

ABSTRACT

Title: EXERCISE BEHAVIOR AND MAINTENANCE OF CEREBRAL CORTICAL ACTIVITY DURING COGNITIVE CHALLENGE IN MIDDLE-AGED MEN AND WOMEN GENETICALLY AT RISK FOR DEMENTIA: A MAGNETOENCEPHALOGRAPHIC STUDY

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Exercise is known to protect and enhance cognitive function in normal aging through increased blood flow and upregulation of neurotrophic factors in the brain. One recent study suggests that carriers of a known genetic risk factor for Alzheimer's disease (AD), the apolipoprotein E (APOE) E4 allele, may exhibit a more profound benefit of exercise on neurocognitive function relative to non-E4 carriers. Brain imaging studies in cognitively normal, middle-aged E4 carriers have revealed deficits in temporal and parietal cortical function even in the absence of clinical symptoms of dementia. As exercise has been shown to protect these regions in normal aging, and even enhance cortical functioning, the current study employs magnetoencephalographic (MEG) measures of cortical activation during the Ericksen flanker task and the Sternberg working memory task to examine whether highly physically active 50-70 year old E4 carriers and non-carriers, who are free from dementia, exhibit greater cortical activation in task-related regions relative to their low-active counterparts. The results revealed that high-active participants, regardless

of genotype, exhibited greater activation on the Ericksen flanker task in the right frontal and right temporal regions relative to low-active participants, while performing similarly on accuracy and reaction time (RT). On the Sternberg working memory task high-active E4 carriers exhibited greater activation than low-active E4 carriers in the right temporal region, while being undifferentiated from both the high-active and low-active non-E4 carriers. This effect was most pronounced in the 150-200 ms post-stimulus time window. All groups performed similarly on accuracy and RT. The results suggest that high-resolution brain imaging methods are sensitive to differences in brain function in populations at different genetic risk for dementia prior to any signs of clinical impairment. Furthermore, the relationships between physical activity and brain function are measurable and distinguishable between groups of different genetic susceptibility on tasks and brain regions specific to AD-related neurocognitive decline. The findings support the notion that populations genetically at risk for dementia who remain sedentary may be at greater risk for decline in brain function relative to those who are physically active.

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CHAPTER 1: INTRODUCTION

The purpose of this research is to examine the nature of the relationship between regular aerobic exercise and apolipoprotein E (APOE) genotype with cortical processes during executive control and a working memory task in middle-aged individuals. While animal and human studies strongly support the notion that regular exercise can help to preserve and even enhance brain functioning in the elderly, very little research has been conducted to examine whether exercise can help to slow the progression of pathological aging, such as that in Alzheimer's disease (AD). One published study (Schuit, Feskens, Launer, & Kromhout, 2001) suggests that the impact of physical activity on cognitive decline may be more robust in populations who carry a known genetic risk factor for AD (APOE E4 allele) than in populations who are at lower risk for dementia (non E4 carriers). As exercise has been shown to be associated with greater task-related cortical activation in normal aging, the current study examines magnetoencephalographic (MEG) activation, a neuroimaging technique characterized by high temporal and spatial resolution, to examine whether physical activity is associated with greater cortical activation during tasks known to challenge executive function and working memory in the brain in both carriers and non-carriers of the APOE E4 allele, and whether differences exhibited between high-active and low-active participants are more robust in E4 carriers, as they are at risk for greater neurocognitive decline.

The Aging Brain

One prominent theory of aging of the central nervous system (CNS) is the frontal lobe hypothesis, which suggests that the frontal lobe and associated executive control functions (ECF) such as planning, inhibition, and working memory are the first to undergo significant decline with age (Kramer, Hahn, & Cohen, 1999; West, 1996). While this notion is generally well supported, individuals vary considerably in the specificity and time-course of such age-associated decline. Alternatively, a multiple-factor framework for studying the aging brain proposes distinct aging processes in different brain systems which vary independently in their decline across individuals (Buckner, 2004). In addition to normal aging in frontal-striatal brain circuits, which cause declines in ECF, independent aging of the medial temporal region can result in memory decline and may be accelerated in individuals who ultimately develop dementia such as AD. Therefore this study is designed to examine an ECF inhibition task known to decline in normal aging, and a working memory task known to challenge AD patients.

Alzheimer 's Disease

AD is an advanced form of aging in the brain marked by build-up of extracellular amyloid plaques and development of intracellular neurofibrillary tangles, which appear first in the entorhinal cortex of the limbic system, followed by the hippocampus, the temporal and parietal cortices, and finally the frontal lobes (Braak & Braak, 1991). Cognitive deficits parallel the structural decline and may begin with mildly impaired memory, followed by visual spatial deficits, confusion,

depression, and eventually death. Although considered pathological aging, estimates suggest that 10% of Americans over the age of 65, and 50% of Americans over the age of 85 suffer from some form of clinical dementia, the most common being AD (Evans et al., 1989).

Alzheimer's Disease and the Apolipoprotein E Gene

A variation in the APOE gene on chromosome 19 has been shown to be a significant risk factor for AD (Saunders, 2001). While about 40% of late-onset Alzheimer's patients carry at least one E4 allele, only about 14% of the US population carry the allele (Clark & Karlawish, 2003). Furthermore a dose-response relationship exists such that homozygous E4 carriers (carriers who receive two copies of the E4 allele) are at even greater risk for developing Alzheimer's symptoms than their heterozygous E4 (carriers of only one E4 allele) counterparts (Saunders, 2001). Although a significant risk factor, presence of the E4 allele does not always result in dementia. Therefore, other genes or environmental and lifestyle influences such as engagement in mental and physical activity likely interact with APOE genotype to influence cognitive decline late in life.

Alzheimer's Disease and Brain Imaging

Neuroimaging studies of AD patients versus age-matched controls have shown that AD patients exhibit decreased temporal and parietal activation, and increased prefrontal activation during declarative memory (Grady et al., 2003) and working memory (Maestú et al., 2001) tasks relative to controls. This has commonly been interpreted as compensatory activation, or reallocation of neural resources due to

pathological decline in hippocampal, temporal, and parietal areas of the brain. Figure 1 from Maestú et al. (2001) illustrates the compensatory frontal lobe activation of AD patients in the absence of temporal and parietal activation during a version of the Sternberg Working Memory task.

Figure 1. Taken from Maestú et al. (2001).

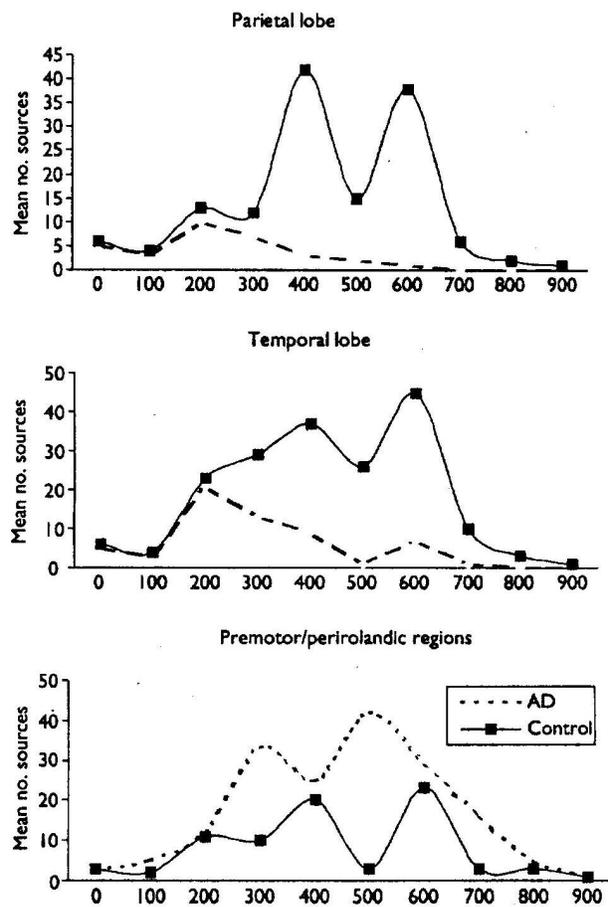


Fig. 1. Temporal course of activation for the two groups of subjects in left hemisphere parietal (upper graph), temporal areas (middle), and premotor/perirolandic areas (collapsed across hemispheres; lower graph) in response to target stimuli.

Brain Imaging in Populations At Risk for Dementia

Further brain imaging studies have focused on cognitively normal individuals who are at risk for AD, as identification of early markers of dementia may facilitate research on interventions to slow the progression of the pathology decades before onset of any clinical symptoms. Reiman and colleagues have used positron emission tomography (PET) to examine glucose metabolism in middle-aged and young carriers and non-carriers of the APOE E4 allele. Reiman et al. (2001) observed that in cognitively normal participants between the ages of 50 and 63, heterozygous E4 carriers exhibited significantly lower cerebral metabolic rates for glucose (CMRgl) than non-E4 carriers, primarily in temporal and parietal regions of the brain. More recently, Reiman et al. (2004) observed the same effect in younger participants between the ages of 20 and 39.

While Reiman and colleagues examined CMRgl in the resting brain (not challenged with a cognitive task), the findings are consistent with the pattern of relative hypoactivation found in the temporal and parietal areas during working memory tasks in older patients with AD (Maestú et al., 2001), and suggest that a similar pattern may be exhibited to a lesser extent in cognitively normal middle-aged individuals who carry the E4 allele. One main goal of the present study is to examine cortical activation during a working memory task to determine if E4 carriers exhibit deficits in temporal and parietal cortical activation, or compensatory frontal activation patterns relative to non-carriers. Furthermore, as outlined below, evidence now exists that exercise exerts protective effects on regions in the brain that decline in both normal and pathological aging. Therefore, the primary goal of this study is to

determine if exercise attenuates any differences in cortical activation patterns that may emerge in the frontal, temporal and parietal areas between middle-aged E4 carriers and non-carriers.

Exercise and the Aging Brain

The evidence is now strong that exercise protects and even enhances specific cognitive functions in the aging populations. Biological mechanisms contributing to maintenance of brain functioning as a result of exercise were initially proposed by Spirduso (1980; 1983). The oxygenation hypothesis proposed that increased cerebral blood flow (CBF) resulting from cardiovascular fitness could help to preserve metabolic functions in the brain. Rogers, Meyer, and Mortel (1990) provided support for this hypothesis reporting that individuals who remained active following retirement exhibited maintained CBF relative to inactive counterparts. Furthermore, the neurotrophic hypothesis which has recently found support in animal studies, suggests that exercise promotes trophic or nourishing effects on the brain. Brain-derived neurotrophic factor (BDNF), which is known to enhance plasticity and long-term potentiation (LTP) in the brain, is upregulated following periods of exercise in rats (Cotman & Engesser-Cesar, 2002). Interestingly, the upregulation of BDNF occurs earliest and is most pronounced in the hippocampal region, an area of the brain which exhibits the earliest and most rapid decline in AD.

Exercise and Cognitive Processing in Normal Aging

A recent meta-analysis of exercise intervention studies revealed that the cognitive functions most enhanced by exercise are, in fact, those that decline earliest

in normal aging, frontally mediated ECF (Colcombe & Kramer, 2003). A recent structural magnetic resonance imaging (MRI) study supports that brain tissue found to exhibit the greatest relative sparing of decline associated with cardiovascular fitness was also the brain tissue shown to decline most rapidly in normal aging, specifically gray matter in the prefrontal, superior parietal, and middle/inferior temporal cortices, as well as anterior white matter tracts (Colcombe et al., 2003). A subsequent functional MRI (fMRI) study was conducted Colcombe et al. (2004) to examine cortical activation during the Ericksen Flanker task, an ECF task requiring inhibition of attention to irrelevant stimuli, prior to and following a six month aerobic exercise intervention. The investigators concluded that exercised participants exhibited more efficient allocation of attentional networks, associated with quicker reaction times relative to non-exercised controls following the intervention. Specifically, the trained group exhibited increased activation in the bilateral superior parietal and right frontal regions, and decreased activation in the anterior cingulate (ACC) region, a region known to monitor attentional conflicts. The authors also reported similar results when comparing aerobically high-fit participants to low-fit participants in a cross-sectional design, suggesting that such designs examining exercise and brain activation may yield similar results to exercise intervention studies. While the previous studies present strong evidence that exercise can protect or even enhance brain functioning in normal aging, little is known about the efficacy of exercise on slowing or preventing pathological decline, such as that in AD.

Figure 2. Taken from Schuit et al. (2001)

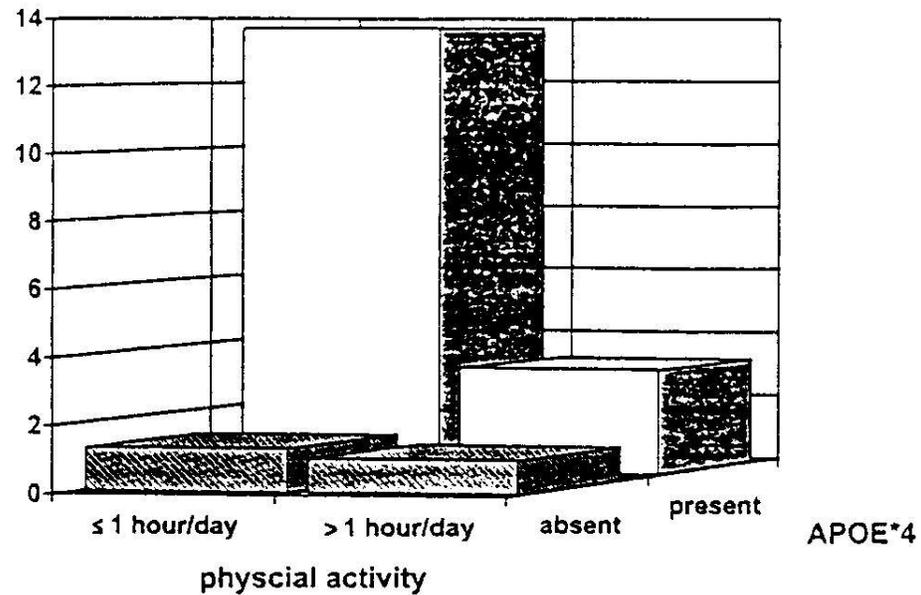


FIGURE 1—Adjusted odds ratios for cognitive decline; adjusted for age and education, MMSE 1990.

Exercise and Dementia in APOE E4 Carriers

Research examining the effects of exercise on pathological aging of the CNS is limited. To date, only one published study has reported on the association between physical activity and risk of dementia in carriers and non-carriers of the APOE E4 allele (Shuit et al., 2000). The authors found that physical activity level had little influence on cognitive decline over a three year period in non-carriers of the E4 allele, while carriers of the E4 allele were four times less likely to show decline if they were physically active (Figure 2). The results suggest that the protective benefits

from exercise may be more apparent in individuals at risk for dementia, as they are more likely to exhibit the most rapid neurocognitive decline.

The current study proposes to extend our understanding of the effects of exercise in populations at-risk for dementia by employing magnetoencephalographic (MEG) measures of cortical activation high and low physically active E4 carriers and non-carriers who exhibit no signs of dementia during cognitive tasks known to challenge areas of the brain susceptible to both normal and AD-related aging. MEG allows for high spatial resolution and exquisite temporal resolution of cortical activity during cognitive challenge

Statement of the Problem

While exercise protects and enhances ECF in normal aging populations, it is unknown whether exercise can slow the decline that occurs in pathological aging such as AD. Recent advances in brain imaging and genetics allow researchers to examine subtle changes in brain processes in populations genetically at risk for dementia several decades prior to any clinical decline. One purpose of this study is to determine whether cognitively normal individuals who carry a known genetic risk factor for AD, APOE E4, exhibit hypoactivation in temporal and parietal regions, or compensatory activation patterns in other cortical regions during performance on executive function and working memory tasks which distinguish them from non-E4 carriers. Secondly, given the neurotrophic effects of exercise, the primary purpose of this paper is to determine if exercise attenuates any main effects for APOE genotype on cortical activation patterns. Two tasks were selected for the brain imaging, the

Ericksen flanker task known to challenge ECF in normal aging, and the Sternberg Working Memory task known to challenge working memory in AD patients.

Hypotheses

Root mean square (RMS) analysis and channel selection for regions is detailed in Chapter 3, Methods.

Sternberg Working Memory Task

APOE E4 carriers will exhibit lower RMS average amplitude in the temporal and parietal regions and greater average RMS amplitude in the frontal region to the probe trials relative to non-E4 carriers. This reduction will be attenuated in the high-active E4 carriers.

Ericksen Flanker Task

High-active individuals will exhibit greater right frontal and bilateral parietal RMS average amplitude compared to the low-active participants. The magnitude of the difference will be greater in E4 carriers than in non-carriers.

Exploratory Analyses

Eight specific regions will be analyzed for RMS on both tasks: right, left, and midline frontal, right and left temporal, right and left parietal, and the central midline region. Regions not addressed in the hypotheses will be analyzed for exploratory purposes.

CHAPTER 2: REVIEW OF LITERATURE

While the overall concept that rigorous physical activity preserves aspects of central nervous system (CNS) functioning has prevailed since the study of exercise and the aging brain began several decades ago, the category of cognitive functions preserved through physical activity were not fully appreciated initially, and the mechanisms by which exercise exerted influence over the aging CNS were somewhat speculative. Early intuition on the topic generated studies that focused on neuromuscular functions and emanated from the assumption that brain regions specifically related to movement functions such as the motor cortex and the cerebellum were likely to benefit most from physical activity (Spirduso, 1980; 1983). More recent studies suggest that the neurotrophic effects of exercise and the associated preservation of brain function are most evident in areas of the brain subserving higher-order decision-making and memory processes (Colcombe & Kramer, 2003). Furthermore, limited but promising research suggests that individuals who possess a genetic risk factor for pathological decline such as Alzheimer's disease (AD) may especially benefit from regular physical activity (Schuit et al., 2001). Now with the advent of a mapped human genome and sophisticated brain imaging procedures the potential exists to identify individuals at risk for cognitive decline several decades prior to onset of any clinical dementia, and to study the effects of exercise on specific cognitive processes while monitoring activation of associated

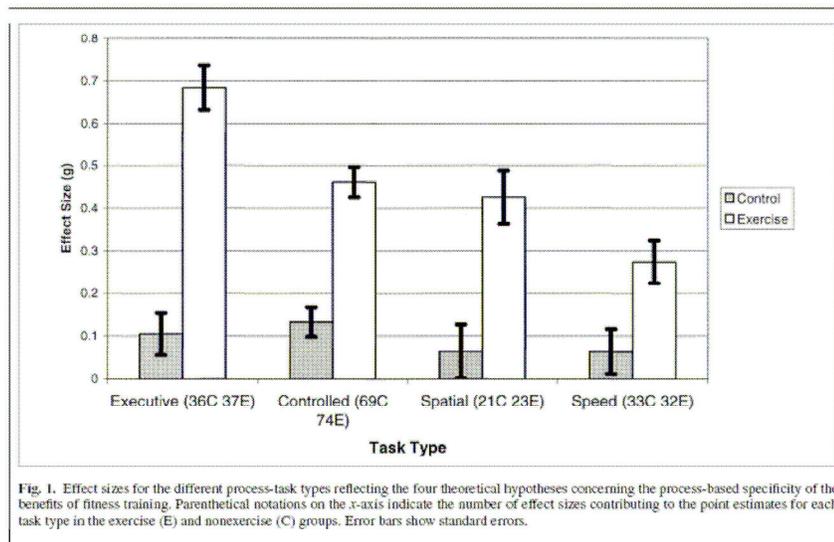
regions of interest in the brain. The following is a review of the current knowledge of the effects of exercise on the brain, the genetics of cognitive decline, and the use of functional brain imaging to detect early deficits in brain activation or metabolism in the absence of behavioral or clinical symptoms.

Exercise and Normal Aging: From Reaction Time to Executive Control

Early studies of exercise and CNS aging focused on neuromuscular tasks such as simple RT and finger tapping, since exercise-induced protective effects on the brain were expected to occur specifically in the motor areas engaged during exercise. Indeed, studies reviewed by Spirduso (1980; 1983) did show a significant relationship between physical fitness and improved RT in the elderly. However, some researchers began to examine the effects of exercise on higher-level cognitive processes based on a paradigm shift from the examination of neuromuscular processes to the examination of cognitive processes that were more susceptible to aging than motor processes. Observing that visuospatial skills decline more rapidly with age than verbal skills, some researchers focused their efforts on examining aerobic fitness and visuospatial tasks (Shay & Roth, 1992; Stones & Kozma, 1989). Other researchers focused on cognitive tasks that require controlled or effortful processing (Chodzko-Zajko & Moore, 1994) as these tasks necessitate greater attentional resources than more automated tasks. Finally, Kramer et al. (1999) proposed that frontally mediated executive control function (ECF) tasks such as planning, coordination, inhibition, and working memory, which have been shown to be most susceptible to normal aging would be most protected and enhanced by aerobic fitness (West, 1996). This notion was supported by a subsequent meta-analysis on exercise intervention studies over

the previous 35 years which reported greater effect sizes for improvements in cognitive function on ECF tasks relative to speed tasks (RT), visuospatial tasks, or controlled processing tasks (see Figure 3) (Colcombe & Kramer, 2003).

Figure 3. Taken from Colcombe & Kramer (2003).



Exercise and Protection of Neural Function: Proposed Mechanisms

Consistent with the early theoretical framework that exercise would primarily influence speed tasks and neuromuscular function, the early proposed mechanisms by which exercise could protect neural function focused mainly on motor and sensory areas of the brain expected to be engaged by physical exertion. Spirduso (1980) proposed two biological mechanisms by which exercise might maintain the integrity of the neuromuscular system. One mechanism, the oxygenation hypothesis, suggested that activation of motor centers in the brain may result in increased blood and oxygen supply, metabolically contributing to maintenance in those regions. Secondly, Spirduso proposed that activation of the muscles may have a trophic

(nourishing) effect on the nerves that activate them, although the specific biological cascades and trophins involved were unknown at the time.

Oxygenation and Neurotrophic Effects in Animals and Humans

The oxygenation hypothesis was supported in animal studies, which showed increased blood flow in the motor cortex of rats during exercise, and angiogenesis in the motor cortex and cerebellum of rats following physical activity (for a review see Churchill et al., 2002). Further evidence in humans was offered by Rogers et al. (1990), who showed that individuals who remained physically active following retirement exhibited greater regional cerebral blood flow (rCBF) in gray matter across both hemispheres relative to individuals who became sedentary during retirement.

The neurotrophic hypothesis received little empirical support until recently, when animal studies by Cotman and colleagues (Cotman & Berchtold, 2002; Cotman & Engesser-Cesar, 2002) revealed that exercising rats exhibit upregulation of brain-derived neurotrophic factor (BDNF), a member of a neurotrophic family that supports the health and functioning of glutamatergic neurons, and is known to maintain longevity of cells, protect cells against insults, and facilitate long-term potentiation (LTP) as well as neuro- and synaptogenesis. Although the most robust upregulation of BDNF was predicted to occur in motor or sensory regions of the brain following exercise, the earliest and most sustained increases in BDNF occurred in the hippocampus, a brain region important to learning and memory, and one which exhibits decline in normal and AD related aging.

Cognitive Stimulation

Although the focus of this review, and the current study, is to understand the impact of exercise on the aging brain, cognitive challenge and stimulation may help to preserve brain functioning as well. Animal studies have distinguished the effects of exercise from learning on the brain by examining changes associated with running versus skill development. Black, Isaacs, Anderson, Alcantara, and Greenough (1990) examined capillary density and number of synapses in the cerebellar region in rats in a motor skill learning group (acrobatic course) compared to an exercise group (treadmill), and found distinct adaptations in the two groups. They found that the exercise group increased capillary density without significant increases in number of synapses, while the opposite was true for the acrobatic group. Studies in humans have also reported beneficial effects of cognitively stimulating activities on the aging brain. Wilson et al. (2002) reported that participation in cognitively stimulating activities resulted in reduced risk of Alzheimer's disease. However, Salthouse, Berish, and Miles (2002) have argued that the relevant literature on the "use it or lose it" hypothesis has resulted in equivocal findings. Although a detailed discussion of the impact of cognitive stimulation is beyond the scope of this study (for a review of the impact of exercise versus experience see Churchill et al., 2002), the research suggests that individuals who remain physically and cognitively stimulated throughout their lives are expected to exhibit the greatest neurocognitive health later in life. In fact, a recent study showed that a combined exercise and cognitive intervention in humans resulted in greater improvement in cognitive performance than either the exercise or cognitive intervention alone (Fabre, Chamari, Mucci,

Massé-Biron, & Préfaut, 2002). Therefore, future efforts should attempt to distinguish between the contributions of physical and mental stimulation.

Exercise and Brain Imaging

Brain imaging studies of physical activity in humans have revealed that brain regions supporting higher order cognition such as the anterior cingulate cortex (ACC) and the insular become active during strenuous exercise (Williamson, McColl, & Matthews, 2003). These changes in activation were shown to be associated with central command and perceived effort, and independent from metaboreflex activation or blood pressure elevation. Activation of these areas during exercise is notable since they are known to be crucial to cognitive functions such as inhibition, decision making and memory. Additionally, Colcombe et al. (2003) reported relative sparing of age-related structural decline in frontal and cortical association areas in aerobically fit individuals. Magnetic resonance imaging (MRI) scans of 55 adults over the age of 55 showed robust declines with increasing age of tissue densities in gray matter in the frontal, parietal, and temporal cortices as well as white matter declines in the anterior tracts. Importantly, the areas exhibiting the greatest decline also exhibited the greatest sparing as a result of cardiovascular fitness.

To study the relationship between physical activity and frontal activation during ECF and non-ECF cognitive challenge, Zimmerman et al. (2004) employed electroencephalographic (EEG) measures to examine P300 amplitude as a function of physical activity level on elderly (age 66-92) participants during an auditory GoNogo ECF task, and an auditory Oddball task. The P300 is a positive event-related brain

potential (ERP) generated during psychological tasks which require discrimination of two stimuli on some dimension (Polich & Kok, 1995). Zimmerman et al. employed a commonly used Oddball task during which subjects count or press a button to rare stimuli (occurring 20% of the time) and ignore common stimuli (80% occurrence). The GoNogo task was generated using the same stimuli, however, subjects were required to respond to the common stimuli by pressing a button, while inhibiting responses to the rare stimuli. While the Oddball task is not considered an ECF task, the GoNogo task requires active suppression of a prepared motor response on the rare trials, and is considered a frontally mediated ECF task. Interestingly, Zimmerman et al. (2004) observed that physical activity in the elderly participants was positively correlated with P300 amplitude in the frontal region during the GoNogo task, while no such effect was observed during on the Oddball task. The results suggest that greater physical activity level in this population was associated with increased ability to generate greater task related activation in the frontal region during the ECF task. Consistent with the notion that exercise effects are greater for ECF tasks than for non-ECF tasks, the relationship between physical activity and P300 amplitude was not observed during the non-ECF Oddball task.

To further examine exercise effects on cortical activation during an ECF task with greater spatial resolution, Colcombe et al. (2004) employed functional MRI (fMRI) during the Ericksen Flanker task, which requires the subject to ignore distracting flanking arrows and determine the direction of a center arrow (<<>>). The paper reported two studies, one cross-sectional design comparing high-fit to low-fit participants, and a second intervention study in which sedentary subjects were

aerobically trained for six months and compared to a stretching group who received no cardiovascular training. Both studies revealed similar fitness effects on cortical activation patterns during the task, with trained participants exhibiting greater activation in the right middle and superior frontal cortical areas, as well as bilaterally in superior parietal cortex. Trained participants also exhibited decreased activation in the anterior cingulate cortex, a deep cortical area associated with resolving conflict and mediating activity in other cortical regions. The authors concluded that increased activation associated with cardiovascular fitness reflected an increased ability to recruit task-related areas of the brain to successfully complete the task, while the decreased activation in the anterior cingulate region reflected reduced conflict in resolving the incongruent stimuli.

While Kramer and colleagues have addressed the question of task specificity by providing compelling evidence for exercise effects on ECF tasks in normal aging, Schuit et al. (2001) addressed the question of population specificity by conducting the first known study examining physical activity and cognitive decline in a population genetically at risk for AD. In the only known published epidemiological study contrasting carriers and non-carriers of a known genetic risk factor for AD, Schuit et al. (2001) suggests that the effect of exercise may be even more robust in at-risk populations genetically predisposed to dementia. The following outlines current understanding of AD, genetic risk factors for dementia, epidemiological studies on exercise and dementia, and recent brain imaging studies of AD patients and those genetically at risk for AD.

Alzheimer's Disease

Although considered pathological aging, recent US estimates suggest that as many as 40% of Americans over the age of 85 may meet the clinical criteria for dementia, the most prevalent form being AD (Clark & Karlawish, 2003; General Accounting Office, 1998). If the current rate holds, by the middle of this century 14 million Americans may suffer from dementia.

The pathology of AD is marked by intracellular neurofibrillary tangles and extracellular neuritic amyloid plaques. These regionally specific plaques and tangles begin in connections between the entorhinal cortex and the hippocampus, and progress to the temporal and parietal cortices, and finally the frontal cortex (Braak & Braak, 1991). Decline of cognitive function parallels the structural decline and begins with mild memory impairment, followed by perceptual impairments, confusion, depression, and ultimately brain failure and death.

Genetics of Alzheimer's Disease

AD has multiple known etiologies as mutations in at least three known genes, the amyloid precursor protein (APP) and the presenilin 1 (PS1) and 2 (PS2) genes seem to be directly causal of the disease (Goate et al., 1991; Levy-Lahad et al., 1995; Sherrington et al., 1995). However, these mutations are rare and only occur in about 2% of Alzheimer's cases. A more common variation of the apolipoproteinE (APOE) gene, found on chromosome 19, has been shown to be associated with susceptibility to late onset AD. Strittmatter et al. (1993) first reported an association between the APOE E4 allele and AD, citing an E4 allele frequency of 52% in late-onset AD patients while finding an E4 allele frequency of only 16% in age-matched controls.

Saunders et al. (1993) replicated the finding through both clinical diagnoses and pathological confirmation in autopsy cases. The robust nature of this association was rapidly and widely confirmed in laboratories across the world (Anwar et al., 1993; Borgaonkar et al., 1993; Houlden et al., 1993; Noguchi et al., 1993; Poirier et al., 1993; Rebeck et al., 1993; Ueki et al., 1993).

The specific role of APOE in the brain is currently under investigation by many, but it is believed to play an important role in lipid and cholesterol transport, and is thought to have an effect on amyloid deposition and stabilization of microtubules, contributing to the formation or lack thereof of the plaques and tangles that mark the disease (Saunders, 2001). While presence of the E4 allele poses a risk factor for AD, and possession of two copies of the allele results in even greater risk with earlier onset of AD, carrying the E4 allele does not always result in dementia. The finding that E4 is a risk factor, but not directly causal of AD suggests that presence of E4 may interact with other genes or lifestyle behaviors such as physical activity in its effect on cognitive decline.

Epidemiological Studies on Physical Activity and Dementia

In a prospective study that focused on the link between physical activity and the incidence of cognitive decline, Laurin et al. (2001) assessed the development of cognitive impairment and incident dementia over a five-year period between 1991-92 and 1996-97 in 4615 men and women, who were over age 65 at study inception, and who completed screening and clinical evaluations of cognitive function at time of entry and at follow-up. Compared to the incidence of cognitive impairment and dementia in non-exercisers they observed that physical activity participation was

strongly associated with reduced incidence for both cognitive impairment and AD in a dose-dependent manner. That is, higher levels of physical activity participation (categorized as none, low, moderate, and high) were associated with progressively smaller odds of risk for impairment as assessed over the 5-year period. More recently, Verghese et al. (2003) followed a group of older men and women over an approximate five-year period in a prospective study of 469 community-dwelling men and women over the age of 75, who were enrolled in the Bronx Aging Study, and who did not have dementia at baseline as assessed by performance on the Blessed Information–Memory–Concentration test. Involvement in leisure activities and cognitive function were assessed at baseline and at follow-up visits at intervals of every 12 to 18 months. After controlling for any differences in cognitive function at baseline assessment leisure activities were associated with reduced risk of dementia. Friedland et al. (2001) compared retrospective accounts from probable AD and age-matched controls in their early seventies and concluded a protective effect from participation in midlife intellectual and physical activities on the risk of AD. Even after controlling for age, gender, income, and educational differences the clinical case group (n=193) reported significantly less engagement in physical activity pursuits between the ages of 20 and 60 as compared to the healthy controls (n=358). Similar effects have been noted in other studies (Albert et al., 1995; Carmelli et al., 1998; Scarmeas et al., 2001).

Exercise and Dementia in Populations at Risk

Schuit et al. (2001) examined whether the influence of physical activity on cognitive decline differs between individuals genetically at higher and lower risk for

AD. The study examined 347 male participants (age 65-84 at baseline) who were either carriers or non-carriers of a genetic marker associated with increased risk of AD, the apolipoprotein E (APOE) E4 allele. The Mini Mental State Exam (MMSE) was administered twice, three years apart, to calculate an odds ratio for cognitive decline during that period. The study revealed that individuals who did not carry the E4 allele were at lower risk for cognitive decline, and exhibited little difference in decline between those physically active during the three years and those who were not. Among the E4 carriers, both high-active and low-active groups exhibited greater decline than the non carriers, however, the high-active E4 carriers were four times less likely to exhibit cognitive decline than their low-active E4 counterparts. The findings indicate that maintaining a physically active lifestyle may be of particular importance to individuals who are at high risk for decline, although further study on the topic is necessary. The findings also suggest that adopting a physically active lifestyle may, in fact, have an effect on slowing the progression of a condition as profound as AD, a notion that likely would not have been seriously considered twenty years ago

Functional Brain Imaging in AD and Populations at Risk

Despite recent progress in examining the influence of exercise on structural and functional changes in the normal aging brain (Colcombe et al., 2003; Colcombe et al., 2004), no published studies to date have employed high temporal or spatial brain imaging procedures to examine the effects of physical activity on dementia, or populations at risk for dementia. However, insights gained from brain imaging studies comparing AD patients to normal controls, and APOE E4 carriers to non-

carriers, combined with the knowledge of exercise, cortical dynamics and normal aging, provide a solid rationale, and directional hypotheses for the study of the influence of exercise on brain activation in populations at risk for AD. The following section outlines recent findings on deficits in brain function and compensatory activation associated with AD or genetic risk factors for AD.

Deficient and Compensatory Activation in Alzheimer's Disease

Functional brain imaging studies comparing AD patients to age-matched controls suggest that AD is characterized by hypometabolism primarily in the temporal and parietal cortices. Hypometabolism in the frontal association areas of the cortex is less pronounced and is typically only apparent in the most severe cases. In contrast to normal aging where the frontal regions exhibit the greatest decline, there is a relative temporary sparing of the frontal region in the early stages of AD compared to temporal and parietal cortices. The areas of the motor cortex, primary visual cortex, basal ganglia, and cerebellum do not differ significantly in AD compared to age-matched controls (Fox, Scahill, Hogg, and Rossor, 2001).

Recent findings provide evidence of the adaptability of the brain under conditions of age-related or AD-related decline to continue to accomplish difficult and attention demanding tasks by engaging alternative brain circuits to compensate (Bruckner, 2004). In fact, evidence from positron emission tomography (PET) research suggests that AD patients exhibit increased activity in prefrontal regions relative to controls when challenged with episodic or semantic memory tasks to compensate for temporal lobe degeneration attributable to AD (Grady et al., 2003).

To examine the spatio-temporal patterns of brain magnetic activity during working memory in AD, Maestú et al., (2001) examined magnetoencephalographically-derived (MEG) measures of brain activation during the Sternberg working memory task in AD patients and controls. The version of the Sternberg task employed required memorizing a set of five letters, followed by a series of 250 probe trials, half of which were members of the memorized set. The subjects were required to lift one index finger if the probe letter was one of the letters in the memorized set. During probe trials where the probe letter matched a letter in the original set the control subjects exhibited the greatest number of active neural sources in the temporal and parietal cortices at 400 and 600 ms, while AD patients exhibited a relative lack of activation in these regions. AD patients, however, exhibited heightened activation in the frontal region, consistent with previous reports of compensatory activation in a region relatively spared by early progression of AD.

Brain Imaging in Cognitively Normal E4 Carriers

Since the identification of the APOE E4 allele as a risk factor for late onset AD researchers have begun to examine functional brain abnormalities in normal functioning E4 carriers several years prior to the potential onset of dementia. Ability to detect changes in brain function in small samples of at risk populations early allows for the opportunity for treatment, as well as research examining the effectiveness of treatments prior to the onset of clinical symptoms.

Using positron emission tomography (PET) Reiman and colleagues have shown that middle-aged heterozygous carriers of the E4 allele who are free from significant cognitive decline or dementia (Reiman et al., 2001) exhibit deficits in

glucose metabolism in the temporal and parietal areas of the brain relative to age matched counterparts who do not carry the E4 allele. More recently, Reiman et al. (2004) observed similar results in 20-39 year old E4 carriers. Detection of such differences allows for future studies to examine the effects of treatments such as drug therapies or exercise interventions on the progression of AD related deficits in normal functioning younger populations. While Reiman and colleagues prefer to examine cerebral metabolic rates for glucose (CMRgl) in the resting brain (not challenged by cognitive demands) to avoid potential confounds of differential strategy application during cognitive tasks across participants, other researchers have chosen to examine cortical activation patterns in cognitively normal E4 carriers during the execution of cognitive tasks known to engage areas of the brain that exhibit early decline in AD (Bookheimer et al., 2000; Smith et al., 1999) These studies have produced seemingly contradictory results.

Smith et al. (1999) examined cortical activation using fMRI in 26 female participants between the ages of 40 and 65, 14 of which were determined to be at high risk for AD based on APOE genotype and family history while 12 were considered at low risk for AD. Both groups performed similarly on a battery of neuropsychological tests as well as on the letter fluency and covert object naming tasks used for fMRI testing. The letter fluency task required participants to generate as many words as they could which began with a randomly selected cue letter. The covert object naming task required participants to recognize and name objects in line drawings which varied in category and complexity. High-risk participants exhibited significantly reduced activation on both tasks in the inferotemporal area relative to the

low-risk participants. Specifically, regions exhibiting decreased activation in the high-risk group were Brodmann's areas 19 and 37, areas on the ventral visual pathway associated with higher order visual processing in object recognition. The authors concluded that the decreased activation in the high-risk group may reflect pre-clinical disruption of neural networks in regions known to demonstrate pathology in AD.

Also employing fMRI, Bookheimer et al. (2000) examined 30 participants between the ages of 47 and 82, 16 of which carried at least one copy of the E4 allele. All participants exhibited memory scores normal for their age range, and as a group exhibited above average intelligence. Functional MRI scanning was conducted during a learning memory task where the participants heard pairs of words, and were required later to recall the second word in a pair given the first. The task was designed specifically to challenge memory and the medial temporal area. Contrary to the results of Smith et al. (1999), the E4 carriers exhibited greater signal intensity and spread of activation in the left frontal region (Broca's area), anterior cingulate cortex, right prefrontal cortex, posterior left temporal and inferior parietal region (Wernicke's area), and the hippocampal regions relative to the non-E4 carriers. The authors concluded that the results support the compensatory hypothesis, suggesting that the E4 carriers, relative to the non-carriers, required greater cognitive effort to accomplish the task and subsequently recruited additional neural resources.

Many factors may have contributed to the seemingly contradictory findings of the Smith et al. and Bookheimer et al. studies. First, while both studies recruited participants in an age range spanning several decades, the average age of participants

in the Smith et al. study was about 10 years younger than those in the Bookheimer et al. study. Additionally the recruitment procedures between the studies differed as high-risk participants in the Smith et al. study differed from low-risk participants in family history as well as APOE genotype, with high-risk participants having at least one first-degree relative with clinical AD in addition to carrying the E4 allele, and low-risk participants possessing neither the E4 allele nor a first-degree relative family history. Assessment of high and low-risk in the Bookheimer et al. study was based solely on APOE genotype with both high and low-risk groups reporting similar family histories of dementia. Finally, the two studies employed different cognitive tasks, which likely differed in level of difficulty. Therefore, the degree of pathology exhibited by the high-risk groups, and the level of cognitive effort required to complete the cognitive tasks likely contributed to the differential findings.

Summary

Exercise causes neurotrophic effects on the brain, which promote plasticity and longevity of cell function. The most pronounced effects of exercise on the aging brain are evidenced in cognitive tasks and regions of the brain prone to normal age-related decline. A recent study suggests that the impact of physical activity may be more robust in a population genetically at risk for AD, carriers of the APOE E4 allele. Brain imaging studies in cognitively normal E4 carriers have revealed differential patterns of activation and glucose metabolism in this population relative to non-E4 carriers several decades prior to onset of cognitive decline. As such, brain imaging studies in middle-aged or younger populations who carry known genetic risk factors

for decline or deficits in brain function represent an important population for studying the impact of physical activity on the progression of dementia or AD related aging. The current study examines cortical activation patterns during ECF and working memory tasks in middle-aged carriers and non-carriers of the APOE E4 allele, who exhibit no signs of cognitive decline, and who are either highly physically active or relatively sedentary. Understanding the association between physical activity and cortical function in populations who are cognitively normal, but at risk for AD is an important move towards understanding the protective effects of exercise on pathological neurocognitive decline.

CHAPTER 3: Manuscript to be Submitted for Publication

ABSTRACT

Exercise is known to protect and enhance cognitive function in normal aging through increased blood flow and upregulation of neurotrophic factors in the brain. One recent study suggests that carriers of a known genetic risk factor for Alzheimer's disease (AD), the apolipoprotein E (APOE) E4 allele, may exhibit a more profound benefit of exercise on neurocognitive function relative to non-E4 carriers. Brain imaging studies in cognitively normal, middle-aged E4 carriers have revealed deficits in temporal and parietal cortical function even in the absence of clinical symptoms of dementia. As exercise has been shown to protect these regions in normal aging, and even enhance cortical functioning, the current study employs magnetoencephalographic (MEG) measures of cortical activation during the Ericksen flanker task and the Sternberg working memory task to examine whether highly physically active 50-70 year old E4 carriers and non-carriers, who are free from dementia, exhibit greater cortical activation in task-related regions relative to their low-active counterparts. The results revealed that high-active participants, regardless of genotype, exhibited greater activation on the Ericksen flanker task in the right frontal and right temporal regions relative to low-active participants, while performing similarly on accuracy and reaction time (RT). On the Sternberg working memory task high-active E4 carriers exhibited greater activation than low-active E4 carriers in the right temporal region, while being undifferentiated from both the high-active and low-active non-E4 carriers. This effect was most pronounced in the 150-200 ms post-stimulus time window. All groups performed similarly on accuracy and

RT. The results suggest that high-resolution brain imaging methods are sensitive to differences in brain function in populations at different genetic risk for dementia prior to any signs of clinical impairment. Furthermore, the relationships between physical activity and brain function are measurable and distinguishable between groups of different genetic susceptibility on tasks and brain regions specific to AD-related neurocognitive decline. The findings support the notion that populations genetically at risk for dementia who remain sedentary may be at greater risk for decline in brain function relative to those who are physically active.

INTRODUCTION

According to recent US estimates as many as 40% of Americans over the age of 85 may meet the clinical criteria for dementia (Clark & Karlawish, 2003; General Accounting Office, 1998), the most common form being Alzheimer's disease (AD). To develop effective strategies to slow the progression of the AD, understanding of brain changes associated with early preclinical susceptibility of dementia in populations at risk can allow for study of intervention strategies before the onset of cognitive impairment.

One published study suggests that physical activity may significantly slow the rate of cognitive decline in carriers of the apolipoprotein E (APOE) E4 allele, a known genetic risk factor for AD. Schuit, Feskens, Launer, & Kromhout (2001) observed that physical activity level had little influence on cognitive decline over a three year period in non-carriers of the E4 allele, while physically active carriers of the E4 allele were four times less likely to exhibit cognitive decline than E4 carriers who were less active. The finding suggests that the impact of physical activity in individuals who are susceptible to AD may be more robust than in individuals who are at lower risk for dementia. Evidence from animal studies suggests that the neurotrophic influences of exercise on the brain may specifically benefit a region afflicted early in AD. Brain-derived neurotrophic factor (BDNF), a growth factor important to healthy functioning, repair, and plasticity in the brain, along with other neurotrophic factors exhibit increased expression following exercise (Cotman & Engessar-Cesar, 2002). This effect is most pronounced in the hippocampus, a region of early decline in AD which is important to learning and memory.

Magnetoencephalographic (MEG) examination of cortical processes during working memory in AD patients versus controls has revealed that patients exhibit decreased temporal and parietal lobe activation relative to controls, and compensatory activation of the frontal region (Maestú et al. 2001), a region relatively spared early in AD. Furthermore, the deficits in temporal and parietal activation were associated with a greater degree of hippocampal atrophy (Maestú et al., 2003).

Although the evidence for the neurotrophic effects of exercise on populations at risk for AD are promising, studies of the effects of exercise on the human brain functioning have been limited to normal aging. Colcombe et al. (2003) reported that the areas of the brain most susceptible to normal age-related atrophy, such as cortical association areas of the temporal, parietal, and frontal lobes, are also those most spared by the neurotrophic effects cardiovascular fitness. Additionally, high-fit individuals have been shown to exhibit greater activation in task-related cortical regions during cognitive challenge on an executive function task relative to low-fit individuals (Colcombe et al., 2004).

Recent brain imaging studies in populations genetically at risk for AD have revealed that cognitively normal APOE E4 carriers between the ages of 50 and 60 (Reiman, et al., 2001) exhibit deficits in resting brain metabolism in the temporal and parietal regions relative to non-carriers. The finding was replicated in 20-39 year olds (2004), suggesting that with high resolution brain imaging, early AD related pathology can be examined several decades prior to clinical decline. As such, cognitively normal middle-aged carriers of the E4 allele represent an ideal population for the study of the effects of physical activity on AD-related decline. If similar

effects of exercise on brain atrophy and activation that occur in normal aging populations are expected to occur in populations at risk for AD, the E4-related deficits in temporal/parietal regions, might be attenuated with greater physical activity level.

The current study is designed to examine whether cognitively normal APOE E4 carriers exhibit decreased activation in temporal and parietal regions, or compensatory activation of the frontal region during executive control and working memory cognitive challenge relative to non-carriers, and whether a high physical activity level is associated with genotype-related differences in cortical activation. The two cognitive tasks were chosen specifically to represent an executive function task known to challenge normal aging, and a working memory task known to challenge AD related aging.

METHODS

Participants

Participants between the age of 50 and 70 years were recruited through newspaper ads, local running events, campus faculty and staff, and other ongoing research studies. Eighty-five participants were initially recruited and screened for physical activity history, APOE genotype, dementia, and health history (Appendix A). High active participants engaged in regular aerobic exercise, had been consistently physically active for the previous 5 years, and scored significantly higher on the exercise portion of the Yale Physical Activity Survey (YPAS; Appendix B)

(Mean=3388.93, SD=1838.79) than the low-active group members (Mean=806.25, SD=786.15), who did not participate in regular strenuous aerobic exercise. APOE genotype was determined based on presence (E4+) or absence (E4-) of at least one E4 allele. Participants possessing the e2 E4 genotype were excluded from analysis as the E2 allele has been associated with decreased risk of dementia. All participants scored in the normal range for their age on the Cambridge Cognitive Examination (CAMCOG) (Mean=95.05, SD=4.20) and no differences emerged between physical activity or genotype groups. Individuals reporting use of psychoactive drugs or neurological disorders were excluded from MEG testing. Additionally participation in the MEG testing was precluded in participants with extensive dental work, metal screws, or prescription glasses that would cause excessive noise in the magnetically shielded room.

Twenty-two participants met the above criteria, three of which were left handed as determined by the Edinburgh handedness inventory. One participant exhibited excessive noise in the signal during the Sternberg Task but not the Ericksen Task, and his Sternberg data were excluded from analysis. One participant in the high-active group was a homozygous E4 carrier (E4 E4), all other E4 carriers were heterozygous (E3 E4). Fourteen participants met the criteria for the high-active group (E4+, n=5; E4-, n=9) and eight participants met the criteria for low-active (E4+, n=4; E4-, n=4). The mean age for the high-active group (7M, 7F) was 60.1 (SD=3.8) and the mean age for the low-active group (1M, 7F) was 58.9 (SD=7.1). The mean age for the E4- group was 61.77 (SD=3.77) and the mean age for the E4+ group was 56.89 (SD=5.82) (Table 1).

Procedures

Participants provided informed consent on a form approved by the University of Maryland Institutional Review Board. Participation in the study required two visits to campus. The first visit was designed to screen for ideal candidates to participate in the second visit, the MEG testing.

Screening

Upon arriving for the first visit a blood draw was conducted for genotyping. Participants were then administered the YPAS (Dipietro et al., 1993) to determine their level of physical activity. The Activity Index (Salthouse et al., 2002; Appendix C) was then administered to determine their levels of cognitive stimulation for potential use as a covariate in data analyses, if appropriate. Finally participants were administered the Cambridge Cognitive Examination (CAMCOG) to screen for any dementia or mild cognitive impairment.

Genotyping

Standard, sterile procedures were used to obtain a 10 ml blood sample from an antecubital vein for consented subjects, and genomic DNA was isolated from peripheral lymphocytes using standard techniques (PureGene DNA Isolation Kit, Gentra, Inc.). The genotyping of the APOE E2, E3, and E4 alleles was performed using restriction enzyme methods as follows. DNA was amplified by PCR using standard conditions and the following primers: F: 5' ACT GAC CCC GGT GGC GGA GGA GAC G 3' and R: 5' TGT TCC ACC AGG GGC CCC AGG CGC TC 3'. Amplified material was digested with both HaeII and AflIII to distinguish the alleles

at the two polymorphisms that comprise the E2, E3, and E4 genotype and genotypes were confirmed for representative samples using direct DNA sequencing.

MEG Testing

MEG testing was conducted using a 160-channel whole-head axial gradiometer system (KIT, Kanazawa, Japan) in a magnetically shielded room. Continuous data was bandpass filtered online from 1-200 Hz with a 60 Hz notch filter at a sampling rate of 500 Hz. Testing was conducted with participants in the supine position able to see a visual display 14 inches above their head. A button pad was placed in each hand for behavioral responses with the right and left thumb.

The participants had instructions read to them for both the Sternberg and the Ericksen task while being shown a visual demonstration of the tasks prior to entering the MEG room, and once inside, they had the instructions read to them again while seeing the instructions on the screen in front of them. The subjects were instructed that to answer as quickly as and accurately as possible. The two tasks were counterbalanced across subjects.

Sternberg Working Memory Task

The Sternberg Working Memory (Figure 1a) task was presented using Presentation software and a modified version of the task which was downloaded from The Neuro-Behavioral Systems website (neuro-bs.com). The task consisted of a pre-stimulus visual cue “+”, followed by five visually presented letters, which when projected on the screen in front of them subtended two inches by two inches. The letters were presented sequentially for 200 ms each with a 1400-ms interval between each letter, and were generated randomly from a set of 21 consonants. Following a

2000-ms pause after the fifth letter, a probe letter was present visually that matched one of the previous five letters 50% of the time. The participants were instructed to press a button with their right thumb if the probe letter matched one of the previous five letters, or to press a button with their left thumb if the probe letter did not. Following another 2000-ms pause, a second probe letter was presented to maximize the number of probe trials in a short time. For each series of trials there were eight stimuli consisting of a pre-stimulus cue, five letters, and two probe trials. Each subject was given three series of practice trials (total of 6 probe trials) and verbally reported understanding the task prior to beginning the trials. The trial sequence was then presented 55 times to produce a total of 110 probe trials.

Ericksen Flanker Task

The Ericksen Flanker task (Figure 1b) was programmed using Presentation software and consisted of a pre-stimulus visual cue “+” for a random duration between 1250 and 1750 ms, followed immediately by a row of five arrows presented visually. On 50% of the trials the arrows were oriented all in the same direction “<<<<<”, while on 50% of the trials the middle arrow was oriented in the opposite direction from the two flanking arrows on either side “<<><<”. The arrow stimuli subtended 0.625 inches in height by 3.75 inches in width. The participants were instructed to press a button with their right thumb if the middle arrow was pointing to their right or to press a button with their left thumb if the middle arrow was pointing to their left, while ignoring the flanking arrows on either side. Each participant was given eight practice trials prior to beginning the trials, and verbally reported understanding the task.

Behavioral Data

Reaction times (RT) were analyzed in a 2 (Activity Level) x 2 (Genotype) x 2 (Condition: Sternberg, correct/incorrect; Ericksen, congruent/incongruent) ANOVA with repeated measures on condition. Percent correct was analyzed in a 2 (Activity Level) x 2 (Genotype) for both the Sternberg and the Ericksen.

MEG Data Analysis

The raw data files were subjected to a noise-reduction algorithm in Matlab 6.0 based on CALM. Following noise reduction the data were epoched and averaged on probe trials for the Ericksen (<<><<, <<<<<<) and Sternberg (match, non-match) conditions from -100 to 1200 ms using MEG160 software (KIT, Kanazawa, Japan). Individual trials were visually inspected, and trials containing amplitudes of > 3 pT were rejected from analysis. The averaged data were then baseline corrected (100-ms pre-stimulus) and low-pass filtered at 20 Hz. The files were then exported into Matlab for further analysis. Channels were selected for each of the eight regions (Figure 2). Root mean square (RMS) for each region was calculated by squaring the time series data from each channel, averaging across channels within the same region (Figure 3b), and taking a square root of the average (Figure 3c). RMS average amplitudes were then calculated from 0 to 600 ms in 50-ms windows for all eight regions of interest (Figure 3d).

Statistical Analyses

Separate 2 (Genotype) x 2 (Physical Activity) x 12 (Time) ANOVAs (Figure 4) with repeated measures on time were conducted separately on RMS for each of the eight regions for both conditions (congruent, incongruent; matching, non-matching)

of both tasks. All analyses were initially run using Age, Gender, and Activity Inventory scores as covariates to control for influence these variables. The variables were removed as covariates from analyses when found not to contribute significantly. Repeated measures analyses where sphericity was violated were Huynh-Feldt corrected, with the adjusted degrees of freedom are reported. Significant omnibus tests were followed up with Tukey HSD post-hoc comparisons.

RESULTS

Behavioral Data

Ericksen Task. No differences emerged between groups for accuracy (Mean=98.86% correct, SD=1.47) or RT (Mean=714.51 msec, SD=164.34). All groups exhibited significantly longer RTs to the incongruent (<<><<) condition (810.89, SD=36.56) compared to the congruent (<<<<<) condition (M=637.71, SD=27.0) ($F(1,18)=55.99$, $p<.001$). For a summary of RT by group see Table 2.

Sternberg Task. No differences emerged between groups for accuracy (Mean=89.75% correct, SD=5.60) or RT (Mean=1098.58, SD=214.94). Condition differences on RT for all groups combined approached significance ($F(1,18)=3.67$, $p=.071$), with a trend towards longer RTs for non-matching probes (Mean=1136.79 msec, SD=57.9) than for matching probes (Mean=1060.67, SD=52.34).

MEG Data

Age, gender, and Activity Inventory scores did not contribute significantly as covariates to any of the analyses reported. As such they were removed from the analyses.

Ericksen Task. Incongruent Condition. A significant main effect emerged for physical activity in the right frontal ($F(1,18)=6.55, p=.020$,) and right temporal regions ($F(1,18)=5.90, p=.026$), with high-active participants exhibiting greater activation. Non-significant trends in the same direction occurred in all other regions (Figure 5).

Also in the right temporal region, the Physical Activity x Genotype x Time interaction approached significance ($F(6.39,115.02)=1.93, p=.078$), and upon visual inspection of the data, the greatest magnitude of difference between groups occurred during the 150-200 ms time window. A subsequent 2 (Physical Activity) x 2 (Genotype) ANOVA examining only the fourth time window (150-200 ms) revealed a significant Physical Activity x Genotype interaction ($F(1,18)=6.33, p=.022$) with high-active E4 carriers exhibiting significantly greater activation than low-active E4 carriers, while being undifferentiated from the other groups (Figure 6).

Congruent Condition. A significant Physical Activity x Time interaction emerged in the left frontal region ($F(5.39,97.03)=2.39, p=.040$,). While post-hoc tests revealed no significant differences between high-active and low-active groups for any given time window, high-active participants exhibited a trend towards greater activation in early time windows (100-250 ms), with the trend reversed in later time windows (300-450 ms) (Figure 7).

A significant Physical Activity x Genotype effect emerged in the left temporal region ($F(1,18)=6.28, p=.022$,). Again, post-hoc tests revealed no significant differences between the four group means, however, the largest magnitude of

difference occurred between the high and low-active E4 carriers, with high-active carriers exhibiting greater activation (Figure 8).

Sternberg Task. Matching Condition. A significant Physical Activity x Genotype effect emerged in the right temporal region ($F(1,17)=9.65$, $p=.006$,) with high-active E4 carriers exhibiting significantly greater activation than low-active E4 carriers, while being undifferentiated from both high and low-active non-carriers (Figure 9a). Although the interaction with time only approached significance, the Physical Activity x Genotype x Time interaction is illustrated in Figure 10, which shows that the largest magnitude of difference emerged in the 150-200 ms time window with low-active E4 carriers exhibiting a relative lack of activation compared to the peaks exhibited by the other three groups.

Non-matching Condition. Similar to the matching condition a significant Physical Activity x Genotype effect emerged in the right temporal region ($F(1,17)=4.90$, $p=.041$,) with high-active E4 carriers exhibiting greater amplitude than the low-active E4 carriers, while exhibiting similar amplitude to both high-active and low-active of non-carriers (Figure 9b).

Genotype significantly interacted with Time in the left frontal region ($F(3,81,64.80)=2.51$, $p=.053$,). Although no direct comparisons between E4 carriers and non-carriers achieved significance, E4 carriers exhibited a trend towards greater activation early (0-250 ms) in the epoch (Figure 11).

Finally, in the mid frontal region a significant Physical Activity x Genotype x Time interaction emerged ($F(11,187)=2.26$, $p=.012$,) with the greatest magnitude of difference early in the epoch being exhibited between high and low-active non-E4

carriers, and the greatest difference late in the epoch emerging between high and low-active E4 carriers. In both comparisons the high-active participants exhibited greater amplitude (Figure 12).

DISCUSSION

The results of the current study support previous findings that high-resolution brain imaging methods are sensitive to differences in brain function in cognitively normal populations who differ in their genetic susceptibility to dementia. Furthermore, the results suggest that the relationships between physical activity and brain function are measurable and distinguishable between groups of different genetic susceptibility to AD, on tasks and brain regions specific to AD-related neurocognitive decline. These findings suggest that future studies of the effects of exercise on AD-related pathology in the brain may be conducted several decades prior to onset of clinical symptoms in relatively young populations who are at risk for dementia.

Importantly, in the current study all participants were free from cognitive decline as they all performed within the normal range on the CAMCOG. Additionally, all groups performed similarly on accuracy and RT for both tasks. High-active participants exhibited a non-significant trend towards faster RT on the Ericksen task.

The hypothesis that high physical activity level would be associated with attenuation of APOE-related differences in activation was generally supported in the right temporal region on the Sternberg task, a task chosen specifically to engage

working memory and recruit the temporal/ parietal regions. During both matching and non-matching probe trials on the task, low-active E4 carriers exhibited the lowest level of right temporal activation of the four groups. High-active E4 carriers exhibited greater activation than their low-active counterparts, while being undifferentiated from both high-active and low-active non-E4 carriers (Figure 5). A similar pattern of activation emerged across groups in the left temporal region on the Erickson congruent condition (Figure 4), with low-active E4 carriers exhibiting the lowest amplitude response while high-active E4 carriers exhibited similar activation to non-E4 carriers. Previous brain imaging studies of cortical activation in APOE E4 carriers have revealed either decreased activation (Smith et al., 1999), or compensatory activation (Bookheimer et al., 2000) in the temporal lobe during cognitive challenge compared to non-carriers. In the current study, low-active E4 carriers exhibited decreased activation of the right temporal region during the recall phase of the working memory task. Consistent with brain imaging studies examining physical activity and cortical activation, which have generally revealed greater activation of task-related cortical areas resulting from increased aerobic fitness (Colcombe et al., 2004), the decreased activation in the right temporal region was attenuated in the high-active E4 carriers. The greatest magnitude of difference between high-active and low-active E4 carriers occurred in the 150-200 ms time window, during which period the low-active E4 carriers exhibited a general lack of the well-defined peak exhibited by the other three groups (Figure 6).

Also in the 150-200 ms time window, high-active E4 carriers exhibited greater activation than low-active E4 carriers on the Erickson incongruent condition, again in

the right temporal region. Once again, the low-active E4 carriers exhibited the lowest amplitude in this time window. However, upon visual inspection of all four groups, the high-active E4 carriers, although statistically undifferentiated non-carriers, exhibited a uniquely high peak activation.

Significant interactions with either physical activity or genotype involving time (0-600 ms) highlight the advantage of brain imaging techniques which allow for high temporal resolution. Although hemodynamic techniques for measuring brain activation such as functional magnetic resonance imaging (fMRI) or positron emission tomography (PET) allow for greater spatial resolution of activation and examination of sub-cortical processes, they require several seconds to obtain, and therefore, do not permit examination of changes in activation occurring on the order of 100 ms or less. Conversely, magnetoencephalographic (MEG) and electroencephalographic (EEG) measures possess exquisite temporal resolution of cortical processes which are time-locked to the presentation of stimuli and measurable in milliseconds. Therefore examination of the time-course of regionally specific high-amplitude responses allows for more specific identification of the cognitive processes being measured.

The peak activations observed in the temporal lobes between 150 and 200 ms on the Sternberg task are consistent with the peaks observed in MEG studies for visual letter and object recognition tasks (Tarkiainen, Helenius, Hansen, Cornelissen, & Salmelin, 1999, Tarkiainen, Cornelissen, & Salmelin, 2002), and are referred to as M170 (peak in amplitude occurring ~170 ms post-stimulus). Source localization analyses have placed the source M170 peaks during symbol or letter viewing in the

occipito-temporal region of the ventral visual stream (Tarkiainen et al., 1999; 2002). A decreased M170 peak in low-active E4 carriers during probe letter-viewing on the Sternberg task may reflect compromised visual recognition during working memory recall relative to the high-active E4 carriers. Smith et al., (1999) also observed deficits in activation in E4 carriers during cognitive challenge in the ventral visual stream (Brodmann's areas 19 and 37). The current findings suggest that high-active E4 carriers may maintain greater integrity in this region relative to sedentary E4 carriers, who exhibit decreased activation in the absence of behavioral deficits.

The region which exhibited the greatest benefit associated with high physical activity in E4 carriers in the current study is the right temporal lobe. Although presentation of letter strings generally results in left-hemisphere dominance of temporal lobe activation (Tarkiainen et al., 1999), the presentation of a single letter (symbol) in the current study elicited differences between groups in the right temporal region. An interaction between physical activity level and APOE genotype specific to the temporal region is consistent with the notion that regular exercise may aid in recovery or protection against brain stress in regions where E4 carriers exhibit metabolic deficiencies. While still under investigation in the literature, one proposed influence of APOE in the brain, and deficiency within E4 carriers, involves recovery from several types of brain stress (Saunders, 2001). One primary known mechanism underlying exercise effects on the brain is upregulation of BDNF, known to contribute to healthy functioning of brain cells and protect against insults such as ischemia and axotomy (Cotman & Egesser-Cesar, 2002). Although the most pronounced upregulation of BDNF is exhibited in the hippocampal region, areas of

the cortex are also known to be protected by aerobic fitness (Colcombe et al., 2003). Deficits exhibited by cognitively normal E4 carriers in the ventral visual stream in previous studies (Reiman et al., 2001; 2004; Smith et al., 1999) were exhibited by the low-active carriers in the current study while integrity of cortical function in this area was relatively spared in high-active E4 carriers.

The notion that the impact of a physically active lifestyle may be more robust on populations genetically at risk for decline was fostered by Schuit et al. (2001), and was more strongly supported in the current study on the Sternberg working memory task than on the Ericksen flanker task. The Ericksen flanker task, and other executive control function (ECF) tasks have previously been implicated as neurocognitive tasks most robustly affected by exercise in normal aging (Colcombe & Kramer, 2003; Colcombe et al., 2004; Kramer et al., 1999). Indeed, main effects for physical activity on the Ericksen task observed in the current study are consistent with increased task-related cortical activation revealed by Colcombe et al. (2004) on the Ericksen task. However, analogous to the notion that ECF tasks, by virtue of susceptibility to early decline in normal aging, are the tasks most likely to be impacted by the protective effects of exercise, neurocognitive tasks susceptible to AD-type decline are those most likely to be those protected by exercise in APOE4 carriers. Therefore, cognitive tasks specific to the effects of exercise on E4 carriers are likely to be memory tasks which engage the hippocampal, temporal and parietal regions, known to decline early in AD.

The Sternberg working memory task was chosen for the current study as AD patients have been shown to exhibit deficits in temporal and parietal activation during

probe trials (Maestú et al., 2001). Although MEG is not conducive to measuring activation of sub-cortical regions such as the hippocampus, decreased temporal and parietal MEG activation in AD patients during the Sternberg task has been correlated with decreased hippocampal volume Maestú et al. (2003). The current findings support the future examination of memory tasks which specifically engage the hippocampal region, as this region is specific to AD-type decline (Braak & Braak, 1991) as well as neurotrophic benefits derived from exercise (Cotman & Engesser-Cesar, 2002).

Compensatory frontal activation during recall on the Sternberg task in AD patients in Maestú et al. (2001) was associated with deficits in temporal lobe activation. As primary circuits of recall engaged by normal controls in the temporal/parietal region were compromised, AD patients exhibited compensatory activation of frontal circuits. Although compensatory frontal activation in E4 carriers in the current study was not prominent, a Genotype x Time interaction emerged in the left frontal region on the Sternberg task in the non-matching probe condition. E4 carriers exhibited a trend towards greater left frontal activation during the first 250 ms. This finding is consistent with compensatory frontal activation in E4 carriers, and may reflect sub-vocal verbal rehearsal of letters resulting from compromised efficiency of primary visual recall circuits. Physical activity level did not significantly impact the effect in this region.

Summary

Consistent with previous findings, physical activity was associated with increased activation in task-relevant regions of the cortex during executive function

challenge. On the Sternberg task, a task specifically chosen to engage working memory and temporal lobe activation, Physical Activity x Genotype effects were specific to the right temporal region, where the magnitude of the difference between high-active and low-active participants was greater in E4 carriers than in non-carriers. Low-active E4 carriers exhibited the lowest amplitude of activation, while high-active E4 carriers were undifferentiated from the non-E4 carriers. The most pronounced differences between groups in the right temporal lobe emerged in the M170 time window suggesting compromised integrity of the ventral visual pathway in low-active E4 carriers, which may be preserved in high-active E4 carriers.

The results confirm the effectiveness of high-resolution brain-imaging for examining differences in brain function in cognitively normal populations who differ in their genetic risk for dementia. Furthermore the results demonstrate the ability to examine relationships between physical activity and brain activation in APOE E4 carriers during working memory in the absence of any behavioral or clinical symptoms of cognitive decline. Future brain imaging studies should address the direct impact of physical activity interventions in populations genetically at risk for decline to assess the impact of exercise on slowing the progression of dementia. A recent study examining the effectiveness of an exercise intervention showed that changes in brain activation associated with increased cardiovascular fitness can occur within the relatively short time span of 24 weeks (Colcombe et al., 2004).

TABLES AND FIGURES

Table 1. Means and standard deviations for Age, CAMCOG, YPAS and Activity Inventory scores. *Represents a significant difference between low-active E4 carriers and non-carriers ($p < .05$). **Represents a significant difference between high-active and low-active participants ($p < .01$).

	n	Age	CAMCOG	YPAS (kcal) Exercise	Activity Inventory
High-Active	14	60.29 (3.90)	95.29 (4.16)	**3388.93 (1838.79)	260.75 (86.50)
E4-	9	60.67 (3.78)	94.44 (4.61)	3361.67 (2008.90)	242.94 (71.52)
E4+	5	59.60 (4.72)	96.80 (3.03)	3438.00 (1706.66)	292.80 (109.96)
Low-Active	8	58.88 (7.01)	94.63 (4.53)	**806.25 (786.147)	369.88 (139.85)
E4-	4	*64.25 (2.63)	94.75 (2.99)	135.00 (270.00)	337.13 (164.38)
E4+	4	*53.50 (5.75)	94.50 (6.25)	1477.4 (409.42)	402.63 (125.53)

Table 2. Means and standard deviations for RT on the Ericksen and Sternberg tasks. *Represents a significance difference between conditions ($p < .05$).

	Ericksen Task (RT)		Sternberg Task (RT)	
	*Congruent	*Incongruent	Matching	Non-Matching
High-Active	599.54 (124.4)	774.88 (169.54)	1045.10 (221.93)	1161.73 (289.38)
E4-	603.27 (147.46)	775.68 (200.25)	1056.12 (266.70)	1210.58 (350.28)
E4+	592.84 (82.07)	773.45 (114.92)	1025.26 (130.60)	1073.80 (108.34)
Low-Active	677.37 (104.36)	847.20 (132.27)	1080.63 (218.86)	1131.74 (162.88)
E4-	724.63 (115.4)	899.07 (168.73)	1080.10 (289.26)	1186.28 (184.71)
E4+	630.12 (78.35)	795.34 (71.54)	1081.17 (167.62)	1077.19 (140.91)

Figure 1. Stimulus presentation for the Sternberg task (a) and the Ericksen Flanker task (b)

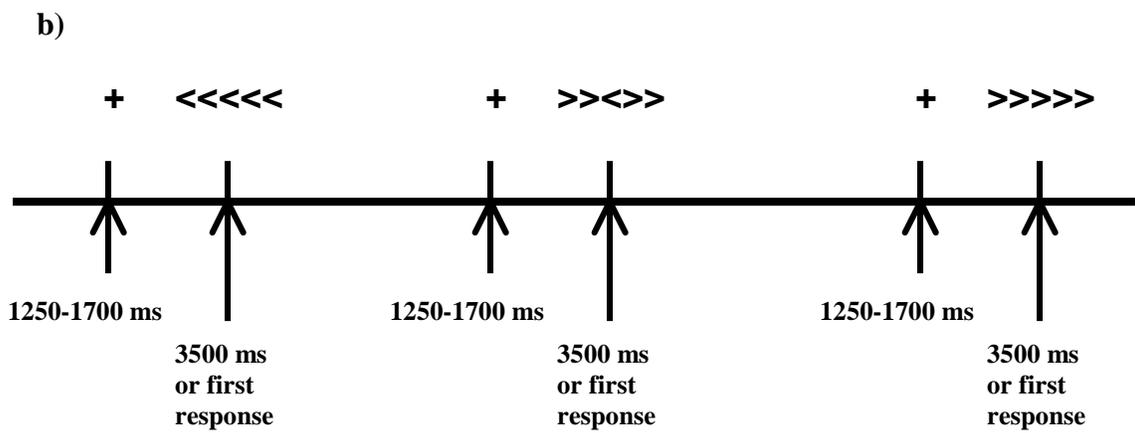
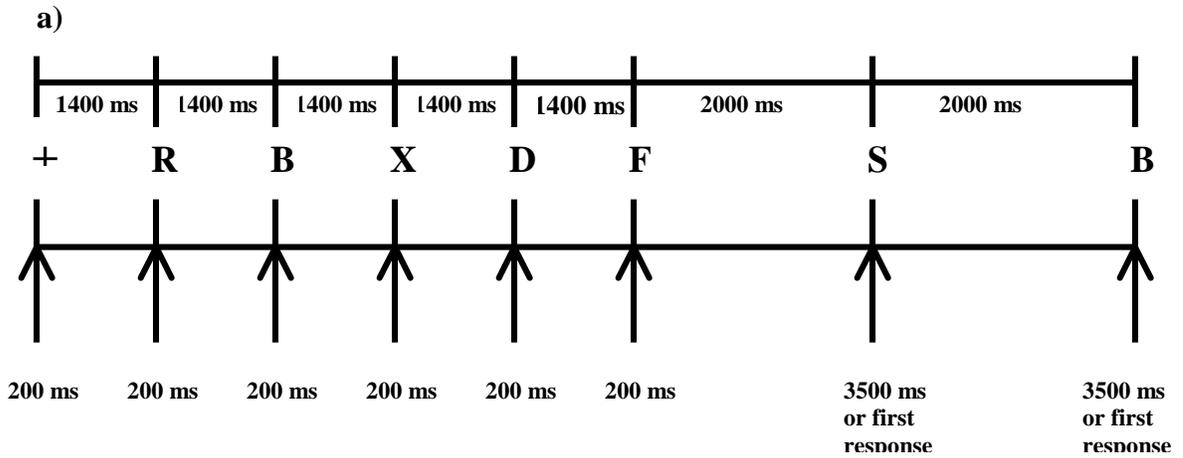


Figure 2. Channel montage for the eight regions. Left and right frontal regions are green, mid-frontal =orange, right and left temporal=light blue, center midline=red, left parietal= blue, right parietal=purple.

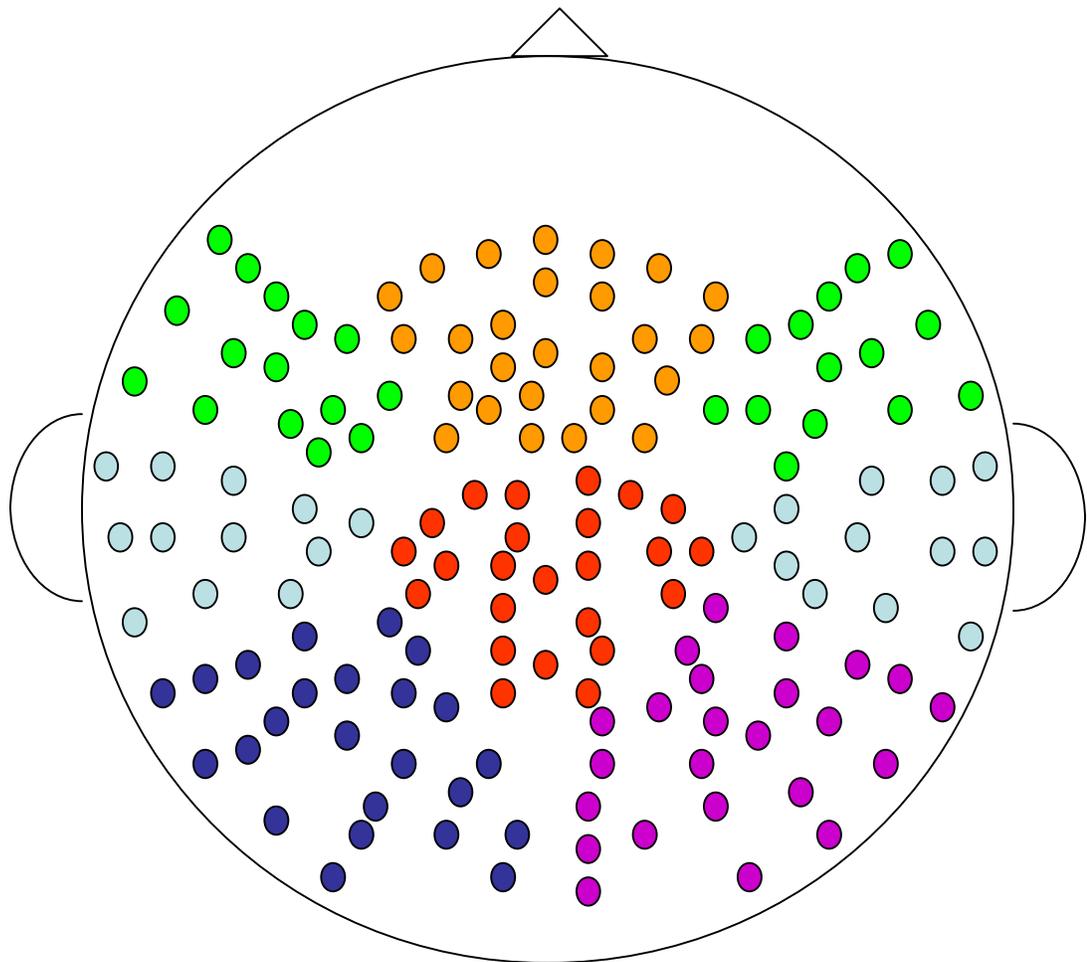


Figure 3. a) Averaged data from all 157 channels b) right temporal channels only c) right temporal RMS d) Average amplitude in 50-ms time windows.

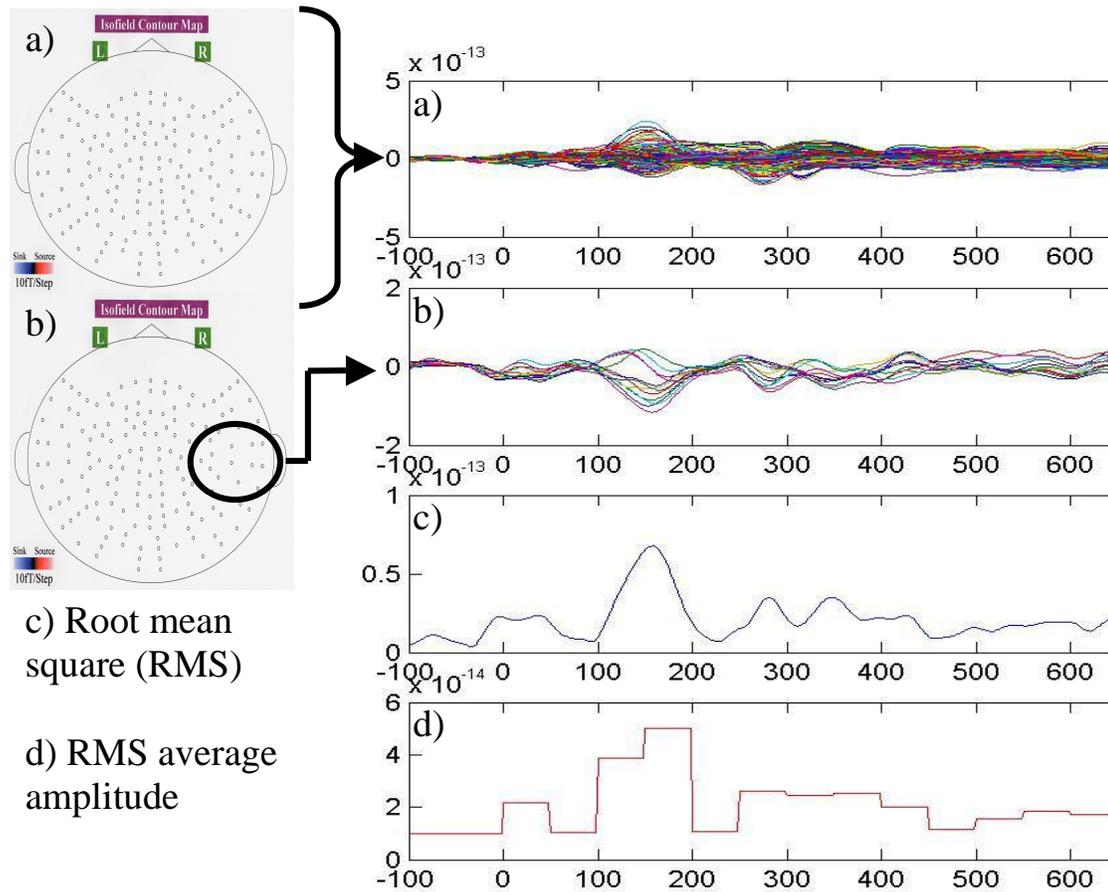


Figure 4. Physical Activity x Genotype x Time design for RMS analysis.

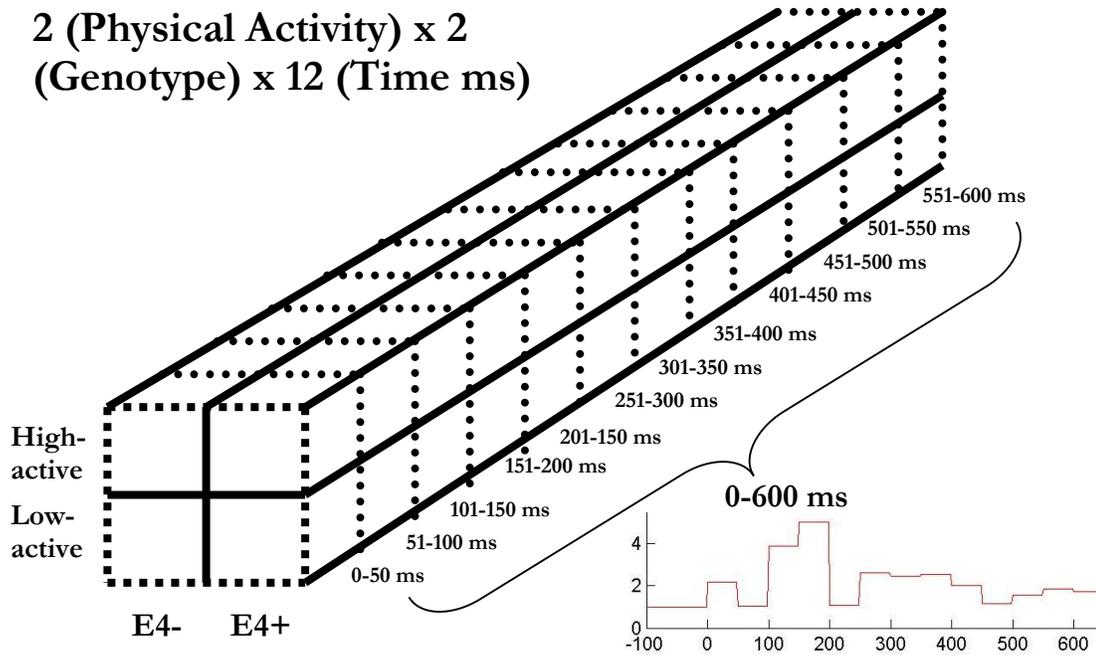


Figure 5. Average RMS (fT) value from 0-600 ms on the Ericksen Incongruent Task.
*Represents a significant difference between groups ($p < .05$).

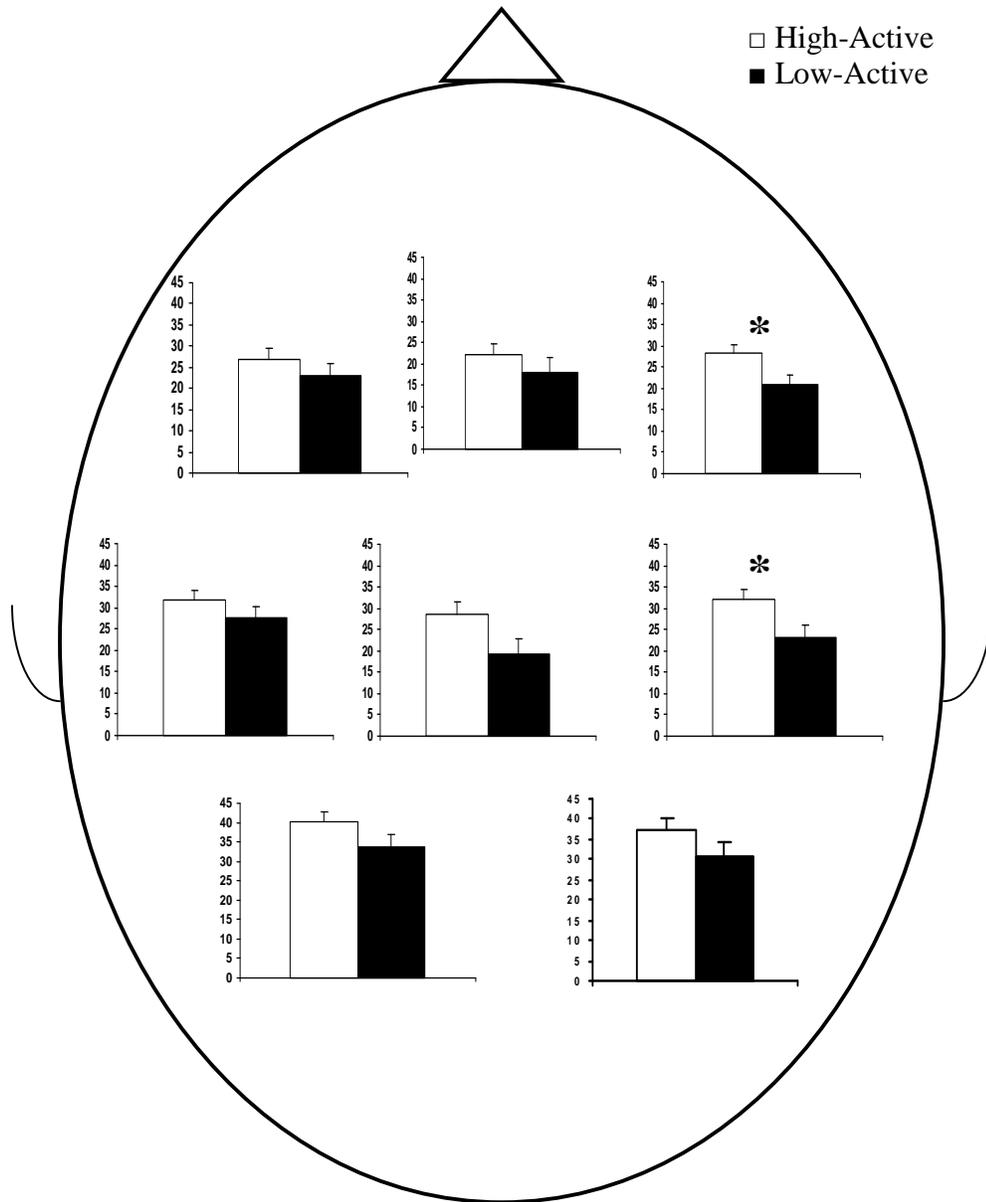


Figure 6. Sternberg matching condition Physical Activity x Genotype x Time interaction in the right temporal region. *Represents a significant difference between high-active and low-active E4 carriers ($p < .05$).

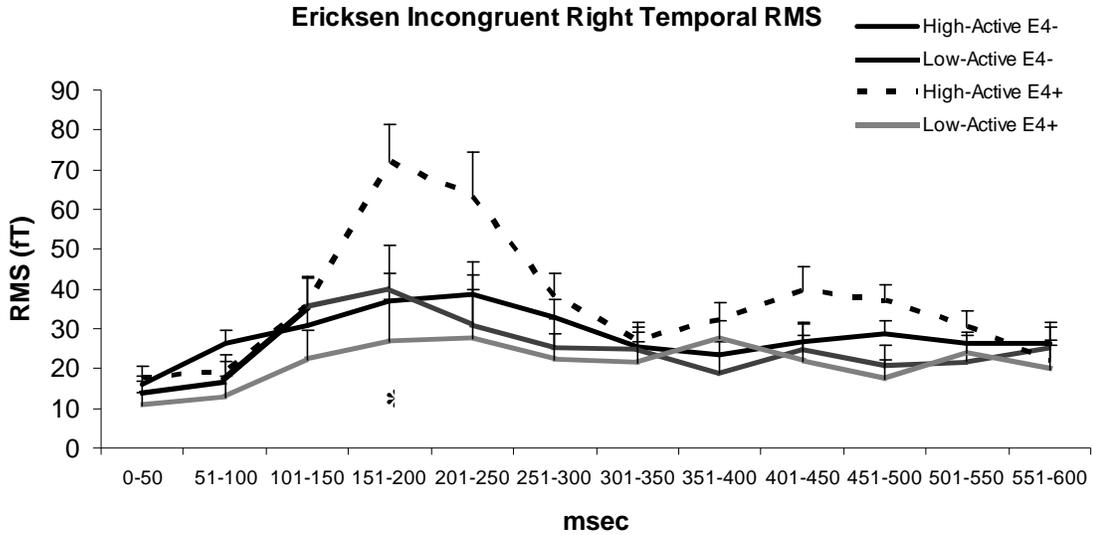


Figure 7. Physical Activity x Time interaction on the Ericksen Congruent condition.

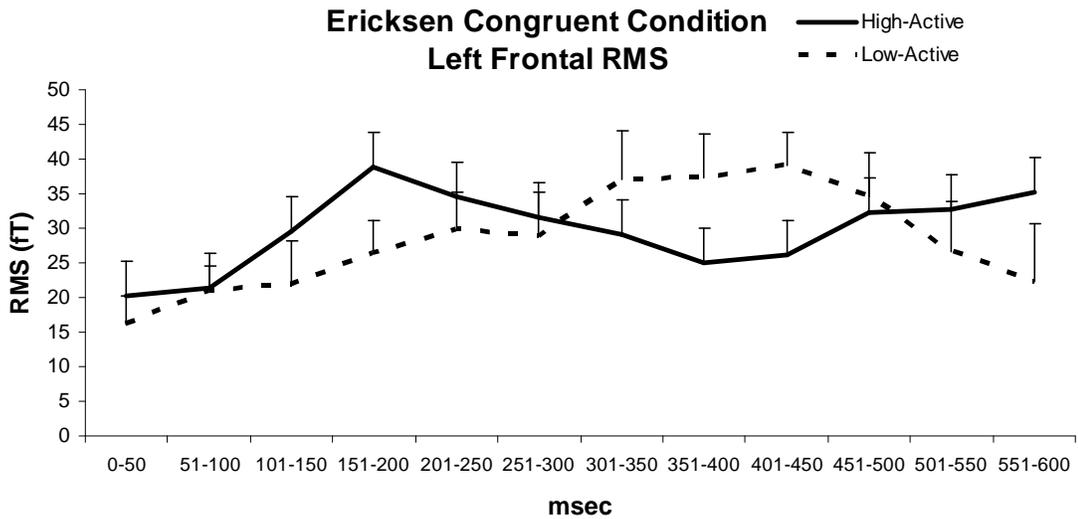


Figure 8. Physical Activity x Time interaction on the Ericksen Congruent condition ($p < .05$).

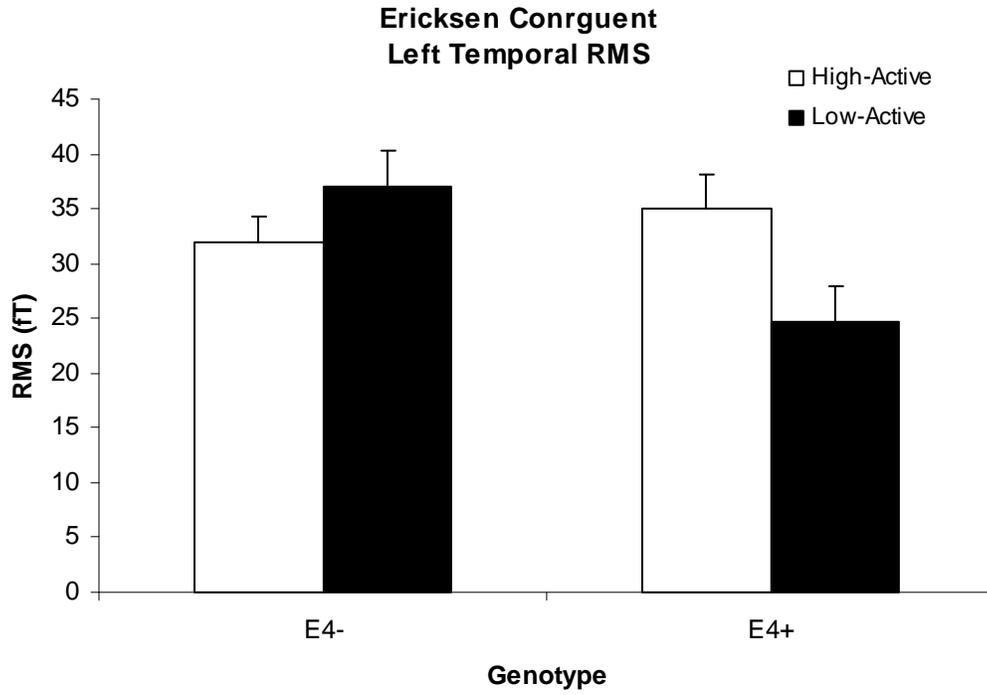
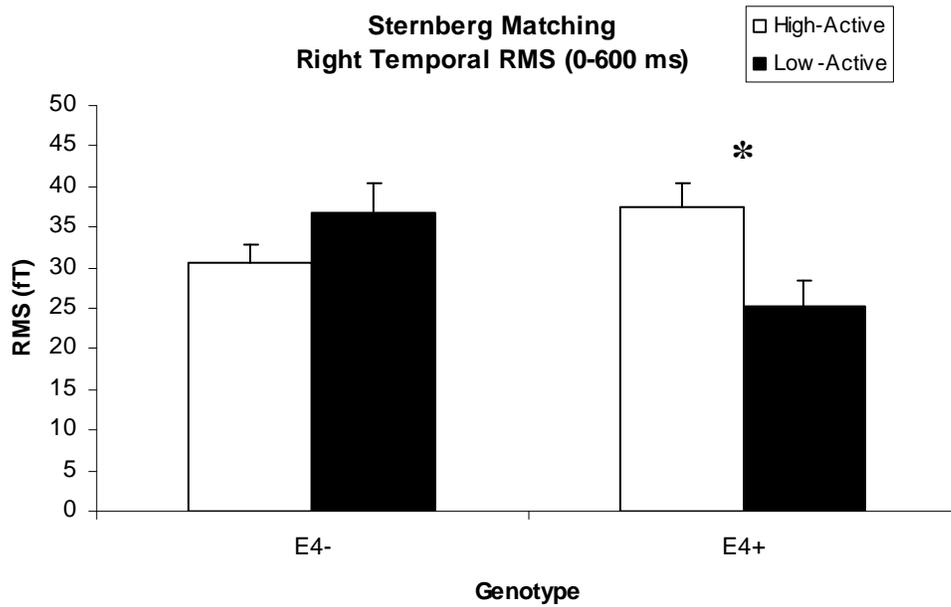


Figure 9. (a) Physical Activity x Genotype Interaction on the Sternberg Matching condition. (b) Physical Activity x Genotype Interaction on the Sternberg Non-matching condition. *Represents a significant difference between high and low-active groups ($p < .05$).

a)



b)

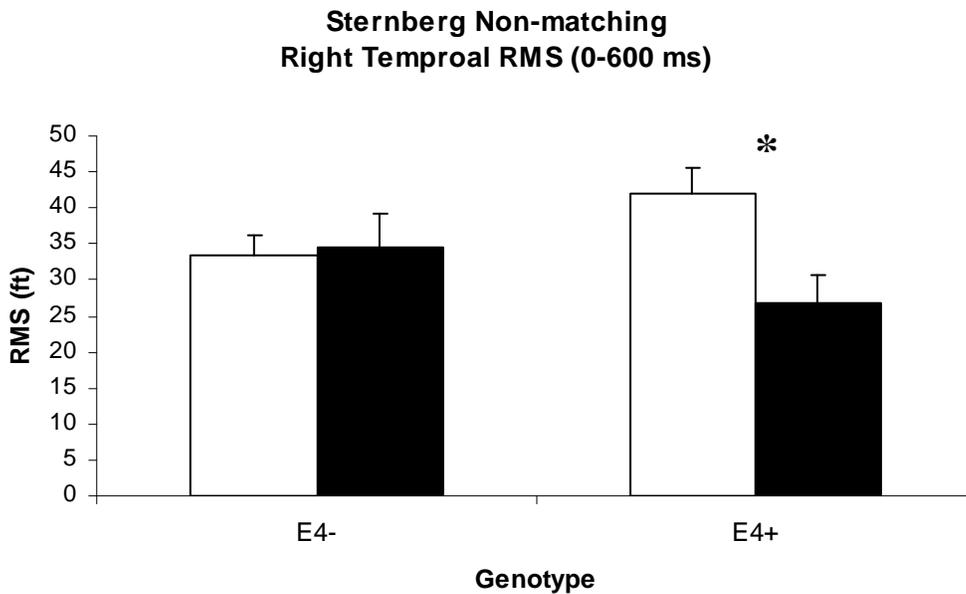


Figure 10. Illustrates peak activation in the 150 and 200 ms exhibited by three of the four groups.

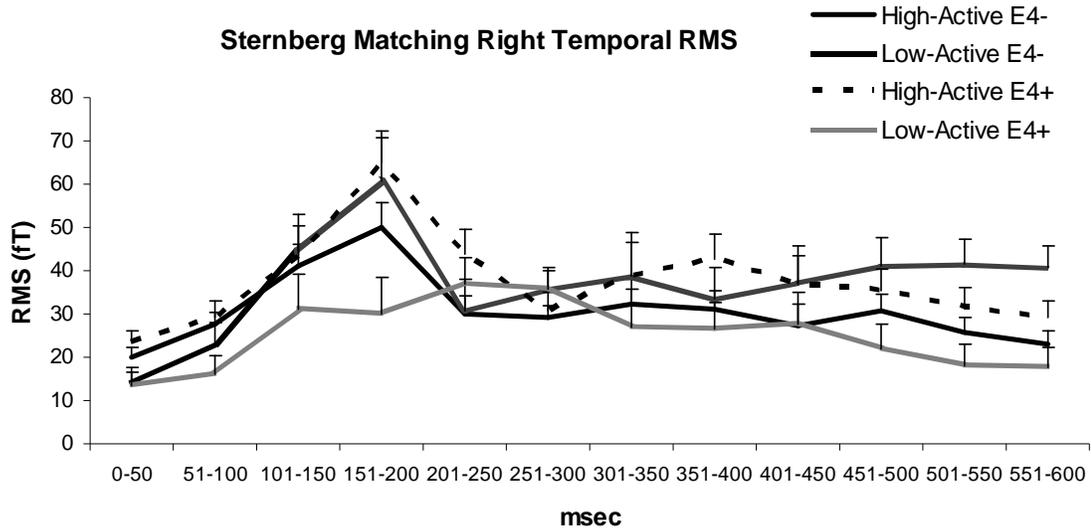


Figure 11. Genotype x Time interaction for the Ericksen Congruent condition in the left frontal region (RMS 0-600 ms).

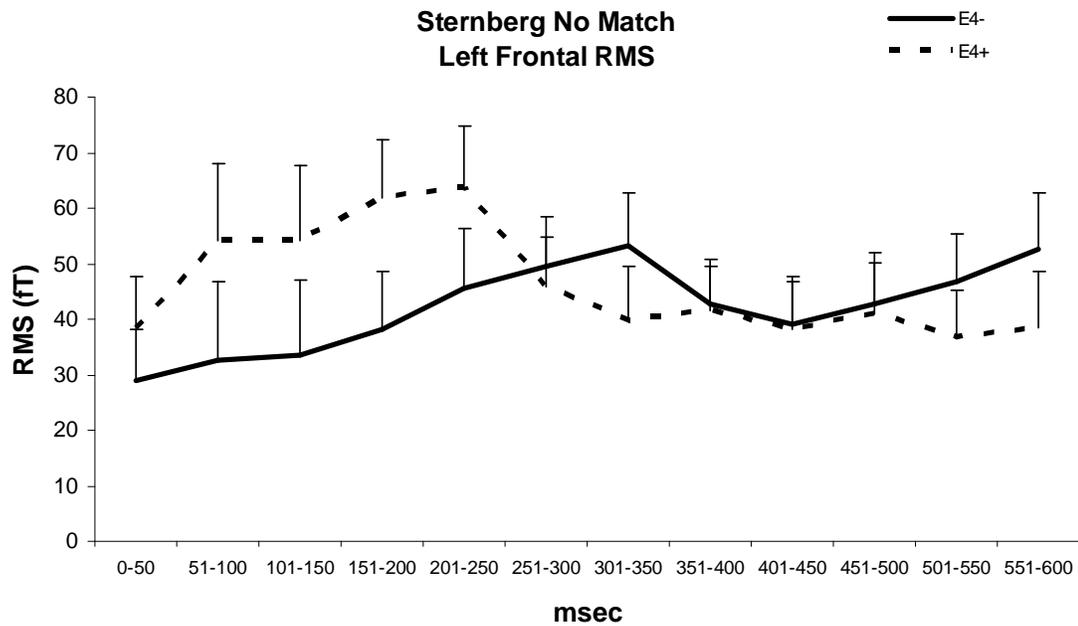
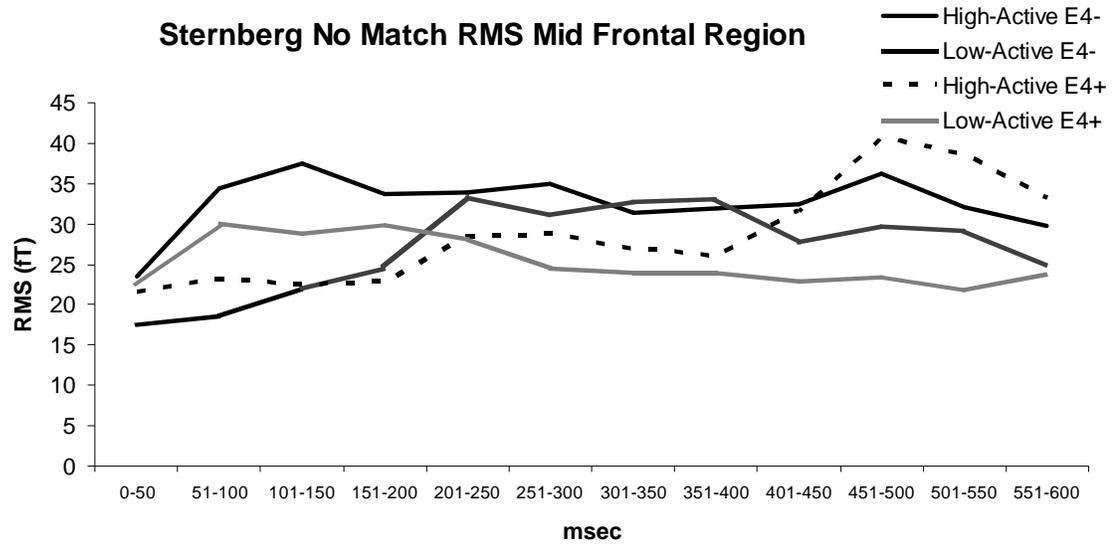


Figure 12. Physical Activity x Genotype x Time interaction in the mid frontal region on the Sternberg Non-matching condition.



APPENDICES

Appendix A: Medical History

Name _____ Telephone _____

Address _____

Date of Birth _____ Age _____ Gender M ___ F ___

Race, ethnicity: _____ Caucasian _____ Black _____ Hispanic
_____ Asian _____ Other

Color Blind Yes ___ No ___

Years of education (High school = 12 years, plus any additional years of college) _____

Please indicate your primary job/career during your lifetime. If you have had multiple careers, please list them:

Medical History Are you currently taking or have you taken any of the following medications within the past two months?

- | | |
|------------------------------|-----------------------|
| Aspirin, Bufferin, Anacin | Tranquilizers |
| Blood pressure pills | Weight reducing pills |
| Cortisone | Blood thinning pills |
| Cough medicine | Dilantin |
| Digitalis | Allergy shots |
| Hormones | Water pills |
| Insulin or diabetic pills | Antibiotics |
| Iron or blood medications | Barbituates |
| Laxatives | Phenobarbital |
| Sleeping pills | Thyroid medicine |
| Other medications not listed | |

Do you currently or have you ever had any of the following medical disorders?

Heart attack	Yes___	No___
Chest pain	Yes___	No___
Hardening of the arteries	Yes___	No___
Irregular heart beat	Yes___	No___
Kidney disease	Yes___	No___
Diabetes	Yes___	No___
Cancer	Yes___	No___
Gout	Yes___	No___
Asthma	Yes___	No___
Epilepsy or seizure disorder	Yes___	No___
Migraine headaches	Yes___	No___
if yes, frequency, intensity___		
Psychiatric disorder	Yes___	No___
if yes, what diagnosis_____		

Physical Activity

___Has your physical activity level remained consistent during the previous 5 years?

a. very consistent b. somewhat consistent c. inconsistent

Have you had any injuries or medical conditions that caused you to be physically inactive for more than 3 months during the past 5 years?

___Yes ___No If yes, explain_____

We are interested in how stable your physical activity level has been over the course of your lifetime. Please use the scale below to rate your level of physical activity for the next five questions.

- 1 Very physically active**, regular aerobic exercise and sports
- 2 Fairly physically active**, sports and active leisure
- 3 Moderately physically active**, hobbies, active leisure activities
- 4 Fairly physically inactive**, very few sports, light physical leisure activities
- 5 Very physically inactive**, no sports, non-physical leisure activities

___How would you characterize your physical activity level between the ages of 20 and 29?

___Between the ages of 30 and 39?

- ___Between the ages of 40 and 49?
- ___Between the ages of 50 and 59?
- ___Between the ages of 60 and 69? if applicable

Memory, Family History

- Do you have difficulty with your memory more than you used to? Y/N_____
- Do you forget where you have left things more than you used to? Y/N_____
- Do you forget the names of close friends or relatives? Y/N_____
- Have you ever been in your own neighborhood and forgotten your way? Y/N_____

If the answer to these questions is no, please skip the next three questions.

- When did this difficulty begin? (Duration in months) _____
- Did it come on gradually or suddenly? _____
- Has it become worse or better since it started? _____

Do you have any biological parents, siblings, or grandparents who have been clinically diagnosed with Alzheimer’s disease? ___Yes No___ If yes, please list them below.

Parents_____

Siblings_____

Grandparents_____

Appendix B: YPAS

The YALE PHYSICAL ACTIVITY
SURVEY FOR OLDER ADULTS

INTERVIEWER: PLEASE MARK TIME: HR__MIN__ SEC__

INTERVIEWER: (Please hand the subject the list of activities while reading this statement.) Here is a list of common types of physical activities. Please tell me which of them you did during a typical week in the last month. Our interest is learning about the types of physical activities that are a part of your regular work and leisure routines.

For each activity you do, please tell me how much time (hours) you spent doing this activity during a typical week. (Hand subject card #1.)

Intensity	Time
Work	
Code	(hrs/wk)
(Kcal/min)	
Shopping (e.g., grocery, clothes)	_____
3.5	
Stair climbing while carrying a load	_____
8.5	
Laundry (time loading, unloading, hanging, folding only)	_____
3.0	
Light housework: tidying, dusting, sweeping, collecting	_____
3.0	
trash in home, polishing, indoor gardening, ironing	
Heavy housework: vacuuming, mopping, scrubbing floors	_____
4.5	
and walls, moving furniture, boxes, or garbage cans	
Food preparation (10+ minutes in duration): chopping,	_____
2.5	
stirring, moving about to get food items, pans	

Food service (10+ minutes in duration: setting table, 2.5 carrying food, serving food	_____
Dish washing (10+ minutes in duration): clearing table, 2.5 washing/drying dishes, putting dishes away	_____
Light home repair: small appliance repair, 3.0 light home maintenance/repair	_____
Heavy home repair: painting, carpentry, 5.5 washing/polishing car	_____
Other: _____	_____

Time

Yardwork

(hrs/wk)

(Kcal/min)

Gardening: planting, weeding, digging, hoeing	_____ 4.5
Lawn mowing (walking only)	_____ 4.5
Clearing walks/driveway: sweeping, shoveling, raking	_____ 5.0
Other: _____	_____

Caretaking

Older or disabled person (lifting, pushing wheelchair)	_____ 5.5
Childcare (lifting, carrying, pushing stroller)	_____ 4.0

Exercise

Brisk walking (10+ minutes in duration)	_____ 6.0
Pool exercises, stretching, yoga	_____ 3.0
Vigorous calisthenics, aerobics	_____ 6.0
Cycling, Exercycle	_____ 6.0

Swimming (laps only) _____6.0

Other: _____

Recreational Activities

Leisurely walking (10+ minutes in duration) _____3.5

Needlework: knitting, sewing, needlepoint, etc. _____1.5

Dancing (mod/fast): line, ballroom, tap, square, etc. _____5.5

Bowling, bocci _____3.0

Golf (walking to each hole only) _____5.0

Racquet sports: tennis, racquet ball _____7.0

Billiards _____2.5

Other: _____

INTERVIEWER: (Please read to subject.) I would now like to ask you about certain types of activities that you have done during the past month. I will ask you about how much vigorous activity, leisurely walking, sitting, standing, and some other things that you usually do.

1. About how many times during the month did you participate in vigorous activities that lasted at least 10 minutes and cause large increases in breathing, heart rate, or leg fatigue or caused you to perspire? (Hand subject card #2)

Score: 0 = Not at all (go to Q3)
1 = 1-3 times per month
2 = 1-2 times per week
3 = 3-4 times per week
4 = 5+ times per week
7 = refused
8 = don't know

Frequency score = _____

2. About how long do you do this vigorous activity(ies) each time? (Hand subject Card #3)

Score: 0 =Not applicable
1 = 10-30 minutes
2 = 31-60 minutes
3 = 60+ minutes

7 = refused
8 = don't know

Duration score = _____ weight= 5

VIGOROUS ACTIVITY INDEX SCORE:

FREQ SCORE _____ x DUR SCORE _____ x WEIGHT

_____ = _____

(Responses of 7 or 8 are scored as missing.)

3. Think about the walks you have taken during the past month. About how many times per month did you walk for at least 10 minutes or more without stopping which was not strenuous enough to cause large increases in breathing, heart rate, or leg fatigue or cause you to perspire'? (Hand subject card #2)

Score: 0 = Not at all (go to Q5)
1 = 1-3 times per month
2 = 1-2 times per week
3 = 3-4 times per week
4 = 5+ times per week
7 = refused
8 = don't know

Frequency score = _____

4. When you did this walking, for how many minutes did you do it? (Hand subject Card #3)

Score: 0 = Not applicable
1 = 10-30 minutes
2 = 31-60 minutes
3 = 60+ minutes
7 = refused
8 = don't know

Duration score = _____ weight = 4

LEISURELY WALKING INDEX SCORE:

FREQ SCORE _____ x DUR SCORE _____ x WEIGHT _____ =

(Responses of 7 or 8 are scored as missing.)

5. About how many hours a day do you spend moving around on your feet while doing things? Please report only the time that you are actually moving. (Hand subject card #4)

Score: 0 = Not at all
1 = less than 1 hr per day

- 2 = 1 to less than 3 hrs per day
- 3 = 3 to less than 5 hrs per day
- 4 = 5 to less than 7 hrs per day
- 5 = 7+ hrs per day
- 7 = refused
- 8 = don't know
- Moving score = _____ weight = 3

MOVING INDEX SCORE:

FREQ SCORE _____ x DUR SCORE _____ x WEIGHT _____ = _____

(Responses of 7 or 8 are scored as missing.)

6. Think about how much time you spend standing or moving around on your feet on an average day during the past month. About how many hours per day do you stand? (Hand subject card #4)

- Score:
- 0 = Not at all
 - 1 = less than 1 hr per day
 - 2 = 1 to less than 3 hrs per day
 - 3 = 3 to less than 5 hrs per day
 - 4 = 5 to less than 7 hrs per day
 - 5 = 7+ hrs per day
 - 7 = refused
 - 8 = don't know
 - Standing score = _____ weight = 2

STANDING INDEX SCORE:

FREQ SCORE _____ x DUR SCORE _____ x WEIGHT _____ = _____

(Responses of 7 or 8 are scored as missing.)

7. About how many hours did you spend sitting on an average day during the past month? (Hand subject card #5)

- Score:
- 0 = Not at all
 - 1 = less than 3 hours
 - 2 = 3 hrs to less than 6 hrs
 - 3 = 6 hrs to less than 8 hrs
 - 4 = 8+ hrs
 - 7 = refused
 - 8 = don't know
 - Sitting score = _____ weight = 1

SITTING INDEX SCORE:

FREQ SCORE _____ x DUR SCORE _____ x WEIGHT
 _____ = _____

(Responses of 7 or 8 are scored as missing:)

8. About how many flights of stairs do you climb up each day?
 (Let 10 steps = 1flight.) _____

9. Please compare the amount of physical activity that you do during other seasons of the year with the amount you just reported for a typical week in the past month.

For example, in the summer, do you do more or less activity than what you reported doing in the past month? (INTERVIEWER: PLEASE CIRCLE THE APPROPRIATE SCORE FOR EACH SEASON.)

	Lot More	Little More	Same	Little Less	Lot Less
Spring	1.30	1.15	1.0	0.85	0.70
Summer	1.30	1.15	1.0	0.85	0.70
Fall	1.30	1.15	1.0	0.85	0.70
Winter	1.30	1.15	1.0	0.85	0.70

SEASONAL ADJUSTMENT SCORE =
 SUM OVER ALL SEASONS/ 4 _____

INTERVIEWER: PLEASE MARK
 TIME:

HR ___ MIN ___ SEC ___

Appendix C: Activity Inventory

For each of the following activities please estimate the number of hours in a typical week you spend on the activity. Also rate how cognitively demanding you feel the activity is on a 5-point scale, where 1 = absolutely no cognitive demands (e.g., sleeping), 3 = moderate cognitive demands (e.g., reading a newspaper), and 5 = high cognitive demands (e.g., completing a tax form).

<u>Activity demands</u>	<u>hours</u> (in a typical week)	<u>cognitive</u> (1 = low, 5 = high)
Reading novels	_____	_____
Watching television	_____	_____
Socializing with friends	_____	_____
Reading newspapers or magazines	_____	_____
Using a computer	_____	_____
Driving a car	_____	_____
Attending meetings	_____	_____
Shopping	_____	_____
Teaching or attending classes or lectures	_____	_____
Housework	_____	_____
Reading nonfiction books or articles	_____	_____

Working on crossword puzzles brain teasers, etc.	_____	_____
<u>Activity</u> <u>demands</u> high)	<u>hours</u> (in a typical week)	<u>cognitive</u> (1 = low, 5 =
Gardening	_____	_____
Playing bridge or other card games	_____	_____
Handling finances (e.g., balancing checkbook)	_____	_____
Hobbies and crafts (e.g., needlework, collecting, etc.)	_____	_____
Volunteering	_____	_____
Supervising activities of others (including children)	_____	_____
Engaging in musical or other artistic activities	_____	_____
Playing chess or other strategy games	_____	_____
Meal preparation	_____	_____
Writing (e.g., letters, creative Writing)	_____	_____
Other (please describe if more than 2 hours per week)	_____	_____

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