Neuroimaging Predictors of Cognitive Decline and Impairment

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Research Abstract

Summary of work: As part of our program of research on early markers of Alzheimers disease,

we are performing serial magnetic resonance imaging (MRI), including measures of vascular changes, positron emission tomography (PET), and neuropsychological assessments in participants from the Baltimore Longitudinal Study of Aging (BLSA) to investigate the neurobiological basis of memory change and cognitive impairment. These evaluations allow us to examine changes in brain structure and function which may be early preclinical predictors of cognitive change and impairment, including Alzheimer's disease (AD). We continue longitudinal testing of older participants and evaluation of new participants, including MRI and neuropsychological assessments of participants younger than 55 years old. For a subsample aged 55 and older, we perform PET measurements of cerebral blood flow, followed by a PET scan using 11-C-Pittsburgh Compound B (PiB) to measure in vivo amyloid deposition. Over the last year we initiated Tau PET (AV-1451) studies of BLSA participants receiving PET amyloid scans. Our progress includes continued acquisition of new neuroimaging assessments and continued analysis of existing data and methods development. We use neuroimaging tools to investigate modulators of cognitive and brain changes, including sex differences in cognitive and brain aging, genetic, metabolic, and inflammatory risk factors, and the effects of sex steroid and other hormones. An understanding of these brain-behavior associations and early detection of accelerated brain changes during the preclinical or asymptomatic stage of disease will be critical in identifying individuals likely to benefit from interventions if a successful treatment for prevention or delaying onset of disease is available. We have published a number of papers describing results from the BLSA neuroimaging study: Longitudinal Change in ABeta and Relation with APOE Genotype. In our PET-PiB amyloid imaging investigations, we continue to highlight the importance of individuals with intermediate amyloid levels that would be considered PiB negative in many binary classification schemes. In our initial longitudinal studies, we pointed out that rates of longitudinal change in PET-PiB retention were a function of baseline levels. We noted that once an individual reached a study-defined threshold, that individual was likely to show longitudinal increases over time. Individuals at intermediate levels, i.e., just above our study-defined threshold, were those in the earliest stages of the development of ABeta neuropathology, a time when a future treatment might be most effective. As our sample sizes and follow-up have increased, it is clear that some individuals maintain no or negligible amyloid burden with advancing age while others cross a threshold and demonstrate steady increases in ABeta over time. In a recent publication, we characterized the spatial progression of PiB retention over time (Bilgel et al 2016). In an important advance (Bilgel et al, 2016), we developed an approach for using longitudinal PET-PiB data to estimate the age at onset of amyloid accumulation on an individual basis, providing an index for each individual that can be used as a dependent outcome to assess factors that may modify age at onset of amyloid accumulation. We applied this approach to demonstrate that APOE e4 positive individuals were 3 times more likely to reach the PiB change point, and on average e4+ individuals began accumulating ABeta 13.3 years earlier than e4- individuals. We believe this approach will be extremely useful in gauging the efficacy of future treatment interventions to delay amyloid accumulation in high-risk samples. Sphingolipids and White Matter Integrity. We have continued our collaboration with Dr. Michelle Mielke to characterize factors related to age-associated changes in sphingolipids, including specific ceramide and sphingomyelin chain lengths. More recently, we used diffusion tensor imaging (DTI) to demonstrate that peripheral sphingolipids are associated with variation in white matter (WM) microstructure in older adults (Gonzalez et al., 2016). We found that elevations in some ceramide species (C20:0, C22:0, C22:1, and C24:1) were associated with lower fractional isotropy (FA) in multiple WM regions, including total cerebral WM, anterior corona radiata, and the cingulum of the cingulate gyrus. Higher

sphingomyelins (C18:1 and C20:1) were associated with lower FA in regions such as the anterior corona radiata and body of the corpus callosum. These findings suggest that plasma sphingolipids are associated with variation in white matter microstructure in older adults. Sleep Duration and Cortical Thinning. We continued collaborative studies with Dr. Adam Spira on the relation between sleep patterns and brain aging. In a recent report (Spira et al., 2016), we examined self-reported sleep duration in relation to rates of cortical thinning in 122 BLSA participants, using data with a mean of 7.6 1.5-T MRI scans and mean follow-up from initial scan of 8.0 y. We observed nonlinear associations between sleep duration and cortical thinning in some regions. Among cognitively normal older adults, sleep durations of < 7 h and > 7 h were associated with increases in rates of subsequent frontotemporal gray matter atrophy. These studies will be expanded, using objective sleep measures to investigate mechanisms linking sleep duration to gray matter loss. Motor Function and Brain Integrity. With Drs. Stephanie Studenski, Luigi Ferrucci and Teresa Tian, we examined the relation between variation in motor function and changes in white matter and gray matter integrity, measured by DTI. We found that higher levels of average MD, associated with reduced gray matter integrity, were significantly associated with higher lap time variability, based on individual trajectories over ten 40-m laps (Tian et al, 2016). These findings suggest that lower gray matter integrity in some brain areas may underlie greater lap time variability in nondemented older adults. In a second study (Tian et al 2016), we examined the effect of age on the associations of regional microstructural white matter integrity with walking variability and speed, independent of macrostructural white matter lesion volume. While macrostructural white matter lesion burden predicts more variable and slower walking in older adults, we found that microstructural white matter disruption was independently associated with more variable and slower fast-paced walking only in the young-old. Thus, disruptions in white matter integrity may contribute to abnormal gait early in the aging process. Methodological Developments. We have continued to optimize our approach for MRI volumetric analysis. In a major methodological advance, we collaborated with Christos Davatzikos on the development of the MUSE, MUlti-atlas region Segmentation utilizing Ensembles of registration algorithms and parameters, pipeline for volumetric MRI analysis. We validated this approach and applied it to cross-sectional data across a studies, including BLSA (Doshi et al, 2016). We demonstrated aging trajectories from infancy to late adulthood in a number of regional volumes. In addition, we applied the approach to longitudinal SPGR MRI data showing longitudinal trajectories of brain aging. In the next phase, we are validating this approach for application to longitudinal MRI data acquired on different scanners with different pulse sequences.

Lay Summary
Further information available at:

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