2018 INTERNATIONAL CONFERENCE

Promoting Healthy Brain Aging and Preventing Dementia

RESEARCH AND TRANSLATION

ORAL AND POSTER ABSTRACTS

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Silent brain infarct manifestations and protective factors against vascular cognitive decline

Romella Durrani, University of Calgary; Eric Smith, University of Calgary; Cheryl McCreary, University of Calgary

Theme 1: New frontiers of biomarker research, early detection and precision health application

Background: Silent brain infarcts (SBI), a manifestation of silent stroke, are 5 times more prevalent than symptomatic strokes. Since symptoms of SBI are subtle, they are clinically unnoticed but are associated with cognitive impairment. Past studies have overlooked middle-aged individuals, focusing instead on the elderly who are at risk for dementia. However, much data points to middle age as a key life period where silent vascular brain injury begins to accrue, leading to increased risk of cognitive decline and later-life dementia. Methods: Our cross-sectional study looks at SBI and cognition in 1500 healthy participants ages 40-75, using MRI, questionnaires, and cognitive assessments. Our objectives are: 1) Determine the association of SBI with hypertension, smoking, diet, excessive alcohol intake, physical activity, diabetes, psychosocial stress, depression, and heart disease. We will determine the odds ratio for the association of SBI with these 9 risk factors. We will also determine the population attributable risk for these individual and aggregate risk factors; 2) Determine whether measures of socioeconomic status (education level, occupational attainment, income), physical activity, diet, engagement in social activities, and stress (modifiable risk factors for cognitive decline) protect against the deleterious effects of SBI on cognition. These pre-specified variables are potentially related to increased cognitive reserve. We will use statistical modeling with test of interactions (SAS 9.4) to determine whether the effect of SBI on cognition is reduced in the presence of these variables; 3) Determine whether brain atrophy (in the thalamus-proper, caudate, putamen, pallidum, hippocampus, ventral diencephalon, cortex volume, and cortical white matter volume) (beyond age-related atrophy) is a consequence of SBI and a modifier (brain reserve variable) of the effects of SBI on cognition. Brain atrophy will be quantitatively measured using Freesurfer 5.3 software, and categorized as volumes that score 1 standard deviation below the age-adjusted mean. Impact: This research can point to possible public health initiatives against cognitive decline and dementia, by uncovering preventable risk factors for SBI, SBI-related brain atrophy, and factors that increase cognitive resilience to lower later risk of dementia.

Modifiable risk factor exposure in late middle-age is associated with increased inflammation 12 years later.

Nicolas Cherbuin, Australian National University; Erin I. Walsh, Australian National University; Kaarin J. Anstey, University of New South Wales and Neuroscience Research Australia; Bernhard T. Baune, University of Adelaide

Theme 1: New frontiers of biomarker research, early detection and precision health application

Introduction:

It is well-established that Alzheimer Disease (AD) pathology develops decades before the onset of symptoms and clinical diagnosis. In the absence of available treatments it is essential that preventative measures be put in place to decrease risk exposure and to delay AD onset. Such interventions require accurate identification of individuals at risk. We have showed in recent research that a validated instrument, the ANU Alzheimer's Disease Risk Index (ANU-ADRI), is predictive of incident MCI and is associated with brain structures particularly affected by AD pathology. This study aims to extend these findings and investigate whether ANU-ADRI risk scores at baseline are predictive of systemic inflammation and oxidative stress (OS) levels 12 years later in the same cohort.

Design and Methods:

380 dementia-free participants (60-64 years, 45% female) were included in the study. Dementia risk was measured with the ANU-ADRI which assesses exposure to modifiable risk factors. Twelve years later, thirteen plasma markers of inflammation/OS were assayed. Principal component analysis (PCA) was conducted to identify the more salient pro-inflammatory components. Associations between dementia risk estimates and principal components of the inflammatory/OS response were investigated through linear regression.

Results:

PCA revealed four factors. Two principal components reflected predominantly broad pro-inflammatory activity (PC1&PC2). The other two components reflected predominantly OS activity. PC1, whose main contributing markers were TNF-R2, TNF-R1, TNF-a, neopterin, IL10, and IL6, was the only component significantly predicted by dementia risk scores (Beta 0.065, p=0.0001). This indicates that higher dementia risk is associated with greater systemic inflammation. To better understand which markers were more implicated in this association post-hoc analyses including only the markers which significantly contributed to PC1 were conducted. They showed that TNF-R2 (Beta 17.869, p=0.0003), TNF-R1 (Beta 18.139, p=0.00005), and log IL6 (Beta 0.019, p=0.005) were the only markers associated with dementia risk.

Conclusions:

Increased risk exposure in cognitively healthy community-living individuals in their early 60s is associated with higher systemic low-grade inflammation 12 years later. These findings confirm that up-regulation of pro-inflammatory pathways, particularly TNF-a and IL6 signalling, which are known to be

associated with a higher risk of neurodegeneration and dementia, are also associated with our validated measure of dementia risk.

Structural connectivity of Neuropsychiatric Symptoms (NPS) in association with cognitive decline and dementia

Sascha Gill, University of Calgary; Eric Smith, University of Calgary; Zahinoor Ismail, University of Calgary; Brandon Craig, University of Calgary; Cheryl McCreary, University of Calgary

Theme 1: New frontiers of biomarker research, early detection and precision health application

Background: Multiple lines of evidence suggest that neuropsychiatric symptoms (NPS) can be early markers of neurodegenerative disease. Although, studies have identified decreased white matter (WM) integrity in regions associated with NPS in Alzheimer's Disease (AD), evidence in pre-clinical populations is sparse. Mild-Behavioural Impairment (MBI) is a neurobehavioral syndrome that describes the later-life onset of NPS as an at-risk state for incident cognitive decline and dementia and could potentially be used for early identification of neurocognitive disorders. Diffusion imaging allows increasingly sophisticated analysis of white matter neurobiology and structural connectivity and has highlighted important pathways within the brain surrounding this field. Although understanding such pathways is informative, exploring changes at the whole brain level may be even more powerful. The whole-brain connectivity (i.e. connectome) approach may also provide biomarkers which can inform individualized predictors of NPS in Mild Cognitive Impairment (MCI) and AD populations.

Aim 1: Describe white matter connectivity alterations in individuals with normal cognition, MCI, and mild AD.

Hypothesis 1: Degree connectivity of relevant nodes (i.e. cingulate, etc.) negatively correlates with disease severity.

Aim 2: Investigate the correlation between NPS clustered into MBI domains and structural connectivity abnormalities in individuals with MCI and AD.

Hypothesis 2: Global and nodal degree connectivity will be inversely correlated with the severity of NPS.

Methods: We recruited participants with normal cognition (n= 20), MCI (n=20) and AD (n= 20) for cross-sectional evaluations (with >40+ scans still to be processed). Participants completed a high-resolution T1-weighted anatomical and diffusion imaging (25 directions; b=850s/mm2) scan. T1 images are parcellated into 99 regions of interest (nodes) using a validated atlas in BrainSuite. Whole-brain WM uses deterministic tractography. Individualized WM connectomes are then quantified by calculating connection strengths (i.e. number of streamlines (NOS) at global (i.e. whole-brain) and nodal levels). Additionally, participants completed validated clinical and cognitive assessments [including Neuropsychiatric Inventory (NPI)]. Using the NPI, NPS will be clustered into the 5 MBI domains, and each domain will be correlated with structural connectome properties.

Significance: Assessing MBI domains in MCI and AD patients will improve understanding of the role of NPS in neurodegenerative disease while potentially uncovering novel imaging biomarkers for early detection/ treatment.

Calgary Normative Study: A Prospective Longitudinal Study to Characterize Potential Quantitative MR Biomarkers of Cognitive Impairment in Ageing

Cheryl McCreary, University of Calgary; Louis Lauzon, University of Calgary; Marina Salluzzi, University of Calgary ; Richard Frayne, University of Calgary; David Gobbi, University of Calgary; Linda Andersen, University of Calgary

Theme 1: New frontiers of biomarker research, early detection and precision health application

Introduction: Numerous neuroimaging biomarkers have been proposed to assess risk, progression and treatment of cognitive impairment in ageing. These markers include measures of brain atrophy, white matter integrity, iron accumulation, and cerebral perfusion. Quantitative measures may be more sensitive to early changes and have reduced variability across equipment platforms. An understanding of how these biomarkers change with age is required. The Calgary Normative Study (CNS) proposes to characterize multiple quantitative MR measures over the adult lifespan in purportedly healthy individuals. Here, we outline the study design and report on progress to date.

Methods: We have incorporated three primary considerations into the design of this ongoing study: 1) evaluation of repeatability of measures in a subset of participants, 2) capability to share image data with other cohort studies as it is collected and 3) protocol flexibility to accommodate emerging quantitative techniques. Volunteers between 18 and 90 years of age, without neurological disease or psychological disorders were recruited. A medical history, Montreal Cognitive Assessment, and magnetic resonance (MR) scans were collected. MR included structural 3D T1-weighted, FLAIR, diffusion, perfusion, quantitative susceptibility mapping (QSM), T1 and T2 relaxometry. Estimates of data stability and variance (repeatability) for each were obtained from 4 volunteers who were scanned 12 times (baseline and 12±2, 18±2, and 48±6 months), including before and after a MR system upgrade. Annual review of recruitment, sequences and MR sequence parameters allows phased-in protocol revisions.

Results and Discussion: To date, 277 participants have consented and data collected. In an initial phase, 52 subjects were recruited. These data were reviewed and the QSM, T1, and T2 mapping sequences were revised for a second phase. In the second phase, 225 subjects were recruited. Additionally, 64 participants have returned for a second scan session after 48 ± 6 months. Over 700 scans have been shared with five investigators at our centre supporting research ranging from depression, inflammatory bowel disease, machine learning, migraine, and stroke; supporting the SND design goal to share data. Further work is ongoing on the evaluation of measurement variability, repeatability, and characterization of potential quantitative neuroimaging biomarkers in ageing.

Decoding Interacting Trajectories of Frailty and Memory Aging: Patterns of Change, Prediction, and Resilience

Sherilyn Thibeau, University of Alberta; Roger Dixon, University of Alberta; G. Peggy McFall, University of Alberta; Kenneth Rockwood, Dalhousie University

Theme 1: New frontiers of biomarker research, early detection and precision health application

Objective: Age-related frailty (cumulative multisystem physiological and health decline) increases the risk of adverse brain and cognitive outcomes, including decline and dementia. Trajectories of both frailty and cognition commonly demonstrate substantial individual variation, prediction differences, and potential opportunities for resilience and intervention.The present objectives are: (1) to examine relationships of both level (statistical centering age) and slope (9-year trajectories) between frailty and memory, and (2) to identify and characterize memory resilience to frailty.

Method: This longitudinal design included older adults (n=626 baseline, Mage=70.7, 66.7% female) from the Victoria Longitudinal Study followed across a 40-year band (53-95) of aging. Latent growth modeling, path analysis, and growth mixture modeling were used to examine (1) variability in level and change in an accumulation-of-deficits frailty index and memory, (2) frailty effects on memory performance and change, (3) subclasses of individuals based on individualized level and slope of (separately) frailty and memory, and (4) resilient and non-resilient participants.

Results: First, for both frailty (higher score=worse) and memory (higher score=better) we observed that individuals varied (all p0.03). Third, two quantitatively separate classes of individual frailty trajectories were identified (all p<.001): (a) Low Frailty: lower level (M = -.12) and negligible decline (M = -.003), and (b) Severe Frailty: higher level (M = -.245) and a more rapid decline (M = -.007). For memory, two classes of individual trajectories were identified (all p<.001): (a) Higher Memory: higher performance (M = 1.98) and slower decline (M = -.13), and (b) Declining Memory: lower performance (M = -4.06) and steeper decline (M = -.19). Fourth, participants were classified as resilient if they were in both Severe Frailty and Higher Memory classes. Ongoing analyses test Alzheimer's risk predictors (genetic, vascular, functional, lifestyle, sex) of memory resilience to frailty.

Conclusion: Among non-demented aging adults frailty is a major risk factor for accelerated decline and dementia. Determining the characteristics and predictors of resilience to frailty may lead to precision solutions that delay its detrimental effects

Alzheimer's Genetic Network Effects on Cognitive Trajectories are Moderated by Modifiable AD Risk Domains

Shraddha Sapkota, Sunnybrook Health Sciences Centre; Roger Dixon, University of Alberta; G. Peggy McFall, University of Alberta; Mario Masellis, Sunnybrook Health Sciences Centre

Theme 1: New frontiers of biomarker research, early detection and precision health application

Introduction/Objective: In a recent genetic network study, we observed that clusters of Alzheimer's disease (AD) and cognitive aging risk genes interactively altered non-demented cognitive trajectories selectively for Apolipoprotein E (APOE)-ε4 carriers. We now examine whether the effects of the AD components of this genetic network on cognitive (executive function (EF)) trajectories are moderated by three modifiable AD risk domains: functional-health, lifestyle, and demographic.

Design and Method: We assembled a longitudinal design (spanning age 53-95) with non-demented older adults (baseline n = 602; Mage=70.63(8.70) years; 66% female) from the Victoria Longitudinal Study. Risk markers for each domain were (1) functional-health (pulse pressure, grip strength, body mass index), (2) lifestyle activities (physical, social, cognitive-integrative, cognitive-novel), and (3) demographic (age, sex, education). All risk factors were categorized from 0-2 (2=greater risk) and summed within domain. AD genetic markers included (1) Apolipoprotein E(APOE; risk=ε4+) with subsequent stratification by (2) low and high AD-genetic risk score [AD-GRS; Clusterin(risk=C+) +Complement receptor 1(risk=A+) +Phosphatidylinositol-binding clathrin assembly protein(risk=T+)]. Statistical analyses included confirmatory factor analysis, longitudinal invariance, latent growth curve modeling, and path analysis.

Results: First, high functional-health risk predicted worse EF performance (β=-0.104, p = 0.033) and steeper decline (β=-0.005, p = 0.028) selectively for the APOE ε4- group. When stratified by AD-GRS, this association was only present in the subgroup with APOE ε4- and high AD-GRS (level:β=-0.160, p = 0.003;slope:β=-0.008, p = 0.006). Second, elevated lifestyle risk was associated with poorer EF performance and decline in selectively the APOE ε4- group for both low (level:β=-0.263, p = 0.013;slope:β=-0.014, p = 0.006) and high (level:β=-0.177, p < 0 .001;slope: β=-0.006, p < 0 .001) AD-GRS. Third, high demographic risk predicted poorer EF performance and decline in the (1) APOE ε4- group with low (level:β=-0.498, p = 0.004;slope:β=-0.031, p = 0.002) and high (level:β=-0.324, p < 0 .001;slope:β=-0.016, p < 0 .001) AD-GRS and (2) APOE ε4+ group selectively with high (level:β=-0.376, p = 0.014;slope:β=-0.022, p = 0.011) AD-GRS.

Conclusion: Multi-modal AD risk analyses showed that modifiable AD risk factors differentially moderated the association of Alzheimer's genetic network effects on EF performance (level) and decline (slope). Distinguishing older adults with high modifiable risk profiles as stratified by a two-component AD genetic network may add an additional level of precision to risk profile calculations than that provided by an overall genetic risk score approach.

Relative Importance of Neuroimaging Biomarkers in Dementia: Predicting Global Cognition by Apolipoprotein E-ε4 Carrier Status

Shraddha Sapkota, Sunnybrook Health Sciences Centre; SAIRA MIRZA, Sunnybrook Health Sciences Centre-University of Toronto; Christopher Scott, Sunnybrook Hospital; Joel Ramirez, Sunnybrook Hospital; Mario Masellis, Sunnybrook Health Sciences Centre; Sandra Black, Sunnybrook Health Sciences Centre-University of Toronto

Theme 1: New frontiers of biomarker research, early detection and precision health application

Introduction/Objective: Recent biomarker research on neurodegenerative diseases has focused on combinations of multiple risk factors to predict development of cognitive impairment and dementia. In the present study, we use a machine learning approach to examine biomarkers from two important domains (genetics and neuroimaging) to predict global cognition in dementia.

Design and Method: We used a ~2-year longitudinal sample (followed annually) of cognitively impaired and dementia patients (baseline N = 363; mean age=70.83 years; range=37-89 years) from the Sunnybrook Dementia Study. The patients represented Alzheimer's disease, Mild Cognitive Impairment, Vascular Cognitive Impairment, Lewy Body Disease, Frontotemporal Lobar Degeneration, and mixed neurodegenerative cases. We used (1)latent growth modeling and class analyses to estimate the number of classes that best represented global cognition over 2 years (using Mini-Mental State Exam [MMSE]) for APOE ε4-(n = 170) and ε4+(n = 193) groups, and (2)Random Forest Analysis to test relative predictive importance of structural brain volumes on global cognition. Neuroimaging biomarkers were examined at two levels using Semi-Automatic Brain Region Extraction, a pipeline that estimates individualized volumetric profiles. First level comprised of global volumes: normal appearing gray matter(NAGM), normal appearing white matter(NAWM), deep white matter hyperintensities(dWMH), periventricular WMH(pWMH), deep lacunes(dLACN), periventricular LACN(pLACN), sulcal cerebrospinal fluid(sCSF), and ventricular CSF(vCSF). Second level included corresponding subregion volumes from 13 regions in the left and right hemisphere (superior, middle, and inferior frontal; medial inferior, superior, and middle frontal; superior and inferior parietal; anterior and posterior temporal; occipital; anterior and posterior basal/ganglia thalamus)

Results: We observed a 2-class model (slow and rapid progressors) for ~2-year MMSE decline in the APOE ε4-(AIC=2088.47;BIC=2113.56;-2LL=2072.47;Entropy=0.80) and APOE ε4+(AIC=2442.13;BIC=2468.23;-2LL=2426.13;Entropy=0.78) groups. First, for global volumes, we observed that slow MMSE progressors had (1)higher dLACN, lower sCSF and vCSF in the APOE ε4- group and (2)higher NAGM and lower sCSF in APOE ε4+ group. Second, out of 208 subregions, 9 subregions in the APOE ε4- and 38 subregions in the APOE ε4+ group significantly discriminated slow and rapid MMSE progressors.

Conclusions: Integration of a machine learning approach across multiple risk domains may (1)identify biomarker profiles of relatively resilient groups across neurodegenerative diseases and (2)lead to personalized medicine to promote healthy brain aging.

Preserved Cognitive Performance Despite Amyloid Burden Amongst Healthy Elderly: Is Cortical Thickness the Explanation?

Catherine Veilleux, Université de Sherbrooke; Sven Joubert, Université de Montréal; Michaël Bernier, Université de Sherbrooke; Pénélope Sévigny-Dupont, Université de Montréal; Marie-Maxime Lavallée, Université de Montréal; Maude Joannette, Université de Montréal; Jim Nikelski, McGill University; Howard Chertkow, McGill University; Kevin Whittingstall, Université de Sherbrooke; Christian Bocti, Université de Sherbrooke

Theme 1: New frontiers of biomarker research, early detection and precision health application

Background: Correlates of cognitive changes in aging are complex. Detecting early Alzheimer's disease (AD) depends on an accurate understanding of the normal aging brain. High cortical amyloid burden, which is thought to reflect preclinical AD, is not always associated with poor cognitive performance. This discrepancy could be explained by the presence of cognitive reserve and brain reserve (BR) measures. We hypothesize that cortical thickness (CoT) could be used as a marker of BR in normal aging and thus provide resistance to expression of cognitive decline.

Methods: 113 cognitively normal elderly subjects recruited in the community were classified as having thin cortex (1 S.D below mean, ALZ+, "higher risk" for preclinical AD) or thick cortex (+/- and >1 S.D over mean, ALZ-, "lower risk" for preclinical AD) in 11 cortical regions involved in AD based on current literature. Amyloid burden was measured with PET scan using Pittsburgh Compound B (PiB); subjects were classified as PiB+ (SUVR>1.24) and PiB-. Episodic memory (EM) score was measured with Rey Auditory Verbal Learning Test (RAVLT) across four ALZ/PiB groups and linear regression was used to determine if CoT and PiB were predictors EM score.

Results: Subjects were aged between 65 and 93 years (mean=73 years). CoT in 11 regions was not associated with PiB ($p=0.351$). ALZ+ was associated ($p=0.011$) with lower EM scores, despite a similar amyloid burden when compared to ALZ- ($p>0.39$). EM score was predicted by ALZ groups ($p=0.03$) and PiB ($p=0.005$), but not by age ($p>0.9$). Amongst ALZ- subjects, there was no difference in EM score regardless of amyloid burden ($p=0.139$).

Conclusions: Our data supports the idea that CoT could represent a proxy for brain reserve in healthy elderly, possibly explaining preserved cognitive performance in the presence amyloid accumulation. We further demonstrated CoT is sensitive to very early EM changes in healthy elderly.

Brain-based age prediction as a cognitive disease biomarker with deep learning: a longitudinal study

Luis Souto Maior, University of Calgary; Mariana Bento, Seaman Family MR Research Centre; Cheryl McCreary, University of Calgary; Marina Salluzzi, University of Calgary ; Richard Frayne, University of Calgary

Theme 1: New frontiers of biomarker research, early detection and precision health application

Introduction

Clinically, FLAIR images are used to identify changes in white matter as shown by a hyperintense signal. The volume and distribution of these white matter hyperintensities (WMH) have been related to small vessel diseases and cognitive decline with age. Presence of moderate to severe white matter changes are correlated with poorer cognitive performance. Progression of WMH volume over time has been shown to be a relatively good predictor of cognitive decline and risk of progression from mild cognitive impairment (MCI) to dementia and Alzheimer's disease (AD). Global brain and cortical atrophy as determined from T1-weighted magnetic resonance (MR) images have been used to predict a participant's age and have been suggested to be a potential biomarker of risk of cognitive impairment. In this preliminary work, we propose to first train a convolutional neural network (CNN) classifier to predict age based on Fluid Attenuated Inversion Recovery (FLAIR) images of normative individuals aged 18-89. We will then incorporate T1-weighted MR images into the CNN before testing on MCI and AD cohorts.

Design and Methods

We used the Calgary Normative Study database comprising 200 brain MR images of patients 18 to 89 years with no known history of neurological injury or psychiatric disorder. The CNN, based on a VGG16 pretrained architecture, used FLAIR images as inputs, and age values from 18-89 years as outputs. The model was trained to classify each slice separately. The dataset was separated into training and testing set: 70% and 30% respectively.

Results and Discussion

Our early results achieved mean error between actual and predicted age of 13 years across 3930 MR slices of the testing set. We expect a decrease in predicted age error when incorporating T1-weighted images on the model training. The model will then be tested on a local dataset that includes AD and MCI cohorts with brain MR images acquired at baseline and 1-year follow-up. Using paired t-test, we will test the hypothesis that the difference between the age predicted by the CNN classifier and the chronological age of the patient will have a statistically significant ($p < 0.05$) increase on the follow-up images when compared to the baseline images.

Lateralization of inhibitory control revealed in VCI patients performing an anti-saccade task

Christopher Scott, Sunnybrook Hospital; Ying Chen, Queen's University; Brian Coe, Queen's University; Donald Brien, Queen's University; Joel Ramirez, Sunnybrook Hospital; Anna Santiago, Baycrest Rotman Research Institute; Donna Kwan, Western University ; Rick Swartz, Sunnybrook Health Sciences Centre; Demetrios Sahlas, Hamilton General Hospital; Wendy Lou, University of Toronto; Rob Bartha, Western University ; Sean Symons, Sunnybrook Health Sciences Centre; ONDRI investigators, Ontario Neurodegenerative Disease Research Initiative; Douglas Munoz, Queen's University

Theme 1: New frontiers of biomarker research, early detection and precision health application

The anti-saccade task has become a popular research tool to assess cognitive functions in neurodegenerative diseases. Unlike pro-saccades (automatic saccades toward a visual stimulus), anti-saccades are saccades made away from a visual stimulus in the opposite direction, requiring robust top-down cognitive control arising from frontal cortex. However, whether an automatic saccade triggered by a visual stimulus appearing in one visual field is suppressed by the frontal cortex on the ipsilateral or contralateral side remains unclear. Here, we describe detailed analysis of anti-saccade behaviour in vascular cognitive impairment (VCI) patients who had strokes in left frontal or parietal cortex to investigate how such unilateral infarcts affect saccade suppression. To localize the specific location of cortical strokes, a semiautomatic brain region extraction technique was used so that 6 cortical lobes (three ROIs in each hemisphere) were parcellated. According to saccade reaction time (SRT: the time from target appearance to the first saccade), some saccades are made at short express latency (SRT: 90-140 ms) while others are driven at longer regular latency (SRTs >140 ms). Corresponding to the two types of saccades, direction errors (looking towards the stimulus) occur either at express latency (express latency direction error) or at regular latency (regular latency direction error), reflecting two different suppression mechanisms. In the current study, VCI patients, recruited from the Ontario Neurodegenerative Disease Research Initiative, completed 240 trials of interleaved pro-/anti-saccade tasks. Frequency of express and regular latency direction errors was calculated. Difference in SRTs (delta SRT) and in frequency of direction errors (delta direction error) between rightwards vs. leftwards targets was analyzed. We compared those differences in patients with strokes only in left frontal cortex (n=5) with age-matched healthy controls (n=13), and patients with strokes only in left parietal cortex (n=8) with age-matched controls (n=16). Our results show left frontal strokes caused higher delta direction error at express latency (p=0.0001), but no laterality of regular latency direction errors. There were no differences between left parietal patients and the controls. This method will be used in VCI patients with strokes in a discrete frontal cortical region to further investigate the lateralization of inhibitory control.

A four-facet model of subjective memory decline in non-demented aging: Selective prediction sensitivity for women

Shannon Drouin, University of Alberta; G. Peggy McFall, University of Alberta; Samantha Fu, University of Alberta; Roger Dixon, University of Alberta

Theme 1: New frontiers of biomarker research, early detection and precision health application

Introduction: Recent studies investigating subjective memory decline (SMD) in aging suggest that self-perceived decline may be an early indicator of future objective decline, Mild Cognitive Impairment and Alzheimer's disease (AD). Typically, two SMD facets are studied: (1) memory complaints and (2) memory concerns. We examine longitudinal profiles and objective memory prediction of the former as well as three others: (3) memory anxiety, (4) memory compensation and (5) memory self-efficacy. Given sex differences in AD biomarkers and prevalence, we test models separately for females and males.

Method: From the Victoria Longitudinal Study we selected cognitively normal participants (n=580, M age = 70.21, 65% female) with up to three waves of data (spanning a 40-year band of aging). The SMD facets were measured with items from established memory inventories. Validated episodic memory measures formed a latent memory variable. Mplus (7.0) was used to investigate latent growth functions and predictions of memory.

Results: First, after item and subscale psychometrics, confirmatory factor analyses revealed a four-factor model of SMD with concerns/anxiety as a combined factor. This demonstrated strict invariance over time. Second, latent growth modeling analyses revealed significant variability in SMD level ($b = 0.013$, $p < 0.001$) and significant SMD change ($b = 0.001$, $p = 0.006$). Third, several SMD facets predicted memory level and change. Both memory complaints ($b = 1.863$, $p < 0.001$) and memory self-efficacy ($b = 1.506$, $p = 0.004$) predicted memory level. However, sex stratification showed these effects were selective for women ($b = 1.867$; $b = 2.191$, respectively). Memory complaints ($b = 0.089$, $p < 0.001$), memory self-efficacy ($b = 0.062$, $p = 0.007$) and memory compensation ($b = 0.109$, $p = 0.022$) predicted memory change. Stratifying by sex, memory complaints ($b = 0.076$, $p = 0.001$) and memory self-efficacy ($b = 0.085$, $p = 0.002$) remained predictors of memory change for women only, along with memory concerns/anxiety ($b = 0.043$, $p < 0.041$).

Conclusion: The subjective experience of memory decline presents as an early marker of objective decline in memory differentially by SMD facet and sex. Identification of specific facets as they function within sex groups allows for precision prevention strategies to target at-risk individuals before the onset of AD-related symptoms.

Less Isn't Always Better: Weight Status Differentially Impacts Semantic Related Cognition as a Function of Age and Sex

Linzy Bohn, University of Alberta; G. Peggy McFall, University of Alberta; Roger Dixon, University of Alberta

Theme 1: New frontiers of biomarker research, early detection and precision health application

Background. Research shows that overweight (OW) and obese (OB) weight status in midlife is a risk factor for accelerated cognitive decline, impairment, and dementia. However, some intriguing inconsistencies have appeared. Some epidemiological work suggests that OW and OB may be protective factors. Inconsistent findings could be partially attributed to differences across studies in precision of sample composition and selection of cognitive domain. For example, we reported that in some conditions language-based tasks might be more sensitive indicators of weight status effects than non-language based tasks.

Method. We examined the impact of age, sex, and weight status on semantic-related cognition (SRC) using cross-sectional data for non-demented participants (n = 886; 66% female) of the Victoria Longitudinal Study. Established semantic-based measures of episodic memory (e.g., story recall), fluency (e.g., figures of speech), executive function (e.g., reading span), and neurocognitive speed (e.g., lexical decision) were indicators of SRC. Participants were classified as normal weight (NW; BMI 18.50-24.99 kg/m2), OW (BMI 25.00-29.99 kg/m2), or OB (BMI ≥ 30.00 kg/m2).

Results. Full-sample confirmatory factor analysis verified a single factor structure of SRC. We examined the independent effects of age category (Young-Old: aged 53 – 74.5 vs. Old-Old: 75 – 95.2), sex, and weight status on SRC factor scores using structural regressions. Overall results showed (1) women (M = -.56) outperformed men (M = -2.18), (2) Young-Old (M = -1.18) outperformed Old-Old (M = -4.16), and (3) weight status was not significant. We subsequently tested weight status as a predictor of SRC as stratified by age and sex. Weight status predicted SRC selectively for Old-Old women such that OB (M = -1.38) outperformed OW (M = -2.20) and NW (M = -3.03) groups. Weight status did not predict SRC for Young-Old women or Young-Old and Old-Old men.

Discussion. These promising cross-sectional findings indicate that weight status may be differentially associated with cognition as a function of age (older) and sex (female). Longitudinal analyses examining differential trajectories as predicted by genetic and other biomarker risk factors are underway and will be reported. A goal is to enhance precision with which intervention protocols may target specific subgroups of older adults.

Alzheimer's genetic and environmental/lifestyle risk scores are differentially associated with latent phenotypes of general cognitive ability (g) and dementia severity (d)

Shea Andrews, Icahn School of Medicine at Mount Sinai ; G. Peggy McFall, University of Alberta; Roger Dixon, University of Alberta; Nicolas Cherbuin, Australian National University; Ranmalee Eramudugolla, Australian National University; Kaarin J. Anstey, University of New South Wales and Neuroscience Research Australia

Theme 1: New frontiers of biomarker research, early detection and precision health application

Introduction: Risk assessment tools for Alzheimer's disease (AD) and other dementias are a key component of dementia prevention strategies aimed at reducing prevalence. It is important to evaluate and compare the sensitivity of AD risk assessment tools for detecting early dementia-related cognitive disturbance. In this study, we investigated the association of the Australian National University Alzheimer's Disease Risk Index (ANU-ADRI) and an AD genetic risk score (GRS) with cognitive performance.

Methods: The ANU-ADRI (composed of 11 risk factors for AD) and GRS (composed of 25 AD risk loci) were computed in 1,061 community-dwelling older adults. Participants were assessed on 11 cognitive tests and activities of daily living. Structural equation modelling was used to evaluate the association of the ANU-ADRI and GRS with: 1) general cognitive ability (g) 2) dementia-related variance in cognitive performance (d) and 3) verbal ability, episodic memory, executive function and processing speed.

Results: A 1SD increase in the ANU-ADRI was associated with worse performance in general cognitive ability ($b = -0.40$, $se = 0.02$, $p < 0.001$), d ($b = -0.40$, $se = 0.04$, $p < 0.001$), verbal ability ($b = -0.29$, $se = 0.04$, $p < 0.001$), episodic memory ($b = -0.34$, $se = 0.03$, $p < 0.001$), executive function ($b = -0.38$, $se = 0.03$, $p < 0.001$) and processing speed ($b = -0.40$, $se = 0.03$, $p < 0.001$). A 1SD increase in the GRS was associated with a worse performance in d ($b = -0.08$, $se = 0.03$, $p = 0.041$) and episodic memory ($b = -0.10$, $se = 0.03$, $p = 035$).

Discussion: A higher ANU-ADRI score is associated with worse performance in dementia-related variance in cognitive task performance in comparison to variance in cognitive function unrelated to dementia processes. Additionally, more specific associations were observed with perceptual speed, executive function, episodic memory and verbal ability. In contrast, an AD GRS was specifically associated with dementia-related variance in cognitive task performance and episodic memory. These results provide additional support for using the ANU-ADRI across the cognitive spectrum in individual patient assessment to inform intervention and treatment strategies aimed at delaying dementia.

Investigating pupil dynamics in patients with neurodegenerative diseases

Jeff Huang, Queen's University; Brian Coe, Queen's University; Donald Brien, Queen's University; Douglas Munoz, Queen's University; ONDRI investigators, Ontario Neurodegenerative Disease Research Initiative; Matthew Smorenburg, Queen's University

Theme 1: New frontiers of biomarker research, early detection and precision health application

Pupillometry is an easy-to-measure method that is increasingly used to assess cognitive processing. Pupil size is modulated by converging bottom-up sensory and top-down cognitive signals, as well as arousal and global luminance. Furthermore, the circuit for pupil control is closely linked to the oculomotor system. Disruptions in neural circuitry due to neurodegeneration or brain injury can therefore affect pupil control and its relationship to the oculomotor system. Here, we examined pupil dynamics in patients diagnosed with one of 6 neurodegenerative diseases (Alzheimer's disease, mild cognitive impairment, Parkinson's disease, amyotrophic lateral sclerosis, frontotemporal dementia, vascular cognitive impairment) as part of the Ontario Neurodegenerative Disease Research Initiative, and hypothesized that components of the pupil response should be altered reflecting disease deficits that affect different parts of the pupillary circuit (e.g., frontal cortex, basal ganglia). Pupil size and eye position were recorded with video-based eye-tracking while subjects performed the interleaved pro-/anti-saccade task, in which subjects were required to make an saccadic eye movement toward a peripheral target (pro-saccade) or to the opposite direction (anti-saccade), with the instruction for each trial indicated by the coloured fixation cue. The pupil constricted shortly after the presentation of the fixation cue following by dilation. Analysis revealed distinct differences between patient groups and age-matched controls in pupil dynamics, including changes in control of pupil constriction and dilation, which may correspond to the different autonomic and executive deficits in these diseases. The results demonstrated changes in pupil dynamics linked to neurodegeneration, showing that pupil measurements can provide valuable insights into processes underlying executive control, and that pupil measurement in visuomotor tasks has the potential to provide relevant behavioural biomarkers for diagnosis of neurodegenerative diseases and tracking disease progression.

Integrating Characteristics of Executive Functions in Non-Demented Aging: Structure, Trajectories, Classification, and Biomarker Predictors

H. Sebastian Caballero, University of Alberta; Roger Dixon, University of Alberta; G. Peggy McFall, University of Alberta

Theme 1: New frontiers of biomarker research, early detection and precision health application

Background: Executive functions (EFs) are mental control processes, associated with neuroanatomical integrity of the brain, that monitor aspects of planning and action in humans. One prominent theory of lifespan EF performance and change has direct implications for both non-demented brain and cognitive aging and dementia. The de/differentiation theory suggests that EFs undergo dramatic structural changes from childhood (unidimensional) to differentiation in adulthood (multidimensional), and then de-differentiating in aging (unidimensional). However, cognitively advantaged aging adults may retain EF differentiation. We investigate EF trajectories, structure, and biomarker predictors.

Objectives: Study 1 goals are to (1a) determine an EF latent growth curve from trajectory distributions, (1b) establish objective stable and declining groups of EF change, and (1c) test predictors (e.g., genetic, vascular, functional, lifestyle, sex) that discriminate these groups. Study 2 goals begin with the results of 1b and then (2a) determine structural dimensionality for each group and (2b) test predictors of EF dimensionality (unidimensional vs multidimensional).

Method: The sample (N = 781; 66.6% female; age 53-95) is from the Alberta-based Victoria Longitudinal Study. Eight standard measures are indicators of three EF dimensions: inhibition, shifting and updating. Mplus 7.0 is used to conduct confirmatory factor analysis, invariance testing, latent growth modeling, and growth mixture modeling. R 3.3.2 is used to perform random forest prediction analysis for goals 1c and 2b.

Results: Foundational results include an overall unidimensional EF structure and longitudinal measurement invariance. Goal 1a results show individual differences in EF performance level ($b = 1.08$, $p < .001$), decline ($M = -.003$, $p = .02$), and individual differences in rate ($b = .001$, $p < .001$). Goal 1b results show two classes: higher level and less declining ($n = 397$, intercept = .90, slope = .02) and lower level and steeper decline ($n = 384$, intercept = -.68, slope = -.03). Preliminary goal 1c results identified three significant EF class predictors.

Conclusion: Trajectory analyses revealed that although (1) EF declines gradually over the 40-year band, there is (2) significant individual variability in change that is (3) clustered in two distinct classes (stable, declining). Biomarker prediction analyses for class discrimination are underway.

Motoric Cognitive Risk Syndrome Differentiates Trajectories of Long-Term Cognitive Change

Stuart MacDonald, University of Victoria; Alison Darnley, University of Victoria; Roger Dixon, University of Alberta

Theme 1: New frontiers of biomarker research, early detection and precision health application

Introduction: Recent evidence implicates slowing gait velocity as a biomarker for detecting cognitive impairment; however, cognitive risk assessments typically do not include motoric signs. To address this issue, Verghese and colleagues (2013) proposed a novel Motoric Cognitive Risk (MCR) syndrome—which replaces the cognitive criterion in Mild Cognitive Impairment (MCI) with diminished gait velocity—and found that MCR participants were at higher risk for developing dementia. The present study extends these findings by examining the association between MCR classification and long-term trajectories of cognitive change spanning up to 20-years.

Design and Methods: Victoria Longitudinal Study (VLS) data were employed to examine associations between current MCR status and retrospective cognitive change for several key domains: episodic memory (word list recall), processing speed (Color Trails 1), executive function (Color Trails 2), and crystallized ability (vocabulary). Eligible participants (n=319; age range=68-98 years; 69% female) spanning all 3 VLS samples completed 4 trials on a 16’ GAITRite computerized walkway. MCR classification was derived by identifying individuals with gait velocities 1 SD below age- and gender-specific group norms.

Results: Upon initial gait assessment, 47 participants (15%) met classification for MCR. For each of the four cognitive outcomes, separate linear mixed models of change were fit as a function of time and MCR status. For word recall and the Color Trails 1 & 2 measures, results yielded (a) no MCR group differences in cognition at baseline gait assessment (independent of age), with (b) significant interactions between time and MCR status indicating that MCR participants exhibited steeper cognitive declines over time compared to non-MCR participants. In contrast, for vocabulary, corresponding estimates of decline were not moderated by MCR status.

Conclusions: By demonstrating associations between MCR status and long-term cognitive change, we have extended recent evidence suggesting that slowing gait velocity is a robust predictor of cognitive impairment. Further, our findings support the supposition that using slow gait velocity as a criterion for assessing risk of cognitive impairment is a valid and potentially useful clinical tool. In ongoing research, we are examining whether the stability of MCR classification over multiple assessments further improves prediction of cognitive decline.

Quantifying Competing Definitions of Intraindividual Variability in Response Times: Associations with Attention Switching and Cognitive Status

Stuart MacDonald, University of Victoria; Robert Stawski, Oregon State University

Theme 1: New frontiers of biomarker research, early detection and precision health application

Introduction: Trial-to-trial variability in response times, response time inconsistency (RTI), reflects both transient (e.g., attentional lapses) and dispositional (e.g., central nervous system integrity) characteristics of an individual. Despite increasing interest in RTI, few systematic comparisons of the multiple quantifications exist and the optimal operationalization of RTI for presaging cognitive impairment requires further study. In the present study, we identify and compare the most commonly-derived quantifications of RTI, contrast their utility for understanding within-person (WP) and between-person (BP) variation in cognition, and explore whether these RTI-cognition associations are further moderated by cognitive impairment status.

Methods: Data from Project Mental Inconsistency in Normals and Demented (MIND) were employed, including various measures of response latency (e.g., choice response time) as well as cognitive function (e.g., attention switching) and impairment. Project MIND (N=302, age 62-94) assessments occurred weekly for 4-5 weeks, with this protocol repeated annually for 4 years. Individuals were classified as cognitively impaired not demented (CIND) if they performed 1 SD below age- and education-specific group norms on reference neuropsychological measures.

Results: Findings from multilevel models revealed that all RTI quantifications exhibited significant variation in RTI between persons as well as within persons across sessions and bursts. RTI quantifications were significant and generally strong and positive BP and WP, with the exception of the coefficient of variation. Independent of covariates (age, education, mean RT), increasing RTI was associated with slower attention switching both WP and BP, with ongoing analyses examining further moderation by CIND classification.

Conclusions: RTI reflects both durable (dispositional) and labile (situational) characteristics of individuals' functioning, and is related to complex cognitive performance and status in theoretically-meaningful ways. Among the most frequently employed RTI quantifications, not all are interchangeable or of comparable predictive utility. These findings support the theoretical and practical value of RTI as an early marker for both normal and pathological facets of cognitive health. In ongoing research, we are examining whether fitting explicit mathematical functions (e.g., ex-Gaussian) to raw RT data yields parameter estimates of variability (tau) that are putatively driven by increased fluctuations in executive control processes and differentially predictive of cognitive impairment.

Predicting cognitive decline after TIA with diffusion tensor imaging and texture analysis of normal appearing white matter

Jake Ursenbach, University of Saskatchewan; Stephen Campeau, University of Calgary; Philip Barber, University of Calgary; Carlson Helen, University of Calgary; Sana Tariq, Calgary Stroke Program, Department of Clinical Neurosciences, University Calgary; Shelagh Coutts, University of Calgary

Theme 1: New frontiers of biomarker research, early detection and precision health application

Introduction:

Patients presenting with a transient ischemic attack (TIA) have a 4-fold dementia risk. We evaluated two potential biomarkers of cognitive decline in this population to inform biomarker research in dementia. Following prior investigations using fractional anisotropy (FA), a marker derived via diffusion tensor imaging (DTI), and grey level co-occurrence matrix (GLCM) texture analysis of MR images, we expanded on these studies by documenting the longitudinal relationship between these markers and cognitive function in a TIA population.

Methods:

Patients (N=86, mean age 65 years, 79% male) with TIA/minor stroke were assessed at three points approximately one year apart. T2-FLAIR (slice thickness of 3.5mm), DTI (14 non-collinear diffusion encoded scanning directions), and neuropsychological data were collected including processing speed (WAIS-IV Digit Symbol Coding), executive function (Trail Making Test Part B), language (Controlled Oral Word Association Task), and verbal/visuospatial episodic memory (California Verbal Learning Test, Rey-Osterrieth Complex Figure Task). Regions of interest were drawn bilaterally in the normal appearing white matter in the medial temporal lobes (MDTL). The GLCM parameter angular second moment (ASM) was used to quantify texture homogeneity in T2-FLAIR images using FSL and ImageJ. Random intercept mixed effects regression (LMER) models were used to analyze changes in FA and ASM while controlling for age.

Results:

We found significant decline in left MDTL FA baseline to 2Y, $t(155.9) = -3.44$, $p < .001$ and baseline to 3Y, $t(157.3) = -3.68$, $p < .001$; however neither right FA and nor ASM declined significantly. When controlling for time and age, lower left MDTL FA predicted poorer executive functioning, $t(282.4) = -2.48$, $p = .014$, verbal learning, $t(265.0) = 2.08$, $p = .039$, and visuospatial memory $t(186.5) = 3.09$, $p = .002$.

Conclusions:

The decline in left MDTL FA suggests demyelination consistent with poorer cognitive performance. Left MDTL FA may be a robust biomarker of cognitive decline after TIA. Future research needs to delineate the aetiology of the change (i.e. vascular vs neurodegenerative processes).

Cerebrovascular reactivity to carbon dioxide in patients with cerebral amyloid angiopathy: Preliminary data from the functional assessment of vascular reactivity to CO2 study (FAVRCO2)

Andrew Beaudin, University of Calgary; Cheryl McCreary, University of Calgary; Erin Mazerolle, University of Calgary; Angela Zwiers, University of Calgary; Anna Charlton, University of Calgary; Richard Frayne, University of Calgary; Zahinoor Ismail, University of Calgary; Bruce Pike, University of Calgary; Eric Smith, University of Calgary

Theme 2: Markers of the pathophysiology and progression of neurodegenerative and vascular cognitive disorders

Introduction: Cerebral amyloid angiopathy (CAA) contributes to dementia risk, but the mechanisms are poorly understood. One potential mechanism is an impaired cerebrovascular reactivity (CVR). We previously reported that CAA patients had a decreased CVR within the primary visual cortex (V1) that was independent of neural activation; thus, implicating reduced vasodilatory function as a primary contributor. Whether CVR is impaired globally in CAA patients is unknown. Hence, the objective of this study was to determine if CAA is associated with global CVR impairment. We hypothesise CVR is impaired globally in CAA patients.

Design and Methods: CVR was quantified for CAA patients and healthy controls using blood oxygen level dependent (BOLD) functional MRI (3T) and a 2-minute 5% CO2 challenge. Individual CVR maps were registered to acquired T1-weighted anatomical images and MNI152 common space. Grey (GM), white matter (WM) and global CVR were calculated using masks generated from skull-stripped anatomical images. CVR within V1 was calculated using a V1 mask within MNI space created from the Juelich Histological Atlas structures. CAA patient and control responses were compared using an analysis of covariance (covariates: age and gender).

Results: Data from 9 CAA patients (75±7y; 4 male) and 20 controls (69±8y; 5 male) were analysed. GM and WM CVR for CAA patients (0.18±0.07 and 0.12±0.04 %Δ-BOLD/mmHg) were lower ($p \leq 0.023$) than controls (0.26±0.06 and 0.15±0.03 %Δ-BOLD/mmHg). Accordingly, global CVR was lower in CAA patients (0.14±0.05 versus 0.19±0.04 %Δ-BOLD/mmHg; $p=0.013$). CVR within V1 was lower in CAA patients (0.20±0.10 versus 0.30±0.12 %Δ-BOLD/mmHg), but this difference was not significant at the current sample size ($p=0.098$).

Conclusions: These preliminary data support our hypothesis that CVR is lower globally in CAA patients. Thus, CVR assessment may provide a novel clinical diagnostic test for CAA. However, additional regional analyses are needed to determine where these differences are the greatest.

Traumatic Brain Injury as a Potential Risk Factor for Developing Parkinson's disease

Julie Joyce, University of Calgary; Oury Monchi, Hotchkiss Brain Institute; Chantel Debert, Hotchkiss Brain Institute

Theme 2: Markers of the pathophysiology and progression of neurodegenerative and vascular cognitive disorders

Introduction: Over 100,000 Canadians are living with Parkinson's disease (PD) in Canada today and approximately 6,600 new cases of PD are diagnosed each year. The exact genetic and environmental influences that lead to PD are still not known.

Hypothesis: First, a history of traumatic brain injury (TBI) increases the risk of developing PD with or without mild cognitive impairment (MCI). Second, patients with a diagnosis of PD with or without MCI would have a history of more TBI's compared to those patients without PD.

Methods: Participants over 60 years old with and without PD and MCI were recruited. Initial assessments included patient characteristics, battery of neuropsychological assessments, Montreal cognitive assessment (MOCA), a clinician-scored motor evaluation of Parkinson's symptoms using Part III of the Unified Parkinson's Disease Rating Scale (UPDRS) and the Brain Injury Screening Questionnaire (BISQ). Summary statistics comparing the four study groups (PD, HC, MCI, PD+MCI) were generated for incidence of TBI over a lifetime using a one-way ANCOVA. A chi-squared test of independence was performed to determine the relation between PD and TBI with loss of consciousness.

Results: Seventy-eight participants (45 males; 33 females) completed the initial assessments. The participants were 60-85 years old ($M = 71.88$, $SD = 6.94$). The number of TBIs sustained in a lifetime had a significant effect on the likelihood of developing PD, $F(3,74) = 3.13$, $p = .03$. Post hoc Tukey HSD tests indicate that the PD + MCI group sustained significantly more TBIs ($M = 5.89$, $SD = 6.82$, $p = .02$) during their lifetime than the non-PD participants without MCI ($M = 1.92$, $SD = 2.30$). When grouped (PD and PD+MCI) these patients were more likely to have sustained a TBI with loss of consciousness compared to the non-PD groups (healthy controls and MCI only), $X2 (1, N = 78) = 6.53$, $p = .01$.

Conclusion: Higher incidence and increased severity of TBI appears to contribute to the risk of developing PD. Participants with PD and MCI sustained significantly more TBIs over their lifetime than the non-PD group without MCI. Continued research is required to investigate TBI as a risk factor for PD.

Assessment of Cortical Thickness and Cerebrovascular Reactivity in Patients with Cerebral Amyloid Angiopathy (CAA)

Arsenije Subotic, University of Calgary; Andrew Beaudin, University of Calgary; Cheryl McCreary, University of Calgary; Angela Zwiers, University of Calgary; Anna Charlton, University of Calgary; Ana Alvarez-Veronesi, University of Calgary; Erin Mazerolle, University of Calgary; Bruce Pike, University of Calgary; Zahinoor Ismail, University of Calgary; Richard Frayne, University of Calgary; Brad Goodyear, University of Calgary; Eric Smith, University of Calgary

Theme 2: Markers of the pathophysiology and progression of neurodegenerative and vascular cognitive disorders

Introduction: Cerebral Amyloid Angiopathy (CAA) is characterized by beta-amyloid deposition in the small vessels of the brain and leptomeninges, and is a leading cause of intracerebral hemorrhage and a contributor to dementia. Previous research has shown impaired cerebrovascular reactivity (CVR) in CAA to be linked to subcortical tissue loss, but its association with cortical thickness, a measure of gray matter atrophy, is not well established. The objective of this study is to analyze cortical thickness changes associated with CAA and the relationship between cortical thickness and cerebrovascular reactivity in CAA patients. It is hypothesized that CAA will be associated with cortical thinning and that decreased cortical thickness will be associated with lower cerebrovascular reactivity.

Methods: As a part of the Functional Assessment of Vascular Reactivity (FAVR) study investigating the relationship between cerebrovascular function, brain structure, and cognition, preliminary data were collected from 23 healthy controls (mean age 70, 17 female) and 12 patients with CAA (mean age 74, 6 female). All participants underwent a comprehensive structural and functional MRI protocol on a 3T scanner. The protocol included acquisition of high-resolution 3D T1-weighted images and assessment of CVR in response to 2 minutes of hypercapnia (5% inspired carbon dioxide) using blood oxygen level dependent (BOLD) functional MRI. Freesurfer version 6.0.0 was used to calculate average cortical thickness of the left and right hemisphere.

Results: Controlling for age and gender, global thickness (average of left and right hemisphere) was found to be lower in patients with CAA compared to controls (2.29 ± 0.14 vs. 2.39 ± 0.12 mm, p=0.02). There were no significant differences in terms of gender, while increasing age was associated with greater thinning. Correlational analyses showed a strong, positive association between cortical thickness and gray matter BOLD-CVR for both CAA (n=8, r=0.95, p=0.003) and controls (n=20, r=0.52, p=0.03) after controlling for age and gender.

Conclusions: Cortical thickness was decreased in patients with CAA, suggesting its role as a possible neurodegenerative biomarker in CAA, and that lower thickness is associated with lower CVR. Ongoing work will further delineate the regional distributions of thinning and its relationship with CVR.

Cortical Microinfarcts on 3T MRI in Cerebral Amyloid Angiopathy: Relations with Other MRI Markers of CAA and Cognition

Hilde van den Brink, University Medical Centre Utrecht; Angela Zwiers, University of Calgary; Aaron Switzer, University of Calgary; Anna Charlton, University of Calgary; Cheryl McCreary, University of Calgary; Brad Goodyear, University of Calgary; Richard Frayne, University of Calgary; Geert Jan Biessels, University Medical Centre Utrecht; Eric Smith, University of Calgary

Theme 2: Markers of the pathophysiology and progression of neurodegenerative and vascular cognitive disorders

Introduction: Cerebral microinfarcts are small ischemic lesions that are found in cerebral amyloid angiopathy (CAA) patients at autopsy. The current study aimed to detect cortical microinfarcts (CMI) on in vivo 3T MRI in CAA patients, to study the progression of CMI over a one-year period, and to correlate CMI with markers of CAA-related vascular brain injury and cognitive functioning.

Design and Methods: 35 CAA patients (mean age 74.2±7.6 years), 13 Alzheimer's disease (AD) patients (67.0±5.8 years) and 26 healthy controls (67.2±9.5 years) participated in the study. All participants underwent a standardized clinical and neuropsychological assessment as well as 3 Tesla MRI. CMI were rated according to standardized criteria, by a single rater blinded to clinical information.

Results: CMI were present in significantly more CAA patients (57.1%) (median number: 1, range 1-9) than in AD (7.7%) or in healthy controls (11.5%) ($p < 0.001$). In participants who had follow-up, new CMI were identified in 9/21 with CAA (total of 16 new CMI), 1/8 with AD-dementia (total of 2 new CMI), and 0/25 controls ($p < 0.001$). CMI did not correlate with any other MRI marker of CAA nor with cognitive function.

Conclusions: In vivo CMI are a frequent finding on 3T MRI in CAA patients and incident CMI are observable after one year-follow up. CMI can be regarded as a new MRI marker of CAA, potentially distinct from other well-established markers. Future larger cohort studies with longitudinal follow-up are needed to elucidate the relationship between CMI and possible causes and clinical outcomes in CAA.

White matter hyperintensities affect activities of daily living differently across dementias-The Sunnybrook Dementia Study

SAIRA MIRZA, Sunnybrook Health Sciences Centre-University of Toronto; Mario Masellis, Sunnybrook Health Sciences Centre; Sandra Black, Sunnybrook Health Sciences Centre-University of Toronto

Theme 2: Markers of the pathophysiology and progression of neurodegenerative and vascular cognitive disorders

Background/Objective: White matter hyperintensities(WMHs) are associated with functional impairment in dementia, but this association has mostly been studied in relation to Alzheimer's Disease(AD). As loss of functional independence is common in patients with all dementia diagnoses, we investigated if WMHs are associated with activities of daily living(ADLs) in a cohort of dementia patients with AD/Dementia with Lewy Bodies(DLB), and if this association is influenced by specific dementia-diagnosis.

Design and Methods: In the Sunnybrook Dementia Study, we investigated if WMHs are associated with ADLs in 214 dementia patients with varying degrees of cerebral small vessel disease(AD=180, DLB=34). All patients underwent standardized volumetric MRI, ADL and neuropsychiatric assessment (assessed within 3 months of each other), and APOE-ε4 genotyping. Total WMH volumes were quantified by semiautomatic segmentation using Lesion Explorer. Basic and instrumental ADLs(BADL and IADL) were assessed by Disability Assessment for Dementia(DAD) scale. Multiple linear regression models adjusted for age, sex, APOE-ε4, global cognition(assessed by Mini-Mental-State Examination-MMSE), and neuropsychiatric symptoms(assessed by Neuropsychiatric Inventory), were used to test if WMH volume predicts ADLs in a cohort of AD and DLB patients combined. After testing an interaction between WMHs and diagnosis, we subsequently tested the association of WMH and ADLs in models stratified for diagnosis.

Results: Of the 214 participants (Mean age 70.8±10.0 years), 52 %(n=142) were women. Patients with AD were older (P=< 0.001), had lower MMSE(P=0.02) and neuropsychiatric symptoms(P=< 0.001), higher WMH volume(AD=mean 6.4±8.3cc(range:0.1-43.5);DLB=mean 3.4±4.5cc(range:0.2-16.5);P=0.036), and a higher percentage of APOE-ε4 carriers compared to DLB patients. In the combined sample, higher WMH volume was associated with worse performance on BADL(Difference:-2.14, 95%CI: -3.87,-0.42) but not on IADL(Difference:-1.09, 95%CI:-4.20,2.01). A significant interaction was observed between WMH and diagnosis of dementia in analysis of both BADL(P-interaction:0.002) and IADL(P-interaction:0.036). In models stratified for diagnosis, higher WMH volume was associated with worse performance on BADL(Difference:-9.39, 95%CI: -16.21,-2.58) and IADL(Difference: -11.37, 95%CI: -19.64,-3.09) in DLB patients only. No associations were observed in patients with AD.

Conclusions: Despite the lower burden of WMHs in DLB patients, WMHs strongly predicted ADLs in this group and less so in AD patients. WMHs possibly interact with DLB pathology differently than with AD pathology consequently influencing functionality.

Longitudinal Changes in Mean Diffusivity along Skeletonized White Matter Tracks in Cerebral Amyloid Angiopathy, Mild Cognitive Impairment, Alzheimer's Disease, and Healthy Controls

Cheryl McCreary, University of Calgary; Andrew Beaudin, University of Calgary; Angela Zwiers, University of Calgary; Anna Charlton, University of Calgary; Richard Frayne, University of Calgary; Eric Smith, University of Calgary

Theme 2: Markers of the pathophysiology and progression of neurodegenerative and vascular cognitive disorders

Introduction: Recently, a novel imaging marker for small vessel disease was proposed that is based on the peak histogram width of skeletonized mean diffusivity (PSMD) tracks. Cross-sectional studies have found significantly higher PSMD measures for patients with cerebral autosomal-dominant arteriopathy with sub-cortical infarcts and leukoencepahlopathy, spontaneous cerebral small vessel disease identified by the presence of white matter hyperintensities and lacunar infarcts on MR images, and cerebral amyloid angiopathy (CAA). However, individual longitudinal changes have yet to be evaluated. We hypothesize that the rate of increase in PSMD will be greater in CAA than mild cognitive impairment (MCI), Alzheimer's disease (AD) and healthy control (HC) participants.

Methods: As part of an ongoing longitudinal cohort study, HCs and participants with probable CAA using validated Boston criteria, AD, and MCI were imaged at baseline and 1 year later. Diffusion images were acquired on a 3.0 T scanner and processed using PSMD marker script (www.psmd-marker.com) and FSL version 5.0. Analysis of variance and Tukey post-hoc tests were used to compare groups with $p<0.05$ considered significant.

Results: HC were significantly younger than the CAA group ($p = 0.001$), but not significantly different from MCI or AD groups ($p = 0.055$ and 0.786, respectively). The PMSD at baseline was significantly greater in the CAA participants (n = 29; PSMD=4.91±1.59 x 10-4 s/mm2) compared to HC (n = 16; PSMD=3.35±0.62 x 10-4 s/mm2), MCI (n = 28; PSMD=4.18±0.27 x 10-4 s/mm2), and AD (n = 13; PSMD=3.68±0.16 x 10-4 s/mm2) [$p < 0.001$]. However, the annualized rate of change was similar for all groups (HC: 0.0394 ± 0.0654 x 10-4, CAA: 0.0494 ± 0.0553 x 10-4, MCI: 0.0321 ± 0.0683 x 10-4, AD: 0.080 ± 0.126 x 10-4; $p = 0.302$).

Discussion: The PSMD results at baseline were similar to previous reports. We were not able to detect a difference in the annualized rate of change in PSMD between groups. This result may be due to the short follow-up period and limitations of the sample size. Some of the variance in the annualized rate of change in PSMD may be attributed to variance in cognitive function within the disease groups. We plan to address this issue in further analyses.

Differences in baseline grading characteristics and episodic memory in individuals on the continuum from subjective cognitive decline to AD: Results from the CIMA-Q study

Olivier Potvin, CERVO Research Center; Louis Collins, McGill University; Simon Duchesne, CERVO Research Center, Mental Health University Institute of Quebec

Theme 2: Markers of the pathophysiology and progression of neurodegenerative and vascular cognitive disorders

Background: Individuals expressing a subjective complaint of cognitive decline (SCD), without objective impairment, may represent a group at risk of developing mild cognitive impairment (MCI), and hence Alzheimer's disease (AD). Patch-based grading is a putative marker of early morphological change, proven to be predictive of progression to probable AD in aged controls and MCI subjects. Our purpose was to determine baseline characteristic of patch-based grading in a cohort of individuals across the AD continuum.

Methods: We compared participants with normal cognitive functioning (CON, n=30), SCD (n=67), early MCI (eMCI, n=22), late MCI (lMCI, n=8), and AD (n=16) from the CIMA-Q study on episodic memory (Rey auditory verbal learning test delayed recall) and patch-based grading from T1w MRIs, extracted with a nonlocal image patch estimator (AlzMETRIX™ score, provided by TPMD Inc.) in the hippocampi (HPC) and entorhinal cortices (EC). The patented AlzMETRIX™ technique (cf. NeuroImage:Clinical 1(1):141-152,2012) scores images by matching patches of voxels within a region to similar neighbourhoods in a pre-labeled set of training images. Each patch is tagged with information known a priori from the selected training images, achieving a grading score expressing the similarity to images of tissue from individuals with probable AD. We hypothesized that there would be gradients of increasing AlzMETRIX™ severity along the episodic memory continuum from CON to AD, with SCD showing a small, but significant difference from CON in the EC and HPC.

Results: A regression predicting episodic memory from the mean AlzMETRIX™ score ($p < .00001$) of the four regions explained 37.2% of episodic memory score variance. Qualitatively, groups showed a gradient of changes from CON to AD. Post-hoc Tukey HSD revealed that all groups were significantly different in terms of AlzMETRIX™ score, however CON-SCD ($p = .900$), eMCI-lMCI ($p = .859$), and lMCI-AD ($p = .075$) were not.

Conclusion: Based on these results, TPMD's AlzMETRIX™ scores for EC and HPC capture some but not all of the differences related to episodic memory impairment across the continuum from CON to AD; and notably does not differentiate at baseline between SCD and CON. Longitudinal follow-up is required to determine its positive predictive values for progression to clinical AD.

High Dose and Delayed Treatment with Bile Acids Ineffective in RML Prion-Infected Mice

Grant Norman, University of Alberta; Jody Campeau, University of Alberta; Valerie Sim, University of Alberta

Theme 3: Cutting-edge rodent models and the path to diagnostics/therapeutics

Prion diseases are a group of neurodegenerative diseases associated with the misfolding of the cellular prion protein (PrPC) into the infectious form (PrPSc). There are currently no treatments for prion disease. Bile acids have the ability to protect hepatocytes from apoptosis and are neuroprotective in animal models of other protein folding neurodegenerative diseases including Huntington's, Parkinson's, and Alzheimer's disease. Importantly, bile acids are approved for clinical use in patients with cirrhosis, and have recently been shown to have therapeutic benefit in trials of patients with amyotrophic lateral sclerosis (ALS). We previously reported that the bile acid, ursodeoxycholic acid (UDCA), given early in disease, prolonged incubation periods in male RML-infected mice. Here we expand on this result to include tauro-ursodeoxycholic acid (TUDCA) treatment trials and delayed UDCA treatment. We demonstrate that, despite a high dose of TUDCA given early in disease, there was no significant difference in incubation periods between treated and untreated cohorts, regardless of sex. In addition, delayed treatment with a high dose of UDCA resulted in a significant shortening of the average survival time for both male and female mice when compared to their sex-matched controls, with evidence of increased BiP, a marker of apoptosis, in treated female mice. Our findings suggest that treatment with high dose TUDCA provides no therapeutic benefit and that delayed treatment with high dose UDCA is ineffective and could potentially worsen outcomes.

Effects of amyloid seeding on Morris water task performance

Sean Lacoursiere, University of Lethbridge; Robert Sutherland, University of Lethbridge; Majid Mohajerani, University of Lethbridge

Theme 3: Cutting-edge rodent models and the path to diagnostics/therapeutics

Seeding of amyloid beta has been shown to increase the aggregation of plaque in rodents; this has been reported in multiple mouse models of Alzheimer's disease (AD). However, the behavioural effects of the seeding have not been reported. This study aimed to investigate the effects of amyloid beta seeding on Morris water task (MWT) behaviour in the single APP knock-in mouse model (APPNL-G-F). The medial entorhinal cortex was injected with a homogenate of brain tissue from fast-spreading AD patients (FAH) or a control homogenate (CH) at two months of age. At three and six months, MWT was completed. At three months, the FAH and CH groups showed no impairment in performance. At six months the FAH group showed robust expression of plaque with 4G8 and GFAP staining; the CH group showed relatively minimal expression of amyloid plaque. At six months no difference in MWT performance between groups was found. Both groups showed deficits in performance. A secondary point of interest which is under investigation is the use of APPNL mice as a control for the APPNL-G-F mouse model. At three months the APPNL mice showed slight impairment, regardless of homogenate group, comparable to the APPNL-G-F group. At six months, the APPNL mice showed equal impairment when compared to the APPNL-G-F mice. These findings suggest amyloid plaque expression does not correlate with spatial memory performance but perhaps other earlier steps in pathogenesis are responsible for cognitive deficits.

Amyloid β may be upregulated during ischemia to reduce pannexin-1 channel opening through an mGluR1-mediated mechanism

Laura Palmer, University of Calgary; Andrew Boyce, University of Calgary; Alexander Lohman, University of Calgary; Connor Anderson, University of Calgary; Roger Thompson, University of Calgary

Theme 3: Cutting-edge rodent models and the path to diagnostics/therapeutics

Introduction: Alzheimer's disease (AD) is associated with over-production of the amyloid β (Aβ) protein. Genetic causes of AD account for ~5% of cases, indicating that there are unknown co-morbidities for the disease. Ischemic stroke has been identified as an important risk factor, and accounts for up to five-fold increase in risk of developing AD. Interestingly, hypoxia upregulates production of Aβ. The purpose for this is unknown, but was previously assumed to be a pathological consequence of ischemia. We hypothesized that Aβ may play a physiological role during hypoxia, such as modulating the anoxic depolarization (aDP). The aDP is a large inward current that occurs in response to excessive hypoxic glutamate release, activating N-methyl-D-aspartate receptors (NMDARs). Previously, our group has demonstrated activation of pannexin-1 (Panx1), a large, non-selective ion channel, downstream of NMDARs during hypoxia. Furthermore, mGluRs are known to regulate NMDARs, and also play a role in hypoxia. Since NMDARs/mGluRs are a known target of Aβ, we hypothesized that Aβ could protect against ischemic Panx1 opening.

Methods: Using whole-cell patch clamp electrophysiology in rat hippocampal slices, the aDP was assayed using low oxygen (~5 mmHg) artificial cerebral spinal fluid. Ionic dysregulation was quantified by calculating area under the curve of the aDP.

Results: We found that low concentrations (pM to nM) of exogenous Aβ attenuated the aDP (nAβ = 10; ncontrol = 8; p < 0 .001), and also blocked Panx1 opening on an NMDA overstimulation assay (nAβ = 9; ncontrol = 9; p < 0 .05). Reducing endogenous Aβ levels using L-685,458 increased aDP severity (nL-685,458 = 9; nvehicle = 9; p < 0 .05). Human Aβ also had a protective effect on the aDP (nAβ(HUMAN) = 8; ncontrol = 12; p < 0 .01), and mice slices overexpressing Aβ oligomers were protected compared to those of wild-type littermates (n5xFAD = 10; nWT = 8; p < 0 .05). Lastly, the protective Aβ effect on the aDP was reversed with co-application of mGluR1 antagonists (nAβ+JNJ = 8; nAβ+vehicle = 8; p < 0 .01).

Conclusions: These data suggest a novel modulation of Panx1 opening by mGluR1, which is regulated by Aβ. Aβ production could be increased under hypoxia in order to prevent activation of Panx1, thereby attenuating the aDP and downstream cell death pathways. With prolonged/repeated ischemic events, Aβ could reach toxic levels and coincide with hallmark pathophysiology of AD.

Stress During Gestation Augments Females' Prone to Develop Alzheimer's Disease Later in Life

Zahra Jafari, University of Lethbridge; Bryan E Kolb, University of Lethbridge; Majid Mohajerani, University of Lethbridge

Theme 3: Cutting-edge rodent models and the path to diagnostics/therapeutics

Alzheimer's disease (AD) consists approximately half of the dementia cases. Besides well-known risk factors for the AD, stress, and in particular noise stress (NS) is a lifestyle risk factor common today. Stress causes neurotoxic damage to cells in the hippocampus and elsewhere in the brain that may increase AD risk. Stress also has a causative association with multiple risk factors for the AD. As evidence is persistently and extensively collecting to confirm women are at significantly greater risk of developing AD than men, as well as, because maternal stress is a common adversity during pregnancy, we aimed to investigate whether gestational NS, as a common source of environmental stresses, could exacerbate development of the AD in female stressed mice than control animals. Pregnant APPNL-G-F mice were randomly assigned to either the stress condition or control group. The experimental group was exposed to the NS on gestational days 12, 14, and 16 for 24 hours. The NS paradigm caused the HPA-axis hyperactivity and increased amyloid-β (Aβ) deposition in various brain areas involved in both AD and stress regulation, especially in limbic structures; i.e., the hippocampal formation, medial prefrontal cortex, and amygdala, as well as cortical and subcortical regions. It also developed an anxiety-like behavior, deficits in learning and memory, and impaired performance in balance and motor coordination. The findings suggest the significance of protecting women against gestational stressors as a potential risk factor in accelerating AD-like neuropathological changes later in life.

The structural biology of misfolded proteins guides the design of novel, structure-based vaccines for neurodegenerative diseases.

Holger Wille, University of Alberta; Andrew Fang, University of Alberta; José Miguel Flores Fernández, University of Alberta

Theme 3: Cutting-edge rodent models and the path to diagnostics/therapeutics

Introduction:

Alzheimer's disease, Parkinson's disease, the prion diseases, as well as other neurodegenerative diseases are caused by the misfolding of specific proteins. In the misfolded state these proteins adopt a beta-sheet rich conformation and often form amyloid fibrils. These proteins, or short peptides thereof, have been studied as vaccine candidates, but in most cases the structure of the antigens were poorly controlled, resulting in a lack of vaccine specificity or even harmful autoimmune responses. Here, we present a new approach to design structure-based vaccine candidates that present specific antigenic sequences in a structurally controlled form.

Design and Methods:

An innocuous scaffold protein that natively adopts a beta-sheet rich conformation is engineered as a vaccine candidate to express antigenic determinants from these disease-causing proteins in a structurally controlled manner. These vaccine candidates were produced in E. coli, purified, refolded, analyzed for their structural fidelity, and injected into indicator animals. The resulting immune response was tested against the initial, recombinant antigen, healthy control samples, as well as disease-relevant samples.

Results:

Proof-of-principle experiments targeting the infectious conformer of the mammalian prion protein were conducted in mice of varying genetic background. A rationally designed vaccine candidate, which adopted a disease-relevant conformation, elicited an immune response that was specific for the infectious conformer, but did not react with the cellular prion protein conformer. Thus, a rationally designed, structure-based vaccine targeting prion diseases in humans and animals may be feasible. Experiments to test the efficacy of this first, structure-based vaccine candidate against a prion disease are underway in an oral infection model.

Conclusions and implications:

The overall similarities in the structural biology of the protein misfolding diseases suggests that our approach of rationally designed, structure-based vaccines should be applicable to the medically important and more common neurodegenerative diseases such as Alzheimer's or Parkinson's disease. Future work will try to extend this approach with antigenic determinants derived from the experimentally determined structures of amyloid beta peptide, the tau protein, as well as alpha-synuclein.

The CNS in inbred transgenic models of 4-repeat Tauopathy develops consistent Tau seeding capacity yet focal and diverse patterns of protein deposition

Ghazaleh Eskandari-Sedighi, University of Alberta; Nathalie Daude, University of Alberta; David Westaway, University of Alberta; Hristina Gapeshina, University of Alberta; Jing Yang, University of Alberta; Razieh Kamali-Jamil, University of Alberta; Holger Wille, University of Alberta; Christopher Janus, University of Alberta

Theme 3: Cutting-edge rodent models and the path to diagnostics/therapeutics

Background. Mutations in the Tau gene can cause neurodegenerative diseases such as frontotemporal dementia but, strikingly, patients with the same mutation may have different clinical phenotypes. The cause of this heterogeneity amongst human kindreds in not understood. Methods. Given heterogeneities observed in a transgenic (Tg) mouse line expressing low levels of mutant human P301L Tau, we backcrossed founder stocks of mice to C57BL/6Tac, 129/SvEvTac and FVB/NJ inbred backgrounds to discern the role of genetic versus environmental effects on disease-related phenotypes. We then investigated biochemical characteristics of Tau fibrils extracted from the brain of these animals to unravel the molecular mechanisms responsible for the heterogeneity we observe amongst individual Tg mice. Results: Three inbred derivatives of a TgTauP301L founder line manifest homogeneity in Tau protein production, accumulation of abnormally phosphorylated Tau species from 90 days of age onwards and neuronal loss in aged Tg mice. However, in other regards, the aged Tg mice were heterogeneous; there was incomplete penetrance for Tau deposition despite maintained transgene expression in aged animals and, for animals with Tau deposits, distinctions were noted even within each subline. We classified the animals into five classes (I-V) based on the pattern of Tau deposition in the brain. The mean ages of mice scored as class I, II or III were not significantly different and, hence, did not fit with a predictable progression from one class to another defined by chronological age. Other pathology-positive Tg mice of similar age not falling within classes I-V presented with focal accumulations in additional caudal neuroanatomical areas including the locus coeruleus. Electron microscopy revealed that brains of Classes I, II and IV animals all exhibit straight filaments, but with coiled filaments and occasional twisted filaments apparent in Class I. Most strikingly, Class I, II and IV animals presented with distinct western blot signatures after trypsin digestion of sarkosyl-insoluble Tau. Conclusions: Qualitative variations in the neuroanatomy of Tau deposition in genetically inbred slow models of primary Tauopathy suggest that non-synchronous, focal events contribute to the pathogenic process. Phenotypic diversity in these models suggests a potential parallel to the phenotypic variation seen in P301L patients.

Biomarkers of disease progression in a non-human primate model of Alzheimer's Disease

Susan Boehnke, Queen's University; Douglas Munoz, Queen's University; Fernanda De Felice, Queen's University; Robert Wither, Queen's University; Joseph Nashed, Queen's University; Ron Levy, Queen's University; Cook Douglas J., Queen's University; Andrew Winterborn, Queen's University; Sergio Ferreira, Federal University of Rio de Janeiro; Emma Robertson, Queen's University; Natalia Lyra e Silva, Queen's University; Leticia Forny-Germano, Federal University of Rio de Janeiro

Theme 3: Cutting-edge rodent models and the path to diagnostics/therapeutics

In order to develop novel therapeutic strategies, there is an urgent need for development of viable animal models of neurodegenerative disease, especially in non-human primates (NHP) where there is some homology with humans in the higher cortical circuitry and cognitive functions. We have developed and validated a NHP model of Alzheimer's Disease (AD) that recapitulates key molecular aspects of human pathology (Forny-Germano et al., J.Neurosci, 2014, Batista et al, J.Pathology, 2018). AD pathology was induced via intracerebroventricular (icv) injection of neurotoxic soluble amyloid beta oligomers (AβOs). To track biomarkers of disease progression we have embarked on experiments to evaluate the changes in behavioural, neuroimaging, blood and CSF biomarkers in animals repeatedly injected with AβOs. Male rhesus macaques received chronic or acute injections of AβOs or vehicle. To measure cognition, we employed a cage-side touch-screen device with cognitive tasks from the CANTAB AD battery, which assesses memory using validated visuospatial tasks. To track behavior, animals wore a collar-affixed activity tracker and their cage activity was examined by recording 24/7 video. To track synaptic loss, we analyzed structural and resting state functional connectivity via fMRI. To track molecular biomarkers in the CSF we quantified Aβ1-40, Aβ1-42, tTau, pTau and neurofilament light chain (NFL) using ELISA. A variety of blood biomarkers were also tracked.

Impairments in spatial working memory were observed in animals receiving (AβOs). AβO injections also decreased functional connectivity across different brain networks measured by resting state fMRI, consistent with our previous neuropathological results showing loss of synapses in NHPs receiving AβO injections. Increases in Aβ 1-42, pTau, tTau, and NFL were observed in the CSF of NHPs receiving ICV injections of soluble amyloid-beta oligomers. We are in the progress of relating these in vivo metrics to each animal's post-mortem brain pathology, and have confirmed the presence of tangle pathology. The long-term goal is to generate a viable NHP model presenting multiple facets of human AD for use in testing therapeutics. These multimodal platforms can easily be translated to track disease in other NHP models of neurodegenerative diseases.

Epigenetic Programming by Ancestral Stress via Inflammatory Systems Alters Age-Related Physical and Mental Health Decline in a Sexually Dimorphic Manner

Ambeskovic Mirela, University of Lethbridge; Yaroslav Ilnytskyy, University of Lethbridge; Olena Babenko, University of Lethbridge; Kovalchuk Igor, University of Lethbridge; Gerlinde Metz, University of Lethbridge

Theme 3: Cutting-edge rodent models and the path to diagnostics/therapeutics

Introduction: Biological age is determined by the rate of mental and physical health decline. One of the risk factors associated with premature aging and disease incidence is prenatal stress. Recent literature has demonstrated that biological signatures of prenatal stress may propagate across multiple generations and compromise the chances of healthy aging in unexposed offspring. Here we investigated age-dependent changes in depression and anxiety-like behaviours, stress response and epigenetic regulation by microRNA (miRNA) expression. We proposed that ancestral prenatal stress can accumulate across multiple generations to accelerate aging in terms of mental and physical health via epigenetic regulation.

Methods: In this study, F4 generation male and female offspring were derived from a lineage in which their ancestral mothers (F0-F3) were stressed during pregnancy. Depression and anxiety-like behaviours were assessed at the age of 6 (young), 12 (middle aged) and 18 (aged) months using a forced swim task and open field task. Physical health was assessed across the lifespan using open field task and ladder run task. Behavioural outcomes were related to plasma corticosterone levels and cortical miRNA profiling via deep sequencing to identify epigenetic regulatory pathways. Morbidity and mortality were also recorded. Three-way ANOVA with sex, stress, and age as factors was run for behavioural tasks, corticosterone levels, and lifespan. For, miRNA analysis, raw count data was normalized and regularized with log transformation using statistical routines implemented in the DESeq2 bioconductor package. Pairwise comparisons were performed using DESeq2 with default settings.

Results: Our findings indicate that aging increases the incidence of both depression- and anxiety-like behaviours, which were further exacerbated by stress. Aging and stress synergistically disturbed the stress response and accelerated age-associated decline in overall health and longevity with sex-specific disease incidence. Moreover, ancestral stress altered cortical miRNA expression in a sex-specific manner, in particular markers related to major depressive disorder, stress-related immune deficiency longevity.

Conclusion: The findings suggest that ancestral programming by stress is a significant determinant of lifetime mental health trajectories and risk of common age-related diseases through altered epigenetic regulation. Disease incidence may be regulated by sex-specific pathways. MiRNAs may represent predictive biomarkers of age-related diseases.

Effects of six-month aerobic exercise intervention on sleep in healthy older adults

Veronica Guadagni, University of Calgary; Cameron Clark, University of Calgary; Amanda Tyndall, University of Calgary; Jill Raneri, University of Calgary; Jillian Parboosingh, University of Calgary; Patrick Hanly, University of Calgary; Marc Poulin , University of Calgary

Theme 4: Exercise and cognitive interventions for healthy brain aging and prevention of dementia

Introduction: Dementia is the fifth greatest cause of mortality in high income countries. Research on risk factors and effective interventions is critical. Recently, research focus has shifted to primary interventions targeting cognitively healthy individuals at increased risk of developing Alzheimer's disease (AD) due to factors such as genetic and lifestyle factors. In this study, we examined the effects of a six-month aerobic exercise intervention on sleep quality in individuals who carry the risk allele apolipoprotein (APOE) ε4. Poor quality of sleep, and sleep fragmentation have in fact been recognized as early indices of AD, and associated with reduced amyloid clearance with APOE ε4 carriers showing lower quality of sleep.

Methods: 203 healthy older adults completed the six-month exercise intervention and their sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI) pre- and post-intervention. A subset of participants (n = 29) underwent two nights of in-home polysomnography (PSG) before and after the intervention. Sleep architecture and respiratory variables were measured. Genotyping was characterized in 199 participants: 50 individuals were classified as APOE ε4 carriers (carriers of at least one risk allele) and 149 individuals as non-carriers (carriers of no risk alleles). Paired samples t-tests were used to compare scores from baseline to the end of the exercise intervention.

Results: We found significant positive effects of the exercise intervention on individuals' subjective sleep quality (PSQI total score, $t202 = 3.346$, $p = .001$, Cohen's $dz = .27$) sleep efficiency ($t199 = -4.448$, $p = .000$, Cohen's $dz = .32$) and sleep latency ($t194 = 3.005$, $p = .003$, Cohen's $dz = .20$). Moreover, the intervention showed significant improvements on objective PSG recordings (n = 29) of total sleep time ($t6 = -3.880$ $p = .008$, Cohen's $dz = 1.47$), sleep efficiency ($t6 = -2.615$, $p = .040$, Cohen's $dz = .99$), and sleep latency ($t6 = 3.702$, $p = .010$, Cohen's $dz = 1.38$) solely in APOE ε4 carriers (n=7).

Conclusions: These results highlight the importance of physical activity in potentially mitigating salient risk factors in the pathogenesis of AD, including poor sleep quality, and sleep fragmentation, even in APOE ε4 carriers

Sociodemographic and Health-Related Factors Associated with Physical Activity Levels and Participation Barriers in Canadian Older Adults.

Lauren Bechard, University of Waterloo; Laura Middleton, University of Waterloo

Theme 4: Exercise and cognitive interventions for healthy brain aging and prevention of dementia

INTRODUCTION: Lack of physical activity (PA) is the largest risk factor for dementia among Canadians. Despite its importance for the maintenance of brain health in older adults, older adults remain largely inactive. Developing public health policy and practices to address this evidence-behaviour gap requires a detailed understanding of PA behaviours and barriers to participation.

OBJECTIVE: The objective of this study was to provide a national profile of PA participation levels and barriers among cognitively healthy adults aged 45-86 years.

DESIGN & METHODS: This study was an analysis of the Canadian Longitudinal Study on Aging (CLSA) comprehensive cohort. The Physical Activity Scale for the Elderly (PASE) was used to collect PA participation data by phone at baseline. Only participants who reported the PASE as well as individual sociodemographic (e.g., age, sex, education, retirement status, income, marital status), and health-related variables (e.g., comorbidity, perceived general and mental health, pain, falls) were included. Relationships between individual sociodemographic and health-related factors and PA participation were determined using regression modelling.

RESULTS: The sample (n=12,199) had a mean age of 60.1 (SD=9.5) years and was 51.26% female. Participants reported an average of 4.23 hours/week of walking, 0.85 hours/week of light PA, 1.85 hours/week of moderate PA, 1.34 hours/week of vigorous PA, and 0.97 times/week of muscle-strengthening PA. The most commonly reported barriers to PA were lack of time (44.91%), lack of motivation (19.96%), and health conditions (16.18%). Older age group was associated with reduced PA levels for all types except light PA in the full model ($p < 0 .001$). No sociodemographic or health characteristics were uniquely associated with walking or moderate-intensity PA level. Being retired was associated with increased light PA level compared to employed participants ($p < 0 .001$). Higher educational achievement, self-rated health, and perceived healthy aging were associated with increased level of vigorous PA and frequency of muscle-strengthening PA ($p < 0 .001$).

CONCLUSIONS & IMPLICATIONS: These findings suggest there are differences in the sociodemographic and health profiles associated with participating in different types of PA. Promoting brain health through PA in older adults may require tailored approaches targeting specific types of PA and perceived barriers for groups with different sociodemographic & health characteristics.

Design, Synthesis and Biological Evaluation Novel Polyfunctional Flavonoids based Derivatives as potent Acetylcholinesterase Inhibitors and Anti-Amnestic agents

MANJINDER SINGH, Chitkara college of Pharmacy, Chitkara University, Punjab Campus; OM SILAKARI, Molecular Modeling Lab, Department of Pharmaceutical Sciences and Drug Research, Punjabi University

Theme 4: Exercise and cognitive interventions for healthy brain aging and prevention of dementia

Flavonoids has emerged as a ‘master key’ due to its presence in wide range of therapeutic activitoes along with its role in various complex diseases like Alzheimer’s disease (AD). Polyfunctional compounds comprise a novel class of therapeutic agents for the treatment of multi-factorial disease like AD. Following this approach integrated with polyfunctional nature of flavonoids, total 33 chromen-4-one derivatives were designed and synthesized by making modifications at different positions of chromen-4-one using Baker-Venkatraman rearrangement with slight modifications. The synthesized derivatives were primarily evaluated for in vitro acetylcholinesterase (AChE) inhibitory, advanced glyacation end products (AGEs) inhibition and antioxidant activity and showed that the majority of synthesized derivatives inhibited AchE with IC50 values in the nanomolar range with additional AGEs inhibitory and radical scavenging activities. The most active compounds FLV-16, FLV-31 and FLV-32 (IC50 = 6.33, 6.48 and 5.83 nM, respectively) were also ameliorated scopolamine-induced amnesia in mice in terms of restoration of time spent in target quadrant (TSTQ) and escape latency time (ELT) and also reversed the changes of various oxidative stress markers (GSH and TBARS). The molecular docking study displayed that most potent compounds simultaneously bind to catalytic active site (CAS) and peripheral anionic site (PAS) of AChE. Moreover, the in silico pharmacokinetic profiles were predicted and revealed that all compounds have drug-like properties with good penetration in brain and good oral absorption. After MD simulations, the Root mean square deviation (RMSD) plots showed that the docked complexes were quite stable for the specified time of 10 ns with minor fluctuations. Thus, newly designed poly-functional flavonoids have the ability to act on different targets or exhibit multiple pharmacological activities related to AD and the poly-functional attribute of these compounds make them potential candidates for the development of drugs for AD.

Sleep intervention and risk of cognitive decline: A systematic review

Roxanne Sterniczuk, RS Psychological Services; Susan Vandermorris, Baycrest Health Sciences

Theme 4: Exercise and cognitive interventions for healthy brain aging and prevention of dementia

Objectives:

There is growing evidence that disrupted sleep is a risk factor for cognitive decline. Older adults who exhibit better sleep tend to have better cognitive ability. However, it is not known whether improving sleep in people with sleep disturbance (i.e., insomnia) using non-pharmacological means, reduces the risk of cognitive decline as people age. This systematic review aimed to explore the relationship between intervention to improve sleep and cognitive decline.

Design and Methods:

Original published material indexed by Ovid MEDLINE, Cochrane and EBM Reviews, Pubmed, and PsycINFO were systematically searched to identify randomized controlled trials that investigated if treating insomnia in cognitively healthy adults aged ≥ 45 years minimizes the risk of cognitive decline later on in life.

Results:

Five randomized controlled trials were identified that met our eligibility criteria. The identified interventions for sleep disturbance included cognitive behavioural therapy for insomnia, behavioural approaches, and cognitive training. However, no study provided findings that answered our question of interest. The studies either lacked a design with a sufficiently long enough follow-up time point to determine cognitive decline, or did not explore the relationship between sleep and cognitive variables.

Conclusions:

At this time, there is a lack of evidence to characterize the impact of treating insomnia symptoms on risk of cognitive decline later in life. Future research should focus on developing a greater understanding of non-pharmacological treatments for insomnia in relation to changes in cognition, including longer treatment and follow-up times. Incorporating neuropsychological examination will also further our understanding of the objective cognitive correlates of improved sleep.

Investigating links between volunteering in the community and cognitive performance in older adulthood

Hayley Guiney, University of Otago; Liana Machado, University of Otago

Theme 4: Exercise and cognitive interventions for healthy brain aging and prevention of dementia

Introduction/Objective

Recent research suggests that volunteering in the community has the potential to promote healthy cognitive aging via the stimulation of social, cognitive, and physical activity. However, only a handful of relevant studies exist and thus little is known about potential relationships between older adults' volunteering engagement and their cognitive functioning. To address this knowledge gap, we investigated volunteering-cognition links in a sample of nondemented older adults.

Design and Methods

Ninety-one retired, community-dwelling 65 to 75-year-olds attended our laboratory, where they provided sociodemographic information and completed measures of wellbeing and activity engagement, as well as a computer-based battery of cognitive tests that incremented in difficulty and tapped specific functions known to decline with age. For analysis, participants were categorised as 'volunteers' (volunteered at least monthly; n = 58) or 'nonvolunteers' (volunteered less often or not at all; n = 33).

Results

Volunteers performed better than nonvolunteers on the most difficult cognitive task, which assessed working memory ($p = .018$, $d = .57$). However, there was little or no evidence that volunteers performed better on tasks requiring inhibitory control ($p = .348$), task switching ($p = .498$), or selective attention ($p = .087$). There were no group differences in age, education, income, self-rated health, depressive symptoms, self-esteem, or quality of life, indicating that those potential covariates did not account for the association between volunteering and working memory. Although the volunteer group had a higher proportion of females, the observed volunteering-cognition relationship held adjusting for sex ($p = .009$, partial $\eta 2 = .09$). Finally, consistent with the idea that volunteering promotes activity engagement, volunteers reported higher levels of social ($p < .001$, $d = .97$) and cognitive ($p = .002$, $d = .69$) activity.

Conclusions

After taking into account potential covariates, volunteering was modestly associated with working memory. However, there was little or no evidence of a positive link with tasks that tapped other cognitive domains known to decline with age. Future work will be needed to test whether volunteering-cognition relationships are causal, but these novel findings nevertheless provide initial insight into the potential benefits for some aspects of cognition.

Cardiorespiratory fitness modifies intrinsic network connectivity in older adults differently for men and women

Christina J. Dimech, York University; John A.E. Anderson, York University; Gary R. Turner, York University; R. Nathan Spreng, McGill University

Theme 4: Exercise and cognitive interventions for healthy brain aging and prevention of dementia

Cardiorespiratory fitness (CRF) has been shown to slow or reduce age-related changes in the brain. However, little research has examined whether sex differences modify this relationship. In this study, we investigated how the interaction of sex and CRF affects the intrinsic functional connectivity of the brain in older adults. We examined this directly in three networks associated with changes in aging and fitness level. These were the default, fronto-parietal, and cingulo-opercular networks. Fifty-one healthy older adults (31 female) were scanned during the resting state with fMRI to obtain measures of intrinsic connectivity within and across these networks. Global efficiency, a metric of network integration, and local efficiency, a metric of regional specialization, were derived from the resting state fMRI data using graph theoretical methods. We found that (i) males had lower levels of local efficiency across the networks and (ii) CRF was positively associated with local efficiency for males. No reliable associations between CRF, sex, and network efficiency were observed for any individual network. Our findings suggest that for older adults, intrinsic network connectivity is associated with cardiorespiratory fitness in a sex-dependent manner. These results underscore the importance of considering sex differences when examining associations between fitness and brain health in aging research.

Preventing Functional and Cognitive Decline in Normal Aging: The Impact of Physical Exercise and Cognitive Multisensorial Stimulation in a Dual-Task Intervention Program

Natáli Valim Oliver Bento-Torres, Federal University of Pará; Naina Yuki Vieira Jardim, Federal University of Pará; Victor Oliveira da Costa, Federal University of Pará; Josilayne Patrícia Ramos Carvalho, Federal University of Pará; João Bento-Torres, Federal University of Pará; Cristovam Wanderley Picanço-Diniz, Federal University of Pará

Theme 4: Exercise and cognitive interventions for healthy brain aging and prevention of dementia

Introduction: In face of the worldwide aging rate and the silent epidemic cognitive decline and dementia in elderly, the need for intervention strategies to protect and/or improve the functionality and cognitive performance on aging increased. Recent studies suggested that as compared with single stimulation protocols, dual task interventions involving physical exercise and cognitive tasks are more efficient by improving cognitive performance and ability in functional tasks. Although preliminary results in the literature are promising, there are few research using dual-task stimulation protocols. Objective: To investigate the effects of a dual-task intervention program (physical exercise and multisensorial stimulation) on cognitive performances, functionality and quality of life of healthy old adults. Methods: 28 community-dwelling old adults (66.14 ± 1.00 years old) underwent cognitive, physical and quality of life assessments at baseline and post-intervention. Cognition was evaluated through Mini Mental State Examination (MMSE), Semantic and Phonological Verbal Fluency, CERAD word list and automated neuropsychological tests (CANTAB); physical assessments included cardiorespiratory fitness (Six-Minute Walk Test), functional mobility (Timed-up and go Test), lower (30-seconds Chair Stand Test) and upper (dynamometer Jamar®) limbs muscle strength; Dual task functional test were performed by Walking While Talking test and quality of life questionnaire (SF36) were also applied. Subjects participated in dual-task intervention program composed by physical exercise (aerobic and strength training) and multisensorial stimuli, composed by 24 sessions, conducted twice a week for 75 minutes each. Outliers values were excluded and T-test was applied to investigate possible differences between baseline and post-invention assessment. Results: After intervention, subjects showed increased cognitive performance (MMSE, verbal fluency, short-term memory, working memory, sustained visual attention, learning, short-term visual recognition memory), better physical and functional parameters (upper limb strength, cardiorespiratory fitness, functional mobility), improved performance in the dual task functional test and personal perception about improved physical function and diminished limitations due to physical problems (SF36). Conclusions: A 24-session dual task intervention program, based on aerobic and strength exercises and multisensorial stimulation, improves cognition, functional exercise capacity, quality of life and ability to perform dual task activities, as normally required in the daily routine of the old adults.

Basal ganglia and hippocampus volumes are associated with aerobic fitness and intra-individual variability in working memory performance in older adults

João Bento-Torres, Federal University of Pará; Natáli Valim Oliver Bento-Torres, Federal University of Pará; Kirk Erickson, Department of Psychology, University of Pittsburgh,

Theme 4: Exercise and cognitive interventions for healthy brain aging and prevention of dementia

Introduction: Intra-individual variability (IIV) reflects performance fluctuations from within-individual trials on a test. Higher IIV has been associated with poor performance on cognitive assessments, and predicts memory failures, dementia and mortality. White matter degeneration and intracortical demyelination are associated with increased IIV on a Flanker test, simple and complex reaction time tests, and can be used to identify neuroanatomical correlates of cognitive performance in healthy aging and early-stage Alzheimer's Disease. Sedentary behavior increases IIV and aerobic fitness modulates the association between aging and intra-individual Reaction Time (RT) variability. Until present, there is no study regarding the relationship between intra-individual reaction time variability, cardiorespiratory fitness, and volumetric measures of subcortical structures. Objective: To investigate the relationship between physical fitness, MRI volumetric data of the thalamus, hippocampus and basal ganglia, and IIV RT on a spatial working memory task. Methods: Older adults 59 to 76 years old (N = 25) underwent a maximal oxygen consumption test to assess physical fitness (VO2) and a computerized spatial memory task. T1-weighted brain images were acquired using a 3D magnetization-prepared rapid gradient echo imaging protocol. IIV was assessed as standard deviation of RT (SDRT), RT, accuracy and coefficient of variation of RT (CVRT). Normality was assessed by using the Shapiro-Wilk test and Pearson correlations were used to assess the relationships between variables. Results: The volume of right putamen (r=-0,4624, p=0,0199) were correlated with CVRT. Thalamus (left: r=-0,4313, p=0,0354; right: r=-0,4246, p=0,0386), right hippocampus (r=-0,4804, p=0,0175), right pallidum (r=-0,4379, p=0,0323), putamen (right: r=-0,5944, p=0,0022; left: r=-0,4845, p=0,0164) were correlated with SDRT. VO2 was correlated with right (r=0,498, p=0,0133) and left (r=0,4927, p=0,0144) pallidum and right hippocampus (r=0,5518, p=0,0052), as well SDRT (r=-0,5158, p=0,0099) and RT (r=-0,5685, p=0,0037). No correlation was found between accuracy and volumes or VO2. Conclusions: Higher physical fitness was associated with increased volumes and reduced RT and IIV. Lower basal ganglia and hippocampus volumes were associated with higher IIV RT on a working memory test.

The association between physical activity and executive function and memory in older adults

Kayla Hauck, University of Lethbridge; Jennifer Copeland; Lara Coelho; Claudia Gonzalez; Robbin Gibb; Irene Kan, Villanova University; Kimiko McKenzie

Theme 4: Exercise and cognitive interventions for healthy brain aging and prevention of dementia

Executive Function (EF) is a blanket term encompassing socio-emotional control, inhibition, working memory, goal-setting, and mental flexibility. These functions develop during the early years of life and decline among older adults. Preservation of EF is critical as it allows us to plan, shift, and organize our everyday behaviors. Physical activity is known to benefit cognitive function and studies have shown positive correlations between exercise training programs and EF in childhood and adulthood. To examine whether physical activity may protect EF and memory among older adults, a total of 75 participants (M age = 75 years; 15 males and 60 females) were stratified based on their self-reported physical activity using the Godin Leisure Time Exercise Questionnaire. 37 and 38 subjects were classified as high active and low active, respectively. All participants completed a battery of EF assessments, including both paper-based (Behavior Rating Inventory of Executive Function (BRIEF) and Amsterdam Executive Function Inventory) and hands-on (Stroop effect, Tower of Hanoi, and Snap - a version of the Wisconsin card sorting test) tasks, as well as a memory test (Wechsler Memory Scale). In addition, participants reported their perceived handedness, habitual physical activity, and time spent in sedentary behaviour. Results showed that seniors who report more physical activity had superior EF and memory compared to seniors who report less; this suggests that physical activity could help preserve cognitive ability (specifically executive function and memory) as we age. It is well known that physical activity can benefit physical health; our results suggest that leisure-time physical activity is also positively associated with intellectual function among older adults.

Evaluation of the Minds in Motion Program

Megan O'Connell, University of Saskatchewan; Joanne Michael , Alzheimer Society of SK; Vanina Dal Bello-Haas, McMaster

Theme 4: Exercise and cognitive interventions for healthy brain aging and prevention of dementia

We evaluated Minds in Motion (MIM), an 8-week community-based exercise and socialization program for persons with dementia and their informal caregivers, which was implemented by the Alzheimer's Society of Saskatchewan. We explored whether participants appeared engaged, measured with observations (Menorah-Park Engagement Scale; M-PES), and whether participants exercised at the desired level of intensity, measured with BORG Perceived Exertion Scale), at week 1, week 3, week 5, and week 8. After completion of MIM, participants' impressions of their participation were gathered with semi-structured interviews. High levels of engagement were seen across all observed sessions. These data are notable for their consistency across weeks of the MIM sessions, with consistently high levels of engagement observed in most M-PES domains. The expression of pleasure, however, demonstrated more individual variability with most expressing pleasure during the activity. Although we saw considerable between person variability, on average, the MIM participants reported a moderate (i.e., above 3 on the modified Borg scale of perceived exertion scale) during exercise. The response to the MIM was overwhelmingly positive with all indicating they would enroll again. Exercise was mentioned most often in response to the general query of what they liked the most about the MIM program. Second most often reported as the best part of the MIM was the opportunity for socialization. A notable minority mentioned the accommodating nature of the MIM program as a positive due to participants with vast differences in abilities – both in physical ability and cognitive/functional ability. Some mentioned exposure to persons with a wide range of cognitive abilities as educational and helpful for planning for the future. Many positive comments revolved around the theme of inclusiveness and the 'non-threatening' environment, including explicit mention of being in a group with others who also have dementia and with other care partners of persons diagnosed with dementia. In summation, the evaluation of the MIM was overwhelmingly positive, but we suggest improvements through individualized goal setting to ensure exercise is at an appropriate intensity and to attain the target of 150 minutes weekly of moderate intensity of exercise to obtain maximal benefits for cognition and function.

Alpha-Klotho protein correlates with hippocampal volume related cognitive changes induced by aerobic exercise in older adults

Andreas Becke, Institute of Cognitive Neurology and Dementia Research, Otto-von-Guericke University, Magdeburg; Anne Maass, German Center for Neurodegenerative Diseases; Emrah Duezel, Institute of Cognitive Neurology and Dementia Research, Otto-von-Guericke University, Magdeburg

Theme 4: Exercise and cognitive interventions for healthy brain aging and prevention of dementia

Aerobic exercise is an important component to delay neurodegeneration in old age. One mediating factor is the expression of neurotrophic and vascular growth factors as well as life extension factors namely Alpha-Klotho proteins. A reduced level of Alpha-Klotho is related to cognitive decline, while increased values with slowing progression of cancer and dementia. Animal studies show that a down regulation of hippocampal Klotho inhibits adult hippocampal neurogenesis. While human studies on structural and functional changes in the hippocampus show controversial findings on the effects of exercise mediated peripheral levels of neurotrophic and vascular growth factors, we were interested in the relation of exercise induced Alpha-Klotho level changes on the effect of hippocampus volume and memory performance.

Forty healthy older humans (mean age=68.4±4.3 years, 55% female) were pseudo-randomly assigned to either an aerobic exercise group (indoor treadmill, n=21) or to a control group (indoor progressive-muscle relaxation/stretching, n=19). Hippocampus Volumes were gained from manual segmentations of 7Tesla-T1 images (0.6 mm isometric voxels) which were acquired along a cognitive test battery, serum fasting blood samples for analysis of human soluble Alpha-Klotho protein and ergospirometry measures (volume of oxygen consumption) at the beginning and the end of a 3-month aerobic exercise intervention.

Mean values of individual changes of hippocampal volumes, memory scores for delayed memory recognition in complex figure task (RCF), Alpha-Klotho and oxygen consumption at ventilatory threshold were compared between groups and further used for regression analysis, corrected for age and gender. Residuals show a significant positive correlation between RCF scores and Alpha-Klotho levels as well as a positive correlation of hippocampal volume and Alpha-Klotho. These findings were irrespective of fitness changes but more prominent in the exercise training group. The results provide additional evidence for the function of Alpha-Klotho mediating adult hippocampal neurogenesis. Further studies need to examine how physical exercise modulates this process specifically, thereby exploiting its full potential in supporting healthy aging.

Preliminary Results: Preventing Language Decline in Dementia

Alita Fernandez, Rotman Research Institute; Regina Jokel, Rotman Research Institute; Malcolm Binns, Rotman Research Institute

Theme 4: Exercise and cognitive interventions for healthy brain aging and prevention of dementia

The purpose of this clinical trial was to examine whether language intervention can improve word finding abilities in individuals with a diagnosis of primary progressive aphasia (PPA) who have difficulty with word retrieval. The design allowed us to explore the differential benefits of semantic versus phonological cues. Participant enrolled in the study received 12 sessions of language therapy (2 sessions/week) for items that were relevant to their life, but they were no longer able to name. Six therapy sessions were phonologically based and six sessions were semantically based. Experimenter-provided errorless learning paradigm was utilized. Twenty participants completed individual therapy, 17 of them had a diagnosis of logopenic (lPA) or non-fluent (nPA) and three had a diagnosis of fluent/semantic (sPA) PPA. With prominent phonological deficits present in lPA and nPA participants, we predicted a significantly greater success rate of re-learning words in phonological therapy than in semantic therapy. Likewise, due to the dominant semantic deficits present in sPA participants, we predicted a significantly higher success rate from the semantic therapy than the phonological therapy. A Wilcoxon signed-rank test showed a statistically significant higher success rate of re-learning words after phonological therapy ($M = 15.00$, $SD = 5.244$) vs semantic therapy ($M = 13.26$, $SD = 6.37$) for lPA/nPA participants ($Z = -1.939$, $p = 0.052$), with an effect size of $r = -0.47$ (large effect size). In our sPA group ($Z = -1.0$, $p = 0.317$), no statistical significant difference was observed for re-learning words between phonological therapy ($M = 9.83$, $SD = 4.25$) and semantic therapy ($M = 12.00$, $SD = 5.0$), however a large effect size was noted ($r = -0.57$). We also tested all participants on a set of untreated control words after each therapy approach and found a significantly greater acquisition of naming in treated words, in comparison to the non-treated words ($p > 0.00$). The results of this study give rise to a viable treatment option that promotes the maintenance of language function and one's communication skills, as well as improve our understanding of preferential learning mechanisms and individualized treatment methods for persons with PPA.

The Brain in Motion II randomized controlled trial: An aerobic exercise intervention for older adults at increased risk of dementia

Cameron Clark, University of Calgary; Veronica Guadagni, University of Calgary; Samantha Hall, University of Calgary; Stewart Longman, Alberta Health Services; Marc Poulin , University of Calgary; Gail Eskes, Dalhousie University; Heather Hanson, Alberta Health Services; Meaghan McDonough, University of Calgary; Michael Hill, University of Calgary; David Hogan, University of Calgary; Tolulope Sajobi, University of Calgary; Patrick Hanly, University of Calgary

Theme 4: Exercise and cognitive interventions for healthy brain aging and prevention of dementia

Introduction:

Despite extensive previous and ongoing research efforts, there remains no effective intervention capable of curing, reversing, or preventing dementia. For this reason, current research is beginning to focus on intervening in neurodegenerative processes before the cognitive and clinical symptoms of dementia manifest. Here we describe the methods of an upcoming randomized controlled trial (RCT) which aims to assess the individual and joint effects of aerobic exercise and behavioural support interventions on older adults at increased risk of dementia.

Methods:

A total of 264 participants (aged 50-80 years) at elevated risk of dementia will be recruited from the community, and randomized to either: 1) an aerobic exercise intervention group; or 2) a stretching-toning active control condition – each 6-months in length. The exercise intervention will consist of a three supervised walking/jogging sessions per week, and increase in intensity and duration over the intervention period. In contrast, participants randomized to the stretching-toning active control group will devote an equal amount of time to sessions focussed on stretching-toning rather than aerobic exercise. Following exercise intervention, participants will be re-randomized to receive 12-months of ongoing behavioural support (i.e. six 15-30 minute supportive phone calls aimed at increasing adherence to an active lifestyle), or not. Assessments covering a variety of cerebrovascular/physiological, neuroimaging, cognitive, lifestyle, and psychological variables will be conducted at each of 0, 3, 6, and 18-months.

Specific aims of the Brain in Motion II study are to: 1) determine the independent effect of exercise on cognitive performance in older adults at increased risk of dementia; 2) determine underlying biological mechanisms that influence cognitive performance after exercise training, and; 3) determine the extent to which changes in cerebrovascular physiology and function persist 12 months after a 6-month exercise intervention.

Implications:

Stated simply, the Brain in Motion II study seeks to determine if aerobic exercise, with or without behavioural support, can improve cognitive functioning in older adults at elevated risk of dementia –

and if so, elucidate the physiological and cerebrovascular mechanisms by which it does. Definitive answers to these questions hold massive clinical and practical importance in the continued search for a cure for dementia.

Effects of 6-months aerobic exercise on cerebrovascular function and oxidative stress in older adults with and without Metabolic Syndrome

Chantal Rytz, University of Calgary; Marc Poulin , University of Calgary; Vincent Pialoux, Univ Lyon, Université Claude Bernard Lyon 1, Laboratoire Interuniversitaire de Biologie de la Motricité (LIBM); Agnès Martin, Univ Lyon, Université Claude Bernard Lyon 1, Laboratoire Interuniversitaire de Biologie de la Motricité (LIBM); Mathilde Mura, Univ Lyon, Université Claude Bernard Lyon 1, Laboratoire Interuniversitaire de Biologie de la Motricité (LIBM); David Hogan, University of Calgary

Theme 4: Exercise and cognitive interventions for healthy brain aging and prevention of dementia

Introduction: Physical inactivity is the fourth leading modifiable risk factor for global mortality, and one of the most prevalent cardiovascular risk factors in Canada. Increasing age in adults is associated with decreased physical activity & cerebrovascular function and increased content of reactive oxygen species (ROS) & level of oxidative stress (OS). Individuals with metabolic syndrome (MetS), for their age, show increased ROS production & decreased cerebrovascular function. We examined the effects of exercise on OS and cerebrovascular function, and the differences amongst these factors after an exercise intervention in individuals with and without MetS.

Methods: 167 middle-aged and older sedentary participants completed a study to determine the effects of 6 months of aerobic exercise on maximal aerobic capacity (VO2max) cerebrovascular function, and cognition. Of this group, 39 individuals met standard criteria for MetS. Cerebrovascular function was assessed using transcranial Doppler ultrasound during hypercapnia and submaximal exercise. Blood samples were used to assess the following oxidative stress and antioxidant biomarkers - Advanced Oxidation Protein Products (AOPP), Ferric Reducing Antioxidant Power (FRAP), Catalase, Glutathione Peroxidase (GPx), Superoxide Dismutase (SOD), nitrotyrosine, malondialdehyde (MDA) and nitric oxide metabolites (NOx). Paired samples t-tests were used to compare changes in cerebrovascular function and OS pre- and post-intervention. One-way ANOVA was used to compare group effects.

Results: VO2max (ml/kg/min) and percent predicted VO2max (ml/kg/min) were significantly higher in participants without MetS pre- and post-intervention ($p < 0.01$). AOPP ($p < 0.001$) and NOx ($p=0.009$) were significantly lower post-intervention in those without MetS. Among those without MetS, women had lower AOPP ($p=0.05$) and men had lower AOPP ($p=0.02$) and NOx ($p=0.046$) post-intervention. Catalase ($p=0.05$) was significantly lower in men with MetS post-intervention. The effects of the exercise intervention on cerebrovascular function, and the cerebrovascular function-OS relationship remain to be determined.

Conclusions: These results suggest that the presence of MetS could blunt the ability of exercise to reduce OS. Interesting sex differences were noted that require exploration. The analyses, when completed, may provide insight on the influence of exercise on cerebrovascular function, OS-cerebrovascular relationships, & potential effect modification by sex &/or the presence of MetS.

Behavioral correlates of striatal improvements following 20 weeks of dance-based exercise in older African Americans

Ashlee Shaw, Rutgers University-Newark; Mark Gluck, Rutgers University-Newark; Neha Sinha, Rutgers University-Newark

Theme 4: Exercise and cognitive interventions for healthy brain aging and prevention of dementia

Introduction/Objective

African Americans have two to three times the prevalence of Alzheimer's disease compared to white Americans. This increased risk of Alzheimer's is thought not to be purely genetic, but due, in part, to health and lifestyle factors (i.e., increased sedentary behavior and obesity, lower physical activity). Aerobic exercise is known to improve the function of brain regions that decline with age; however, there are gaps in the literature that must be addressed.

Firstly, while most research to date has focused on frontal and hippocampal regions, the striatum, which is also known to decline with age, is understudied. Additionally, most aerobic exercise interventions focus on well-learned, repetitive behavior (i.e., walking or cycling), which may cause a relative under-engagement of striatal areas in these interventions. Finally, African Americans, while among those most at risk for Alzheimer's disease, are underrepresented in biomedical research, due to real and perceived past abuses by researchers.

Design and Methods

As part of a larger brain health research and outreach initiative, we evaluate a five-month dance-based aerobic exercise intervention for its ability to improve cognition and brain function in healthy African-American seniors, aged 55 and older, who at high risk for cognitive decline due to obesity and/or sedentary lifestyles. Dance aerobics was chosen because it requires movement learning (and therefore may engage the striatum in a way that well-learned movements do not), and has increased cultural appeal to participants. Pre- and post-intervention, all participants receive a full health (i.e., VO2 max, blood pressure, etc.), lifestyle (i.e., diet, sleep, etc.), neuropsychological (i.e., dementia risk, working memory, depressive symptoms, etc.), and cognitive battery, which includes a reward- and punishment-learning task that is known to tap into striatal function.

Results

At present, preliminary behavioral results suggest improvements in punishment learning after only 5 months of dance-based exercise ($F(1,82)= 3.34$, $p = 0.07$; $n=42$) when compared to non-exercising controls ($F(1,28)= 0.27$, $p = 0.61$; $n=15$).

Conclusions

The current work suggests that moderate-intensity dance-based aerobic exercise may improve behavioral correlates of striatal function in healthy older adults at risk for dementia due to sedentary lifestyles. Future work will examine dosage effects.

The Utility of the Mild Behavioral Impairment-Checklist in Detecting Mild Cognitive Impairment and Dementia

Sophie Hu, University of Calgary; Zahinoor Ismail, University of Calgary; Scott Patten, University of Calgary

Theme 5: Applied research in dementia

INTRODUCTION: By 2036, 1 in 4 Canadians will be 65 or older and many will suffer cognitive decline and/or dementia. Although memory loss is a hallmark of dementia, neuropsychiatric symptoms (NPS) are early markers. Mild Behavioral Impairment (MBI) is a syndrome of sustained NPS as an at-risk state for cognitive decline and dementia. However, NPS have been historically viewed in the context of dementia populations rather than pre-dementia populations with mild cognitive impairment (MCI). The MBI Checklist (MBI-C) was developed with applicability to populations with normal cognition or MCI. The MBI-C assesses motivation, mood, impulse control, social appropriateness and perception. As the MBI-C is a new instrument, its utility will be compared to the gold standard Neuropsychiatric Questionnaire (NPI-Q) for normal cognition, MCI and dementia patients.

RESEARCH QUESTION: How does the MBI-C compare to the NPI-Q in detecting NPS in a cognitive neurology clinic?

OBJECTIVE: To determine the sensitivity of MBI-C scores in comparison to the NPI-Q to detect NPS in normal cognition, MCI and dementia.

METHODS: The MBI-C is routinely administered in the Cognitive Neuroscience Clinic at the University of Calgary. We will retrospectively analyze MBI-C and NPI-Q scores in normal cognition, MCI and dementia patients using 2-sample t-tests and logistic regression.

RESULTS: Normal cognition patients (n=18) had an average NPI-Q score of 3.22 ± 0.83 (p=0.22) and MBI-C score of 9.56 ± 1.76 (p=0.25). MCI patients (n=92) had an average NPI-Q score of 3.86 ± 0.43 (p=0.63) and MBI-C score of 12.02 ± 1.03. Dementia patients (n=58) had an average NPI-Q score of 4.72 ± 0.63 (p=0.06) and MBI-C score of 12.28 ± 1.28 (p=0.14).

CONCLUSIONS: As cognitive decline progresses, NPI-Q and MBI-C scores increase. The MBI-C may be used to detect NPS in normal cognition and MCI patients, and to predict incident cognitive decline and dementia. Historically, NPS have been exclusion criteria for dementia clinical trials, but this may change if evidence supports the utility of MBI in dementia prognostication.

What works in dementia training and education for the health and social care workforce?: findings from a UK study

Claire Surr, Centre for dementia Research, Leeds Beckett University; Cara Sass, Centre for Dementia Research, Leeds Beckett University; Michelle Drury, University of Leeds; Sarah Smith, Centre for Dementia Research, Leeds Beckett University; Sahdia Parveen, University of Bradford; Natasha Burnley, Centre for Dementia Research, Leeds Beckett University; Andrea Capstick, University of Bradford; Alison Dennison, University of Bradford; Jan Oyebode, University of Bradford

Theme 5: Applied research in dementia

Background:

Creating an informed and effective dementia workforce has been a UK government priority since it was included in the National Dementia Strategy in 2009. A range of policies and programmes over recent years have sought to increase the availability and reach of dementia training, however this has been with limited evidence about what constitutes high quality, effective training.

Aims:

The What Works? study was commissioned by the UK Department of Health Policy Research programme on behalf of Health Education England, in order to investigate the ingredients associated with effective dementia education and training.

Methods:

Kirkpatrick's four level model (learner reaction, learning, behaviour change, outcomes) for the evaluation of training underpinned the study. It was comprised of a number of components including: 1) a systematic review of existing international literature (n=152 papers), 2) a national audit of dementia training undertaken with care and training providers and commissioners (n=420), 3) survey of staff (n=553) who had undertaken dementia training to assess knowledge, attitudes and barriers and facilitators to implementation and 4) in-depth, mixed-methods case studies (n=10) in health and social care organisations who demonstrated hallmarks of good practice.

Results:

Training that led to positive outcomes across the four Kirkpatrick levels was delivered face-to-face, was interactive, tailored to the service setting and role of learners and delivered by an experienced training facilitator with clinical dementia experience. There were a range of barriers to training implementation including a lack of time and resources, poor staff attitudes towards training and poor planning in terms of release of staff to attend training. Facilitators for training implementation included a supportive organisational culture and management, clear and strong leadership for dementia training and a whole systems approach that connected managers, trainers and learners.

Implications for policy/practice:

Dementia training will form a component of any care quality improvement strategy. There are a number of training features and setting conditions that are more likely to lead to positive outcomes across the four Kirkpatrick levels. Care provider organisations, training providers, commissioners and policy makers should consider these in any training policy, strategy or implementation plan.

Creating Dementia-Friendly Exercise: Experiences, Perceptions, and Needs of Community Exercise Providers.

Lauren Bechard, University of Waterloo; Cheyenne Marie Mitchell, University of Waterloo; Aidan Holley McDougall, University of Waterloo; Kayla Regan, University of Waterloo; Maximillian Bergelt, University of Waterloo; Laura Middleton, University of Waterloo

Theme 5: Applied research in dementia

INTRODUCTION: Dementia prevalence in Canada is expected to exceed 1 million people by 2038. Exercise is associated with reduced dementia risk and sustained functional abilities in persons with mild cognitive impairment (MCI) and dementia. Despite these benefits, persons with MCI/dementia are frequently inactive due to poor support and accommodation of their needs in exercise programs. Community exercise providers delivering programming to persons with MCI/dementia could mitigate these barriers by improved accommodation of their needs.

OBJECTIVE: To explore the experiences, perceived barriers and facilitators, and educational needs of exercise providers for delivering exercise to persons with MCI/dementia.

DESIGN & METHODS: Semi-structured focus groups were held with community exercise providers who delivered exercise to older adults (≥55 years). Focus groups were audio-recorded, transcribed verbatim, and analyzed using thematic analysis. RESULTS: Five focus groups were conducted with a total of 30 exercise providers. Three themes emerged from analysis. (1) Unique experiences lead to diverse perceptions of dementia. Exercise providers reported a variety of personal and professional experiences with MCI/dementia, which informed their perception of and strategies used to deliver exercise to persons with MCI/dementia. (2) Learning as you go, adapting exercise prescription and instruction "case-by-case" for people with dementia. Exercise providers perceived cognitive and behavioural dementia symptoms as barriers to participation in exercise, but many developed their own strategies for program design and delivery to adapt to the abilities and preferences of individual clients with MCI/dementia. (3) Determining best practices while accommodating dementia heterogeneity. Exercise providers identified a need for more education and best practice guidance on dementia-friendly exercise, but noted the progressive and heterogeneous nature of dementia as a challenge to standardized approaches.

CONCLUSIONS & IMPLICATIONS FOR PROGRAMS: Exercise providers support the creation of inclusive community spaces for exercise for persons with MCI/dementia, but have little dementia education and/or training in best practices for dementia-friendly exercise provision. Standardized education and best practice sharing networks could reduce reliance on disparate experiences and trial-and-error approaches in programming. Developing structured educational resources and training opportunities for exercise providers may broaden their scope of knowledge and increase accessibility of exercise programs to persons with MCI/dementia.

COMPAs - An iPad app that supports communication in dementia

Michele Masson-Trottier, Université de Montréal, Centre de recherche de l'IUGM; Ana Inés Ansaldo, Université de Montréal, CRIUGM

Theme 5: Applied research in dementia

Over 402 000 Canadians are living with dementia1; and the numbers will increase significantly in years to come. Along with behavioural disorders, communication impairment is a main feature of dementia. Communication breakdown between the person living with dementia (PWD) and their caregivers has a deleterious influence on the quality of life of PWD and their proxies, increasing isolation for all the people involved, and burden in the caregivers, a factor that accelerates the process leading to institutionalization. Given the poor results with pharmacological interventions, most efforts are presently focused on behavioural interventions adapting communication tools to facilitate communication between PWD and their caregivers. New technologies represent an interesting support to adapted communication, as they are portable, can stock a lot of significant material, while favouring intergenerational relationships2. Based on this research and others in the field of neuroscience3-5, we have developed COMPAs, an iPad application designed to facilitate communication between PWD and their caregivers. COMPAs gathers personalized contents such as images, photos, musical excerpts and videos related to the life trajectory of the person in an organized and user-friendly manner. Easy access to this content provides significant elements to support communication and enhance the quality of life of the PWD and his or her caregivers. COMPAs also allows the caregiver to subjectively rate the communication of the PWD and compiles these ratings in the online file. A health professional can therefore have an idea of the evolution of the symptoms, directly from his office. The advantages of COMPAs are numerous, such as giving the caregivers a tangible communication support and encouraging them to use effective communication strategies. There is also an online training website to guide the caregiver in using COMPAs. We will illustrate the use and benefits of COMPAs, while presenting pilot data on communication changes secondary to the use of COMPAS in dyads of PWD and their caregivers.

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The Incremental Healthcare Costs of Dementia and Frailty among Home Care Recipients

Colleen Maxwell, University of Waterloo; Luke Mondor, Institute for Clinical Evaluative Sciences; David Hogan, University of Calgary; Susan Bronskill, Institute for Clinical Evaluative Sciences; Michael Campitelli, Institute for Clinical Evaluative Sciences; Walter Wodchis, University of Toronto

Theme 5: Applied research in dementia

Introduction: Timely data on the healthcare use and costs of dementia in Canada are essential for informed clinical and public policy programs. Current cost estimates for dementia in Canada are lacking and no studies have yet to examine the incremental healthcare costs associated with both dementia and frailty, despite evidence of increasing prevalence of both conditions and their bidirectional association.

Methods: Using linked clinical and administrative health databases in Ontario, we conducted a retrospective cohort study of all long-stay home care clients aged 50+ years with an index clinical assessment between April 1, 2014 and March 31, 2015 and who met key eligibility criteria (n=160,209). At baseline, prevalent dementia was defined using a validated case ascertainment algorithm and frailty categories (robust, pre-frail, frail) were defined based on a modified frailty index from 66-items derived from clinical assessment data. Clients were followed prospectively for 1-year (divided into bi-monthly intervals), for which we obtained total- and sector-specific public healthcare costs for all encounters. We calculated differences between dementia-frailty groups using a three-part, regression-based, survival- and covariate-adjusted cost estimator described by Manning and Basu (2010) that included dementia-frailty interactions. All figures are reported in $2015CAD.

Results: Prevalence of dementia was 26.8% and 33.3% of these clients were frail (vs. 26.9% among clients without dementia). Approximately 15% of the cohort died over the 1-year follow-up. The average 1-year estimated total health system cost was $26,965. On average, home care clients with dementia categorized as frail incurred $14,291 (SE=$139) more in charges than similar robust clients ($35,381 vs. $21,091, respectively). In contrast, frail persons without dementia incurred $12,796 (SE=$95) more in charges that similar robust clients ($33,659 vs. $20,864, respectively). Among frail persons, those with dementia incurred $1,722 (SE=$149) more in expenditures, on average.

Conclusions: Dementia and frailty pose significant challenges to healthcare systems and society. Although costs are elevated for clients with dementia, our findings illustrate much larger incremental cost associated with frailty, regardless of dementia status. Our data are limited to public healthcare costs in Ontario and further research is needed to explore the joint impact of these two conditions on formal and informal care costs across different regions and care settings.

Examining the relevance of frailty to cholinesterase inhibitor (ChEI) use and discontinuation during transition to long-term care: a population-based cohort study

Colleen Maxwell, University of Waterloo; Laura Maclagan, Institute for Clinical Evaluative Sciences; Susan Bronskill, Institute for Clinical Evaluative Sciences; Jun Guan, Institute for Clinical Evaluative Sciences; Michael Campitelli, Institute for Clinical Evaluative Sciences; Nathan Herrmann, Sunnybrook Hospital; Kate Lapane, University of Massachusetts Medical School; David Hogan, University of Calgary; Joseph Amuah, University of Ottawa; Dallas Seitz, Queens University; Sudeep Gill, Queens University

Theme 5: Applied research in dementia

Objectives:

Understanding the determinants of continued use or withdrawal of ChEIs during the transition into long-term care (LTC) may help in assessing the appropriateness of this decision-making. Patterns of ChEI use at and following LTC admission among persons with dementia are described. We examined whether frailty, among other factors, was associated with discontinuation.

Approach:

Linked clinical and administrative health databases were used to conduct a retrospective cohort study of 47,851 adults (aged 66+) with dementia newly admitted to LTC in Ontario between April 2011-March 2015. ChEI use at admission and during the following year was identified. Frailty when admitted was calculated using a validated 72-item index derived from the Resident Assessment Instrument (RAI-MDS 2.0). Discontinuation was defined as a 30-day period when no dispensations occurred and no supply of ChEI was available. Subdistribution hazard models were used to estimate the association between resident characteristics and discontinuation, accounting for the competing risk of death.

Results:

Over a third (36.7%) of residents were receiving a ChEI at admission and this proportion was lower among those defined as frail (33.6%) vs.non-frail (40.7%) at admission. Among those on a ChEI at admission, 82.3% continued use and 17.7% discontinued during the following year. After accounting for resident characteristics, ChEI type and history of use, the incidence of discontinuation was 15% higher in frail residents compared to non-frail residents (hazard ratio (HR)= 1.15, 95% confidence interval (CI) [1.01,1.30]). Residents with severe aggressive behaviours (HR=1.82, 95% CI [1.60, 2.07]), and higher levels of cognitive impairment (HR=1.29, 95% CI [1.10, 1.51]) were also more likely to discontinue. Residents aged 85+ (HR=0.69, 95% CI [0.61, 0.77]) and those who were widowed (HR=0.84, 95% CI [0.77, 0.91]) were less likely to discontinue.

Conclusions:

Most LTC residents who entered LTC on a ChEI continued treatment during the subsequent year. Frailty, severity of cognitive impairment and aggressive behaviours were associated with ChEI discontinuation; whereas selected sociodemographic factors predicted continued use. Future work should examine long-term outcomes associated with cholinesterase inhibitor discontinuation in this population.

Longitudinal evaluation of dual-task walking in patients with Alzheimer's Disease (AD).

Angela Juby, University of Alberta; Christopher Davis, University of Alberta

Theme 5: Applied research in dementia

Introduction

Patients with AD are known to have increased risk of falls, not only due to cognitive/judgement issues but also specific gait problems. AD is associated with executive function impairment, and hyper-excitability of the motor cortex which is known to affect their gait. This results in lower gait speed. In mild cognitive impairment (MCI) longitudinal evaluation of dual-task walking has been shown to identify those who are more likely to develop AD. To date, no longitudinal evaluation of AD patients has been reported.

Objectives

Longitudinal evaluation of gait in AD patients to assess the association between preferred walk (PW) speed and dual-task walking (DTW) speed and cognition.

Methods

AD patients were timed over a 6m walking mat for their PW and DTW. The DTW was counting aloud backwards from 100 by 1's. The change in these times over the 6 month study period was evaluated (baseline, 3 and 6 months), and compared to the change in their cognition over the same time (using the MMSE and MoCA). No specific gait and balance interventions were done.

Results

19 AD patients with an average age of 72.7yrs (54-84), including 8 women and 11 men participated. Their average baseline MMSE was 20.7 (5-30) and M0CA was 17.6 (0-25). PW time at baseline varied from 4.6 to 12s (average 6.6s), DTW 5.3 to 15.5s (average 8.3s). Over 6 months there was no trend for increased walking times. There was no correlation between baseline MMSE or MoCA and PW and DTW time (R=-0.00 to -0.44). There was no correlation between percentage change in MMSE and change in DTW (R=0.335) or between MoCA and DTW (R=-0.363). The percentage difference between the PW time and DTW time was moderately negatively correlated with MMSE at baseline and 3 months (R=-0.55 to -0.71), but not at 6 months.

Conclusions

Walking time (PW vs serial 1's DTW) alone is not discriminatory enough to assess the relationship between DTW and cognition in patients with established AD. Further analysis of more challenging DT activities may be more discriminatory; however, this analysis will also require correction for the number of responses.

Association Between Surgery with General or Regional Anesthesia and Subsequent Development of Dementia

Dallas Seitz, Queens University; Maria Hussain, Queen's University; Marlo Whitehead, Institute for Clinical Evaluative Sciences; Sudeep Gill, Queens University; Roderick Eckenhoff, University of Pennsylvania; Miles Berger, Duke University; Clive Velkers, Queen's University; Cara Reimer, Queen's University

Theme 5: Applied research in dementia

Background: Surgical procedures and the type of anesthesia administered for surgery have been proposed as potential risk factors for development of dementia. Observational studies conducted to date have shown conflicting results and have had methodological limitations small sample sizes and limited control of potential confounders. Our study evaluated the association between receipt of elective surgeries using either general anesthesia (GA) or regional anesthesia (RA) among older adults in Ontario.

Methods: We conducted a retrospective cohort study of adults aged 66 and older who did not have dementia or prior history of surgery and underwent one of five common elective surgical procedures (hip replacement, knee replacement, inguinal hernia repair, prostatectomy, or hysteretomy) in Ontario. Individuals who had surgery with GA or RA were then matched 1:1 to a surgical consult only group on age, gender, type of surgeon, calendar year, and propensity score. Participants were followed for a minimum of one year and up to 5 years for the development of dementia. Cox proportional hazards models were used to determine the hazard ratio (HR) and 95% confidence intervals (CI) for the associations between surgery and anesthesia.

Results: There were a total of 15,800 pairs of GA:controls and 16,193 pairs of RA:controls. The matched groups were well balanced on potential confounders. Survival analysis demonstrated a reduced risk of the development of dementia for individuals who underwent surgery with either GA (HR: 0.91, 0.85 – 0.95, P=0.04) or surgery with RA (HR: 0.72, 95% CI: 0.61 – 83, < 0 .0001).

Conclusions: In this observational study, receipt of surgery with either GA or RA was not associated with an elevated risk of developing dementia. Additional studies are required to determine if there are specific patients populations who may be susceptible to the development of dementia following major surgical procedures.

Depressive Symptoms in Long Term Care Facilities in Western Canada: A Cross Sectional Study.

Zahra Goodarzi, University of Calgary ; Abi Heninger , University of British Columbia; Matthias Hoben, University of Alberta; Jayna Holroyd-Leduc, University of Calgary; Carole Estabrooks, University of Alberta; Jennifer Knopp-Sihota, Athabasca University

Theme 5: Applied research in dementia

Objectives: The main objective is to better understand the prevalence of depressive symptoms, in long-term care (LTC) residents with or without cognitive impairment across Western Canada. Secondary objectives are to examine comorbidities and other factors associated with of depressive symptoms, and treatments used in LTC.

Design: Cross-Sectional Study

Setting & Participants: 11,445 residents across a random sample of 91 LTC facilities, from 09/2014 to 05/2015, were stratified by owner-operator model (private for-profit, public or voluntary not-for-profit), size (small: 120 beds), location (Calgary and Edmonton Health Zones, Alberta; Fraser and Interior Health Regions, British Columbia; Winnipeg Health Region, Manitoba).

Methods: Random intercept generalized linear mixed models with depressive symptoms as the dependent variable, cognitive impairment as primary independent variable, and resident, care unit and facility characteristics as covariates were used. Resident variables came from the Resident Assessment Instrument – Minimum Data Set (RAI-MDS) 2.0 records (the RAI-MDS version routinely collected in Western Canadian LTC). Care unit and facility variables came from surveys completed with care unit or facility managers.

Results: Depressive symptoms affect 40.1% of all LTC residents and 34.8% of LTC resident have both, depressive symptoms and cognitive impairment. Hypertension, urinary and fecal incontinence were the most common comorbidities. Cognitive impairment nearly doubles the risk for depressive symptoms (adjusted odds ratio 1.91 [95% confidence interval 1.68; 2.17]). Pain, anxiety and pulmonary disorders were also significantly associated with depressive symptoms. Pharmacologic therapies were commonly used in those with depressive symptoms, however there was minimal use of non-pharmacologic management.

Conclusion: Depressive symptoms are common in LTC residents –particularly in those with cognitive impairment. Depressive symptoms are an important target for clinical intervention and further research to reduce the burden of these illnesses.

The relationship between mild cognitive impairment and driving ability

Anthony Singhal, University of Alberta; Reyhaneh Bakhtiari, University of Alberta; Michelle Ehmig, University of Alberta; Stephen Langor, University of Alberta; Joanna Scanlon, University of Alberta; Aaron Granley, DriveABLE Company

Theme 5: Applied research in dementia

Introduction/Objective: Mild cognitive impairment (MCI) is considered an intermediate condition between normal aging and dementia. Research suggests that people with MCI have a high rate of progression to dementia, which manifests quickly. MCI affects cognition domains including deficits in attention, memory, judgment, and language. An important related area of research is MCI and associated diminished driving abilities that can lead to increased risk for automobile collisions and injury. The present study compared MCI and healthy older aged adults on several indices of driving and cognitive performance to investigate the nature of the relationship between MCI and specific cognitive impairments underlying deficits in driving ability.

Design/Methods: Twenty-five MCI individuals (8 female, 73.9±9.7 yr) and 44 control participants (20 female, 65.3±7.0 yr) participated in this study. Their driving skills were measured with a 45 minute on-road evaluation with a driving instructor, and several computer-based cognitive tasks. The computer tasks were designed to test response-speed, memory, perceptual-motor skills, and decision making.

Results: As expected, analyses of covariance (ANCOVA) with age as a covariate indicated a significant difference between the MCI and control participants in the on-road driving task, where the MCI participants were consistently driving more poorly. Moreover the MCI participants showed an interesting convergence of performance on the computer tasks. Reaction time on several of the tasks was consistently higher for the MCI participants. This pattern was also observed for increased decision-making time on some of the judgement tasks. Performance on the memory tasks showed an interesting shift in the speed-accuracy function, indicating a multi-dimensional deficit in memory performance. Performance on the bimanual perceptual-motor tasks also showed a unique response pattern by the MCI participants' obstacle avoidance and visual-tracking.

Conclusions: The MCI individuals performed significantly worse than the controls on most of the computer-based tasks, as well as on the in-car driving assessment. Taken together, the results across all the tasks show a unique pattern of deficits in cognition and perceptual-motor performance that may underlie the low driving scores. These findings are important to further our understanding of this disease, and foster the development of new strategies for MCI assessment for road safety.

A theoretical framework for using humor to reduce the effects of chronic stress on cognitive function in older adults: An integration of findings and methods from diverse areas of psychology

Sasha Mallya, Ryerson University; Maureen Reed, Ryerson University; Lixia Yang, Ryerson University

Theme 6: All other research and translation approaches to dementia, healthy brain and cognitive aging or other neurodegenerative diseases (eg. FTD, PD/LBD) not covered within themes 1-5

Many older adults experience some degree of cognitive decline, which is associated with reductions in functional status, independence, and overall quality of life. These losses can result in considerable stress that is chronic in nature. Chronic stress, in turn, increases the brain's vulnerability to additional cognitive decline. This theoretical discussion proposes humour as a technique that older adults may use to reduce stress and protect cognitive abilities. Humour here is described as a form of cognitive reappraisal, allowing older adults to reappraise daily stressors. Further, it is speculated that humour's protective value is in the reduction of chronic activation of the physiological stress response systems, which in turn may protect functional integrity of the hippocampus and prefrontal cortex. Because older adults appear to have difficulty solving more complex jokes, we propose that low complexity, self-enhancing humour may be the most useful form of humour to promote healthy brain aging.

Comparing mindfulness and psychoeducation interventions for family caregivers: The impact on cognitive function

Sasha Mallya, Ryerson University; Alexandra Fiocco, Ryerson University

Theme 6: All other research and translation approaches to dementia, healthy brain and cognitive aging or other neurodegenerative diseases (eg. FTD, PD/LBD) not covered within themes 1-5

Approximately 14.9% of Canadians aged 65 and older are living with cognitive impairment, including dementia, which means that there is likely an equal or even greater number of Canadians involved in their care. Relative to non-caregivers, caregivers of persons with dementia typically show more cognitive difficulties (e.g., executive function, memory), and report increased perceived stress, depression, and poor quality of life. The aim of this study was to assess whether a standardized mindfulness-based stress reduction (MBSR) intervention could improve cognitive function and well-being in caregivers, compared to a psychoeducation control group. Family caregivers (N = 57) completed a battery of cognitive and psychosocial measures and were subsequently randomized into an eight week MBSR program (n = 33) or a psychoeducation control group (n = 24). At post-program, all participants completed a re-assessment of cognitive and psychosocial functioning. Results showed that both interventions were associated in improvement in cognitive performance, resulting in no statistically significant differences between groups. However, MBSR was associated with a significantly larger reduction in self-reported depressive symptoms and perceived stress relative to psychoeducation. Results of this randomized controlled trial provide preliminary evidence for the selective benefits of MBSR relative to psychoeducation in a group of older caregivers of individuals with dementia.

Fine tuning cognitive assessment in the elderly using an online test battery

Avital Sternin, University of Western Ontario; Emily S. Nichols, University of Western Ontario; Jessica A. Grahn, University of Western Ontario; Adrian M. Owen, University of Western Ontario

Theme 6: All other research and translation approaches to dementia, healthy brain and cognitive aging or other neurodegenerative diseases (eg. FTD, PD/LBD) not covered within themes 1-5

Assessing cognitive capacity has become a large part of caring for the elderly. Full cognitive capacity assessments are difficult and time-consuming to administer. Shorter tests are used to gain a snapshot of an individual's capacity. Currently, the most widely used short tests are the Montreal Cognitive Assessment (MoCA) and the Mini Mental State Examination (MMSE). In this study, we compared how an online battery of 12 tests (Cambridge Brain Sciences Battery; CBSB) performed compared to these two traditional tests. The CBSB was developed based on existing neuropsychological test literature and has been administered to more than 74 000 individuals.

34 older adults, age 70-92, participated in this study. They completed the CBSB, a MoCA, and a MMSE. All testing occurred in one day.

As in previous studies, we found a high correlation between MoCA and MMSE scores (r = 0.78, p<0.001). Using step-wise multiple regression we investigated which combination of CBSB tasks best predicted MMSE and MoCA scores. MMSE scores were best predicted by two tests (R^2 = 0.46): a verbal reasoning task and a deductive reasoning task. MoCA scores were best predicted by two different tests (R^2 = 0.64): a feature match (FM) test of attentional processing and a test of spatial working memory (TS).

Using MoCA scores, the participants' data were split into three groups: unimpaired (27-30), borderline (23-26), impaired (<22). The FM and TS test scores of the borderline participants were compared to the mean FM and TS scores of the other two groups to determine whether the borderline participants could be further categorized using their scores on either, or both, of the two tasks. This resulted in 8/18 (44%) participants categorized out of the borderline group.

The results showed that different CBSB tests best predicted MoCA and MMSE scores and that CBSB scores could be used to fine tune the MoCA test diagnosis. The regression results suggest that the traditional tests are capturing changes in different cognitive abilities. These results underscore the importance of understanding which components of cognition are measured by the traditional (short) tests and how those components relate to impairments in patient populations.

Diagnosis, Treatment, and Management of Apathy in Parkinson's Disease: A Scoping Review

Bria Mele, University of Calgary; Jayna Holroyd-Leduc, University of Calgary; Zahinoor Ismail, University of Calgary; Tamara Pringsheim, University of Calgary; Zahra Goodarzi, University of Calgary

Theme 6: All other research and translation approaches to dementia, healthy brain and cognitive aging or other neurodegenerative diseases (eg. FTD, PD/LBD) not covered within themes 1-5

Introduction/Objective

Parkinson's disease (PD) is commonly understood to be a movement disorder, however is associated with a variety of non-motor symptoms including depression and apathy. Apathy is present in 17 to 70% of those with PD. Apathy has been observed to decrease quality of life more than the motor symptoms of PD. Despite this, there is no consistently utilized definition for apathy and limited understanding of how to best diagnose and manage apathy. The objective of this scoping review was to synthesize available literature regarding the diagnosis, treatment, and management of apathy in PD and to identify gaps in this knowledge.

Design and Methods

MEDLINE, EMBASE, PsychINFO, CINHAL, Cochrane Central Register of Control Trials, and Cochrane Database of Systematic Reviews were searched to May 17, 2017. The grey literature was searched using the CADTH Grey Matters tool. Original peer-reviewed research was included if it included individuals with PD and apathy. Information regarding diagnosis, treatment, and management was extracted. Non-original data was only included if it was in the form of meta-analysis. Citation/manuscript screening and extraction were performed in duplicate.

Results

From 10,872 citations, 325 articles were included in the final review. Most citations were general epidemiological information on apathy or non-motor symptoms in PD (41%). Fifteen percent described apathy after deep brain stimulation (DBS), and 26% addressed diagnosis, and management of apathy in PD. Seventeen screening tools for apathy were identified. Eight were specific to screening for apathy and nine assessed apathy as part of a larger non-motor symptom-screening tool. Under half the treatment studies identified were randomized control trials (RCTs) (40%). Treatment focused studies utilized a variety of treatment methods including: exercise, mindfulness, Rotigotine (Neupro) transdermal patch, Rivastigmine (Exelon), and Galantamine (Razadyne).

Conclusions and Implications

Although we identified a large body of literature for apathy, most studies were focused on risk factors and prevalence with few studies examining treatment. Future research should aim to detect an ideal screening tool for apathy, to identify the best treatment options for apathy and the variety of co-

morbidities it may present with, and finally aim to better understand post-operative apathy in those with DBS.

Brain slice culture: a tool for characterizing different strains of prion disease

Grant Norman, University of Alberta; Hailey Pineau, University of Alberta; Jody Campeau, University of Alberta; Debbie McKenzie, University of Alberta; Holger Wille, University of Alberta; Valerie Sim, University of Alberta

Theme 6: All other research and translation approaches to dementia, healthy brain and cognitive aging or other neurodegenerative diseases (eg. FTD, PD/LBD) not covered within themes 1-5

Prion diseases, or transmissible spongiform encephalopathies (TSEs), are neurodegenerative diseases that are invariably fatal and for which there are no treatments. TSEs can affect many mammals, including cervids (Chronic Wasting Disease; CWD), sheep (scrapie), cattle (Bovine Spongiform Encephalopathy; BSE), and humans (Creutzfeldt-Jakob Disease; CJD). These diseases result from the conversion of the normal prion protein (PrPC) to a misfolded form (PrPSc) that can template itself and spread through the brain, triggering neurodegeneration. PrPSc can fold into a number of different conformations, each of which can have its own biophysical properties and cause distinct neuropathologies, giving rise to unique prion strains. Traditionally, strains are generated in animals infected with prion disease; however, these are lengthy experiments, often taking several months. Fortunately, Aguzzi and colleagues developed an ex vivo model of prion disease, called the prion organotypic slice culture assay (POSCA), which can faithfully recapitulate prion disease in a dish and on a shortened timescale – 40-50 days. This makes POSCA an ideal method for propagating prion strains. Originally POSCA was developed to test mouse-adapted scrapie strains. Here, we report the adaptation of POSCA to other strains, including CWD strains from deer and elk and CJD strains from human patients. By generating these prion strains ex vivo, we have the opportunity to test strain-specific properties as pathogenesis proceeds, and develop and test strain-specific therapeutic interventions at discrete disease time points and without the confounder of blood-brain barrier.

Epigenetic deregulation through abnormal processing of SINE non-coding RNAs in aging brain and dementia: An integrative RNA genomics approach.

Athanasios (Athan) Zovoilis, University of Lethbridge; Chris Isaac, University of Lethbridge; Babita Gollen, University of Lethbridge; Majid Mohajerani, University of Lethbridge; Jogender Mehla, University of Lethbridge; Yubo Cheng, University of Lethbridge; Kumari Alka, University of Lethbridge; Cody Turner, University of Lethbridge; Travis Haight, University of Lethbridge

Theme 6: All other research and translation approaches to dementia, healthy brain and cognitive aging or other neurodegenerative diseases (eg. FTD, PD/LBD) not covered within themes 1-5

As the human life span increases, the number of people in Canada suffering from aging associated cognitive impairment and dementia is expected to rise dramatically. In a previous work we have shown that learning impairment is connected with hippocampus–specific epigenetic changes of gene expression including Immediate Early Genes (IEGs),(Peleg*, Sanabenesi*,Zovoilis* et al, Science 2010). However, the molecular mechanisms associated with this epigenetic deregulation remain largely unknown. Among mechanisms that have recently attracted attention are those involving epigenetic regulation by non-protein-coding RNAs (non-coding RNAs), including RNAs derived by repetitive DNA (Zovoilis et al, Cell 2016). Repetitive DNA accounts for ~50% of the noncoding sequences, with Short Interspersed Nuclear Elements (SINEs), being among the most frequent repeats. Here, we applied an integrative RNA genomics and bioinformatics approach to dissect any connection of SINE non-coding RNAs with aging associated learning impairment and neurodegeneration. Using cell culture models, mouse models and next-generation sequencing data from dementia and aging patients, we demonstrate that SINE RNAs are associated with dementia and aging associated cognitive impairment. Our study reveals that SINE RNAs are subject to abnormal RNA processing both in rodents and humans, revealing a potential biomarker and a novel molecular mechanism associated with neurodegeneration and learning impairment.

Silent Brain Infarcts and Cognition: A Systematic Review and Meta-Analysis

Feeha Azeem, University of Calgary ; Romella Durrani, University of Calgary; Eric Smith, University of Calgary

Theme 6: All other research and translation approaches to dementia, healthy brain and cognitive aging or other neurodegenerative diseases (eg. FTD, PD/LBD) not covered within themes 1-5

Background: Dementia is the worldwide leading cause of disability in the elderly population, and its prevalence is estimated to triple by 2050, reaching 132 million cases worldwide. Cerebrovascular disease is the second most common cause for dementia after Alzheimer's disease. Evidence based on current literature identifies vascular abnormalities, such as silent brain infarctions (SBI), as an important contributor to cognitive impairment, and to the development of dementia. Additionally, patients with Alzheimer's disease exhibit a greater number of asymptomatic (silent) brain infarctions via magnetic resonance imaging (MRI) compared to control participants without dementia. According to various epidemiological studies, SBI are remarkably common in the elderly population. However, the true incidence and prevalence of SBI remains controversial due to discrepancies amongst epidemiological literature. Over the past decade, research has focused on the etiology of vascular cognitive impairment (VCI) and dementia. However, studies relating the incidence of SBI with cognitive impairment are scarce, and little is known about their accurate association.

Objective: To undergo a systematic review and meta-analysis to statistically summarize the association between SBI and cognitive decline. The results of this systematic review and meta-analysis aim to provide a more precise quantification of the relative risk of cognitive decline in the presence of SBI.

Methods: We conducted a sensitive literature search using two primary databases: MEDLINE and EMBASE using the Ovid Technologies interface. A highly sensitive search strategy composed of controlled vocabulary, text words, and proximity searching was used to deliver 3942 citations. After the removal of 1453 duplicates, 2489 citations were identified and imported onto Covidence to undergo title and abstract screening. Moreover, 113 studies met the inclusion criteria and were selected to undergo a full-text review. Currently our team is conducting the full text review stage. The entire systematic review and meta-analysis is expected to be completed before June 2018.

Expected Results and Conclusion: We expect to find evidence associating prevalent and incident SBI with cognitive impairment, steeper decline in cognitive function, and higher risk for dementia. Our study will provide the most accurate estimates of the effect of SBI on cognition, useful for planning clinical trials to preserve cognition by preventing SBI.

Predictors of daily life functionality in dementia patients differ by APOE-ε4 carrier status –Results from The Sunnybrook Dementia Study

SAIRA MIRZA, Sunnybrook Health Sciences Centre-University of Toronto; Sandra Black, Sunnybrook Health Sciences Centre-University of Toronto; Mario Masellis, Sunnybrook Health Sciences Centre; Shraddha Sapkota, Sunnybrook Health Sciences Centre

Theme 6: All other research and translation approaches to dementia, healthy brain and cognitive aging or other neurodegenerative diseases (eg. FTD, PD/LBD) not covered within themes 1-5

Introduction/Objective: The role of APOE-ε4 in predicting functional independence in dementia is debated. In a cohort of dementia patients with Alzheimer's disease (AD).and Dementia with Lewy Bodies (DLB), we examined the relative importance of age, sex, education, global cognition, neuropsychiatric symptoms, and white matter hyperintensities (WMHs) in predicting Activities of Daily Living (ADLs) by APOE-ε4 status.

Design and Method: In the Sunnybrook Dementia Study, we examined various predictors of ADLs by APOE-ε4 status in 214 dementia patients with varying degrees of cerebral small vessel disease (AD=180, DLB=34). Using Random Forest Analysis (RFA), relative predictive importance of the following variables were tested: age, sex, education, APOE-ε4, global cognition (assessed by Mini-Mental State Examination-MMSE), WMH volume as a proxy of vascular pathology (quantified by semiautomatic segmentation-Lesion Explorer), neuropsychiatric symptoms (assessed by Neuropsychiatric Inventory-NPI), and dementia diagnosis. Basic and instrumental ADLs (BADL and IADL) were assessed with the Disability Assessment for Dementia (DAD) scale and scores were dichotomized as low and high using a median-split for RFA. In an RFA stratified on APOE-ε4 carrier-status, we examined which predictors discriminated the low and high ADL groups.

Results: Of the 214 study participants (mean age 70.8±10.0), 52 %(n = 142) were women, and 55%(n = 117) were APOE-ε4 carriers. 59%(n = 69) of all carriers were women, however, mean BADL and IADL scores as well as other study characteristics did not differ between APOE-ε4 carriers and non-carriers. In order of significance, in non-carriers of APOE-ε4 allele, worse BADL performance was predicted by (i) higher NPI scores and (ii) DLB, whereas worse IADL performance was predicted by higher NPI score only. In APOE-ε4 carriers, worse BADL performance was predicted by (i) higher NPI scores, (ii)male sex, (iii)increasing age, and (iv) lower MMSE score. Worse performance on IADL in carriers was predicted by (i) higher NPI scores, (ii)lower MMSE score, and (iii) male sex.

Conclusion: Predictors of functionality differed by APOE-ε4 status in dementia patients. Remarkably, neuropsychiatric symptoms most strongly predicted functionality in both APOE-ε4 carriers and non-carriers.

Identifying relative importance of commonly examined demographic and clinical variables on functionality stratified by APOE-ε4 genotype may lead to novel pathophysiological insights, and guide personalized interventions in dementia patients.

A Novel ex vivo Model for Characterization of Alzheimer's Disease Strains

Hailey Pineau, University of Alberta; Grant Norman, University of Alberta; David Westaway, University of Alberta; Valerie Sim, University of Alberta

Theme 6: All other research and translation approaches to dementia, healthy brain and cognitive aging or other neurodegenerative diseases (eg. FTD, PD/LBD) not covered within themes 1-5

Objectives: Affecting >48 million people worldwide, Alzheimer's disease (AD) is the leading cause of dementia. Evidence suggests that both amyloid β (Aβ) and tau, the proteins associated with neurodegeneration in AD, exist in many different conformations (strains), which may explain variation in pathology and phenotype between AD patients. Specifically, we are interested in whether strain differences underlie differences in rate of disease progression. Using biophysical techniques and prion-based slice culture assays, we hope to elucidate Aβ properties and plaque morphology characteristic of typical and rapidly progressive AD, and to develop a novel ex vivo model that can replicate strain features.

Methods: The organotypic slice culture assay (OSCA) is a mouse brain slice culture that can be infected with different strains of prions and undergoes pathology as seen in vivo. Because Aβ and tau possess prion-like infectivity, we are adapting this technique to AD using coronal brain slice cultures from 5xFAD and CRND8 mice. These mice express human mutant amyloid precursor protein and develop plaques and other neuropathology by 2 and 3 months of age respectively. Typical or rapidly progressive AD brain homogenate will be applied to these slice cultures to induce strain-specific aggregates. Using confocal microscopy, we will quantify plaque burden, morphology, localization and adjacent pathology. Asymmetric flow field flow fractionation (AFFFF) will be used to isolate and quantify oligomeric size distributions of Aβ from rapidly progressive and typical AD samples. ELISA will be done to quantify levels of Aβ40 and Aβ42 in the AD brain samples and slice culture. Guanidinium denaturation curves will allow for comparison of Aβ conformational stability between typical and rapidly progressive AD brain samples.

Results: Confocal images of Aβ plaques stained with thioflavin S and/or 6E10 in fresh and cultured slices will be compared, and the effects of exposure to rapidly progressive AD brain homogenate will be shown. ELISA results demonstrating a positive correlation between Aβ42: Aβ40 and disease duration will be demonstrated, and AFFFF data on oligomer size distribution may also be presented.

Conclusions: An ex-vivo model of AD that can replicate strain features will facilitate investigation into AD pathogenesis and strain-specific treatments.

Grading-driven brain age estimation in healthy individuals using 3D anatomical MRI

Iman Beheshti, CERVO Research Center, Mental Health University Institute of Quebec; Pierre Gravel, CERVO Research Center, Mental Health University Institute of Quebec; Olivier Potvin, CERVO Research Center; Simon Duchesne, CERVO Research Center, Mental Health University Institute of Quebec

Theme 6: All other research and translation approaches to dementia, healthy brain and cognitive aging or other neurodegenerative diseases (eg. FTD, PD/LBD) not covered within themes 1-5

Grading-driven brain age estimation in healthy individuals using 3D anatomical MRI Iman Beheshti1, PhD, Pierre Gravel1, PhD, Olivier Potvin1, PhD, and Simon Duchesne, PhD1,2

1 Centre de recherche CERVO, 2601, de la Canardière, Québec, Canada, G1J 2G3

2 Département de radiologie, Faculté de médecine, Université Laval, 1050, avenue de la Médecine, Québec, Canada, G1V 0A6

Background:

An estimated brain age metric based on anatomical magnetic resonance imaging (MRI) processing is introduced to monitor and trace the brain's morphological alterations across the adult lifespan, as well as early detection of age-related cognitive decline.

Methods:

We propose a novel and robust grading-driven procedure on the basis of the non-local patch-based MRI segmentation framework proposed by the team of Coupé and Collins (NeuroImage 54 (2011)) for estimating brain age in individuals. Using the fully automated Freesurfer segmentation procedure (version 5.3) and the Desikan-Killiany-Tourville parcellation protocol, we first decomposed the entire cortex into 62 lateralized sub-structures (labels). We then computed the association for each patch (a 7X7X7 voxel block) of unknown labels to similar patches from known labels of a training set, based on intensity similarity. The chronological age of known labels was then back-propagated and averaged over all patches of the unknown label to form the estimated age metric.

Results:

We tested our approach using a leave-one-out train/test strategy on 97 individuals from the MindBoggle dataset (age range: 19 to 61 years old), and computed the regression fit between chronological (real) and estimated cortical ages for all participants. The proposed method yields an excellent correlation of 0.92 (r2 = 0.85) between real and estimated ages, as well as a mean absolute error of only 2.48 years.

Conclusions:

These experimental results demonstrated the reliability of our technique at estimating brain age from structural MRI over the 19-61 years old range, with superior correlation than other competing, state-of-the-art techniques.

“Alberta Dementia Research Futures”: The Alberta experience of developing a provincial dementia research framework

Heather Hanson, Alberta Health Services; Billy Zhao, University of Alberta

Theme 6: All other research and translation approaches to dementia, healthy brain and cognitive aging or other neurodegenerative diseases (eg. FTD, PD/LBD) not covered within themes 1-5

Introduction: Research is essential to our understanding of preventing or delaying the onset of dementia, mitigating its consequences, and managing the health system and societal costs of the disease. To address dementia research at the provincial level, a strategic framework is crucial for setting a direction of travel and identifying key steps to achieving the desired future state. “Alberta Dementia Research Futures” (ADRF) was launched to develop a provincial dementia research framework, with the aim of positioning Alberta as a leader in dementia research, promoting the development of innovative solutions, and encouraging the translation of research into practice to improve health outcomes for Albertans.

Methods: Framework development began with early stakeholder input to ensure provincial readiness. A Steering Committee of experts guided the framework development process. Informed by horizon scanning activities, they identified the current state of dementia research and a desired future state, along with critical success factors needed to reach the desired future state. Stakeholder input on an initial draft framework was obtained through an external consultation process, including dementia researchers, funders, advocacy organizations, industry/provider representatives, and individuals and caregivers living with dementia. After the Steering Committee incorporated the consultation input into the final draft, the framework was presented to the Ministry of Health for endorsement and planning for implementation of key actions.

Results: The framework targets a 5-year time horizon to reach the desired future state for dementia research outcomes. It also advocates for monitoring of health outcomes on a 20-year time horizon for research outcomes to translate into health outcomes. The full spectrum of dementia research, and translational research, is valued. This framework proposes five key aims necessary to achieve the future state.

Conclusions: This dementia research framework outlines a direction of travel for Alberta. The framework should be reviewed against its critical success factors in 3-yrs to ensure that Alberta is on-target to meet its objectives. ADRF may serve as a model for other jurisdictions interested in developing a dementia research framework with robust stakeholder involvement. We gratefully acknowledge the support of the ADRF Co-Chairs and Steering Committee is completing this work.

Mapping age-related changes in brain organization using high-field rs-fMRI

Stanislau Hrybouski, University of Alberta; Fraser Olsen, University of Alberta; John McGonigle, Imperial College London; Rawle Carter, University of Alberta; Peter Seres, University of Alberta; Nikolai Malykhin, University of Alberta

Theme 6: All other research and translation approaches to dementia, healthy brain and cognitive aging or other neurodegenerative diseases (eg. FTD, PD/LBD) not covered within themes 1-5

Introduction: The predominant theory of brain aging suggests that the association cortices are most affected by the aging process, while primary sensory and motor systems of the brain are fairly preserved in healthy older individuals. Seed-based fMRI network analyses revealed disruption of functional connectivity between the association cortices in healthy aging. Here, we tested the hypothesis that functional networks, which are localized to frontal, temporal, and parietal association cortices are more vulnerable in healthy aging than the primary sensory and primary motor networks. Participants: A total of 105 healthy volunteers (18-85 years old) were recruited for the study. Participants were excluded if they had unstable medical illness, history of psychiatric or neurological disorders and the use of medications that might affect brain structure or function. Data acquisition and analysis: 200 functional volumes were collected axially in an interleaved order on a 4.7T Varian Inova scanner using a custon-written T2*-sensitive Gradient Echo Planar Imaging (EPI) pulse sequence [TR = 3 s; TE = 19 ms; flip angle = 90°; FOV = 216×204 mm2; voxel size = 3×3×3 mm3; number of slices = 45]. SPM12, FSL 5.0, ANTS, and GIFT (v4.0) software packages were used to preprocess and analyze the imaging data. We evaluated age-related changes in functional connectivity by (1) examining independent component (IC) spatial maps to study intra-network properties and (2) examined age-related changes in network signal amplitude by comparing standard deviations of scaled network time courses. Twenty-two ICs were identified as likely network components. These included primary visual, primary somatosensory, primary auditory, secondary visual, dorsal attention, ventral attention, frontoparietal control, and default networks. Results: Although small age-related differences in within-network connectivity were present in spatial maps of most networks, these were relatively mild compared dramatic age-related reductions in network amplitude. Age-related reduction in network amplitude was present in all resting-state networks (30-75% reduction in BOLD signal amplitude); however, was most prominent in the primary somatosensory and the primary visual areas (> 60 % reduction in BOLD signal amplitude). Similar to our results from intra-network connectivity, the default system (esp. its MTL subsystem) was most resilient to aging (20-30% reduction in BOLD signal amplitude).

Selective effects of healthy aging on limbic white matter tracts: A diffusion tensor imaging tractography study.

Arash Aghamohammadi-Sereshki, University of Alberta; Fraser Olsen, University of Alberta; Rawle Carter, University of Alberta; Peter Seres, University of Alberta; Nikolai Malykhin, University of Alberta

Theme 6: All other research and translation approaches to dementia, healthy brain and cognitive aging or other neurodegenerative diseases (eg. FTD, PD/LBD) not covered within themes 1-5

Introduction: Success in diagnosis and treatment of age-related brain diseases depends on understanding healthy-aging. Diffusion tensor imaging (DTI) can provide in-vivo measurements of white-matter tracts non-invasively. The goal of the present study was to investigate the relationship between age and white matter microstructure of the limbic tracts in a large sample of healthy participants.

Method: 140 healthy participants (62 men, 78 women; age range:18-85) were recruited, excluding those with unstable medical illness, history of psychiatric or neurological disorders and use of medications that might affect brain structure. Images were acquired on Siemens Sonata 1.5-T scanner. The program DTI-studio was used for the DTI-tractography of the following limbic white matter tracts: uncinate fasciculus, rostral, dorsal and parahippocampal cingulum.

Results: Fractional anisotropy (FA) showed significant negative linear relationship with age for the uncinate fasciculus (adjusted R2 = 0.143, p 0.5). Mean diffusivity (MD) showed significant positive non-linear relationship with age for the uncinate fasciculus (adjusted R2 = 0.229, p 0.06). Radial diffusivity (RD) showed significant positive relationship with age for the uncinate fasciculus (adjusted R2 = 0.226, p 0.2). Age was associated with significant reduction in tract volume of the all studied limbic white matter tracts (all ps < 0 .03). Number of fibers declined with age in all of the limbic white matter tracts (all ps < 0 .03) except for the rostral cingulum. Fiber length was significantly reduced with age only in the rostral cingulum (adjusted R2 = 0.042 p < 0 .05).

Conclusion: Our findings demonstrate that limbic white matter tracts are not uniformly affected by healthy aging. Overall, the parahippocampal cingulum is the least affected tract by aging compared to other limbic tracts.

Validating the Pictorial Fit-Frail Scale (PFFS) in a Memory Clinic Setting

Lindsay Wallace, Dalhousie University; Olga Theou, Dalhousie University; Melissa Andrew , Dalhousie University; Lisa McGarrigle , Dalhousie University; Emma Squires, Dalhousie University; Kenneth Rockwood, Dalhousie University

Theme 6: All other research and translation approaches to dementia, healthy brain and cognitive aging or other neurodegenerative diseases (eg. FTD, PD/LBD) not covered within themes 1-5

Objective: The purpose of this study was to validate the PFFS tool in a memory clinic setting. This tool was developed to be a simple, user-friendly tool that could overcome patient communication barriers. Here, we evaluate the feasibility and inter--rater reliability of this tool, as well as its relationship with cognition. Methods: We plan to recruit 60 patients and their caregivers from the memory disability and geriatric ambulatory care clinic in Halifax, Nova Scotia. Each enrolled participant will complete a demographic questionnaire and the PFFS. A nurse and geriatrician will each complete the PFFS on every patient participant. Feasibility will be evaluated by timing the length of time participants took to fill out the form, and by qualitative participant comments. Intra-class correlation coefficient and repeated measures ANOVA were performed to evaluate the agreement between raters. Results: Currently, 20 patients and 23 caregivers were enrolled in the study. Mean age (years) of patients and caregivers was 73.7±10.3 and 60.0±14.5, respectively, 61% of patients and 83% of caregivers were female. Mean MMSE was 22.1±7.7. Mean time taken to complete the scale (min:sec) was 4:12±2:23, 3:14±1:09, 1:07±0:25, 0:59±0:32 for patients, caregivers, nurses, and geriatricians, respectively. The PFFS score theoretically ranges from 0- to 43. Mean PFFS scores were 22.3±2.3, 24.5±6.8, 22.8±4.1, 23.9±5.9 for patients, caregivers, nurses, and geriatricians, respectively; these scores did not significantly differ. Inter--rater reliability between nurses and geriatricians was good (ICC=0.67, p=0.04). Conclusions: Our preliminary results suggest that the PFFS is a feasible, reliable, and valid tool for use with patients, caregivers, nurses, and health care professionals. Further analysis is needed to determine cut-offs beyond which PFFS is unreliable due to cognitive impairment.