Genetic and Lifestyle Determinants of Cognitive Resilience in Midlife

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Research Abstract

? DESCRIPTION (provided by applicant): Advancing age and the apolipoprotein E ?4 (APOE4) allele are key determinants of the accumulation of pathophysiological abnormalities related to Alzheimer’s disease (AD), as well as the clinical manifestation of AD syndrome. However, there

is substantial interindividual heterogeneity in cognitive aging and the accrual of AD pathology such that some individuals remain cognitively intact and harbor minimal AD-related brain changes even into old age, and despite being APOE4 positive. Further, although there is replicable evidence for an association between AD pathophysiological changes and cognitive impairment, this relationship is imperfect. Some individuals continue to exhibit intact cognition despite harboring substantial AD pathology. These findings underscore the existence of factors that confer resilience to (i) the influence of age and APOE4 on cognitive course and biomarker profile, and (ii) the impact of biomarker alterations on cognitive trajectory. In this project, we leverage the wealth of multimodal genetic, neuroimaging, biomarker, cognitive, and lifestyle data acquired in the Wisconsin Registry for Alzheimer's Prevention and the Wisconsin Alzheimer's Disease Research Center to study three such factors: the aging-suppressor gene KLOTHO and its systemic expression, the neuroplasticity-promoting gene brain-derived neurotrophic factor (BDNF) and its systemic expression, and physical activity. Our investigations are organized around two integrative and translational aims that seek to ascertain the extent to which KLOTHO, BDNF, and physical activity singly or jointly modify the effect of age and APOE4 on cognitive trajectory (Aim 1) and neuroimaging and fluid biomarkers of AD (Aim 2) in middle-aged adults (N ? 2000) at increased risk for AD. We will also determine whether these resilience factors alter the pernicious influence of biomarker changes on cognitive course. Together, this complementary set of studies will provide critical insights into putative avenues for promoting brain and cognitive health, particularly against the constraints imposed by advancing age and APOE4 genotype.

Further information available at:

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