**Supplemental Materials**

**Impact of age and apolipoprotein E ε4 status on regional white matter hyperintensity volume and cognition in healthy aging**

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Description of the Overall Study

The goal of the overall study (Brain Aging and Memory Study; BAMS) from which the data for the present study was derived, was to investigate how individual differences in health status and genetic risk for cognitive impairment affect the regional distribution and severity of brain changes associated with aging and age-related cognitive decline. Differences in blood pressure, aerobic fitness, and the presence of the apolipoprotein E (APOE) e4 allele, a common susceptibility gene for Alzheimer's disease, were factors of particular interest.

Participants were recruited from the Tucson-metro area by newspaper advertisement. Before they were enrolled in the study, participants underwent an extensive medical screen to exclude significant neurological, psychiatric, and medical disorders that could affect cognitive function. Information on their medical history and medication status were obtained by self-report and they had a physical and neurological examination performed by a neurologist who specializes in age-related cognitive disorders (Franchetti et al., 2021; Nguyen et al., 2016; Van Etten et al., 2020). During this medical screen, their height, weight, and blood pressure readings were obtained. The participants also completed rating scales and questionnaires to assess functional capacity (Lawton and Brody, 1969), self-reported family history, quality of sleep (Buysse et al., 1989), and the presence of current symptoms of depression with the Hamilton Depression Rating Scale (HAM-D; Hamilton, 1960). Participants were excluded from participating in the overall study if they had a HAM-D score ≥10 or MMSE score <26. Procedures for this study were approved by the University of Arizona Institutional Review Board and all participants gave their informed written consent for participation.

After the screening visit, 210 community dwelling, neurologically healthy older adults met our inclusion criteria and were enrolled into the study. The participants returned to the laboratory to complete tests of aerobic fitness assessed by a graded exercise treadmill test, magnetic resonance imaging (MRI) scans, a blood draw for APOE genotyping, and assessments of cognitive function using a battery of standardized neuropsychological tests. During the MRI session, multiple scans were acquired on a 3T GE Signa scanner (HD Signa Excite, General Electric, Milwaukee, WI), including volumetric T1-weighted Spoiled Gradient Echo (SPGR) scans, a T2 Fluid-Attenuation Inversion Recovery (FLAIR) scan, and diffusion tensor imaging (DTI) scans. A neuropsychological battery included tests across a variety of cognitive domains of global cognition, intelligence, memory, processing speed, executive functions, language, and motor functions. Participants were asked to return every two years for follow-up MRI scans, medical and cognitive assessments, and health status rating-scale questionnaires.

Overall, the BAMS study aimed to determine how age interacts with three potentially modifying factors: a) blood pressure, b) aerobic fitness, and c) APOE genotype to alter the regional distribution and severity of gray and white matter changes in aging; and to evaluate how specific brain regions identified by the interactive effects of aging with health status and genetic risk for cognitive impairment are associated with cognition. The study was designed to enhance our understanding of the brain changes associated with aging and related cognitive decline, help to identify those at greatest risk for age-related cognitive dysfunction, and provide a foundation to develop and test focused strategies to delay or prevent the brain changes that lead to cognitive decline in aging.

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