2011 Pilot Seed Grant Award Recipients

Project Title: On the Move: Optimizing Elder Exercise inside the Health Care System

Principal Investigator: Jennifer S. Brach, PhD, PT

Co-Investigators: Pamela Peele, PhD, Subashan Perera, PhD

ABSTRACT

Brief Background: Walking difficulty is a common, costly program in older adults. Exercise is beneficial to physical and mental health and may prevent walking difficulty in older adults. Interventions to prevent walking difficulty have mainly focused on improving strength and endurance and have overlooked two important components of walking, the timing and coordination of movement. We have preliminary data to suggest that exercise interventions targeting the timing and coordination of movement have a bigger impact on walking than standard exercise programs that focus on strength and endurance. Currently, the UPMC for Life Health Plan sponsored fitness program entitled Silver and Fit focuses primarily on improving strength and endurance. Our long term goal is to incorporate a timing and coordination exercise program into the Silver and Fit program. Specifically, we plan to conduct a randomized clinical trial within the UPMC health system to compare the effects of a standard exercise program (Silver and Fit) versus a standard PLUS exercise program (Silver and Fit plus timing and coordination) in improving gait speed, preventing walking difficulty, and decreasing healthcare usage and costs. This would be the first trial to model exercise promotion and walking difficulty prevention within a Medicare product.

Specific Aims: We propose to use the Aging Institute Pilot Funding Program to prepare for this long-term goal. The objectives of this application are to continue to build the research team with members of UPMC, to determine the feasibility of recruiting and retaining older adults into the study, to document variability of the outcomes of the Silver & Fit intervention, and to develop the system to obtain the necessary exercise adherence, healthcare utilization, and cost information.

Summary of Methods: To achieve these objects we will complete three tasks: 1) survey eligible members of the UPMC for Life program to determine the number of subjects who meet study inclusion/exclusion criteria and are potentially eligible and willing to participate, 2) recruit and enroll 30 older adults to participate in the Silver and Fit program and record outcomes (i.e. gait speed) at baseline and after 12 weeks of exercise, and 3) electronically obtain healthcare usage and cost information for the 30 older adults participating in the Silver and Fit program.

Future Use of Data: We plan to submit an R01 application to AHRQ to fund the future randomized clinical trial comparing the standard to the standard PLUS exercise program within the UPMC health system. We have designed this pilot 1) to collect necessary pieces of information (i.e. screen to recruit ratio, variability of the gait speed outcome in the control group), 2) to demonstrate that we can work within the UPMC system, and 3) to develop the system to collect adherence and healthcare usage and cost data; factors that are critical to the R01 application.

Project Title: Development of a Protocol for Disclosing Amyloid Imaging Results in Mild Cognitive Impairment

Principal Investigator: Jennifer Hagerty Lingler, PhD, RN, FNP

Consultants: Scott Roberts, PhD, Keith Johnson, MD, Jason Karlawish, MD, **Amanda Gentry, MPH, Project Director**

Abstract

Specific Aims: 1) To develop a standardized protocol for the disclosure of amyloid imaging results in the context of MCI using an iterative approach involving a panel comprised of local and external experts in neuroimaging, risk communication, regulatory affairs, and bioethics; and 2) To establish the acceptability of an amyloid imaging results disclosure protocol among patients with mild cognitive impairment and their immediate family members.

Brief Background: In the near future, amyloid imaging tools will play an unprecedented role in determining how dementia and preclinical dementia are diagnosed and ultimately treated. As the use of amyloid imaging tools expands from research settings into clinical practice, it will be critically important to identify effective approaches to communicating the results of such brain scans to patients and their family members.

Summary of Methods: Both aims will be addressed using iterative processes, methodologically grounded in the principles of qualitative research. After addressing Aim 1 by convening an expert panel to develop the content of amyloid imaging results disclosure sessions, Aim 2 will be pursued by engaging up to 10 patients and their family members in mock (hypothetical) amyloid imaging results disclosure sessions and focus groups to evaluate the acceptability of a standardized process for imparting such information.

Future Use of Data: The development of an expert informed and patient validated protocol through the proposed pilot study is a critical preliminary step in the applicant's forthcoming R01 application. The applicant's planned R01 will examine the psychosocial and behavioral impact of amyloid-beta (Aβ) biomarker testing for AD in the context of MCI.

Project Title: Inflammation in Cognitive Aging

Principal Investigator: Anna L. Marsland, PhD

Co-Investigators: Peter J Gianaros, PhD

Abstract

Specific Aim: The goal of the current proposal is to collect pilot data examining whether peripheral inflammation in midlife is associated with white matter atrophy and microstructural alterations, which have been associated with cognitive aging.

Background: Normal aging is associated with changes in brain structure and function that result in declines in cognitive performance. These changes begin in early adulthood, are relatively large, and culminate in debilitating functional impairment for many. Yet, little is known about the biological bases of age-related changes in cognitive function. Converging animal findings suggest that systemic inflammation may play a role, being associated with activation of central inflammatory mechanisms that result in hippocampal neurodegeneration and related impairment of memory function. Consistent with animal findings, we have shown an inverse association of plasma interleukin (IL)-6, a relatively stable marker of systemic inflammation, with working memory and executive function, and with grey matter volume in the hippocampus and medial prefrontal cortex among cognitively-normal middle-aged adults. Interestingly, these are the regions of the brain where IL-6 receptors are densely concentrated, suggesting a plausible neurobiological pathway by which inflammation could impact the brain systems implicated in memory and executive function.

Methods:

The primary goal of the proposed study is to extend our work to an initial examination of whether IL-6 is also associated with microstructural white matter tissue integrity, as assessed by diffusion tensor imaging among a sample of 160 cognitively-normal mid-life adults. We also propose examining whether brain derived neurotrophic factor (BDNF) is assocaited with white matter structure independently of markers of inflammation. We plan to assay plasma IL-6 and BDNF levels in frozen samples collected from 160 adults on whom we have already obtained structural diffusion tensor images.

Future Use of Data: We recently submitted an R01 proposal to conduct a longitudinal study of IL-6 as a predictor of changes in structure (and function) of the hippocampus and prefrontal cortex. The grant was well received (12th percentile), but was not funded. Reviewers suggested that the proposal would be strengthened considerably if we expanded our focus to examine whether white matter alterations relate to neurocognitive outcomes through inflammatory mechanisms. In this regard, we anticipate that the current pilot will provide preliminary data for our R01 resubmission.

Project Title: Elucidating the role of Lamin B1 in aging dependent demyelination

Principal Investigator: Quasar Saleem Padiath, PhD

Abstract

(a.)Specific Aim: Generation and characterization of mice models for Autosomal Dominant Leukodystrophy (ADLD).

Background: ADLD is a disorder of aging as patients only show the onset of the disease in the 4th or 5th decade of life. It is a progressive disease characterized by demyelination of the Central Nervous System (CNS) and ultimately results in death. The late age of onset suggests mechanisms that specifically involve age dependent myelin regulation might be affected. We have recently shown that ADLD is caused by a duplication of the gene Lamin B1. Lamin B1 is an integral part of the nuclear lamina, a structure that plays an important role in both normal aging and accelerated aging phenotypes such as progeria. Myelin or white matter lesions have been recognized as being a key feature of the aging brain. The involvement of the nuclear lamina both in demyelination and aging suggests that it might have an important role to play in myelin loss in the aging brain. Understanding the mechanism underlying ADLD might thus give us clues to age related white matter lesions.

Summary of Methods: No animal model exists for ADLD. I propose to generate and characterize 2 types of transgenic mice that over express Lamin B1 in a cell specific and inducible manner. Firstly, I propose to generate mice in which Lamin B1 is under the control of an tetracycline inducible promoter. By crossing these mice to appropriate driver lines, we can drive the expression of Lamin B1 in different CNS specific cell types and control the timing of expression. As Lamin B1 is thought to be ubiquitously expressed, it is unclear which cell type is responsible for the demyelination phenotype. By targeting the over expression of Lamin B1 to different cell types we can determine which cell type is responsible for ADLD. The second type of transgenic mouse is one in which Lamin B1 is specifically over expressed in oligodendrocytes. As oligodendrocytes produce myelin in the CNS it is possible that this cell type is uniquely susceptible to Lamin B1 over expression and its dysfunction leads to demyelination. Both these mouse models will be characterized at the behavioral, histopathological and molecular level

Future use of Data: The results generated from these mice will be used as preliminary data for extra mural grants such as an R01. The availability of the mice will allow us to test specific hypotheses for ADLD disease mechanisms and submit grant proposals to fund such hypothesis driven research.

Project Title: Use of functional MRI to validate NIRS Investigation of brain control during urgency and urge urinary incontinence

Principal Investigator: Stasa Tadic, MD

Co-Investigators: Resnick, Neil MD, Schaefer, Werner PhD, Huppert, Theodore PhD, Griffiths, Derek PhD, Clarkson, Becky PhD

Structured Abstract

Specific Aims: Our goal is to assess whether functional near-infrared spectroscopy, fNIRS can reliably record responses in the brain concordant with functional magnetic resonance imaging, fMRI, in areas known to be relevant for bladder function during filling of the bladder and urge sensation. Thus our specific aims are: to show that activations and deactivations demonstrated on fMRI agree with fNIRS measurements within known technical limits; and to show that the areas of the brain where both fMRI and fNIRS measurements agree are among those known to be important and relevant in control of the lower urinary tract (LUT).

Background: Urge urinary incontinence, UUI, is prevalent, morbid and costly, especially in the older population. Current medical treatments only provide modest management of symptoms, focus on the bladder and do not consider the cerebral factors inherent in loss of control of the bladder. We have begun to study key brain areas involved in bladder control using fMRI, but have yet to combine brain imaging with simultaneous comprehensive urodynamic evaluation due to technical restrictions. Functional near infrared spectroscopy, fNIRS, allows real time brain imaging in less restrictive environments than fMRI and is therefore a logical progression.

Methods: In order to validate use of fNIRS as a tool for investigating central bladder control, it must be evaluated against our current gold standard of fMRI. fNIRS measurements will be made on subjects with urgency and urge incontinence simultaneously with fMRI measurements during a standardized bladder filling and emptying protocol.

Future use of Data: This data will quantify the degree of agreement between fMRI and fNIRS for this particular application. It will confirm use of fNIRS to further investigate brain control of the bladder in more realistic settings. This data would establish the validity of fNIRS to measure from these brain regions, which we believe to be crucial to introducing this novel technique into the urodynamics field.