RESEARCH SCHOLAR PROGRAM – 2018

SUPERVISOR & PROJECT INFORMATION FORM

Please complete and return, via email only (crems.programs@utoronto.ca) by ***November 3rd 2017*** *(forms received after this date will not be posted).*

Supervisor Information

Name: Andrew Lim

Email: andrew.lim@utoronto.ca

Degree: MD, MMSc

SGS Appointment (IMS, IHPME, LMP etc..): IMS

Academic Rank: Assistant Professor

Field of Research: Dementia, Sleep, Circadian Rhythms, Genetics

Research Institution Affiliation (if applicable): Sunnybrook Research Institute

Allocation of student contact time (number of hours per week YOU are available to the student for any concerns or to review progress): I am available in the laboratory at least 30 hours a week. At least 2 hours per week is spent in formal group lab meetings. An addition 2-4 hours a week is available for formal face-to-face instruction of each student.

Project Information

Title: The Ontario Sleep and Brain Health Study - An Extension of the Ontario Sleep Health Study to Examine the Links Between Sleep and Brain Health in Working-Age Ontarians

Description (max 500 words):

Quantifying the contribution of sleep and circadian disruption to cognitive impairment and dementia in Ontario, and identifying their brain correlates, is a public health priority with important therapeutic implications. Sleep and circadian disruption, including sleep apnea, sleep deprivation, sleep fragmentation, and circadian disruption from shift work, affect millions of Ontarians and may be contributing to the growing burden of Alzheimer's disease (AD) and other dementias. Studies in model organisms and studies in humans suggest that sleep and circadian disruption impair cognition and may predispose to dementia-associated brain damage including accumulation of toxic proteins, brain vessel damage, brain atrophy, and brain white matter injury. In large studies of older adults, circadian irregularity, sleep fragmentation, and sleep apnea are associated with impaired cognition and AD, suggesting that targeting 1) common treatable causes of sleep or circadian disruption (e.g. sleep apnea), or 2) their brain consequences, may delay or prevent impaired cognition and AD. However, most studies have focused on older adults, which is problematic since AD-related brain damage appears many years before AD onset. Moreover, logistical and technological limitations have made it difficult to obtain sleep and circadian measures in large numbers of working-age adults with detailed brain imaging and long-term follow-up. These factors have left gaps in our knowledge regarding which specific forms of sleep/circadian disruption most affect dementia risk, when in the lifespan they act, and via what mechanisms, impeding strategies to prevent cognitive decline and dementia by targeting sleep and circadian disruption or their brain consequences. **This study is quantifying the contributions of 4 key forms of mid-life sleep and circadian rhythm disruption to cognitive impairment, dementia-associated structural brain changes, and the risk of late-life dementia.** In compelling preliminary work, we have shown that higher late-life sleep fragmentation, measured with a novel metric we developed, is linked to 1) a higher risk of future AD, 2) more brain arteriolosclerosis, 3) a greater impact of genetic factors on AD risk and AD-related brain damage, and 4) smaller frontal lobes on MRI. However, fragmentation is only one type of sleep disruption, and its impact cannot be understood without simultaneously examining common sleep disorders such as sleep apnea. Moreover, few studies have examined the impact of mid-life sleep or circadian disruption on cognition and dementia-associated brain structural changes. Leveraging resources from two ongoing Ontario-based cohort studies, we are cost-effectively addressing these gaps by measuring 4 key forms of sleep and circadian disruption in 2400 adults aged 35-69 with wearable devices, and linking these data to cognitive impairment, dementia-associated brain changes, and late life dementia risk. Our **specific aims** are: **Aim 1**: Determine the burden and severity of a) sleep apnea, b) sleep deprivation, c) sleep fragmentation, and d) circadian irregularity in working-age Ontarians using wearable devices, and examine their impact on cognition and function. **Aim 2:** Evaluate the associations of these 4 forms of sleep and circadian disruption with dementia-related brain damage including regional atrophy, white matter hyperintensities, lacunes, cerebral microbleeds, and enlarged perivascular spaces visualized using brain MRI.

This study is funded by CIHR grant MOP125934 (PI Lim) and Ontario Ministry of Innovation grant ER-16-12-034

If human subjects are involved, have Ethics been obtained?

☒ YES ☐ NO ☐ Application Submitted ☐ N/A

Do you expect this work will be published within the 20 months?

☒ YES ☐ NO ☐ Uncertain

Student's roles and responsibilities (please be specific)

Please indicate who will serve as the student's direct report (PI, PhD student, technician etc…)

The student will report directly to the PI. Sleep (accelerometry, nasal pressure, pulse oximetry, heart rate) and cognitive data have already been collected from >800 participants, with MR imaging on >300. The student will be responsible for writing code in MATLAB and R to process already collected physiologic and neuropsychological data, utilize an existing pipeline to process the MR imaging data, and relate the two. Anticipated manuscript(s) will describe the impact of sleep and circadian rhythm disruption on 1) cross-sectional neuropsychological performance and 2) MR imaging metrics as described in the project summary above. As the work will involve a reasonable degree of programming and data analytics, the ideal student will have programming (especially R and MATLAB, although any language acceptable) and statistics experience, coupled with an undergraduate-level knowledge of mathematics and neurobiology.

Examples of manuscripts from a previous medical student working in this area in the laboratory include:

1. Sohail S, Yu L, Schneider JA, Bennett DA, Buchman AS, Lim AS. Sleep Fragmentation and Parkinson's Disease Pathology in Older Adults Without Parkinson's Disease. Mov Disord. In Press [Accepted September 15, 2017].
2. Sohail S, Yu L, Bennett DA, Buchman AS, Lim AS. Irregular 24-hour activity rhythms and the metabolic syndrome in older adults. Chronobiol Int. 2015 Jan 1;32(6):802-13.

Other recent manuscripts from the laboratory related to this area include:

1. Lim AS, Yu L, Schneider JA, Bennett DA, Buchman AS. Sleep Fragmentation, Cerebral Arteriolosclerosis, and Brain Infarct Pathology in Community-Dwelling Older People. Stroke. 2016 Feb 1;47(2):516-8.
2. Lim AS, Fleischman DA, Dawe RJ, Yu L, Arfanakis K, Buchman AS, Bennett DA. Regional Neocortical Gray Matter Structure and Sleep Fragmentation in Older Adults. Sleep. 2016 Jan 1;39(1):227-35.

3. Lim AS, Ellison B, Wang J, Yu L, Schneider JA, Buchman AS, Bennett DA, Saper CB. Sleep is related to neuron numbers in the ventrolateral preoptic/intermediate nucleus in older adults with and without Alzheimer's disease. Brain. 2014 Oct 1;137(10):2847-61.
4. Lim AS, Yu L, Kowgier M, Schneider JA, Buchman AS, Bennett DA. Modification of the Relationship of the Apolipoprotein E ε4 Allele to the Risk of Alzheimer Disease and Neurofibrillary Tangle Density by Sleep. JAMA Neurol. 2013 Dec 1;70(12):1544-51.
5. Lim AS, Kowgier M, Yu L, Buchman AS, Bennett DA. Sleep Fragmentation and the Risk of Incident Alzheimer's Disease and Cognitive Decline in Older Persons. Sleep. 2013 Jul 1;36(7):1027-1032.
6. Lim AS, Yu L, Costa MD, Buchman AS, Bennett DA, Leurgans SE, Saper CB. Quantification of the fragmentation of rest-activity patterns in elderly individuals using a state transition analysis. Sleep. 2011 Nov 1;34(11):1569-81.