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: Sleep and Circadian Rhythms;

Dementia; 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: Sleep, Circadian Rhythms, and Mechanisms of Cognitive Decline in the Human Brain

Description (max 500 words):

Sleep and circadian disruption, including sleep apnea, sleep fragmentation, and circadian rhythm irregularity, affect millions of Americans, and are associated with impaired cognition and Alzheimer's disease (AD). Challenges in applying standard techniques (e.g. polysomnography) in ambulatory settings to quantify sleep and circadian disruption in large numbers of community-dwelling older adults, and in obtaining detailed cognitive assessments and brain tissue from the same individuals, have left knowledge gaps. Thus, although sleep and circadian rhythm disruption affect millions of older Americans, there are few data concerning the contribution of their different forms to the growing number of older adults with cognitive impairment and dementia, and associated brain mechanisms. This study is filling fill these gaps. **The overall goal of this study is to quantify the contributions of, and identify brain mechanisms linking, sleep and circadian rhythm disruption to cognitive decline and incident AD in older adults.** In compelling preliminary work, we developed and applied a new method of measuring sleep fragmentation in the community setting using actigraphy, the non-invasive continuous measurement of movement using a watch-like device. In older adults, we found that higher sleep fragmentation is associated with 1) a greater risk of incident AD, 2) more brain arteriolosclerosis and subcortical strokes at autopsy, and 3) a higher burden of AD pathology in APOE ε4 carriers. However, sleep fragmentation is only one type of sleep disruption, and its impact cannot be understood without simultaneously examining the impact of common sleep disorders such as sleep apnea, which may affect up to half of older adults. To extend these findings, we are using a portable battery of 2 wearable devices measuring continuous peripheral arterial tonometry, oximetry, and actigraphy to simultaneously quantify 5 key forms of sleep and circadian disruption in 780 older adults in the Rush Memory and Aging Project (R01AG17911). These will include 1) sleep apnea, 2) sleep duration, 3) sleep architecture, 4) sleep fragmentation, and 5) circadian irregularity. These measurements are being combined with donated cognitive and other clinical data, as well as post-mortem histopathology and brain MRI indices from decedents, to elucidate the brain correlates of sleep and circadian disruption in community-dwelling adults, and their impact on cognitive impairment and incident AD dementia. By overcoming key translational barriers, this study is filling important gaps in our knowledge concerning the burden and brain correlates of 5 key forms of sleep and circadian disruption in old age. This offers the potential to leverage sleep and circadian interventions to decrease the growing burden of cognitive impairment and AD, and for targeted therapies to improve brain health for the millions of Americans who experience sleep or circadian rhythm dysfunction.

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. Longitudinal accelerometric, neuropsychological, and clinical data have already been collected from >1000 participants of whom >300 also have post-mortem histopathology. Collection of peripheral arterial tonometry data and next-generation accelerometric data is anticipated to begin in January 2018. Data collection is overseen by dedicate research staff. The student will primarily use R and MATLAB to analyze already-collected data, relating sleep measures to cognitive, imaging, and neuropathological outcomes, and prepare manuscripts describing the results. 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 on this project 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 project 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.