, 3, 4)**

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- 9- Department of Biomedical Engineering, University of Alberta, Edmonton, Alberta, Canada
- 10- Neuroscience and Mental Health Institute, University of Alberta, Edmonton, Alberta, Canada

**Introduction:** Cerebral amyloid angiopathy (CAA) causes intracerebral hemorrhage, cerebral microbleeds, white matter hyperintensities and cortical superficial siderosis, and is associated with increased risk of cognitive impairment and dementia. A reduced cerebrovascular reactivity (CVR) is proposed to contribute to the hemorrhagic, ischemic, and cognitive consequences of CAA, but it has not been measured directly. Employing a global vasodilatory stimulus (hypercapnia) this study assessed the relationships between CVR and MRI markers of CAA and cognitive function.

**Methods:** Individuals with probable CAA (n=31; 74.7±7.6y; 13 female), mild cognitive impairment (n=24; 72.8±8.3y; 9 female), Alzheimer disease (n=16; 69.8±6.2y; 5 female) and healthy controls (n=48; 69.9±6.3y; 35 female) underwent neuropsychological testing and an MRI at 3T that included a 5% carbon dioxide (CO<sub>2</sub>) challenge. Cerebrovascular reactivity to CO<sub>2</sub> (quantified as the percent change in blood oxygen level dependent (BOLD) signal per millimeter of mercury increase in end-tidal partial pressure of CO<sub>2</sub>) was compared across groups controlling for age and sex. In addition, its associations with MRI markers of CAA in CAA patients and with cognition across all participants were determined using multivariable linear regression adjusting for group, age, sex, and education.

*Continued on the next page*

# Abstract Oral Presentations

Theme 5: Other (this includes research that is relevant to healthy brain aging and dementia but does not fit in the other theme categories)

## ABSTRACT #19:

### Impaired cerebrovascular reactivity is a core feature of cerebral amyloid angiopathy

Results: Grey and whiter matter CVR averaged across the entire brain was lower in participants with CAA and Alzheimer disease compared to healthy controls, with a predominantly posterior distribution of lower reactivity in both groups. Cerebrovascular reactivity within the primary visual cortex was lower in only CAA participants compared to healthy controls. Higher white matter hyperintensity volume was associated with lower white matter CVR (standardized coefficient [ $\beta$ ], 95% confidence interval): -0.45, -0.88 to -0.01. Higher gray matter reactivity was associated with better global cognitive function ( $\beta$ : 0.19, 0.03-0.35), memory ( $\beta$ : 0.21, 0.07- 0.35), executive function ( $\beta$ : 0.21, 0.02-0.40), and processing speed ( $\beta$ : 0.29, 0.12- 0.46); and higher white matter reactivity was associated with higher memory ( $\beta$ =0.21, 0.07-0.35) and processing speed ( $\beta$ =0.25, 0.08-0.41).

Conclusions: Reduced cerebrovascular reactivity is a core feature of CAA, and its assessment may provide an additional biomarker for disease severity and cognitive impairment.



# Abstract Oral Presentations

Theme 5: Other (this includes research that is relevant to healthy brain aging and dementia but does not fit in the other theme categories)

## ABSTRACT #20:

### Contribution of hypercapnia to cognitive impairment in severe sleep-disordered breathing

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On behalf of the Canadian Sleep and Circadian Network (CSCN)

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**Introduction:** Although cognitive impairment in obstructive sleep apnoea (OSA) is primarily attributed to intermittent hypoxemia and sleep fragmentation, hypercapnia may also play a role in patients whose OSA is complicated by hypoventilation. This study investigated the impact of hypercapnia on cognitive function in severe sleep-disordered breathing (OSA accompanied by hypoventilation).

**Methods:** Patients with severe OSA (apnoea-hypopnea index (AHI)>30; n=246) underwent evaluation for accompanying hypoventilation with polysomnography that included continuous transcutaneous carbon dioxide (TcCO<sub>2</sub>) monitoring and awake arterial blood gas analysis. Patients were categorized as having no hypoventilation (n=84), isolated sleep hypoventilation (n=40) or awake hypoventilation (n=122). Global cognitive function was evaluated using the Montreal Cognitive Assessment (MoCA); memory with the Rey Auditory Verbal Learning Test (RAVLT); and processing speed with the WAIS-IV Digit Symbol Coding sub-test (DSC).

**Results:** AHI was similar across groups (p=0.15), but the sleep and awake hypoventilation groups had greater nocturnal hypoxemia compared to the no hypoventilation group (p<0.01). Within all groups, mean MoCA scores were <26 which is the validated threshold to indicate mild cognitive impairment; RAVLT scores were lower than age-matched norms only in the awake hypoventilation group (p≤0.01); and DSC scores were lower than age-matched norms within all groups (p<0.01). In multivariable regression analyses, higher arterial PCO<sub>2</sub> and TcCO<sub>2</sub> during wakefulness were associated with lower MoCA and DSC scores (p≤0.03), independent of confounders including overlap syndrome (OSA+ chronic obstructive pulmonary disease).

**Conclusions:** Awake hypoventilation is associated with greater deficits in cognitive function in patients with severe sleep-disordered breathing.

# Abstract Oral Presentations

Theme 5: Other (this includes research that is relevant to healthy brain aging and dementia but does not fit in the other theme categories)

## ABSTRACT #21:

### Does the Montreal Parkinson Risk of Dementia Rating Scale Predict Dementia in a Geriatric Parkinson's Disease Cohort?

**Linzy Bohn (1), G. Peggy McFall (1, 2), Myrlene Gee (3), Roger A. Dixon (1, 2)\*, and Richard Camicioli (2, 3)\***

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\*Co-senior authors

**Introduction:** Parkinson's disease (PD) is associated with an increased risk for dementia and associated downstream negative outcomes. The 8-item Montreal Parkinson Risk of Dementia Rating Scale (MoPaRDS) was developed as a rapid, in-office screening tool for Parkinson's disease dementia (PDD). The present study examines (1) predictive validity of the MoPaRDS in an older PD cohort, (2) whether education improves predictive validity of the MoPaRDS, (3) predictive validity of alternate configurations of the MoPaRDS, (4) prediction patterns as stratified by sex, and (5) longitudinal level and change trajectories of overall MoPaRDS scores.

**Methods:** We assembled three waves of data collected at 18-month intervals for 48 non-demented PD patients (27 males; Mage = 70.61years). After a 36-month follow-up, 14 participants were diagnosed with PDD. This enabled baseline prediction analyses comparing two subgroups, PD with incipient dementia (PDID) and PD with no dementia (PDND). Longitudinal data for eight risk variables that paralleled items used in the original MoPaRDS report were compiled: age (>70 years), sex (male), falls and/or freezing, bilateral disease onset, rapid eye movement sleep behavior disorder, orthostatic hypotension, mild cognitive impairment (MCI), and visual hallucinations. Baseline data included education and performance on eight neuropsychological tests.

**Results:** The 8-item MoPaRDS discriminated between PDID and PDND (AUC = 0.81). Education did not improve predictive validity (AUC = 0.77). Age, orthostatic hypotension, and MCI independently discriminated the groups. Accordingly, a reduced 3-item configuration of the MoPaRDS discriminated the groups at a level exceeding the 8-item configuration (AUC = 0.88). Performance of the 8-item configuration varied across sex (AUCfemales = 0.91; AUCmales = 0.74), whereas performance of the 3-item configuration was similar across sex (AUCfemales = 0.88; AUCmales = 0.91). Participants with a positive screen result on the 3-item (total score > = 2) or 8-item (total score > = 4) MoPaRDS showed generally worse neuropsychological task performance. Risk scores on both configurations of the MoPaRDS increased over the three waves.

**Conclusions:** The full and the reduced versions of the MoPaRDS may have selective applications for early dementia risk detection in PD patients differing in age and sex.

# Abstract Oral Presentations

Theme 5: Other (this includes research that is relevant to healthy brain aging and dementia but does not fit in the other theme categories)

## ABSTRACT #22:

### Data-Driven Approaches to Executive Function Performance and Structure in Aging: Integrating Person-Centered Analyses and Machine Learning Risk Prediction

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**Introduction:** Executive function (EF) performance (level) and structure (single or multidimensional factor) in non-demented aging are frequently examined separately with variable-centered approaches. Person-centered approaches combined with data-driven analytics can contribute unique information about classes of persons based on simultaneous considerations of both EF performance and structure. Machine learning technology can be applied to determine the relative importance of a set of aging-related risk predictors for discriminating the observed classes. We assembled one-wave data from the Victoria Longitudinal Study to examine two data-driven research goals: (1) detecting underlying classes based on indicators of both EF performance and structure and (2) testing and comparing risk factor predictors that best discriminate these classes.

**Methods:** We used a classification sample ( $n = 778$ ,  $M$  age = 71.42,  $SD = 9.07$ , range = 53.24 – 95.25, 66.5% female) for the first goal and a prediction sub-sample ( $n = 570$ ,  $M$  age = 70.10,  $SD = 8.50$ , range = 53.24 – 95.25, 66.5% female) for the second goal. Eight neuropsychological measures represented three EF dimensions (inhibition, updating, shifting). Fifteen candidate predictors represented five domains of risk for exacerbated brain and cognitive impairment (genetic, functional, lifestyle, mobility, demographic). We used factor mixture modeling (Mplus 8.2) for the first goal and random forest analysis (R 3.3.2) for the second goal.

**Results:** First, within a two-factor solution, we observed two distinct classes: (1) lower EF performance and multidimensional structure (Class 1) and (2) higher EF performance and multidimensional structure (Class 2). Second, eight predictors discriminated the two classes. Class 2 was predicted by younger age, more everyday novel cognitive activity, more education, lower body mass index, lower pulse pressure, female sex, faster balance, and more everyday physical activity.

**Conclusions:** Previous speculations about EF aging have included a “healthy brain aging” sub-type characterized as displaying both preserved EF performance and sustained multidimensional structure. Our sequence of data-driven modeling approaches detected two latent classes of older adults, one of which was concordant with this previously unobserved sub-type. The subsequent machine learning prediction models objectively discriminated the two classes, showing that the more successful EF aging class was associated with multiple risk reducing factors.

# Abstract Oral Presentations

Theme 5: Other (this includes research that is relevant to healthy brain aging and dementia but does not fit in the other theme categories)

## ABSTRACT #23:

### The Role of Cognitive Reserve and Lifestyle Factors in Vascular Cognitive Impairment

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**Introduction:** Compared to individuals with lower cognitive reserve, when individuals with higher reserve (i.e. high education) develop a cognitive disorder their brain pathology is more severe, suggesting some resistance to the deleterious effects of the pathology. Most studies on cognitive reserve focus on Alzheimer's disease, while few studies focus on whether cognitive reserve can mitigate the adverse effects of vascular brain pathology, such as white matter hyperintensities (WMHs). This is important because vascular pathology accounting for 20% of dementia cases.

**Methods:** We analyzed 197 participants aged 50-90 years from 31 sites across Canada, within the Comprehensive Assessment of Neurodegeneration and Dementia (COMPASS-ND) study (part of the Consortium on Neurodegeneration in Aging [CCNA]). Cognition was measured using the Montreal Cognitive Assessment tool, memory composite z-score, processing speed composite z-score, and executive function composite z-score. Participants either had mild cognitive impairment, vascular mild cognitive impairment, subjective cognitive impairment or were cognitively intact elderly. Vascular brain injury was assessed using MRI and was defined as brain infarcts or white matter hyperintensities (WMHs). Cognitive reserve variables included: education, occupational attainment, marital status, social activities, religious activities, physical activity, annual household income, and multilingualism.

**Results:** Mean age was 73 years and 50.8% of participants were female. We found that having a university degree, professional/managerial/qualified non-manual occupations, annual household income  $\geq$  60K, being married/common law, and being multilingual (more than one language) were each independently associated with higher cognition. Additionally, WMH was associated with lower cognition (processing-speed) (beta-coefficient: -0.17 [95% CI: -0.31, -0.03]), but the association was not modified by the cognitive reserve composite score (interaction p-value=0.50).

**Conclusions:** Markers of cognitive reserve (income, education, occupation, marital status, and multilingualism) are associated with higher cognition. Vascular brain injury, specifically WMH, is associated with lower cognition. However, cognitive reserve does not mitigate the effects of WMH on cognition. Therefore, public health efforts should promote improvement of lifestyle factors, in addition to preventing vascular brain injury, as lifestyle factors alone may not mitigate the effects of vascular brain injury.

# Abstract Oral Presentations

Theme 5: Other (this includes research that is relevant to healthy brain aging and dementia but does not fit in the other theme categories)

## ABSTRACT #24:

### The Relationship Between Subjective Hearing Impairment and Mild Behavioral Impairment – A Study of Older Adults Without Dementia in the COMPASS-ND Study

**Dylan X. Guan (1), Penny Gosselin, PhD (2), Hung-Yu Chen, PhD (3), M. Kathleen Pichora-Fuller, PhD (1, 4), Natalie Phillips, PhD (5), Eric E. Smith, MD, MPH (6), and Zahinoor Ismail, MD (6)**

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**Introduction:** Hearing loss and mild behavioral impairment (MBI) are both early warning signs of cognitive decline and dementia in older adults and have been recommended for use as non-cognitive markers of dementia. To date, few studies have directly investigated the relationship between these two markers.

**Methods:** Baseline data from 219 non-demented participants (10 cognitively normal; CN, 48 subjective cognitive decline; SCD, 161 mild cognitive impairment; MCI) in the COMPASS-ND study (February 2020 release) were analyzed. Hearing impairment was measured in three ways: with a 10-item self-report measure using the Hearing Handicap Inventory for the Elderly – Screening Version (HHIE-S), with a speech and noise test using the Canadian Digit Triplet Test (CDTT), and with screening audiometry using 2 discrete input levels at 2000 Hz to generate 6 hearing loss categories. Global and domain-specific MBI burden was approximated using the Neuropsychiatric Inventory Questionnaire (NPI-Q) with a published algorithm. Multivariable linear regressions were conducted to examine the association between the three hearing impairment measures and global MBI burden, adjusting for sex, age, education, hearing aid use, and Montreal Cognitive Assessment (MoCA) score or diagnosis. Multivariable logistic regressions were used to investigate whether the hearing variables could predict MBI domains.

**Results:** Half of all participants showed MBI symptoms (Figure 1). Greater self-reported hearing impairment measured by the HHIE-S was significantly associated with greater global MBI burden and the presence of apathy and affective dysregulation when controlling for global cognition or diagnosis (Table 1). These associations remained significant in analyses restricted to MCI alone. Performance on CDTT and screening audiometry, were not associated with global or domain-specific MBI burden.

**Conclusions:** The HHIE-S, which was designed to capture the emotional and social aspects of hearing loss, was positively related to global MBI burden and more specifically to apathy and affect. Unlike audiometry and speech and noise measures, self-reported measures of hearing impairment can be influenced by age, sex, other comorbidities, and social factors. Our findings underscore that value of self-report measures of hearing impairment as distinct from audiometry and speech and noise measures in their association with behavioral impairment and as non-cognitive markers of dementia.

# Abstract Oral Presentations

Theme 5: Other (this includes research that is relevant to healthy brain aging and dementia but does not fit in the other theme categories)

## ABSTRACT #25:

### Dual-Task Gait and Mild Behavioral Impairment: Findings on the Interface Between Non-Cognitive Dementia Markers in the COMPASS-ND Study

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**Introduction:** Mild behavioral impairment (MBI) and poor dual-task gait performance are non-cognitive markers for dementia. Both MBI and dual-task gait performance have been associated with an increased risk of cognitive decline, but to our knowledge the relationship between them has yet to be investigated.

**Methods:** Cross-sectional data from 193 non-demented participants (10 cognitively normal, 48 subjective cognitive decline, 135 mild cognitive impairment; MCI) in the COMPASS-ND study (February 2020 release) were analyzed. MBI was approximated using the Neuropsychiatric Inventory Questionnaire (NPI-Q) using a published algorithm. Dual-task gait cost (DTGC), operationalized as the percentage difference between dual-task and preferred walking speeds, was assessed under three cognitive tasks: animal naming, counting backwards by one, and serial seven subtractions. Multivariable linear regression was used to determine the association between global MBI burden and DTGC, adjusting for age, sex, years of education, and Montreal Cognitive Assessment (MoCA) score, or diagnosis. Models were additionally fitted for the subgroup of participants with MCI alone. Mediation analyses were conducted using bootstrapping to determine if the association between MBI and DTGC was mediated by global cognition (MoCA), executive function (Trail Making B), verbal (Rey Auditory Verbal Learning Test) or working (Digit Span) memory.

**Results:** Participants on average were 72.4 years old (52.8% female) and had completed 15.8 years of education. MBI symptoms were observed in 46.6% of participants. Greater overall MBI burden was associated with reduced gait speed and higher DTGC for all three gait conditions in MCI, and in all participants without dementia when controlling for diagnosis or MoCA (Table 1), except for DTGC under animal naming conditions when controlling for MoCA. The associations between MBI and DTGC were mediated by executive function but not global cognition, verbal or working memory (Table 2).

**Conclusions:** In this group of older adults at risk but without dementia (SCD and MCI spectrum), MBI is associated with DTGC, which in itself is a dementia risk marker. Our findings support the role of these non-cognitive dementia markers in the detection of at-risk individuals. Identification of older adults at risk of incident dementia may be enhanced by considering MBI and DTGC in conjunction.

# Abstract Oral Presentations

Theme 5: Other (this includes research that is relevant to healthy brain aging and dementia but does not fit in the other theme categories)

## ABSTRACT #26:

### Gender Mediates the Relationship Between Sex and Memory in Cognitively Normal Older Adults

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**Introduction:** Research with cognitively normal older adults often reveals that women have higher episodic memory performance than men. Do these results indicate differences in sex, gender, or an interaction? Typically, in biomedical research, differences are attributed to sex (biological attributes), whereas gender (psychosocial attributes) is under-studied. The Victoria Longitudinal Study (VLS) focuses on the multifaceted and dynamic nature of brain health in aging and dementia. It includes a binary sex variable but no explicit gender measures. We attempt to integrate sex and gender into a single study by extracting gender-related items from VLS data archives and testing if gender mediates the sex-memory association.

**Methods:** We (1) identified a 56-item pool of gender-based items in VLS inventories on metacognition, memory compensation, demographics, subjective cognitive impairment, lifestyle activities, health behaviours; (2) used a cross-sectional sample ( $n=825$ ;  $M$  age=72; 53–95 years) and principal component analysis (PCA) to identify gender components; (3) tested the sex difference on episodic memory performance; (4) used SPSS PROCESS to test gender components as mediators of the sex-memory association. Memory was measured by standard episodic memory tests: Word recall and Rey Auditory Verbal Learning Test.

**Results:** PCA analysis revealed 6 gender components representing 45 items (accounted for 36% of total variance). We confirmed that females had higher memory performance than males ( $t(663)=6.8$ ,  $p < 0.001$ ,  $d=0.48$ ). Sex-memory association was mediated separately by five gender-related lifestyle components (% mediated): (1) Traditional male activities (62.4%), (2) Traditional female activities (34.2%), (3) Creative community opportunities (8.5%), (4) Leisure time (6.5%), (5) Health seeking behaviour (2.9%).

**Conclusions:** Archival databases in brain and cognitive aging may not have explicit gender measures. We show that gender-related items can be extracted from such databases and perform informative research functions. Integrating gender and sex in brain health and dementia research advances both scientific and equity goals.

# Abstract Oral Presentations

Theme 5: Other (this includes research that is relevant to healthy brain aging and dementia but does not fit in the other theme categories)

## ABSTRACT #27:

### Effects of lamin A progeric mutation in tau reporter cell lines

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**Introduction and Methods:** Tauopathies are a family of neurodegenerative disorders pathologically that feature insoluble intracellular tau inclusions in the central nervous system (CNS) and are characterized clinically by dementia and/or parkinsonism. As a microtubule-associated protein, tau is predominantly expressed in the axons of neurons. In disease states, hyperphosphorylated tau detaches from the microtubule and migrates to the soma, forming aggregates that are neurotoxic. Certain tauopathies may associate with impaired lamin-enriched nuclear lamina and thus are also considered as laminopathies, at least in the experimental context of *Drosophila melanogaster*. Hutchinson-Gilford Progeria Syndrome (HGPS) is an autosomal dominant disorder of premature aging. A single substitution mutation of the LMNA gene results in the production of a truncated form of lamin A (progerin). Although a brain-specific microRNA downregulates the expression level of lamin A in the CNS, recent research demonstrated a positive correlation between progression of Alzheimer's disease (AD) and the hippocampal level of LMNA. It remains unclear if progerin has synergistic, deleterious effects regarding tau misfolding. To investigate this possibility, we are using the HGPS mutation of lamin A to accelerate cellular aging in a HEK293 cell line expressing a TauRD-YFP reporter protein. We hypothesize that LMNA-mediated pathological aging may accelerate the formation of intracellular tau aggregates.

**Results and Conclusions:** Our fluorescent seeding assay with pathogenic tau shows a significant increase in the frequency of tau misfolding events in cell lines stably expressing progerin. This may be explained by a progerin-induced increase in tau expression level. Interestingly, when progerin expresses in a HEK293 tau reporter cell line that is chronically infected with preparations of pathogenic tau, progerin results in a decrease in tau level. As expected, cells that are positive in both tau inclusion and progerin expression display dramatic nuclear dysmorphology, suggesting a synergistic interaction between progerin and aggregated tau. Furthermore, our proteomic analysis reveals multiple significantly up/downregulated proteins associated with progerin expression, providing insights in the involvement of LMNA in tau cell biology. Taken together, this study demonstrates that progerin has potential roles in tau misfolding events and may provide an explanation for elevated hippocampal level of LMNA in late AD stages.



# Abstract Oral Presentations

Theme 5: Other (this includes research that is relevant to healthy brain aging and dementia but does not fit in the other theme categories)

## ABSTRACT #28:

### Assessing The Utility Of The Mild Behavioral Impairment Checklist: The Association of Neuropsychiatric Symptoms With Cognitive Impairment

**Sophie Hu, MSc (1, 2), Scott Patten, MD, PhD (1,2,3,4,5), Anna Charlton, MSc (2), Karyn Fischer, BSc (2) Gordon Fick, PhD (1, 5), Eric E. Smith, MD, MPH (2, 4), and Zahinoor Ismail, MD (1,2,3,4,5)**

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**Introduction:** Mild Behavioral Impairment is characterized by later life emergent and persistent neuropsychiatric symptoms (NPS). MBI domains include impaired drive/motivation, affective dysregulation, impulse dyscontrol, social inappropriateness, and psychosis. We aimed to compare the relationship between NPS and cognition in patients with subjective cognitive decline (SCD), mild cognitive impairment (MCI) and dementia, using the Mild Behavioral Impairment-Checklist (MBI-C) and Neuropsychiatric Inventory Questionnaire (NPI-Q). MBI domains were derived from the NPI-Q using a published algorithm.

**Methods:** Data was examined from 1238 patients in the PROMPT Cognitive Neurology Clinic registry at the University of Calgary. NPS was characterized at baseline using the MBI-C (n=474) and NPI-Q (n=1040). Forward stepwise linear regression models were conducted to compare MBI-C and NPI-Q total and domain scores with cognition as assessed using the Montreal Cognitive Assessment (MoCA). Age, diagnosis, sex and education were included as covariates.

**Results:** Overall, 90% of patients had an MBI-C total score >0 and 55.91% of patients scored above cutoff (>7). MBI prevalence (based on cutoff) was 37% in patients with SCD, 54% in MCI, and 62% of dementia patients scored above the cutoff. By domain, over half had impaired drive/motivation (59.57%), affective dysregulation (68.66%) or impulse dyscontrol (64.11%), while relatively fewer had social inappropriateness (33.97%) or psychotic symptoms (22.25%). For the NPI-Q, 67.98% of patients had a total score >0 including 60.36% of SCD, 60.00% of MCI and 74.95% of dementia. By domain, over half had affective dysregulation (61%) or impulse dyscontrol (58.50%) while less than half had impaired drive/motivation (44.31%), social inappropriateness (23.19%) or psychosis (10.18%). With increasing diagnostic severity, age, MBI-C and NPI-Q scores increased, while MoCA scores decreased. Greater MBI-C and NPI-Q total and domain scores were significantly associated with lower MoCA score. Of all domains, psychosis had the strongest association with impaired cognition using both measures. Age, sex and diagnosis were modifiers for the MBI-C.

**Conclusions:** NPS are associated with poorer cognition regardless of diagnostic status. MBI domain scores are more strongly associated with impaired cognition than total scores. These findings suggest that the MBI-C has utility in capturing NPS in this clinic population, as a complement to the NPI-Q.

# Abstract Oral Presentations

Theme 5: Other (this includes research that is relevant to healthy brain aging and dementia but does not fit in the other theme categories)

## ABSTRACT #29:

### Mnemonic Training for older adults: Alternatives to the Method of Loci

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**Introduction:** Research on memory training in aging populations, a crucial precursor to efforts at alleviating memory impairments in Alzheimer's disease and amnesic mild cognitive impairment, has hit a roadblock. Moreover, seniors (and memory-impaired patients) fail to transfer strategies to their daily life. We suggest that this is because the Method of Loci, a visuospatial mnemonic strategy that has been the dominant method in previous mnemonic training approaches in older adults, is ill-suited for aging populations. Reasons for this may include reduced self-efficacy and age-related decline in visuospatial cognition.

**Methods:** In a set of three experiments with younger adults, we investigated alternatives to the Method of Loci that are based on autobiographical memory (Autobiographical Method) and a sequence of body parts (Body Method).

**Results and Conclusions:** In younger participants, the Body Method was equally effective as the Method of Loci and the Autobiographical Method also showed a significant improvement compared to uninstructed baseline memory. These findings suggest that there are alternatives to the Method of Loci which may be better suited for older adults.

# Abstract Oral Presentations

Theme 5: Other (this includes research that is relevant to healthy brain aging and dementia but does not fit in the other theme categories)

## ABSTRACT #30:

### Contributions of Prefrontal White Matter Integrity to Cognitive Performance in Healthy Aging

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**Introduction and Methods:** Previous diffusion tensor imaging (DTI) studies have confirmed the sensitivity of prefrontal cortex (PFC) white matter (WM) to aging. The PFC is composed of several subregions including the medial prefrontal (MPFC), dorsolateral prefrontal (DLPFC), and the medial and lateral orbitofrontal cortices (MOFC/LOFC). These subregions facilitate unique cognitive processes and changes in their WM may explain the age-related decline of certain cognitive functions. Few aging studies have investigated the role of PFC WM in cognitive functions involving the PFC, such as executive functions, which are particularly vulnerable to aging. The objective of this DTI study was to examine the relationship between PFC WM integrity and PFC function in aging and determine whether age-related changes in fractional anisotropy (FA) mediate the cognitive decline that occurs with age. 140 cognitively healthy participants aged 18-85 (62 men, 78 women) were recruited. Imaging was performed on a Siemens Sonata 1.5T MRI scanner, PFC WM was manually segmented into subregions and average tract FA was extracted. Executive functions were tested using the Delis-Kaplan Executive Functions System, and factor analysis was used to reduce exam data into 4 executive function variables: Conceptual Flexibility, Inhibition, Monitoring Fluency, and Monitoring Switch. Structural equation modeling (SEM) was conducted to assess relationships between age, FA, and cognition; followed by mediation analysis of tract specific FA.

**Results and Conclusions:** FA values in all PFC subregions declined linearly with increased age. Age was negatively associated with scores on all executive function scores, sex differences were found in Monitoring Switch scores. SEM analysis revealed that while global PFC FA did not significantly mediate performance of any cognitive domain, tract specific mediation analysis found the left LOFC FA produced a significant indirect effect on Conceptual Flexibility. While increased age was related to declines in WM integrity and performance in certain cognitive domains, our results suggest that these effects were mostly independent, with global PFC FA not serving as a mediator between age and cognition. However, the left LOFC may influence specific cognitive functions as measured by Conceptual Flexibility. These results demonstrate that certain PFC subregions may differentially contribute to specific cognitive functions.

# Abstract Oral Presentations

Theme 5: Other (this includes research that is relevant to healthy brain aging and dementia but does not fit in the other theme categories)

## ABSTRACT #31:

### Longitudinal Study of Cognition and Brain Atrophy Rates in Transient Ischemic Attack Patients

**Meaghan Reid (1, 2, 3, 4), Noah Reaume (2, 3, 4, 5), Pauline Wu (2, 3, 4, 5), Alex Pan (2, 3, 4), Arooj Aftab (2, 3), Rani Gupta (2, 3, 4, 6), Richard Frayne (3, 4, 6), Shelagh Coutts (2, 3, 4), Tolulope Sajobi (2, 7), Stewart Longman (5), Christopher D. d'Esterre (2, 3, 4), Meng Wang (7), and Philip Barber (2, 3, 4, 6)**

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**Introduction:** Transient ischemic attack (TIA) is associated with increased cerebral atrophy and a 4-fold increased risk of late-life cognitive decline. We aim to corroborate the percent brain volume (PBVC) and ventricular volume change (PVVC) of TIA patients and controls over 1-year, identify vascular and demographic risk factors associated with PBVC, and explore the relationship between PBVC and cognitive outcomes over the follow-up period.

**Methods:** A sample of age and sex-matched TIA (n=82) and control (n=52) participants without clinical cognitive impairment underwent structural T1-weighted MRI, cognitive assessment and demographic screening at baseline and 1-year follow-up. TIA patients had their initial assessments within 14-days of symptoms. FSL SIENA was used to measure PBVC and PVVC. Wilcoxon Rank-Sum tests were used to compare TIA and control groups and backwards stepwise linear regression was used to determine the association between risk factors (demographic and clinical) and annualized rates of PBVC. Multivariate multiple linear regression was used to examine the association between annualized PBVC and annualized change in cognitive performance.

**Results:** TIA patients had significantly greater annualized PBVC, compared to controls (Mdn = -0.80%/year, -0.37%/year, respectively;  $p < 0.001$ ). Differences in annualized PVVC were not observed between groups. At baseline, TIA patients performed significantly worse on all tests, excluding TMT-A ( $p = 0.096$ ), and at follow-up, performed worse on ACE-R (Total, Verbal Fluency), BVMT (Total, Delayed), RAVLT, TMT (A, B) ( $p < 0.05$ ). Over the follow-up period, TIA participants significantly improved on BVMT (Total, Delayed) and WAIS-IV DS Coding ( $p < 0.05$ ). TIA, increased age and higher systolic blood pressure were significantly associated with an increased rate of percent brain volume loss (adjusted  $r^2 = 0.197$ ). Annualized PBVC was not associated with a change in cognitive performance across time points ( $p > 0.05$ ).

**Conclusions:** TIA patients experience more than double the annualized percent brain volume loss, compared to controls, over a 1-year period. Increased annualized percent brain volume loss was associated with TIA status, systolic blood pressure and age, but not with changes in cognitive performance. Future studies are needed to determine whether increased cerebral volume loss predicts an increased risk of cognitive decline, and what clinical, biological, and MRI parameters predict increased longitudinal atrophy rates.

# Abstract Oral Presentations

Theme 5: Other (this includes research that is relevant to healthy brain aging and dementia but does not fit in the other theme categories)

## ABSTRACT #32:

### Self-reported and informant-reported depressive symptoms are independent and divergent predictors of new onset dementia in older adults

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**Introduction:** Depressive symptoms in older adults are important predictors of incident dementia. Symptoms can be assessed in several ways, including self-reported or informant-reported measures. It is unclear whether one is superior in predicting dementia onset or how to interpret discordant reports. Here, in a large sample of non-dementia older adults for whom depressive symptoms were assessed via both self-report and informant-report, we test independent and divergent prognostic utility for dementia.

**Methods:** Data from 10,684 non-dementia subjects from the National Alzheimer's Coordinating Centre were analysed. This included individuals with normal cognition (NC; CDR=0) and Mild Cognitive Impairment (MCI; CDR=0.5). Geriatric Depression Scale-15 (GDS) was used for self-report and the Neuropsychiatric Inventory Questionnaire depression item (NPI-Q-D) was used for informant-report. Cox regression and Kaplan Meier (KM) survival analyses were used to explore the measures as independent predictors of dementia, and the putative interaction between them. Outcome was defined as change to CDR $\geq$ 1 at follow-up. The cox model was adjusted for age, sex, and education. CDR category was included to determine applicability of findings across cognitive categories. GDS-15 and NPI-Q-D scores were added as continuous predictors. For the KM analysis, depressive symptoms were dichotomized as GDS+/GDS- and NPI-Q-D+/NPI-Q-D- using cut-off scores of  $\geq$ 5 for GDS-15 and  $\geq$ 2 for NPI-Q-Depression.

**Results:** GDS (HR: 1.096; CI: 1.070–1.122) and NPI-Q-D (HR: 1.428; CI: 1.291–1.580) independently predicted dementia, with a significant interaction between them ( $p<0.000$ ) even after controlling for CDR. KM analyses showed that in the self-reported non-depressed group (GDS-), there was a significant difference in the hazard of incident dementia based on the informant report. The discordant group i.e., GDS-/NPI-Q-D+ progressed to dementia significantly faster (9.6yrs; SD=0.292) compared to the GDS-/NPIQ-D- group (12.0yrs; SD=0.055) ( $p<0.000$ ; Log-rank test). No significant difference was found based on informant reports in the GDS+ group ( $p=0.114$ ).

**Conclusions:** Self-reported and informant-reported depressive symptoms are not duplicative, and independently predict dementia risk across cognitive categories. Informant report is particularly important when self-report is negative, to detect individuals with compromised insight at higher risk for progression. Discordance of self-informant reports require greater clinical and research consideration in NC and MCI populations.

# Abstract Oral Presentations

Theme 5: Other (this includes research that is relevant to healthy brain aging and dementia but does not fit in the other theme categories)

## ABSTRACT #33:

### Transgenerational Prenatal Stress Programs Gene Expression Detectable in Early Life Directly Related to Neurodegenerative Disease

**Nicola A. Schatz (1), Stephanie E. King (1, 2), Olena Babenko (1, 3), Yaroslav Ilnytskyy (3), Igor Kovalchuk (2, 3), and Gerlinde A.S. Metz (1, 2)**

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2- Southern Alberta Genome Sciences Centre, University of Lethbridge, Lethbridge, Alberta, Canada

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**Introduction:** Prenatal stress has been shown to increase the susceptibility to long-term chronic conditions including neurological diseases in a sex-specific manner. Changes in placental function from prenatal stress can impact neurodevelopment and increase the susceptibility to neuropsychiatric disorders. Exposure to prenatal stress can generate transgenerationally inheritable alterations to the transcriptome linked to neurological health. The objective of this study was to investigate the sex-specific effects of transgenerational prenatal stress on pathways in the brain and placenta known to increase the susceptibility to neurodegenerative diseases.

**Methods:** Four generations of Long-Evans rats were bred for this study. The parental (F0) generation gestating rats were exposed to stress during gestational days (G) 12-18. The transgenerational lineage was bred to the F3 generation without any further stress exposure. Control and transgenerational stress lineage fetuses and placentas were collected at G21 from males and females. Both the fetal cortex and placenta of the F1-F3 generations were used for transcriptome analysis.

**Results:** Differentially expressed genes were compared and about 41-46% of the genes overlapped between the cortex and placenta in both the male and female groups. An analysis of variance identified that many of the genes have a similar alteration in fold change compared to control. Pathway analysis was performed on the dataset and several genes common between the brain and placenta were identified as having a key role in the etiology of neurodegenerative disease. There appeared to be a sex-specific effect with 7 genes unique to the females and 12 genes unique to the males with 16 genes differentially expressed in both male and female cortex and placenta.

**Conclusions:** While there were sex-specific alterations in genes, both datasets appeared to have genes involving alterations to the proteasome, ubiquitination, and oxidative phosphorylation pathways which are vital for mitochondrial function. However, males appeared to have an increased number of genes directly involved with Alzheimer's, Parkinson's, and Amyotrophic lateral sclerosis (ALS) pathways. The overlap in transcriptomic changes related to neurodegenerative disease between the placenta and fetal cortex suggesting that the placenta may be used as a potential biomarker to predict sex-specific molecular changes in the brain correlated with neuropathologies in adulthood.

# Abstract Oral Presentations

Theme 5: Other (this includes research that is relevant to healthy brain aging and dementia but does not fit in the other theme categories)

## ABSTRACT #34:

### Towards the development of rationally-designed, structure-based vaccine candidates for Alzheimer's Disease

**Aishwarya Sriraman (1, 2), José M. Flores-Fernández (1, 2), YongLiang Wang (1, 2), and Holger Wille (1, 2, 3)**

1- Centre for Prions and Protein Folding Diseases, University of Alberta, Edmonton, Alberta, Canada

2- Department of Biochemistry, University of Alberta, Edmonton, Alberta, Canada

3- Neuroscience and Mental Health Institute, University of Alberta, Edmonton, Alberta, Canada

**Introduction:** Alzheimer's disease (AD) is mainly caused by the misfolding of the amyloid beta (A $\beta$ ) and tau proteins, which both adopt a beta-sheet rich conformation and form amyloid aggregates. Diverse attempts were made to develop vaccines as prophylactics for AD employing these proteins and peptides in their linear form, but which lacked structural specificity and functionality. We have used a novel approach to design vaccine candidates based on the folded structure of A $\beta$  peptides and tau proteins. These vaccine candidates are expected to provide disease-specific antigenicity.

**Methods:** We have used the currently available structures of A $\beta$  peptides and tau proteins deposited in the protein data bank (PDB). We used a fungal prion, HET-s, as an innocuous scaffold, which can adopt a beta-sheet rich conformation natively. The vaccine candidates are constructed by engineering the antigenic determinants on the HET-s scaffold in a structurally controlled manner. The constructs were expressed in *E. coli* (BL21) cells, purified and refolded. The proper folding was confirmed by negative staining electron microscopy. The constructs that formed amyloid fibrils similar to HET-s fibrils were injected in to wild-type mice to assess the specificity of the immune response.

**Results:** Based on the recent structures of A $\beta$  peptide and tau protein deposited in the PDB, we made several recombinant constructs to use as vaccine candidates. The engineered proteins that were purified and refolded exhibited the expected self-assembly into amyloid fibrils by negative stain electron microscopy for the constructs, designed based on the structures A $\beta$  peptide (Gremer et al., 2017; Kollmer and Fandrich, 2019) and tau proteins (Fitzpatrick et al., 2017; Falcon et al., 2018).

**Conclusions:** The self-assembled recombinant constructs will be injected into mouse models of Alzheimer's disease. The antisera from these mice will be tested against control HET-s, the engineered recombinant fibrils, and brain homogenates from AD patients to determine their ability to bind disease-specific antigens.

# Abstract Oral Presentations

Theme 5: Other (this includes research that is relevant to healthy brain aging and dementia but does not fit in the other theme categories)

## ABSTRACT #35:

### Brain-wide neuronal activation and functional connectivity are modulated by prior exposure to repetitive learning episodes

Dylan J. Terstege, Isabella M. Durante, and Jonathan R. Epp

Department of Cell Biology and Anatomy, Hotchkiss Brain Institute, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada

**Introduction:** Prior learning has been shown to induce structural and functional changes in the brain, often coinciding with changes in memory performance. Changes in functional connectivity can alter the efficiency and resiliency of networks underlying cognitive function, changing vulnerability to cognitive decline with deterioration. While different types of memory rely on different overall networks, they have many points of overlap. The extent to which changes in memory performance through cognitive stimulation are generalizable to other types of memory through these points of overlap is unknown. In the present study, we investigate whether cognitive stimulation in one task would increase the efficiency of the functional networks underlying a different form of memory.

**Methods:** Cognitive stimulation was provided by training mice in a repeated acquisition variant of the Morris Water Task for 10 weeks. Following training, mice who had received cognitive stimulation and untrained controls underwent contextual fear conditioning (CFC). A retention test was performed the next day and mice were perfused 90 minutes later. Brains were serially sectioned and stained for c-Fos which was quantified in 98 brain regions. Regional cell counts were cross-correlated to generate functional networks which were then analyzed using graph theory. We analyzed, network centrality, clustering global efficiency and performed targeted node deletions to determine network resilience.

**Results:** During CFC, memory retention was similar between groups. However, analyses of c-Fos expression revealed differences in the functional connectome supporting these behavioural outputs. Across the brain, prior cognitive stimulation decreased c-Fos expression. In maintaining the same behavioural output with less neuronal activation, prior cognitive stimulation made memory recall more efficient. This was supported by an increase in global efficiency and a shift in the distribution of region centrality within the network. Targeted node deletion revealed that prior cognitive stimulation rendered networks better able to preserve global efficiency.

**Conclusions:** The results of this study suggest that chronic learning has generalized effects on the functional connectome. Enhanced network efficiency and resilience suggest that learning itself may be neuroprotective against deterioration. These findings have important implications for mitigating cognitive deterioration in Aging and Alzheimer's disease.



# Abstract Oral Presentations

Theme 5: Other (this includes research that is relevant to healthy brain aging and dementia but does not fit in the other theme categories)

## ABSTRACT #36:

### A Reelin-ApoER2-CD2AP axis in brain endothelial cells controls neurovascular coupling and is compromised in Alzheimer's disease

Milène Vandal (1), Colin Gunn (1), Adam Institoris (2), Philippe Bourassa (3, 4), Ramesh C. Mishra (2), Govind Peringod (2), Camille Belzil (1), Yulan Jiang (1), Louise Reveret (3, 4), Cyntia Tremblay (4), Mada Hashem (5), Wilten Nicola (6), Jeff F. Dunn (1, 2, 5), Andrew P. Braun (2), David Bennett (7), Grant R.J. Gordon (2), Frédéric Calon (3,4), and Minh Dang Nguyen (1)

1- Departments of Clinical Neurosciences, Cell Biology and Anatomy, and Biochemistry and Molecular Biology, Hotchkiss Brain Institute, University of Calgary, Calgary, Alberta, Canada

2- Department of Physiology and Pharmacology, Hotchkiss Brain Institute, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada

3- Faculté de pharmacie, Université Laval, Québec City, Québec, Canada

4- Axe Neurosciences, Centre de recherche du centre Hospitalier de l'Université Laval (CHUL), Québec City, Québec, Canada

5- Department of Radiology, Hotchkiss Brain Institute, University of Calgary, Calgary, Alberta, Canada

6- Departments of Cell Biology and Anatomy, Hotchkiss Brain Institute, University of Calgary, Calgary, Alberta, Canada

7- Rush Alzheimer's disease Center, Rush University Medical Center, Chicago, Illinois, United States

**Introduction:** Genome-wide association studies have uncovered CD2-associated protein (CD2AP) as an important predisposition factor for Alzheimer's disease (AD). However, the physiological role of the protein in the brain and its contribution to AD pathogenesis remain largely unresolved.

**Methods:** In this study, we investigated the association between CD2AP and AD using isolated brain microvessels from volunteers of the religious order study cohort, cultured brain endothelial cells (BECs) and awake two-photon microscopy in mice.

**Results:** We demonstrate that lower levels of CD2AP in brain microvessels of AD subjects are strongly associated with cognitive dysfunction, and decreasing CD2AP expression in BECs impairs neurovascular coupling and cerebral blood flow in mice. In BECs, CD2AP interacts with apolipoprotein receptor 2 (ApoER2); lowering the levels of CD2AP in cultured cells reduces ApoER2 levels and deregulates Reelin-mediated ApoER2 signaling. In awake mice, Reelin causes a robust, nitric oxide-dependent vasodilation of penetrating arterioles and increases neurovascular coupling. These in vivo effects of Reelin are both heightened in mice with microvessels depleted of CD2AP, in line with the overshoot in Reelin signaling observed in BECs lacking CD2AP. Finally, the vascular levels of ApoER2 in AD volunteers are associated with cognitive dysfunction, lower levels of platelet-derived growth factor receptor beta, the presence of cortical infarcts and the accumulation of amyloid-beta in brain vessels.

**Conclusions:** Thus, the Reelin-ApoER2-CD2AP axis in BECs represents a novel pivot for neurovascular coupling, and its dysregulation may contribute to the brain vascular and cognitive dysfunction in AD.

# Biographies of Speakers



## KEYNOTE

### Kaarin Anstey

**University of New South Wales – Sydney, Australia**

Professor Kaarin Anstey is Director of the UNSW Ageing Futures Institute, and a Senior Principal Research Scientist at Neuroscience Research Australia. Anstey also co-Directs the Australian Dementia Centre for Research Collaboration and is Chair of the International Research Network on Dementia Prevention. Anstey's research programs focus on the causes, consequences and prevention of cognitive ageing, and dementia. She has developed risk assessment tools and is an investigator on several multidomain dementia risk reduction trials. A second focus of her work is on how sensory and cognitive ageing impact driving, disease pathophysiology and memory impairment.



## KEYNOTE

### Alison Goate

**Icahn School of Medicine at Mount Sinai – New York, United States of America**

Dr. Alison Goate is the Jean C and James W. Crystal Professor and Chair of the Dept. of Genetics and Genomic Sciences at the Icahn School of Medicine at Mount Sinai (ISMMS). She has worked on the genetics of neurodegenerative diseases including Alzheimer's disease (AD) and Frontotemporal Dementia (FTD) since 1987, and is the founding director of the Ronald M. Loeb Center for Alzheimer's disease at ISMMS. Over the last three decades she has been part of many gene finding teams that have successfully identified disease causing variants for both AD and FTD. Whilst working at Imperial College she reported the first mutation to cause familial Alzheimer's disease and early studies at Washington University identified the mutation in the Colombian families that are now part of the API clinical trial. Her lab was also part of the team that first reported MAPT mutations in FTD. Dr. Goate is also a leader in the study of late onset AD genetics using integrative genomic approaches to identify novel genetic risk factors. Her work led to the identification of Trem2 as a risk factor for AD and has highlighted the enrichment of AD risk variants in microglial enhancers, regulatory elements in DNA that control gene expression in immune cells of the brain. She is now building upon these insights using genome-editing in induced pluripotent stem cells to understand the molecular mechanisms of disease and to develop novel therapeutics. Dr. Goate has received the Potamkin Award, the Khalid Iqbal Lifetime Achievement Award from the Alzheimer's Association and the MetLife Award for her research on AD. She was elected a fellow of AAAS in 2012 and a fellow of the National Academy of Medicine in 2016.

# Biographies of Speakers



## Dorthe Stensvold

**Norwegian University of Science and Technology – Trondheim, Norway**

Stensvold works as a professor in the cardiac exercise research group (CERG), and her key research areas are healthy aging and aerobic exercise. Stensvold is the principal investigator for the Generation 100-study.



## Bryce Anthony Mander

**University of California, Irvine – Irvine, United States of America**

Dr. Mander utilizes a multimodal neuroimaging approach to examine relationships between sleep physiology, cognitive aging, and dementia pathophysiology. His research program aims to characterize how and when sleep interacts with neurodegenerative pathology and medical disorders to impact dementia risk, and to determine if sleep interventions can effectively promote healthy brain aging in older adults with or at risk for neurodegenerative dementias.



## Laura Middleton

**University of Waterloo – Waterloo, Canada**

Laura Middleton is an associate professor in the Department of Kinesiology at the University of Waterloo. She is also a research scientist at the Schlegel Research Institute for Aging and an affiliate scientist at the Toronto Rehabilitation Institute. Her research aims to identify strategies to prevent dementia and promote wellbeing and independence among those living with dementia. Her work in the area was instigated when her aunt was diagnosed with early onset Alzheimer's disease at 47 years of age. Dr. Middleton focuses on the influence of lifestyle, and specifically on the role of exercise alone and in combination with other therapeutic approaches (for example, cognitive training or healthy diet). Her research integrates epidemiological, experimental, clinical trial, and qualitative approaches towards this aim. Her recent work has explored the creation and evaluation of exercise interventions to improve the cognitive, physical, and social health of people living with mild cognitive impairment or dementia in the "real-world". She involves people living with dementia, health care professionals, and community service providers as co-researchers to create accessible and effective solutions for people living with dementia in Canadian communities. One recent project (the "Dementia-Inclusive Choices for Exercise" project) aims to increase the quality and quantity of exercise programs accessible to people living with dementia by improving understanding of dementia, decreasing stigma, and promoting use of inclusive practices. She completed her PhD at Dalhousie University and postdoctoral fellowships at University of California San Francisco and Sunnybrook Research Institute. She is also an avid rower who, in a prior life, competed for the Canadian national team.

# Biographies of Speakers



## Miia Kivipelto

**Karolinska Institutet – Stockholm, Sweden**

Miia Kivipelto, MD, PhD, is Professor in Clinical Geriatrics at Karolinska Institutet (KI), Center for Alzheimer Research and senior geriatrician and Director for Research & Development of Medical Unit Aging at Karolinska University Hospital, Stockholm, Sweden. Part of her Nordic Brain Network multidisciplinary research team (around 100 researchers and clinical staff) is located at University of Eastern Finland and Imperial College London, UK, where she has part time position as Professor. Her frontline research findings have been published in leading journals (330+ publications, H-index 75) and she has received numerous prestigious awards.

Dr. Kivipelto's translational research focuses on the prevention, early diagnosis and treatment of cognitive impairment, dementia and Alzheimer's disease (AD). Through epidemiological studies, Prof. Kivipelto has identified various lifestyle and vascular risk factors for dementia and interactions with genetic factors and clarified underlying mechanisms. She is the PI of the landmark FINGER trial and founder and scientific leader of World-Wide FINGERS network. Professor Kivipelto is often invited to leading global dementia conferences and task forces.



## Adrian M. Owen

**Western University – London, Canada**

Adrian M. Owen OBE, PhD is currently a Professor of Cognitive Neuroscience and Imaging in the Departments of Physiology & Pharmacology and Psychology at the University of Western Ontario, Canada, after ending his term as a Canada Excellence Research Chair. His research combines structural and functional neuroimaging with neuropsychological studies of brain-injured patients and has been published in many of the world's leading scientific journals. Adrian is best known for showing that functional neuroimaging can reveal conscious awareness in some patients who appear to be entirely vegetative and can even allow some of these individuals to communicate their thoughts and wishes to the outside world. He has published over 300 peer-reviewed articles and chapters and a best-selling popular science book *Into the Gray Zone: A Neuroscientist Explores the Border Between Life and Death*. Adrian was recently awarded Officer of the Most Excellent Order of the British Empire (OBE) in the Queen's Honors List, 2019, for services to scientific research.

# Biographies of Speakers



## **Teresa Liu-Ambrose**

**University of British Columbia – Vancouver, Canada**

Dr. Teresa Liu-Ambrose, PhD, PT, Professor, is a physical therapist and a Canada Research Chair at the University of British Columbia, Department of Physical Therapy. She directs the Aging, Mobility and Cognitive Health Laboratory as well as the Vancouver General Hospital's Falls Prevention Clinic.

Dr. Liu-Ambrose's research focuses on healthy aging, with a focus on cognitive health and mobility in aging. Her research expertise are in randomized controlled trials, exercise prescription for older adults, cognitive neuroscience, and mobility aging. Her research findings have been implemented into clinical practice, community programs, and influenced international practice guidelines to promote healthy aging.



## **Dallas Seitz**

**University of Calgary – Calgary, Canada**

Dr. Seitz is an Associate Professor of Psychiatry and Community Health Sciences, in the Cumming School of Medicine, University of Calgary. He was the Provincial Medical Lead for Dementia Capacity Planning in Ontario and immediate past president of the Canadian Academy of Geriatric Psychiatry. His research examines health service utilization of older adults with psychiatric disorders; evaluation of the safety and efficacy of treatments for geriatric mental health conditions; and, knowledge translation in geriatric mental health. Dr. Seitz is actively involved in the development health system strategies, guidelines and policies related to seniors and mental health at both the provincial and national level.



## **Richard H. Swartz**

**Sunnybrook HSC, University of Toronto – Toronto, Canada**

Dr. Swartz is a stroke neurologist and clinician-scientist with expertise in vascular cognitive impairment, stroke in young adults and atypical causes of stroke. His pragmatic research includes clinical trials in hyperacute stroke, embedding cognitive endpoints in clinical trials, facilitating widespread cognitive screening after stroke and improving cognitive endpoints in clinical trials. Recently, he has been investigating COVID as a possible cause of covert and overt VCI.

# Biographies of Speakers



## David Wishart

**University of Alberta – Edmonton, Canada**

Dr. David Wishart (PhD Yale, 1991) is a Distinguished University Professor in the Departments of Biological Sciences and Computing Science at the University of Alberta. He also holds adjunct appointments with the Faculty of Pharmaceutical Sciences and with the Department of Pathology and Laboratory Medicine. He has been with the University of Alberta since 1995. His research interests span many areas including structural biology, bioinformatics, prion biology, nanobiology and metabolomics. From 2006-2009, Dr. Wishart led the “Human Metabolome Project” (HMP), a multi-university, multi-investigator project that catalogued all of the known metabolites in human tissues and biofluids. Using advanced methods in NMR spectroscopy, mass spectrometry, multi-dimensional chromatography and machine learning Dr. Wishart and his colleagues identified or found evidence for more than 8500 endogenous metabolites. This information has been archived on a freely accessible web-resource called the Human Metabolome Database (HMDB). The methods and ideas developed for the HMP have helped lay the foundation for a number of clinical metabolomics projects currently being pursued in his lab. These include studies of several cancer biomarkers, identifying organ transplant biomarkers, exploring wound healing mechanisms, identifying early biomarkers of prion and prion-like diseases, and investigating biomarkers of common diseases in cows. Over the course of his career, Dr. Wishart has published more than 430 scientific papers covering many areas of protein science including structural biology, protein metabolism and computational biochemistry. These papers have been cited more than 78,000 times. Dr. Wishart has been identified as one of the world’s most highly cited scientists for each of the past 7 years.



## AmanPreet Badhwar

**CRIUGM, Université de Montréal – Montréal, Canada**

Dr. Badhwar’s PhD work at McGill University employed multimodal research to tease apart the contributions of neuronal and cerebrovascular damage on cognitive dysfunction in Alzheimer’s disease (AD). Her PhD work at CRIUGM sought to characterize the heterogeneity in AD using resting-state fMRI connectivity. Currently, Dr. Badhwar’s lab focuses on integrating observations from in-vivo imaging and molecular ‘omics’ in the study of AD and other age-related dementias, with the goal of discovering new biomarkers/therapeutic targets.

# Biographies of Speakers



## Yasser Iturria-Medina

**McGill University – Montréal, Canada**

Dr. Yasser Iturria-Medina holds a Canada Research Chair in Multimodal Data Integration in Neurodegeneration. He is an Assistant Professor in the Montreal Neurological Institute (McGill). He is also an associate member of the Ludmer Centre for Neuroinformatics and Mental Health, and the McConnell Brain Imaging Centre (McGill). Iturria-Medina's Lab, Neuroinformatics for Personalized Medicine, focuses on defining and implementing multiscale and multifactorial brain models for further understanding neurological disorders from a multifactorial perspective and identifying effective personalized interventions. The lab combines molecular, imaging and cognitive data using integrative mathematical/computational approaches to create both individual and population-based mechanistic brain models. These approaches underpin his work in precision medicine aimed at identifying individual brain signatures, personalized therapeutic fingerprints for the human brain.



## Michelle M. Mielke

**Mayo Clinic – Rochester, United States of America**

Michelle M. Mielke, Ph.D. is a Professor of Epidemiology and of Neurology at the Mayo Clinic in Rochester, MN. Dr. Mielke works as a translational epidemiologist to understand the etiology and epidemiology of neurodegenerative diseases, and the utility of blood-based biomarkers. Another focus of her research is on understanding sex and gender differences in the development and progression of aging-related conditions. She directs the Mayo Clinic Specialized Center of Research Excellence on Sex Differences.



## Michael Sasner

**The Jackson Lab – Bar Harbor, United States of America**

Michael Sasner is a Senior Research Scientist and the Center Manager for the MODEL-AD program at the Jackson Lab. He obtained his B.A. in Biology and Biochemistry from Colby College, and his Ph.D. in Physiology & Neurobiology at the U. of Connecticut. In addition to the MODEL-AD program, he is currently developing novel mouse models of familial Alzheimer's disease, reporter strains specific for microglial activation states, and models to study the effect of APOE alleles on Alzheimer's disease risk. He is a co-organizer of a workshop Improving Preclinical Translation in AD.

# Biographies of Speakers



## Fernanda De Felice

**Queen's University – Kingston, Canada**

Fernanda DE FELICE is an Associate Professor at Queen's University, Canada. DE FELICE has been investigating Alzheimer's disease (AD) and its intersection with metabolic diseases. Her studies on insulin and other hormones such as GLP1 and exercise-linked irisin highlight the importance of the periphery-to-brain cross talk in AD development. She is a Guggenheim fellow, Senior Editor of Neuropharmacology and Handling Editor of The Journal of Neurochemistry. De Felice has 110 peer-reviewed publications (including Nat Med., Trends in Neurosci. JCI, Cell Metab., Mol. Psych., J. Neurosci., EMBO Mol. Med., Diabetes), and has a current h-index of 50 and more than 11,000 citations.



## Gerold Schmitt-Ulms

**University of Toronto – Toronto, Canada**

Dr. Gerold Schmitt-Ulms, Associate Professor, trained with Dr. Stanley Prusiner at UCSF, San Francisco, before joining the Tanz Centre for Research in Neurodegenerative Diseases at the University of Toronto. His work focuses on Alzheimer's disease, prion disorders and related dementias. His main interests are the molecular events that lead to toxic A $\beta$  assemblies, signaling of A $\beta$  to Tau, and the mechanism of cell death in these disorders with a view to derive mechanism-based early diagnostics and disease interventions.



## Matthew Macauley

**University of Alberta – Edmonton, Canada**

Trained as a biochemist, my laboratory at the University of Alberta is developing and applying chemical, biochemical, and genetic approaches to study and modulate immune responses through a family of glycan-binding proteins called Siglecs. Rooted in a biochemical understanding of how glycans have the potential to modulate the function of glycan-binding proteins, I am leveraging my knowledge as an immunologist to further elucidate roles Siglecs in immune responses under diseased conditions. I am particularly interested in genetic links between Siglecs and human disease and modeling this in mouse models. A large aspect of this work also involves developing chemical and biochemical tools to study Siglecs. The ultimate goal of my laboratory is to better understand the immunomodulatory properties of Siglecs in order to modulate immune cells for improving human health.



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