

PILOT AWARDS – FISCAL YEAR 19

Institute on Aging Pilots

1. Psychosocial Stress Exposure, Biological Functioning, and Cognitive Change across the Life Course

PI: Courtney E. Boen, PhD, MPH

Abstract: A growing body of research has focused on population patterns, causes, and consequences of cognitive impairment and chronic disease. Still, critical gaps in the literature remain. In particular, few studies have examined the factors that shape trajectories of cognitive and biological change using nationally-representative, population-level data that spans the life course. Further, because of data limitations, the relationship between biological and cognitive change remains to be better understood, as do the factors that promote biological and cognitive resiliency and healthy aging in the face of adversity. Drawing on nationally-representative, population data from four longitudinal studies collectively spanning from birth through old age, the proposed project employs a unique life course design to examine the prospective relationships between diverse measures of psychosocial stress exposure, biological functioning, and cognitive change across early-, mid-, and late-life. In addition to examining the psychosocial stressors that shape trajectories of biological and cognitive development, we will also identify the social, environmental, and behavioral factors that buffer against stress exposure and promote resiliency at each life stage and across the life course. By utilizing population-level, longitudinal data on psychosocial stress exposure and biological and cognitive change, this research will contribute new knowledge of the role of stress in producing population disparities in biological and cognitive functioning across the life span; improve understanding of the relationship between biological and cognitive functioning at different life stages; and shed new light on the factors that promote biological and cognitive resiliency in early-, mid-, and late-life. Findings from the proposed project will both identify the factors that impede biological and cognitive development across the life course and provide new insights into possible leverage points and life course stages to target with prevention and intervention efforts. Given the aging of the U.S. population and age-related increases in cognitive impairment and related disease in later life, improving understanding of the determinants of biological dysfunction and cognitive decline, as well as the factors that support healthy aging, is of critical scientific, public health, and social policy importance. Further, the project will provide preliminary results for an NIA-grant application on this topic.

2. Defining the epidemiology and functional outcomes after surgery of older adults with cognitive impairment and dementia

PI: Timothy G. Gaulton, MD, MSc

Abstract: There is increasing epidemiologic evidence of a link between surgery and reductions in cognitive function in older adults. While the exact definition of cognitive decline and its mechanisms are unclear, there are strong associations between having cognitive impairment prior to surgery and a decrease in cognitive performance after surgery. Unfortunately, we have only a limited understanding of how patients with preexisting cognitive impairment recover following surgery despite evidence of their potential vulnerability. At present, we do not know how many adults who present for surgery have cognitive impairment. With the expected increase in the size of elderly population in the next several decades, there is likely a large and growing number of adults with cognitive impairment and dementia who have surgery every year. These patients are at high risk of perioperative morbidity and mortality and the potential economic and societal impact is substantial. Accurate estimates of the prevalence of cognitive impairment are therefore a critical start to shaping perioperative health policy. At the patient level, we lack an understanding of how adults with cognitive impairment recover their ability to function after surgery. Loss of independent function is a debilitating consequence of surgery and can create a significant and unexpected burden on patients and their families. Decisions made in the perioperative setting are especially difficult for these patients and their families, and healthcare providers. We therefore need to learn more about their postoperative recovery to allow for an informed and comprehensive decision to be made about the choice of surgery and about the expectations of recovery. With that framework in mind, the research proposed for the pilot grant aims to: 1) define a national prevalence of dementia and cognitive impairment with no dementia in older adults who present for surgery and 2) to determine risk of long-term functional decline in patients with preexisting cognitive impairment following surgery. We will conduct a retrospective cohort study of older adults who underwent surgical procedures while enrolled in the Health and Retirement Study (HRS), a nationally representative survey of aging and health funded by the National Institute on Aging (NIA) that contains more than 37,000 US adults since 1992. The survey data will be linked to Medicare claims to create a patient cohort with detailed information on cognition, surgery, and functional outcomes. The findings from his research will help us better understand how patients with cognitive impairment recover after surgery. This work will also provide preliminary data needed by the investigators to obtain future extramural funding for research that will use quantitative and qualitative analyses to determine the mechanisms that underlie the link between cognitive impairment, surgery, and post-operative functional recovery. This future work will help guide clinical practice and inform effective policy interventions to reduce loss of independence in patients with cognitive impairment.

3. Development of a Goal-Directed Behavior App: Changing Apathy into Action in Neurodegenerative Diseases

PI: Dawn Mechanic-Hamilton, PhD

Abstract: Patients with Alzheimer's Disease and Related Dementias (ADRD) present with a constellation of cognitive and neuropsychiatric symptoms. Impairment of goal-directed behavior (GDB), often labeled apathy, is one of the symptoms that has a significant negative impact on a patient's ability to engage in everyday activities and care partner burden. This project will develop a mobile app to engage both patients and care partners in order to increase goal-directed behavior to improve functional and neuropsychiatric outcomes for patients and decrease care partner burden. The mobile app will target key and distinct components of GDB (motivation, planning and initiation), incorporate individualized patient goals, and measure outcomes in both the patient and care partner. Subjects – patients and care partners – will be recruited from the Penn Memory Center and the Penn Frontotemporal Degeneration Center. This project will include two stages: Stage 1 will include building the app and collecting focus group responses to the app utility and content and Stage 2 will include pilot testing the app in a small group of patients and care partners with mild behavioral variant Frontotemporal Dementia (bvFTD) and mild Alzheimer's Disease (AD). The impact of the intervention on patients and care partners will be assessed before, during and after the four-week intervention.

4. The role of telomeric protein TRF2 in dilated cardiomyopathy

PI: Foteini Mourkioti, PhD

Abstract: Dilated cardiomyopathy (DCM) in elderly patients have a worse prognosis and the medical management is often more difficult. Telomere length has been suggested to be a major determinant of aging. However, the effects of telomere biology in adult cardiac cells remain equivocal. The goal of this study is to investigate how telomere dysfunction affects cardiac failure in the dilated cardiomyopathy seen in Duchenne muscular dystrophy (DMD) patients. This proposal builds up on strong preliminary data and a new mouse model to investigate a previously unexplored, proliferation-independent, mechanism in dystrophic dilated cardiomyopathy. Our experiments are designed to uncover the role of the telomeric protein TRF2 in the progression of dystrophy that could provide fresh strategies for therapeutics to prevent or diminish the destructive cardiac processes in DCM. Success of our studies will open the door for mechanisms that likely would be applicable to other cardiovascular diseases affecting the elderly population.

Alzheimer's Disease Core Center Pilots

5. Sleep modification to transform brain aging in health and disease

PI: Matthew S. Kayser, MD, PhD

Abstract: The impact of age on the brain can be devastating, leading to cognitive decline and dementia. Recent evidence indicates that sleep is a crucial variable in dementia: disrupted sleep worsens brain degeneration, and disease progression worsens sleep. And yet, sleep represents a potentially powerful untapped therapeutic modality through which neurodegeneration—and perhaps brain aging itself—can be mitigated. In humans, behavioral therapies to modify sleep are the first-line treatment for insomnia, particularly in the aging population. Such behavioral therapies, however, can be challenging to implement broadly. Molecular insight into the mechanisms of behavioral sleep interventions, therefore, could guide new avenues for treatment. We propose an innovative approach using the fruit fly *Drosophila* to uncover conserved pathways targeted by sleep modification to achieve healthful brain aging and protection from disease. By incorporating principles of human clinical sleep methods to *Drosophila*, we developed a behavioral paradigm that markedly improves sleep quality in fly models of insomnia. We applied this approach to an Alzheimer's disease (AD) model to show that sleep impairments displayed in the model are reversible with behavioral sleep modification [importantly, AD animals with improved sleep also show lifespan extension. In parallel, we have identified a highly conserved small RNA (a microRNA) that impacts brain aging and will assess how sleep modification mechanistically shifts the brain aging profile. Our goals in this proposal are to determine mechanistically how behaviorally-induced sleep improvements transform the molecular trajectory of brain aging in health and disease.

6. Intercellular coordination of autophagy between neurons and glia in models of neurodegenerative disease

PI: Sandra Maday, PhD

Abstract: Most of the neurons in the human brain must last a lifetime of ~90+ years. To maintain function in the face of aging, neurons rely heavily on robust housekeeping pathways to routinely take out their cellular trash. In fact, alterations in these pathways are associated with the progression of neurodegenerative disease in humans. Thus, restoring the efficiency of these processes in disease represents an avenue for therapeutic intervention. This proposal will investigate how housekeeping pathways are coordinated between the two main cell types in the brain, neurons and glia, particularly in response to cellular stress associated with neurodegeneration. Findings from this study will identify new pathways that may be targeted therapeutically to mitigate neurodegenerative disease.