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# Interactive effects of physical activity and APOE-ε4 on BOLD semantic memory activation in healthy elders

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ABSTRACT

Evidence suggests that physical activity (PA) is associated with the maintenance of cognitive function across the lifespan. In contrast, the apolipoproteinE-ε4 (APOE-ε4) allele, a genetic risk factor for Alzheimer's disease (AD), is associated with impaired cognitive function. The objective of this study was to examine the interactive effects of PA and APOE-ε4 on brain activation during memory processing in older (ages 65–85) cognitively intact adults. A cross-sectional design was used with four groups ($n = 17$ each): (1) Low Risk/Low PA; (2) Low Risk/High PA; (3) High Risk/Low PA; and (4) High Risk/High PA. PA level was based on self-reported frequency and intensity. AD risk was based on presence or absence of an APOE-ε4 allele. Brain activation was measured using event-related functional magnetic resonance imaging (fMRI) while participants performed a famous name discrimination task. Brain activation subserving semantic memory processing occurred in 15 functional regions of interest. High PA and High Risk were associated with significantly greater semantic memory activation (famous>unfamiliar) in 6 and 3 of the 15 regions, respectively. Significant interactions of PA and Risk were evident in 9 of 15 brain regions, with the High PA/High Risk group demonstrating greater semantic memory activation than the remaining three groups. These findings suggest that PA selectively increases memory-related brain activation in cognitively intact but genetically at-risk elders. Longitudinal studies are required to determine whether increased semantic memory processing in physically active at-risk individuals is protective against future cognitive decline.



## Introduction

Emerging evidence suggests that increased leisure-time physical activity (PA) is associated with enhanced cognitive function and preservation of brain tissue volume (Colcombe and Kramer, 2003; Kramer et al., 2006) in healthy older adults. In contrast, possession of one or more ApolipoproteinE-ε4 (APOE-ε4) alleles is a risk factor for Alzheimer's disease (AD) and has been associated with accelerated cognitive decline, reduced neurite outgrowth, and amyloid β aggregation (Kim et al., 2009). Interestingly, the protective effects of PA on neurocognitive test performance appear to be greater in carriers than non-carriers of the APOE-ε4 allele. Specifically, high PA APOE-ε4 carriers experience less cognitive decline and a lower risk of being diagnosed with mild cognitive impairment (MCI) (Etgen et al., 2010; Geda et al., 2010) and AD (Laurin et al., 2001) than more sedentary carriers and non-carriers (Etnier et al., 2007; Schuit et al., 2001). Thus, PA may protect against cognitive decline, especially among healthy older adults at genetic risk for dementia (Kivipelto et al., 2008).

The precise mechanisms by which PA influences brain structure and function are unclear. One hypothesis, based on animal research, posits that PA produces neurogenic (van Praag et al., 1999) and angiogenic (Pereira et al., 2007) brain changes. In a functional magnetic resonance imaging (fMRI) study, greater activation in response to an executive control task was observed in the prefrontal and parietal cortices of high functioning older adults who were more physically active at study entry and in persons who had become more physically fit over the course of the study (Colcombe et al., 2004). These limited findings contrast with a complete absence of data addressing the brain mechanisms influencing the possible interaction of PA and APOE status.

*Abbreviations:* PA, physical activity; APOE-ε4, ApolipoproteinE-epilson4; AD, Alzheimer's disease; MCI, mild cognitive impairment; SBAS, Stanford Brief Activity Survey.

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The purpose of this study, therefore, was to examine the interactive effect of PA and APOE status on brain activation patterns, as measured by task-activated fMRI. Four groups of cognitively intact older adults were studied based on self-reported frequency and intensity of PA (active versus inactive) and genetic risk for AD (presence versus absence of an APOE-ε4 allele). The fMRI task involved a low-effort, high accuracy semantic memory task that involved discrimination of famous from unfamiliar names. Previous work by our group (Seidenberg et al., 2009) has shown that healthy elders with the APOE-ε4 allele demonstrate greater semantic memory activation (famous>unfamiliar names) than non-carriers in the posterior cingulate/precuneus, lateral temporal–parietal and medial prefrontal regions. Furthermore, greater semantic memory activation at study entry was shown to be protective against future cognitive decline measured 18 months post-scanning (Woodard et al., 2010). Based on our previous work, we hypothesized that brain activation patterns would show an interaction between PA and APOE status, with the greatest amount of semantic memory brain activation occurring in physically active, genetically at-risk older participants.

## Methods

This study was approved by the institutional review board at the Medical College of Wisconsin and conducted in accordance with the Helsinki Declaration. Written informed consent was obtained from all participants.

### *Participants*

Healthy adults between the ages of 65 and 85 were recruited from newspaper advertisements. A telephone screen was administered initially to 459 individuals to determine eligibility based on inclusion/exclusion criteria (see Inclusion and exclusion criteria). Of those who met criteria, 109 agreed to undergo APOE genotyping from blood samples, a physical activity questionnaire, neuropsychological testing, and an fMRI scanning session. From this initial pool, four subgroups of equal sample size ($n = 17$), carefully matched on demographic variables (age, sex, education), were formed based on the presence/absence of at least one APOE-ε4 allele and self-reported amounts of leisure-time physical activity: (1) Low Risk/Low PA, (2) Low Risk/High PA, (3) High Risk/Low PA, and (4) High Risk/High PA. Potential Low Risk participants were excluded if they reported a family history of AD. The sample sizes were equated to avoid potential biases in the group image analyses.

### *Physical activity status*

Frequency and intensity of leisure time PA was measured using the Stanford Brief Activity Survey (SBAS) (Taylor-Piliae et al., 2006). The SBAS has demonstrated validity for assessing habitual PA (Taylor-Piliae et al., 2006, 2007). Those individuals endorsing items indicating two or fewer days of low intensity PA (ranging from no PA to slow walking or light chores) were classified as physically inactive (Low PA). Participants who endorsed items indicating moderate to vigorous intensity PA three or more days per week (ranging from brisk walking, jogging or swimming for 15 min or more, or moderately difficult chores for 45 min, to regular jogging, running, bicycling or swimming for 30 min or more, or playing sports such as handball or tennis for an hour or more) were classified as physically active (High PA).

### *Genetic risk*

APOE genotype was determined using a PCR method described by Saunders et al. (Mayeux et al., 1998; Saunders et al., 1996). DNA was isolated with Gentra Systems Autopure LS for Large Sample Nucleic Acid Purification. Participants with one or both APOE-ε4 alleles were classified as at-risk for developing AD (High Risk); the remaining participants were classified as not at-risk (Low Risk). APOE genotype results for the four groups were as follows: Low Risk/Low PA (1 ε2/ε3; 16 ε3/ε3); Low Risk/High PA (1 ε2/ε3; 16 ε3/ε3); High Risk/Low PA (2 ε2/ε4; 15 ε3/ε4); and High Risk/High PA (15 ε3/ε4; 2 ε4/ε4).

### *Inclusion and exclusion criteria*

Potential participants were excluded if they reported a history of cognitive deterioration and/or dementia, neurological disease, medical illnesses, major psychiatric disturbance meeting DSM-IV Axis I criteria, a Geriatric Depression Scale score greater than 15 and substance abuse meeting DSM-IV Axis I criteria. Participants were allowed to take cardiovascular drugs. No between-group differences were observed in the percent of participants taking blood pressure medications. A blood chemistry screen (TSH, homocysteine, vitamin B12, folate, and creatinine) indicated all participants were within normal limits, and there were no significant differences between the groups on these measures. Only right-handed participants, based on the Edinburgh Handedness Inventory (Oldfield, 1971), were included.

### *Procedures*

Neuropsychological testing and the fMRI scanning were conducted on the same day. Participants were asked to refrain from alcohol use 24 h and caffeine use 12 h prior to testing. All participants received financial compensation.

### *Neuropsychological testing*

The neuropsychological test battery consisted of the Mini-Mental State Examination (Folstein et al., 1975), Mattis Dementia Rating Scale 2 (DRS-2) (Jurica et al., 2001); Rey Auditory Verbal Learning Test (RAVLT) (Rey, 1964), Geriatric Depression Scale (GDS) (Yesavage, 1988), and Lawton Activities of Daily Living (ADLs) (Lawton and Brody, 1969).

### *Functional MRI*

#### *Famous name recognition task*

The task stimuli consisted of 30 names of easily recognized famous persons (e.g., Frank Sinatra) and 30 names of unfamiliar individuals chosen from a local phone book. Only names with a high rate of identification (> 90% correct for targets and foils) were selected from an original pool of 784 names (Douville et al., 2005). A trial consisted of the visual presentation of a single name for 4 s. Participants were instructed to make a right index finger key press if the name was famous and a right middle finger key press if the name was unfamiliar. Both accuracy (% correct) and reaction time (in ms) were recorded. The 60 name trials were randomly interspersed with 20 4-s trials in which the participant was instructed to fixate on a single centrally placed crosshair in order to introduce "jitter" into the fMRI time course. The imaging run began and ended with 12 s of fixation. Total time for the single imaging run was 5 min and 24 s.

#### *fMRI Acquisition*

Whole-brain, event-related fMRI was conducted on a General Electric (Waukesha, WI) Signa Excite 3.0 Tesla short bore scanner equipped with a quad split quadrature transmit/receive head coil. Images were collected using an echoplanar pulse sequence (TE = 25 ms; flip angle = 77 degrees; field of view (FOV) = 240 mm; matrix size = 64 × 64). Thirty-six contiguous axial 4-mm-thick slices were selected to provide coverage of the entire brain (voxel size = 3.75 × 3.75 × 4 mm). The interscan interval (TR) was 2 s. High-resolution, three-dimensional spoiled gradient-recalled at steady-state (SPGR) anatomic images were acquired (TE = 3.9 ms; TR = 9.5 ms; inversion recovery (IR) preparation time = 450 ms; flip