

ABSTRACT

Title of Document: THE RELATIONSHIP BETWEEN PHYSICAL
ACTIVITY AND EXECUTIVE CONTROL
FUNCTIONING AS MODIFIED BY
GENOTYPE

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As we age, the structure of the brain deteriorates and cognitive functioning declines. The region of the brain that begins to age the fastest is the frontal lobe, in which the dorsal-lateral prefrontal cortex is involved in executive control functions such as planning, organizing, initiating behaviors, and working memory. For some individuals, the brain declines more rapidly with age because of genetic factors. Apolipoprotein E (APOE) is a gene that assists in the transport of cholesterol and repair of the brain when it is damaged. Presence of the $\epsilon 4$ allele impairs cholesterol transport and puts its carriers at risk for increased cognitive decline and possibly dementia of the Alzheimer's type (DAT). Physical activity can slow the aging process of the brain and delay the onset and severity of cognitive decline and DAT as it increases oxygenation and blood flow, neuronal growth and synaptogenesis, and it

increases the expression of genes helpful to the functioning of the brain such as brain-derived neurotrophic factor (BDNF). Therefore, individuals at greater genetic risk for age-related cognitive decline (i.e., $\epsilon 4$ carriers) should receive increased benefit from physical activity. Accordingly, this study examined the relationship between physical activity and executive control functioning, assessed by the Wisconsin Card Sort Test (WCST) in middle-aged APOE $\epsilon 4$ carriers and non-carriers. High-active participants were predicted to perform better than their low-active counterparts, and this difference should be even greater among APOE $\epsilon 4$ carriers. While most research studies on this topic have focused on general cognitive performance, the present study is specific in its focus on executive control functioning. Sixty-seven cognitively normal middle-aged adults between the ages of 50 – 70 years were assessed on medical history, overall cognitive functioning, APOE genotype, level of physical activity, and executive control functioning (WCST). Using hierarchical regression, seven WCST variables were regressed on age, genotype, physical activity, and the interaction between genotype and physical activity. Analysis revealed that as level of physical activity increased, performance significantly improved on all seven WCST variables for APOE $\epsilon 4$ carriers, but not for non-carriers. These results reveal that the benefits of physical activity to cognitive performance in this age group are specific to those who are genetically at-risk for cognitive decline.

THE RELATIONSHIP BETWEEN PHYSICAL ACTIVITY AND EXECUTIVE
CONTROL FUNCTIONING AS MODIFIED BY GENOTYPE

By

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Chapter 1: Introduction

Benefits of Physical Activity on the Aging Brain and Genetically At-Risk Adults

Overview

With the increase in the number of individuals over the age of 65 in the United States, there will be an increase in the number of people who suffer from dementia. By 2030, the older population is expected to account for approximately 20 percent of the U.S. population, largely due to the Baby Boomers' generation beginning to turn 65 in 2011 (Federal Interagency Forum on Aging-Related Statistics, 2004). Currently, it is estimated that 4.5 million Americans are living with Alzheimer's disease (Alzheimer's Association, 2004^a). It is expected that there will be a 44 percent increase in this number by 2025 (Alzheimer's Association, 2004^b). These increasing numbers not only put a burden on the people who suffer from dementia, but also on those who care for these individuals. Alzheimer's disease is a disease that affects the forebrain, causing a decrease in cognitive functioning and memory loss. Atrophy of the hippocampus, temporal lobe, parietal lobe, and frontal lobe occur (Braak and Braak, 1991; Maestú et al., 2003). This disease is defined by the amyloid plaques and neurofibrillary tangles that form in the brain (Roth, 1994).

Some people are at greater risk genetically for developing dementia than others. Apolipoprotein E or APOE, is a gene that results in the formation of lipoproteins that aid in the transport of cholesterol throughout the brain and assist with repairing the brain when damaged (Nathoo et al., 2003). The $\epsilon 4$ allele of this gene, a polymorphic variation, has been found to put those who carry it at a higher risk for developing dementia (Podewils et al., 2005). The $\epsilon 4$ allele results in a

deficiency that disrupts the transport of cholesterol and does not properly repair the brain. It has been estimated that approximately 40% of the cases of late-onset AD patients carry this allele. More generally, subclinical brain and cognitive dysfunction occur in carriers of this allele even though such individuals are classified as normal functioning (Reiman et al., 2001, 2004).

Intellectual and physical activities during the middle ages of life have been examined to be protective and reduce the risk of Alzheimer's disease in the elderly (Friedland et al., 2001). In this regard, physical activity has been found to be a cost-effective and natural way of delaying the onset of dementia, along with slowing the aging process of the brain. In a five-year prospective study of older men and women, leisure activities were associated with reduced risk of dementia (Verghese et al., 2003).

Leisure activities involving physical activity may be particularly beneficial. Through increased oxygenation and blood flow to the brain, the number of capillaries and synapses in the brain are increased, creating a cognitive reserve that helps to preserve the health of the brain (Colcombe et al., 2004; Black et al., 1990; Swain et al., 2003). Maintenance of neurotransmitters and neurotrophic factor synthesis also assist in maintaining cognitive functioning (Dustman et al., 1990; Cotman and Engesser-Cesar., 2002). These neurobiological benefits of exercise, which have been most often observed in animals, likely slow the aging of the human brain by countering the presence of age-related decline and this effect should be most apparent in carriers of APOE ϵ 4 due to accelerated age-related decline.

Aging Process of the Brain

The brain declines with age resulting in decreased cognitive performance (Colcombe et al., 2003^a; Lezak 1995). Brain volume decreases and there is a loss of white matter, especially in the frontal lobe (Colcombe et al., 2003^b; Van Petten et al., 2004). Thinning of the cerebral cortex becomes apparent by middle age, with significant reductions in the primary sensory, primary somatosensory, and motor cortices (Salat et al., 2004). This process may be due to common diseases that occur with age such as hypertension and cardiovascular disease that result in less blood, oxygen, and glucose reaching the brain (Lezak 1995; Dywan 1992).

In special cases such as dementia of the Alzheimer's type (DAT), neurofibrillary tangles and amyloid plaques begin to form in the cerebral cortex (Roth, 1994). Cognitive examinations have shown that non-demented elderly people perform significantly better than demented elderly people, with the most pronounced areas of cognitive decline being memory, attention, and abstract thinking (Williams et al., 2003). These functions of the brain, along with other aspects of executive control functioning begin to decline with age, whether a person is demented or not. The use of positron emission tomography (PET) has revealed hypoactivation in a number of brain regions in healthy young adults and middle aged adults who are asymptomatic for cognitive impairment, especially in those who possess the apolipoprotein $\epsilon 4$ allele (Reiman et al., 2001, 2004). This would imply that the brain is declining years before any behavioral symptoms occur, but detection of such subtle change on a behavioral level may be achieved if the appropriate mental challenge is employed (i.e. executive task).

Executive Control Functions

The region of the brain that has been found to be responsible for executive control functioning is the frontal lobe, and more specifically, the prefrontal cortex (Royall et al., 2002). Executive control functioning (ECF) involves cognitive processes such as planning, organizing, controlling, initiation, and monitoring behaviors related to goals (Royall et al., 2002). Working memory and attentional shift are major processes involved with executive control functioning accordingly, the prefrontal cortex has more connections to other areas of the brain than any other brain region, making it that much more important in the planning and execution of thought processes. The prefrontal cortex is composed of the dorsolateral region, orbital or medial region, and the anterior cingulate or mesiofrontal region. Each of these areas receives information from other regions of the brain that are specific to those areas. These are the regions of the brain that exhibit dramatic decline in APOE ϵ 4 carriers.

Apolipoprotein E ϵ 4

Apolipoprotein E (APOE) is involved with the transfer of lipids within the brain, maintaining the structural integrity of microtubules within neurons, and helping with neural transmission (Nathoo et al., 2003). It has also been found to assist in repairing the brain after suffering traumatic brain injury. Possession of the ϵ 4 allele has been found to raise plasma cholesterol and low-density lipid (LDL) concentrations. Individuals who are heterozygous for this allele are at an increased risk of developing Alzheimer's disease, and those who are homozygous are at an even higher risk. APOE ϵ 4 has been linked to increased release of amyloid beta protein, which comes from amyloid precursor protein (APP). This increased release of

amyloid beta protein and the improper transportation of lipids places carriers of this gene at risk for cognitive decline and AD (Nathoo et al.). Brain injury in people possessing APOE ϵ 4 results in increased release of amyloid beta protein, which leads to the decreased ability of the brain to protect itself from further damage and the inability to repair the damage that has already been done. In this regard, Kutner et al. (2000) found that older football players who possessed the APOE ϵ 4 gene had significantly lower cognitive tests scores than players who did not possess this gene, and younger players who possess the gene. A study that examined severe head trauma found that those who possessed the gene had an increased likelihood for severe disability, vegetative state, or death, than those without the gene (Caulfield, 1999). In a sense, the head trauma that occurs in such combative sports may be analogous to an extreme rate of aging.

The Influence of Physical Activity on the Aging Brain

Being physically active is one factor that can help in maintaining cognitive functioning and the structural integrity of the brain (Colcombe et al., 2003^b; Colcombe et al., 2003^b). Exercise increases neurotrophic factor synthesis in the central nervous system with increased gene expression (Van Hoomissen, 2005). Brain-derived neurotrophic factor (BDNF), a member of the nerve growth factor family, is increased in the hippocampal region as a result of physical activity (Van Hoomissen, 2005; Cotman et al., 2002; Neeper et al., 1996). BDNF enhances the function of different neurons, promotes neuronal activity and plasticity, and helps build more synaptic connections.

Cortical plasticity is the development of synaptic connections and new neurons that lead to a more adaptive and efficient brain (Colcombe et al., 2004). Cardiovascular activity has been shown to slow the aging process of the brain, increase cortical plasticity, and improve cognitive performance (Colcombe et al.). Colcombe et al. found that cognitive performance mediated by the prefrontal and parietal cortices was greater in highly fit and aerobically trained individuals than in low-fit and non-aerobic individuals. Through a meta-analysis, Colcombe and Kramer (2003^a) displayed that older adults who exercised performed better than controls on executive control tasks, controlled processing tasks, visuospatial tasks, and speed tasks.

As such, cardiovascular exercise reduces the loss of tissue in the brain as we age (Colcombe et al., 2003^b). This reduced loss of tissue helps to maintain cognitive performance. Cardiovascular disease has been linked to poorer cognitive performance (Dywan et al., 1992), therefore it is important for people to keep their cardiovascular system healthy. Prolonged exercise increases blood flow in the motor cortex region, and a consistent exercise regimen can promote angiogenesis in the cerebral cortex (Black et al., 1990, Swain et al., 2003).

Physical activity is protective of cognitive decline in carriers of the apolipoprotein E ϵ 4 allele (Schuit et al., 2001). In a group of elderly men, the risk of cognitive decline for active and inactive non-carriers was similar, but the risk of decline in inactive carriers was much greater when compared to active carriers (Schuit et al.). Being physically active slowed down the cognitive decline that is associated with possessing APOE ϵ 4. Another study by Podewils et al. (2005)

revealed that physical activity decreased the risk of dementia in active non-carriers, but did not have the same effect on active carriers. The apparent contradiction of Schuit et al. and Podewils et al. are resolved by noting that Schuit et al. measured rate of cognitive decline and Podewils et al. measured risk of incident dementia. Another finding from this study was that variety of activities seemed to be just as important as frequency, intensity, and duration of physical activity, in decreasing the risk of dementia. Because of the rapid decline of the frontal lobe with aging, physical activity should prove to be extremely beneficial in slowing this process. One way we can measure frontal lobe functioning is through the use of cognitive behavioral tests such as the Wisconsin Card Sorting Test.

Wisconsin Card Sorting Test: A Test of Executive Control Functions

The Wisconsin Card Sorting Test (WCST) is recognized by many researchers as the best measure of executive control functioning (Hartman et al. 2001; Konishi, S. 1999; Lezak 1995; Royall 2002). It known for its sensitivity to frontal lobe dysfunction and lesions (Dywan et al. 1992; Hartman et al. 2001; Green 2000; Konishi et al. 1999; Royall et al. 2002). Patients with frontal lobe lesions and brain injured patients have been found to perform worse on the WCST than control participants (Green 2000; Lezak 1995)

The WCST also challenges working memory and attentional set shifting (Green 2000; Hartman et al. 2001; Konishi et al. 1999; Lezak 1995). Participants are asked to match cards based on three dimensions—color, number, and shape. When the dimension that the participant is matching on changes, they have to remember what other two dimension they have to choose from, select the correct dimension, and

continue matching on the dimension until it changes again (Green 2000; Lezak 1995). People with frontal lobe dysfunction tend to forget what the three dimensions are, and are likely to continue with the same wrong response, or perseverative response. A perseverative response is the repetition of a response that is no longer in effect.

As the brain declines with age, so does cognitive performance, in a manner that resembles the cognitive performance of patients with lesions and/or brain injury. The WCST is also sensitive to age differences in cognitive functioning (Green 2000; Lezak 1995), such that older adults display poorer performance than younger controls (Hartman et al. 2001).

Statement of the Problem and Hypothesis

A classic study by Kramer et al. (2001) provides a foundation for the present study. Their results revealed that increased exercise improved performance on tasks measuring executive control processes. Therefore, high-active men and women in the current study should perform better on a test of executive control function, such as the Wisconsin Card Sorting Test, than low-active participants. Furthermore, the strength of the relationship between physical activity and cognitive functioning should be greater in those who are at genetic risk of cognitive decline. As such, the present study provides a replication and extension of the work reported by Kramer et al. Therefore, we predict that high-active participants will perform better than the low-active participants on the WCST, and that the magnitude of difference will be greater in the carriers of APOE $\epsilon 4$. The specific hypothesis for this study is:

The number of perseverative errors (absolute and percent) committed during the Wisconsin Card Sorting Test will be negatively related to the level of self-

reported physical activity (Yale Physical Activity Survey), and that the magnitude of this relation will be greater in APOE ϵ 4 carriers than in non-carriers.

Limitations

One of the limitations of this study is that it is a cross-sectional study, and cannot address causal influence of the various factors on mental performance. Furthermore, the study failed to assess the participants' level of physical activity earlier in life as it was confined to a period comprised of the last five years just prior to testing. In most cases the participants reported stable activity patterns during this period. Only using a middle aged population does not allow us to examine how their cognitive performance will be once they become older adults. Our purpose for studying middle aged adults is that they are old enough to display age-related effects of cognitive decline, but young enough to offset these problems with physical activity. Richards et al. (2003) reported that physical activity and spare-time activities reported at the age 36 were significantly associated with the preservation of memory later in middle life.

Chapter 2: Review of Literature

Introduction

In this review of literature, we will first examine the aging process of the brain. More specifically, how the frontal lobe – the fastest region to age – which is primarily responsible for executive control functions begins to decline. We will then investigate how genetic factors put some people at a higher risk for cognitive decline than others. Research on how physical activity effects the brain will be presented, along with studies debating the benefits of physical activity for people who are genetically at-risk for increased cognitive decline. Finally, we will look at how executive control functioning is measured using a card sorting task that is considered to be the “gold standard” for testing executive control processes.

Brief Anatomy of the Brain

The anatomy of the brain is very complex. Making up approximately 2% of the total body weight, the brain is either responsible for or plays a role in many functions including (but not limited to) memory, motor activity, emotions, thoughts, and more. The brain is made up of three major subdivisions – the cerebral hemispheres, the cerebellum, and the brain stem. Since this study is primarily concerned with the frontal lobe, which is located in the cerebral hemisphere, the latter two subdivisions will not be discussed. The two highly convoluted cerebral hemispheres are made up of overlying gray matter and underlying white matter. The convolutions are referred to as gyri, and the grooves that separate the convolutions are called sulci. Together, these gyri and sulci separate the cerebrum into six regions

called lobes. The six lobes are the frontal, temporal, parietal, occipital, insular, and limbic.

Physical Activity

For the purpose of this study it is important to define what is meant by physical activity. Physical activity in this study includes deliberate exercise such as going to the gym or going outside for a run, as well as our activities of daily living such as gardening, doing laundry, or walk up steps to name a few. A person can be extremely physically active, but not engage in deliberate exercise, and still gain positive benefits such as angiogenesis, synaptogenesis, neurotrophic effect, and an overall preservation of the brain. Some physical activities may also involve problem solving or learning something new (i.e. rock climbing, construction work) which gives us the benefits of being cognitively engaged in a task.

Aging Brain

As we age, our brains decrease in size due to reductions in gray and white matter (Van Petten et al., 2004). This can be observed as early as our third decade of life and appears to start with the most anterior regions of the brain (Salat et al., 2004; Van Petten et al., 2004). Salat and colleagues (2004) used magnetic resonance imaging (MRI) to scan participant brains for a measure of cortical thickness. The study consisted of 106 participants from three age groups: younger (18-31), middle-aged (41-57), and older participants (60-93). All participants were asymptomatic for neurologic, psychiatric, or medical illness that could have a negative affect on their results. Cortical thickness was measured by calculating the distance from the

gray/white matter boundary to the cortical surface. This was done across the surface of the cortex to obtain global and regional measures of cortical thinning. The results showed that age had a significant effect on thickness and volume. That is, as age increased, thickness and volume decreased. They found an approximate loss of ~0.016mm of thickness per decade in the age range examined. Regional measures revealed that significant thinning was apparent in the occipital lobe, pre/post central gyrus and central sulcus, and the inferior lateral prefrontal cortex. The most statistically significant thinning was observed in the inferior prefrontal, precentral and supramarginal regions of the cortex, indicating that these are the regions that begin to deteriorate first with age.

Demented aging is different from normal aging. While amyloid plaques and neurofibrillary tangles are present during both normal and demented aging, they become the hallmark for demented aging. Roth (1994) reported that when senile plaques per microscopic field are on average at 15 or below, no clinical symptoms of dementia are present. He considers this to be the threshold for dementia of the Alzheimer's type (DAT). Below this threshold neurofibrillary tangles are primarily found in the hippocampus and parahippocampal gyrus. It is beyond this threshold of plaques and tangles that DAT becomes evident.

Head and colleagues (2004) used MRI to examine the corpus callosum (CC) and hippocampus (HC) regions of the brain in normal aging and demented aging. The study consisted of a younger participants ranging in age from approximately 19-28, a nondemented older sample ranging from approximately 65-93 years in age, and a demented older sample ranging in age from about 69-87. The corpus callosum was

divided into five subregions from the most anterior region (CC1) to the posterior region (CC5). Results revealed that all five subregions of the CC in younger adults were significantly larger than those in nondemented older adults. No significant differences were found in these subregions between nondemented and demented older adults. A significant group by brain region interaction was also observed between the younger sample and nondemented older sample when comparing regions CC1 and CC5. The difference in CC1—the most rostral region—was greater than the difference in CC5—the most posterior region. This gives us evidence that age-related deterioration starts in the most rostral regions of the brain. Analysis of the hippocampal region revealed that demented adults had significantly smaller HC volumes than nondemented adults. No significant differences were found between the HC regions of nondemented adults and younger adults. These results display the regional effect dementia has on the brain.

Executive Control Functioning

The frontal lobe region of the brain has more connections to other areas of the brain than any other region (Royall et al., 2002). More specifically the prefrontal cortex is responsible for planning, organizing, controlling, initiating, and monitoring behaviors (Royall et al., 2002). These cognitive processes are part of what is known as executive control functions. When more than one stimulus is present and allows for a variety of responses, higher-order cognitive processing is needed. Executive control functioning solves these situations by providing goals and instructions, as well as restricting unwanted responses (Hall, Smith, Keele, 2001).

While brain volume and cognitive functioning begin to decline with age, the frontal lobe has been suggested to be the fastest region of the brain to begin declining as a result of aging (Hall, Smith, Keele, 2001). As a result, we see a more significant decline in executive control functioning than in non-executive control functioning on measures of cognitive performance (Hall et al., 2001). This is thought to be due to the reduction in gray matter volume in the frontal lobe region that Van Petten and colleagues (2004) witnessed, along with a reduction in blood flow to that region of the brain resulting in reduced cognitive processing speed (Hall et al., 2001).

To display the effects of age, as well as education, on executive functions in women, Plumet, Gil, and Gaonac'h (2005) tested 133 women ages 50 to 92 on a modified card sorting test (MCST) and a verbal fluency test. The women were separated into three age groups – 50 to 59, 60 to 69, and 70 and above. Each age group was split into two education categories – low education level (7-11 years of education) and high education level (12 years or greater). The card sorting test was a modified version of the Wisconsin Card Sorting Test, but is still aimed at testing executive functioning and uses total trials and number of perseverative errors as measurements, along with number of distractive errors and number of sorting errors. The verbal fluency test was used as a second measure of executive functioning. Participants were required to name as many objects as possible from one category (i.e. modes of transportation) for one minute in the first trial, and in the following second trial they were required to alternate between two different categories (i.e. animals and vegetables).

Their results on the MCST revealed that with advancing age the participants needed more trials to complete the task, and committed a greater number of perseverative errors, distractive errors, and sorting errors. When comparing ages in the low education level group, the group that was age 70 and over needed significantly more trials and produced significantly more sorting errors than the 50-59 age group. Significant differences in the number of perseverative errors was also found in this group. In the high education level group, the older subgroup needed significantly more trials to complete the task than the 50-59 age group. There was no significant difference in perseverative errors in this group. Analysis comparing the two education levels revealed that the low education level group required significantly more trials and committed significantly more sorting errors than the high education group. Only in the two oldest age groups did the low education group commit significantly more perseverative errors than the high education group. As for distractive errors, participants in the 70 and over age group committed significantly more errors than the younger groups, and did not differ in regards to education level.

The results of the verbal fluency tests revealed a significant main effect of education on performance, with higher levels of education being associated with a greater total number of words produced and number of atypical words produced. Age revealed a significant decrease on the number of atypical words produced, as well as a significant simple effect in the low education group on spontaneous switches and percentage of semantic associations. There was also a significant main effect of age and education on spontaneous switches and percentage of semantic associations. The researchers' analysis of the relationship between the two executive control tasks

revealed an inverse relationship between perseverative and sorting errors on the MCST with total word fluency scores.

Kramer et al. (2001) recruited 124 older adults ages 60 to 75, who had been sedentary for at least six-months prior to their study being conducted on the effects of improved aerobic fitness on cognition, especially on tasks measuring executive control functioning. This was a six-month randomized exercise intervention in which participants were placed in either a toning group or a walking group.

A cognitive battery was administered to all participants before and after the six-month intervention. Nine of the tasks in this cognitive battery rely on executive control processes carried out in the frontal and prefrontal regions of the brain. The other six tasks were non-executive processing tasks that have been found to rely less on the frontal lobe. The researchers predicted that participants would improve more on the tasks involving executive control processes as a result of improved aerobic fitness than on the non-executive tasks.

VO₂ peak was used to assess aerobic capacity of all participants before and after the exercise intervention. The aerobic exercise group engaged in a brisk walking program three times a week for six-months. Intensity and duration were increased each session until the participants were walking for 40 minutes per session at a moderate level of intensity. The stretching and toning group also met three times a week for six-months, but engaged in stretching and toning exercises for the whole body. Each session lasted approximately 40 minutes, along with ten minutes of warm-up exercises and ten minutes of cool-down exercises.

The results revealed what the investigators initially hypothesized. For the tasks that involved executive control processes, the aerobic group displayed improvements in performance, but the toning group did not. The two groups did not differ on improvements on the non-executive tasks.

Apolipoprotein E ε4

Along with the normal aging process, there are genetic factors that can increase the rate of cognitive decline. A susceptibility gene located at position 19q13.2 on chromosome 19 has been linked to the development of Alzheimer's Disease (AD) (Wasco 2001). This gene is known as apolipoprotein E (APOE). The liver contains the largest amount of APOE mRNA in the body, and the brain has about one-third that amount (Saunders). The primary responsibility of APOE is the transport of lipids in cerebrospinal fluids (Nathoo, Chetty, van Dellen, & Barnett 2003; Saunders 2001). It is also believed to play a role in maintaining the structure of and repairing neurons (Nathoo et al. 2003). APOE is a polymorphic gene with three alleles (Wasco). These three alleles are APOE ε2, APOE ε3, and APOE ε4. Individuals possess two of these three alleles, leading to either a heterozygous phenotype (ε2/ε3, ε2/ε4, ε3/ε4) or a homozygous phenotype (ε2/ε2, ε3/ε3, ε4/ε4). APOE has been studied the most in Caucasian populations and it has been found that the ε3 allele is the most common isoform at 78%, followed by ε4 at 15%, and then ε2 at 7% (Nathoo et al 2003; Wasco). The polymorphism of APOE is the result of two amino acids—cysteine and arginine—at positions 112 and 158 (Wasco). APOE ε3 contains cysteine at position 112 and arginine at position 158. APOE ε2 has cysteine at both positions, while APOE ε4 has arginine at both positions. The presence of the

$\epsilon 4$ allele is what puts individuals at an increased risk for AD. The role of APOE $\epsilon 4$ has not been made clear. It is hypothesized that it does not bind well with cytoskeletal proteins and amyloid β protein (Nathoo, 2003), and does not block the formation of neurofibrillary tangles (Wasco). Previous studies have observed a higher frequency of the $\epsilon 4$ allele in patients who have poor recovery from head trauma (Saunders). These patients exhibited increased levels of amyloid β protein deposition, and were more likely to develop severe disability (Caulfield 1999; Nathoo et al. 2003; Saunders). Individuals who are heterozygous for the $\epsilon 4$ allele are at a greater risk for AD than individuals who do not possess the allele, while individuals who are homozygous $\epsilon 4$ show the greatest risk for AD (Wasco). APOE $\epsilon 2$ is hypothesized to have a protective effect against AD, due to the low frequency of the allele found in late-onset AD patients (Wasco).

In a longitudinal study using positron emission tomography (PET) to examine brain activity in cognitively normal APOE $\epsilon 4$ heterozygotes compared with $\epsilon 4$ noncarriers, Reiman, Chen, Alexander, Brandy, and Frost (2001) found significant declines in cerebral metabolic rate for glucose (CMRgl) over a two year span in various brain regions. Participants ranged in age from 50 to 63 years old, reported a family history of AD, and had a two year interval between test 1 and test 2. The $\epsilon 4$ heterozygotes showed significant declines in the temporal cortex, posterior cingulate cortex, prefrontal cortex, basal forebrain, parahippocampal/lingual gyri, and thalamus. The $\epsilon 4$ noncarriers showed significant declines in the posterior cingulate cortex, parietal cortex, anterior cingulate cortex, and the caudate nucleus. Though both the $\epsilon 4$ heterozygotes and $\epsilon 4$ noncarriers had significant declines, the $\epsilon 4$

heterozygotes declines were significantly greater, and their magnitude of difference was greater.

Yaffe, Cauley, Sands, and Browner (1997) conducted a longitudinal study involving elderly women ages 65 years and older who were enrolled in a study on osteoporosis risk factors. They examined APOE phenotype in relation to performance on a battery of cognitive tests at baseline and repeated the measures six years later. Results revealed that $\epsilon 4$ carriers performed significantly worse than noncarriers on the follow-up tests, and homozygous carriers declined approximately twice as much as heterozygous carriers.

Another study by Haan, Shemanski, Jagust, Manolio, and Kuller (1999) found that the APOE $\epsilon 4$ allele combined with subclinical cardiovascular disease placed elderly individuals ages 65 years and older at an increased risk for cognitive decline than those without the $\epsilon 4$ allele or subclinical cardiovascular disease. Hsiung, Sadovnick, and Feldman (2004) observed that the $\epsilon 4$ allele significantly increased the risk of developing Alzheimer's disease from cognitive impairment without dementia, as well as from normal cognitive functioning.

Wisconsin Card Sorting Test

The Wisconsin Card Sorting Test (WCST) has been considered by some to be the “gold standard” for measuring executive control functioning (Royall et al. 2002). During the WCST, the left dorsolateral prefrontal cortex is activated the most out of the brain regions, along with activation from the right anterior prefrontal region, the mesiofrontal/anterior cingulate, and the orbitofrontal region (Royall et al.). Executive control functions primarily involved in the WCST include working

memory, attentional shift, and response inhibition (Konishi et al., 1999; Hartman et al., 2001; Royall et al., 2002).

Konishi et al (1999) used functional magnetic resonance imaging (fMRI) to examine what region of the brain is activated by the WCST and if that region is activated by both working memory and attentional set-shifting. Seven subjects ages 24-40 performed the original WCST, a modified WCST, and a working memory task. In the modified WCST, the working memory component was removed by informing the subjects of the new correct dimension that should be used. The working memory task that was administered—the N-back Task with card stimuli—was used to replicate previous studies to show that working memory activates the inferior prefrontal region of the brain. The fMRI results revealed that the working memory task and the original WCST both activated the inferior prefrontal cortex. To examine the contribution of working memory to the WCST, the researchers quantified the overlap of the two tasks inferior prefrontal activation. The ratio of overlap in the left and right inferior prefrontal areas was highly significant in all seven subjects. The modified WCST revealed that the inferior prefrontal cortex still displayed activation with the working memory component removed, though the amount of activation was significantly smaller when compared to the original WCST. From this, they concluded that working memory and attentional set-shifting are both involved in performing the WCST and that the WCST is sensitive to frontal lobe functioning, more specifically the inferior prefrontal cortex.

Dywan and colleagues (1992) examined different levels of cardiovascular health and performance on the WCST. Their participants were 34 men and women

ages 55 to 77 years who were part of a larger ongoing study on cognitive functioning across the life span. Based on a health questionnaire and interview, the participants were separated into three groups. Eleven participants with no health problems and no medication formed group 1. Ten participants who reported health problems and were taking medication, but whose problems do not compromise oxygen or blood flow to the brain made up group 2. Group 3 consisted of thirteen participants with cardiovascular health issues such as hypertension, coronary heart disease, transient ischemic attacks, and the use of medication related to these problems. Using a hierarchical multiple regression of age, vocabulary, health, and P300 latency on the percentage of perseverative errors on the WCST, the researchers found that health accounted for a significant 28% of the variance. Group 3 committed a significantly higher percentage of perseverative errors than group 1 and group 2 on the WCST. Group 2 did commit more a few more errors than group 1, but the difference was not significant. This shows us that health issues that decrease oxygenation and blood flow to the brain, such as hypertension and coronary heart disease, can lead to poorer performance on a task such as the WCST, a task that is sensitive to frontal lobe functioning.

Benefits of Physical Activity

Brain function is enhanced and protected by the increased expression of various genes (Cotman & Engesser-Cesar, 2002; Van Hoomissen, 2005). Exercise increases the expression of brain-derived neurotrophic factor (BDNF), a gene that assists in the functioning of glutamatergic neurons (Cotman & Engesser-Cesar, 2002; Van Hoomissen, 2005). The increased expression of BDNF has been observed in

animal studies primarily in the hippocampal region of the brain along with the cerebral cortex (Neeper et al, 1996; Cotman & Engesser-Cesar, 2002; Van Hoomissen, 2005). This is important because the hippocampus is highly involved with learning and memory processes. It is also the region that declines the fastest with Alzheimer's disease.

Neeper, Gomez-Pinilla, Choi, and Cotman (1996) examined the brains increase in BDNF and nerve growth factor (NGF) – another gene that has been found to support the function of neurons – in 39 Sprague-Dawley male rats after physical activity. Exercise in the form of wheel running served as the mode of physical activity. BDNF and NGF mRNA levels were observed after 0 (control group), 2, 4, and 7 nights of exercise. All rats were 3 to 4 months of age and received 3 days of training with the wheel, followed by 10 days without the wheel to reduce any physiological effects from the training. They were then given 0, 2, 4, or 7 nights with access to the wheel before being sacrificed.

There was a significant increase in BDNF mRNA in the frontal cortex after 2 nights with exercise, but then dropped back to control levels after 4 and 7 nights of exercise. No significant increase was observed in the middle cortex, but a 30% increase above control levels was observed in the cerebellum after 4 nights of exercise. The most significant increases in BDNF and NGF mRNA levels were observed in the hippocampus and the caudal cortex. In the hippocampus, BDNF mRNA levels were significantly higher than controls after two nights with the running wheel and remained elevated through seven nights. To be more specific within the hippocampus, Ammon's horn areas CA1 and CA4 had the most significant

increases after seven nights, increasing 80% and 40% respectively, above control levels.

NGF mRNA levels in the hippocampus after 2 nights of exercise were 30% above control levels, but declined after 4 and 7 nights. More specifically, after 7 nights, CA4 and the dentate gyrus areas of the hippocampus were significantly 20-30% higher than controls.

In measuring BDNF mRNA in the cerebral cortex, the caudal 1/3 showed a significant increase of 35% above control levels after 2, 4, and 7 nights with the running wheel. Layers II-III and the retrosplenial cortex increased 90% after 7 nights. NGF mRNA levels were significantly increased after 2, 4, and 7 nights, with the 7-night time point being the highest. Layer II-III had a 60% significant increase over control levels. These results demonstrate that the expression of genes that are beneficial to the brain can be increased through higher amounts of physical activity. The increased expression of the genes is most noticeable in regions involving learning and memory.

In addition to the neurotrophic effect, physical activity also increases cortical plasticity through increases in blood flow and synaptic connections. In animal studies involving rats, researchers have found that not only is physical activity beneficial to brain, but the type of physical activity might have a specific effect on the brain. Swain et al. (2003) found in three different experiments that prolonged exercise in the form of a running wheel 1) increases blood volume in the motor cortex, especially in the regions of the motor cortex associated with running, mainly the forelimbs, 2)

increases capillary reserve in response to elevated levels of CO₂, and 3) induces a healthy amount angiogenesis within 30 days.

Black, Isaacs, Anderson, Alcantara, and Greenough (1990) used rats to compare the effects of acrobatic training to those of physical exercise in the form of wheel running. They found that the learning component of acrobatic training caused a significant increase in synapses per Purkinje cell compared to the exercise group and the inactive control group. The exercise group had greater blood vessel density than the acrobatic group and significantly greater density than the inactive group. These results display the multiple benefits the brain stands to gain from not only increase physical activity, but also from different types of physical activity.

Physical Activity and the Aging Brain

The benefits that the brain receives from physical activity become more important in helping to maintain cognitive functioning as the brain ages. In a meta-analysis done by Colcombe and Kramer (2003^a), they looked at the effects of fitness on cognitive functioning in older adults. They found that older adults who exercised performed better than non-exercising controls on speed, spatial, controlled, and executive cognitive tasks, with the most significant difference being in the executive task category. Among the three age groups studied—young-old (55-65), middle-old (66-70), and old-old (71+)—the middle-old group benefited significantly more than the young-old and the old-old groups. The old-old group benefited significantly more than the young-old group. All three groups were statistically significant from zero. The young-old group may not have benefited as much as the two older groups because their brains are still fairly young and have not declined as much. The old-old

group may be at a point where their brains have declined to a point where exercise is beneficial but only to a degree. The middle-old being statistically greater than the other two groups could be due to them being old enough to display the effects of aging—compared to the young-old—but young enough to offset those effects through exercise—compared to the old-old.

Colcombe et al. (2004) examined the effects of cardiovascular fitness on cortical plasticity in the aging brain in two different studies. The first study was a cross-sectional assessment of 41 high-functioning older adults. Fitness assessments were conducted to put the participants in either a high-fit or low-fit group. Estimates of maximal oxygen uptake (VO_2) were obtained using participants height, weight, heart rate, and performance on the Rockport 1-mile walk test. The researchers measured participants' reaction time on a flanker task. Their percent increase reaction time on incongruent stimuli was compared to that of their average reaction time on congruent stimuli. While engaged in the task, participants' brains were scanned using functional magnetic resonance imaging (fMRI).

From the results, it was revealed that high-fit older adults performed better than low-fit older adults on the flanker task. High-fit older adults displayed 18% interference on the incongruent stimuli compared to 26% interference by the low-fit older adults. The fMRI results revealed that high-fit older adults had significantly higher levels of activation in the right middle frontal gyrus, superior frontal gyrus, and the superior parietal lobule. The anterior cingulate cortex, a region linked to behavioral conflict, displayed significantly less activity in high-fit participants.

The second study was a longitudinal study conducted over six-months. The study included 29 high-functioning older adults ages 58 to 77 years old. One-week before the six-month intervention, all participants completed the same flanker task and fMRI scanning as in the first study. The same task and fMRI scan were also administered one-week after the six-month intervention was completed. For the six-month exercise intervention, participants were randomly assigned to one of two groups—an aerobic exercise group or a stretching and toning control group. These groups met for three times per week for 40 to 45 minutes over six-months and were led by trained exercise personnel. The aerobic exercise group aimed to improve cardiorespiratory fitness by means of a walking activity that increased in intensity throughout the six-months. The stretching and toning group was used as the control group. They engaged in a total body exercise program including stretching, limbering, and toning.

The results showed that the aerobic exercise group had a significant increase in VO_2 compared to the stretching and toning control group after the six-month intervention. On the flanker task from pre-intervention to post-intervention testing, the aerobic exercise group showed an 11% reduction on incongruent stimuli compared to only 2% by the control group. Results from the fMRI revealed that the aerobic exercise group displayed significantly higher levels of activity in the middle frontal gyrus, superior frontal gyrus, and the superior parietal lobule, along with significantly decreased activity in the anterior cingulate cortex when compared with the control group after the six-month intervention.

The fMRI results from Study 1 and Study 2 revealed that both the high-fit group (Study 1) and the aerobic exercise group (Study 2 after the six-month intervention) displayed similar regional activity on the flanker task. This leads the researchers to conclude that the cognitive benefits from increased cardiovascular exercise can become evident in approximately six-months. It is hypothesized that these benefits are the result of increased blood flow and synaptic connections that come from the increase amount of cardiovascular activity. It should also be noted that the frontal and parietal regions associated with the flanker task benefited the most.

For individuals who are genetically at-risk for increased cognitive decline, such as those who are heterozygous or homozygous for APOE ϵ 4, being physically active can be even more important. Schuit et al. (2001) examined the role of APOE ϵ 4 and its relationship to physical activity and cognitive decline. This was a longitudinal study involving 347 men between the ages of 65-84 years old. The study was conducted from 1990 to 1993. The Mini Mental State Examination (MMSE) was used to test global cognitive functioning. A reduction of more than three points on the MMSE over the three year period was considered cognitive decline. Participants were either defined as carriers or noncarriers of the APOE ϵ 4 allele. A self-administered questionnaire was used to assess physical activity in 1990. Questions about deliberate exercise, hobbies, and odd jobs were included on the questionnaire. Participants were categorized into two groups based on their amount of physical activity. The first group was a “maximal of 1 hour per day” (low active), and the second group was “more than one hour per day” (high active). The results revealed

that the risk of cognitive decline from 1990 to 1993 between low active and high noncarriers—those without the APOE ϵ 4 allele—was similar. However, while the risk of cognitive decline for the high active carriers—those with at least one APOE ϵ 4 allele present—came close to those of the noncarriers, the low active carriers risk was approximately four times the risk of the high active carriers. From the results, we can see that while overall, the risk of cognitive decline is greater for low active participants than high active participants, the greatest magnitude of difference was between the high active and low active carriers. This shows us that physical activity has an even greater impact on individuals who carry the APOE ϵ 4 allele.

Podewils and colleagues (2005) examined a similar relationship between physical activity and APOE genotype, but instead of studying cognitive decline, they looked at incident dementia. The study took place from 1992 to 2000 and included 5,888 men and women age 65 and older. Physical activity was assessed by a questionnaire asking participants questions about frequency, duration, and the number of different of activities they engage in. APOE genotype was defined by either being a carrier or noncarrier of the APOE ϵ 4 allele. A number of covariates were measured at baseline and over the time period of the study. Some of the covariates were, but not limited to age, gender, education level, ethnicity, smoking, alcohol, cardiovascular health issues, social networks, height and weight, MRI scans, and cognitive status using the Modified version of the Mini-Mental State Examination (administered annually). Dementia status and type were assessed and classified from 1999 to 2000. Of the many results obtained from this study, the results that we are concerned about for our current study are that those participants who developed

dementia were more likely to be carriers of the APOE ϵ 4 allele, and there was an inverse relationship between leisure-time energy expenditure and dementia risk, as well as the number of physical activities and dementia risk. More importantly for our study, the inverse relationship of energy expenditure and number of activities to dementia risk was only found in APOE ϵ 4 noncarriers, not APOE ϵ 4 carriers.

It is important to note the difference between the Schuit et al. (2001) study and the Podewils et al. (2005) study. Schuit and colleagues measured cognitive decline, while Podewils and colleagues measured incident dementia. This is important to consider when comparing these two studies because a person may ultimately developed dementia, but their rate of cognitive decline leading up to dementia along with the severity of the dementia may be different in APOE ϵ 4 carriers and noncarriers, as well as individuals with varying levels of physical activity. Participating in a variety of activities may be just as effective as having higher energy expenditure because of the amount of learning and memory involved which possibly engages and enhances more neural networks.

Chapter 3: Methods and Procedures

Participants

The participants in this study came from a larger ongoing study investigating physical activity, the aging brain, and genotype. Volunteers were recruited from local running events, health clubs, campus faculty and staff, and newspaper ads.

Participants consisted of 67 men and women, 50 to 70 years of age. Level of education obtained was also recorded. Participants were assessed on their level of physical activity and whether they are a carrier or non-carrier of APOE $\epsilon 4$.

Participants who carried the combination of APOE $\epsilon 2/\epsilon 4$ were excluded from the study.

Screening of Participants

Participants signed a consent form (Appendix B) and were screened for any health problems using a medical history form (Appendix C). Participants accepted for the study were asymptomatic for psychiatric disorders, psychotropic medication, and neurological disorders.

Screening for Cognitive Impairments

Participants were screened for cognitive impairments with the Cambridge Cognitive Examination (CAMCOG, Appendix D). The CAMCOG is a subsection of the Cambridge Examination for Mental Disorders of the Elderly – Revised (CAMDEX-R) (Roth, Huppert, Mountjoy, & Tym; 1998). The CAMDEX-R is a standardized, structured interview and examination used for the diagnosis of mental disorders in older adults. The CAMDEX-R and the CAMCOG were both designed

with special emphasis on dementia. The CAMCOG is used to assess older adults generally ages 65 and up on the following cognitive functions: orientation, language, memory, attention and calculation, praxis, abstract thinking, and perception (Roth et al., 1998). The CAMCOG includes two other widely used tests, the Mini-Mental State Exam (MMSE) and the Abbreviated Mental Test, for purpose of comparison. Subjects who score in the range of 28 to 30 on the MMSE usually show a wide distribution on the CAMCOG. The CAMCOG is scored on a range from 0 – 107, with the total coming from the combined scores of the subsections. This widely used examination has proven useful in assisting with the differential diagnosis of dementia. Significant differences have been found on total CAMCOG scores as well as on each subscale (Williams et al., 2003). In a study conducted by Huppert et al. (1996) using a population aged 75 years and older, the mean total CAMCOG score for non-demented patients was 89.69, 77.95 for patients with minimal dementia, and 65.46 for patients with mild dementia. A cut-point of 80/81 produced the highest levels of sensitivity and specificity of the CAMCOG in predicting dementia diagnosis. For the current study we will be using a cut-point of 28 on the MMSE and 85 on the CAMCOG. The cut-point of 85 will be used to adjust for the younger population that we will be using.

Genetics Methods

Enrolled subjects provided a blood sample to enable comprehensive 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,

Genra, Inc.). Unique identification numbers were used for each DNA sample received, such that the identity of the subjects was not known during any portion of the project, including data analysis. This ID number was linked with all necessary, but similarly blinded, phenotype data.

Genotyping was performed using restriction fragment length polymorphism (RFLP) techniques. The APOE genomic sequence was amplified by PCR using standard techniques in a DNA thermal cycler using the following forward and reverse oligonucleotide primers: (APOE-OP-F: 5' ACT GAC CCC GGT GGC GGA GGA GAC G3' & APOE-OP-R: 5' TGT TCC ACC AGG GGC CCC AGG CGC TC 3'). Amplified product (15 μ l), ~300 base pairs (bp) in length, of study participants was added separately both to 2 units of HAEII enzyme and to 7.5 units of AFLIII enzyme for digestion and incubated at 37 degrees for 24 hours. Each digestion sample was loaded on to a 3% agarose gel containing ethidium bromide and electrophoresed. After electrophoresis the DNA fragments were visualized by ultraviolet illumination and fragment sizes were estimated by comparison to a 1 kb ladder run on the same gel. Genotyping of subjects was based on the following fragment sizes: 2/2: *HAEII*: 267 bp *AFLIII*: 231 bp 2/3: *HAEII*: 267, 232 bp *AFLIII*: 231 bp 2/4: *HAEII*: 267, 232 bp *AFLIII*: 295, 231 bp 3/3: *HAEII*: 232 bp *AFLIII*: 231 bp 3/4: *HAEII*: 232 bp *AFLIII*: 295, 231 bp 4/4: *HAEII*: 232 bp *AFLIII*: 295 bp. Sequence-verified control samples were used with all genotyping assays.

Assessment of Level of Physical Activity

The Yale Physical Activity Survey (YPAS, Appendix E) was administered to study participants during their initial visit for the larger study on physical activity, the

aging brain, and genotype. This survey assesses how physically active a person is. Physical activity in this survey encompasses deliberate exercise as well as the physical activity people engage in on a daily basis such as climbing steps and doing housework. Energy expenditure is recorded as kilocalories, summed, and averaged to calculate a weekly pattern of physical activity. The three scoring dimensions included in the YPAS are total time, energy expenditure, and activity summary scores (Dipietro et al., 1993). Total time is shown as the total number of hours per week for all activities combined. Energy expenditure is calculated by multiplying the time for each activity by an intensity code ($\text{kcal} \cdot \text{min}^{-1}$) and then summing all the activities to create an index ($\text{kcal} \cdot \text{wk}^{-1}$). The activity summary score or Yale index is calculated by multiplying the frequency score by the duration score, and then multiplying by a weighting score for each of the five activities. These five activities are vigorous activity, leisurely walking, moving, standing, and sitting.

Dipietro et al. (1993) report a positive correlation of $r = .58$ between the YPAS activity dimensions summary index and $\text{VO}_{2\text{max}}$, and an inverse relationship of $r = -.43$ with percent body fat. Repeatability coefficients ranged from .42 to .65 between two administrations (two-weeks apart) of the YPAS for the eight summary indices (Dipietro et al.). Shuler et al. (2001) found moderate to good short term repeatability of $R = .70$ to $.82$ for the three survey indices. High-intensity exercise related activities were reported to have a higher repeatability than lower-intensity activities, possibly due to the recall of more structured exercise as compared to the recall of more random activities of daily living (Dipietro et al., Shuler et al.).

Executive Control Task

The Wisconsin Card Sorting Test (WCST) is widely recognized as the best measure of executive control functioning (Hartman et al. 2001; Konishi, S. 1999; Lezak 1995; Royall 2002). The Wisconsin Card Sorting Test was administered to participants using a Gateway PC and software provided by Psychological Assessment Resources, Inc. Four stimulus cards appear across the top of the computer screen. A response card appears at the bottom center of the screen. Using four keys on the keyboard that correspond with the three matching principles—color, shape, and number—participants match the response card to the appropriate stimulus card based on one of the three matching principles. If the participant matches the response card on the wrong principle, the word “wrong” will appear in the middle of the screen. The participant then receives another response card to try to match on the correct principle. Once the correct principle is identified, they keep matching on the principle until the computer notifies them that they are “wrong”, indicating that the principle has changed. The word “right” appears in the middle of the screen when the participant matches the card correctly.

Scoring of the WCST is based on total errors, perseverative errors, and perseverative responses (refer to Appendix F for an example of scoring). Participants must match ten consecutive cards correctly on one principle before the principle changes. Participants receive a minimum of 64 cards and a maximum of 128 cards to complete the test. Errors that count towards the total number of errors occur when participants do not match on the current principle. Perseverative errors occur when a participant continues to match to a principle that is incorrect. Perseverative responses

are the total number of perseverations, correct and incorrect. The computer automatically scores the entire test once it is complete. Machine scoring provides objectivity among the scores.

Participants in the current study first received a coached practice trial with the test administrator's assistance. After the coached trial, they received the actual test trial in which they did not receive any assistance from the test administrator.

Data Analysis

The statistical approach used for the current study was adapted from a previous study conducted by Bixby et al. (2007) examining the unique relationship between physical activity and cognitive functioning in older men and women. The task that was used to examine executive function was regressed on age, education, IQ, physical activity (i.e., Yale index), and the interaction of age X physical activity. Therefore, the current study used hierarchical regression to examine the relationship between physical activity and mental performance on the WCST. Each of the seven performance scores (i.e., trials administered, total errors, percent total errors, perseverative errors, percent perseverative errors, nonperseverative errors, and percent nonperseverative errors) were separately regressed on age, genotype (i.e., presence or absence of APOE ϵ 4), physical activity (Yale index), and the interaction between genotype and physical activity. In the event of such a significant interaction, cognitive performance was regressed on physical activity separately for ϵ 4 carriers and non-carriers.

All statistical analyses were done using SPSS version 14.0. Mean and variability are reported for gender, age, education, overall CAMCOG score, MMSE

score, and Yale index. In addition, differences between genotype groups were assessed with 2-tailed independent sample T-tests for the same variables mentioned above.

In order to assess the logical structure of the data set, inter-correlations were computed between age, education, genotype, physical activity (i.e., Yale Index, Kcal expenditure, and Yale exercise), and each of the seven Wisconsin Card Sorting Test measures (i.e., trials administered, total errors, percent total errors, perseverative errors, percent perseverative errors, nonperseverative errors, and percent nonperseverative errors).

Chapter 4: Results

Descriptive Statistics

No differences were revealed between $\epsilon 4$ carriers and non-carriers in age, education, overall CAMCOG score, MMSE, or physical activity (see Table 1).

Table 1

Descriptive Statistics

| | Total | Non-carriers | $\epsilon 4$ Carriers | F | df | Sig (2-tailed) |
|-----------------------|--------------|---------------------|---|----------|-----------|-----------------------|
| N | 67 | 48 | 19 | - | - | - |
| Male/Female | 36/31 | 22/26 | 14/5 | 11.499 | 65 | 0.04 |
| Age | 60.0 (5.0) | 60.10 (5.0) | 59.74 (5.7) | 0 | 65 | 0.795 |
| Education | 17.37 (2.3) | 17.21 (2.3) | 17.53 (2.4) | 0.04 | 65 | 0.614 |
| CAMCOG Overall | 94.47 (4.1) | 94.33 (4.0) | 94.74 (4.6) | 0.455 | 65 | 0.722 |
| MMSE | 28.04 (1.2) | 28.17 (1.0) | 27.84 (1.4) | 1.462 | 65 | 0.299 |
| Yale index | 60.37 (23.5) | 61.21 (24.3) | 59.16 (22.0) | 0.981 | 65 | 0.751 |

Note. The mean and (standard deviation) reported for the entire group then separately for non-carriers and $\epsilon 4$ carriers.

Correlation Analyses

An initial correlation analyses was conducted on each of the Yale Physical Activity Survey measures with the seven Wisconsin Card Sorting Test variables. The Yale index score was the only measure to yield a significant relationship with any of the WCST variables. Therefore, the Yale index score was used as the assessment of physical activity in the data analysis.

Correlation analysis was conducted on the seven WCST variables with age, education, genotype, and Yale index. The correlation matrix is reported in Table 2 (2-tailed probability).

As expected, positive correlations were found between age and the following executive performance variables: percent total errors ($r = .229$, $p = .056$),

perseverative errors ($r = .232$, $p = .053$), and percent perseverative errors ($r = .232$, $p = .054$).

As expected, negative relationships were observed between Yale index and the following variables: nonperseverative errors ($r = -.254$, $p = .034$), and percent nonperseverative errors ($r = -.232$, $p = .054$).

Table 2

Correlations between WCST variables & Age, Education, Genotype, Yale Index

| | | Trials Admin | Total Errors | % Errors | Perseverative Errors | % Perseverative Errors | Nonperseverative Errors | % Nonperseverative Errors |
|------------|---------------------|--------------|--------------|----------------|----------------------|------------------------|-------------------------|---------------------------|
| Age | Pearson Correlation | .188 | .213 | .229(*) | .232(*) | .232(*) | .172 | .166 |
| | Sig. (2-tailed) | .119 | .077 | .056 | .053 | .054 | .153 | .170 |
| Ed. | Pearson Correlation | -.008 | .011 | .006 | -.039 | -.050 | .042 | .047 |
| | Sig. (2-tailed) | .945 | .925 | .960 | .752 | .683 | .731 | .701 |
| Gene | Pearson Correlation | -.050 | -.019 | -.038 | -.001 | .009 | -.029 | -.069 |
| | Sig. (2-tailed) | .688 | .882 | .762 | .990 | .939 | .813 | .580 |
| Yale index | Pearson Correlation | -.202 | -.199 | -.155 | -.095 | -.021 | -.254(*) | -.232(*) |
| | Sig. (2-tailed) | .094 | .099 | .199 | .432 | .861 | .034 | .054 |

* Correlation is significant at the 0.05 level (2-tailed).

In addition, correlation analyses were conducted on the four YPAS measures with the cognitive screening tools (i.e., CAMCOG and MMSE). This was performed to examine global cognitive integrity. The correlation matrix is reported in Table 3 (2-tailed probability).

The results from this correlation analysis indicated positive relationships between the following: (1) Yale exercise and MMSE ($r = .302$, $p = .011$), (2) Yale index and MMSE ($r = .353$, $p = .003$), and (3) Yale vigor and MMSE ($r = .281$, $p = .018$).

Table 3

Correlations for Physical Activity Variables & Cognitive Screening

| | | CAMCOG overall | MMSE |
|---------------|---------------------|----------------|-----------------|
| Yale kcal | Pearson Correlation | .034 | -.009 |
| | Sig. (2-tailed) | .778 | .941 |
| Yale exercise | Pearson Correlation | .177 | .302(+) |
| | Sig. (2-tailed) | .143 | .011 |
| Yale index | Pearson Correlation | .208 | .353(++) |
| | Sig. (2-tailed) | .084 | .003 |
| Yale vigor | Pearson Correlation | .198 | .281(+) |
| | Sig. (2-tailed) | .100 | .018 |

++ Correlation is significant at the 0.01 level (2-tailed).

+ Correlation is significant at the 0.05 level (2-tailed).

Hierarchical Regression Analyses

Percent perseverative errors.

Regression analysis revealed that age was positively related to percent perseverative errors and accounted for approximately 8% of the variability. No effect was revealed for genotype or physical activity alone. The interaction between genotype and level of physical activity accounted for approximately 6% of the variability in cognitive performance (see Figure 1). Follow-up analysis of the interaction was accomplished by regressing percent perseverative errors on age and physical activity for carriers, and non-carriers, separately. Carriers were characterized by a significant positive relationship between age and percent perseverative errors ($F_{\text{change}}(1,17) = 6.785, p = .018, \beta = .259, r^2 = .285$). Regressions for the non-carriers did not reveal any significant findings for any of the WCST variables.

Perseverative errors.

Regression analysis revealed that age was positively related to perseverative errors and accounted for approximately 11% of the variability. No effect was revealed for genotype or physical activity alone. The interaction between genotype

and level of physical activity accounted for approximately 10% of the variability in cognitive performance (see Figure 2). Follow-up analysis revealed that carriers were characterized by a significant positive relationship between age and perseverative errors ($F_{\text{change}}(1,17) = 10.034, p = .006, \beta = .391, r^2 = .371$), and a significant negative relationship between Yale index and perseverative errors ($F_{\text{change}}(1,16) = 4.353, p = .053, \beta = -.064, r^2 = .134$).

Percent nonperseverative errors.

Regression analysis revealed that age was positively related to percent nonperseverative errors and accounted for approximately 11% of the variability. No effect was revealed for genotype or physical activity alone. The interaction between genotype and level of physical activity for the percent nonperseverative errors was nonsignificant, but accounted for approximately 5% of the variability in cognitive performance (see Figure 3).

Nonperseverative errors.

Regression analysis revealed that age was positively related to nonperseverative errors and accounted for approximately 14% of the variability. No effect was revealed for genotype or physical activity alone. The interaction between genotype and level of physical activity accounted for approximately 10% of the variability in cognitive performance (see Figure 4). Follow-up analysis revealed that carriers were characterized by a significant positive relationship between age and nonperseverative errors ($F_{\text{change}}(1,17) = 10.411, p = .005, \beta = .531, r^2 = .380$) and a significant negative relationship between Yale index and nonperseverative errors ($F_{\text{change}}(1,16) = 4.785, p = .044, \beta = -.089, r^2 = .143$).

Percent total errors.

Regression analysis revealed that age was positively related to percent total errors and accounted for approximately 13% of the variability. No effect was revealed for genotype or physical activity alone. The interaction between genotype and level of physical activity accounted for approximately 8% of the variability in cognitive performance (see Figure 5). Follow-up analysis revealed that carriers were characterized by a significant positive relationship between age and percent total errors ($F_{\text{change}}(1,17) = 9.897, p = .006, \beta = .646, r^2 = .368$).

Total errors.

Regression analysis revealed that age was positively related to total errors and accounted for approximately 15% of the variability. No effect was revealed for genotype or physical activity alone. The interaction between genotype and level of physical activity accounted for approximately 12% of the variability in cognitive performance (see Figure 6). Follow-up analysis revealed that carriers were characterized by a significant positive relationship between age and total errors ($F_{\text{change}}(1,17) = 11.785, p = .003, \beta = .922, r^2 = .409$) and a significant negative relationship between Yale index and total errors ($F_{\text{change}}(1,16) = 5.522, p = .032, \beta = -.153, r^2 = .152$).

Trials administered.

Regression analysis revealed that age was positively related to the number trials administered and accounted for approximately 14% of the variability. No effect was revealed for genotype or physical activity alone. The interaction between genotype and level of physical activity accounted for approximately 9% of the

variability in cognitive performance (see Figure 7). Follow-up analysis revealed that carriers were characterized by a significant positive relationship between age and trials administered ($F_{\text{change}}(1,17) = 14.065, p = .002, \beta = 1.578, r^2 = .453$) and a significant negative relationship between Yale index and trials administered ($F_{\text{change}}(1,16) = 4.424, p = .052, \beta = -.220, r^2 = .119$).

Complete R^2 change and F change results can be found in Table 4.

Table 4

Summary of Hierarchical Regression Analysis for WCST variables. (N = 67)

| | Age | | | Gene | | | Yale Index | | | Gene X Index | | | Total R ² Change |
|---------------------------|-----------------|-----------------|-------------------------------|----------|-----------------|-------------------------------|------------|-----------------|-------------------------------|----------------|-----------------|-------------------------------|-----------------------------|
| | F-Change | R-Square Change | Standardized Beta Coefficient | F-Change | R-Square Change | Standardized Beta Coefficient | F-Change | R-Square Change | Standardized Beta Coefficient | F-Change | R-Square Change | Standardized Beta Coefficient | |
| % Perseverative Errors | 4.972* | <u>0.077</u> | 0.277 | 0.033 | <u>0.001</u> | 0.023 | 0.103 | <u>0.002</u> | 0.041 | 4.132* | <u>0.062</u> | -0.736 | <u>0.142</u> |
| % Nonperseverative Errors | 7.019** | <u>0.105</u> | 0.324 | 0.106 | <u>0.002</u> | -0.04 | 1.281 | <u>0.019</u> | -0.141 | 3.702 | <u>0.053</u> | -0.681 | <u>0.179</u> |
| Perseverative Errors | 7.028** | <u>0.105</u> | 0.324 | 0.07 | <u>0.001</u> | 0.033 | 0.004 | <u>0</u> | -0.008 | 7.197** | <u>0.1</u> | -0.934 | <u>0.206</u> |
| Nonperseverative Errors | 9.520** | <u>0.137</u> | 0.37 | 0.054 | <u>0.001</u> | 0.028 | 1.909 | <u>0.027</u> | -0.168 | 7.387** | <u>0.096</u> | -0.913 | <u>0.261</u> |
| % Total Errors | 9.026** | <u>0.131</u> | 0.362 | 0.001 | <u>0</u> | -0.003 | 0.225 | <u>0.003</u> | -0.059 | 5.742* | <u>0.079</u> | -0.831 | <u>0.213</u> |
| Total Errors | 10.225** | <u>0.146</u> | 0.382 | 0.076 | <u>0.001</u> | 0.033 | 0.685 | <u>0.01</u> | -0.101 | 9.235** | <u>0.118</u> | -1.012 | <u>0.275</u> |
| Trials Administered | 9.765** | <u>0.14</u> | 0.374 | 0 | <u>0</u> | 0 | 0.764 | <u>0.011</u> | -0.107 | 6.783* | <u>0.09</u> | -0.887 | <u>0.241</u> |

Notes: * p < .05

** p ≤ .01

Significant values bolded.

Amount of variance accounted for underlined.

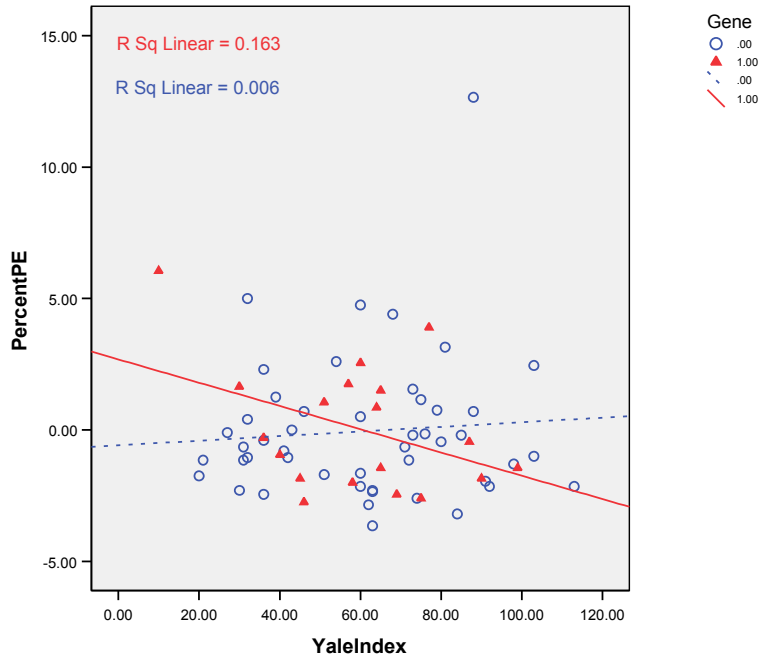


Figure 1. The vertical axis represents percentage perseverative errors, while the horizontal axis represents low to high levels of physical activity. The red triangles and solid red line represent APOE $\epsilon 4$ carriers, and the blue circles and dotted blue line represent non-carriers.

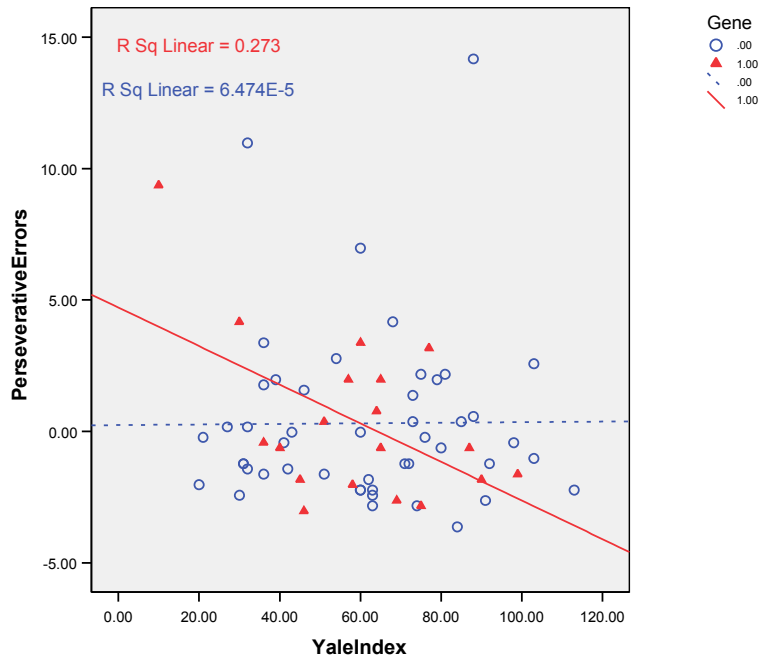


Figure 2. The vertical axis represents number of perseverative errors, while the horizontal axis represents low to high levels of physical activity. The red triangles and solid red line represent APOE $\epsilon 4$ carriers, and the blue circles and dotted blue line represent non-carriers.

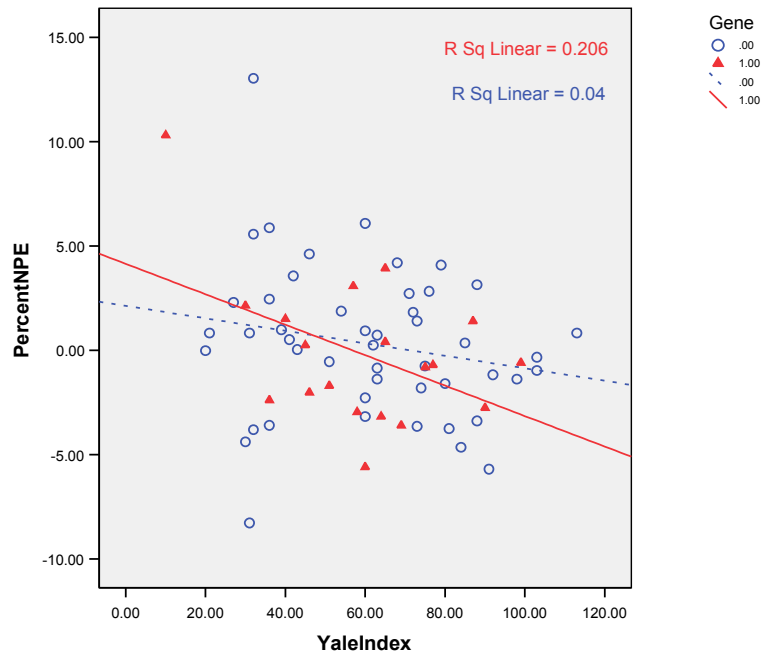


Figure 3. The vertical axis represents percentage of nonperseverative errors, while the horizontal axis represents low to high levels of physical activity. The red triangles and solid red line represent APOE ε4 carriers, and the blue circles and dotted blue line represent non-carriers.

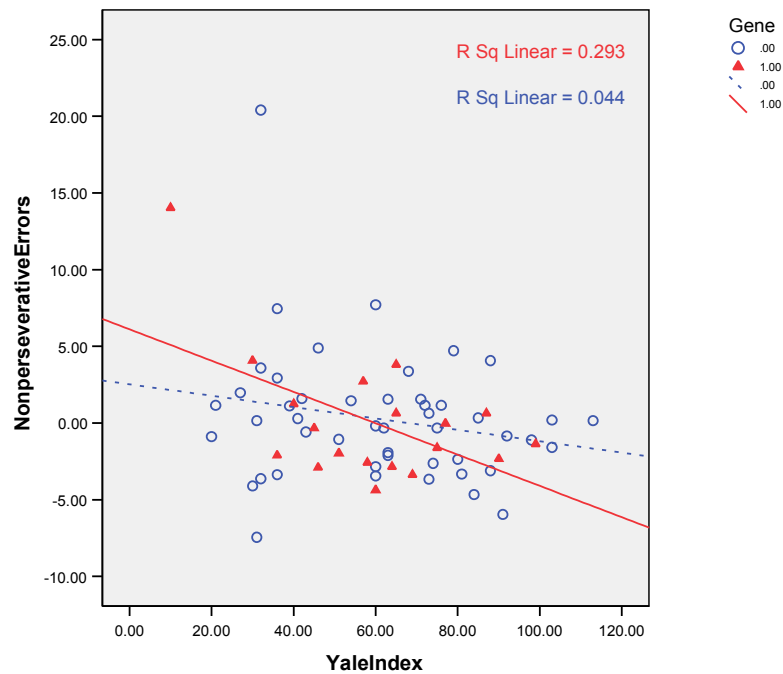


Figure 4. The vertical axis represents number of nonperseverative errors, while the horizontal axis represents low to high levels of physical activity. The red triangles and solid red line represent APOE ε4 carriers, and the blue circles and dotted blue line represent non-carriers.

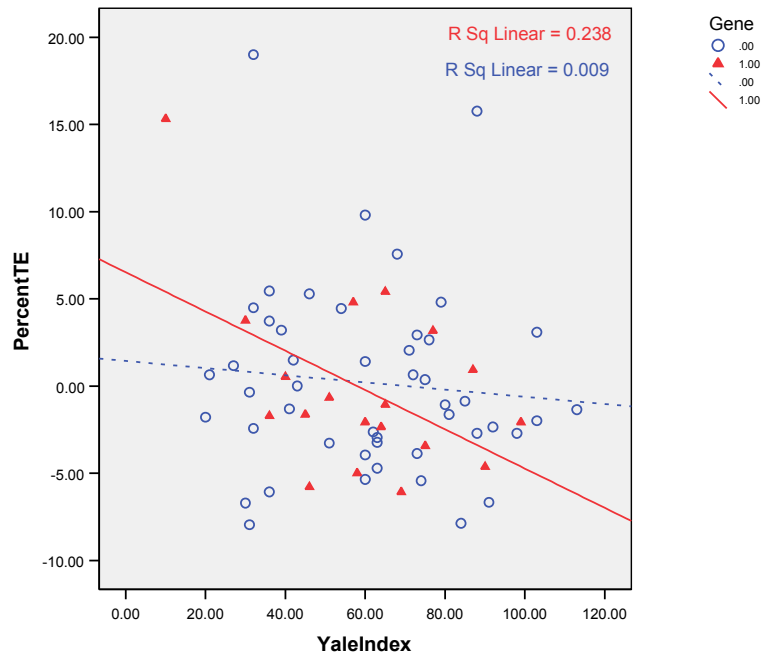


Figure 5. The vertical axis represents percentage of total errors, while the horizontal axis represents low to high levels of physical activity. The red triangles and solid red line represent APOE ϵ 4 carriers, and the blue circles and dotted blue line represent non-carriers.

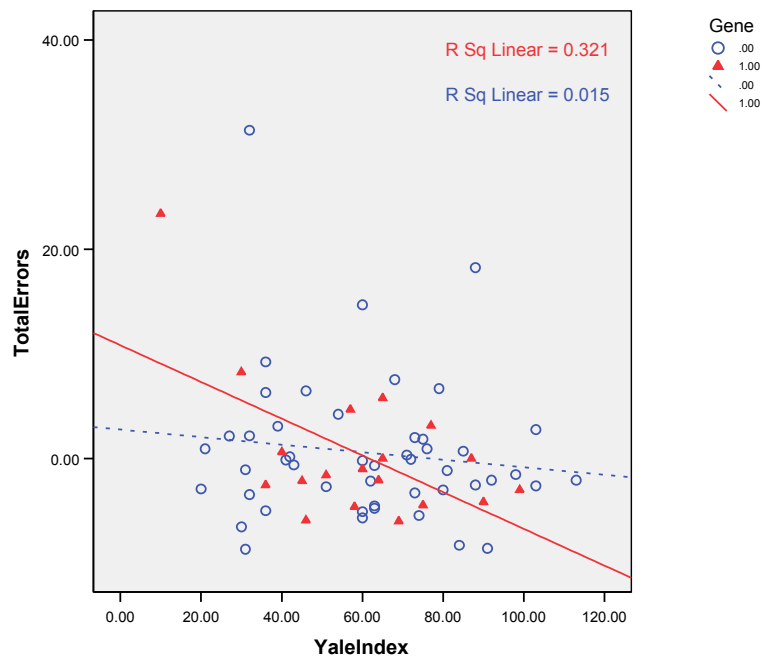


Figure 6. The vertical axis represents number of total errors, while the horizontal axis represents low to high levels of physical activity. The red triangles and solid red line represent APOE ϵ 4 carriers, and the blue circles and dotted blue line represent non-carriers.

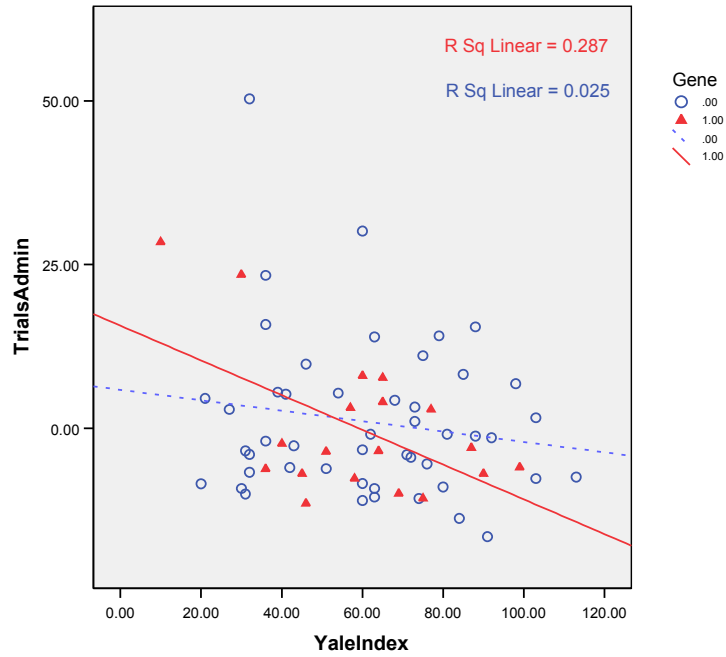


Figure 7. The vertical axis represents number of trials administered, while the horizontal axis represents low to high levels of physical activity. The red triangles and solid red line represent APOE $\epsilon 4$ carriers, and the blue circles and dotted blue line represent non-carriers.

Chapter 5: Discussion

Summary of Findings and Review of the Present Study

In the current study the relationship between physical activity and executive control functioning was examined in 67 adults aged 50 to 70, as modified by APOE ϵ 4 status (carriers and non-carriers). The Wisconsin Card Sorting Test was selected to measure executive control functioning due to its sensitivity to the integrity of frontal lobe function (Dywan et al. 1992; Hartman et al. 2001; Green 2000; Konishi et al. 1999; Royall et al. 2002). It was predicted that APOE ϵ 4 carriers would show the greatest benefit in executive control functioning from physical activity, because of the accelerated age-related neurocognitive decline associated with the ϵ 4 allele. That is, ϵ 4 carriers have more cognitive deficit and, therefore, are more likely to show apparent benefit from physical activity than non-carriers.

The percent and number of errors and trials administered increased as age increased on all seven of the WCST measures (i.e., percent perseverative errors, perseverative errors, percent nonperseverative errors, nonperseverative errors, percent total errors, total errors, and number of trials administered). This result is consistent with previous findings (Hartman et al. 2001; Green 2000; Lezak 1995). Neither genotype nor physical activity, alone, was significantly related to WCST performance. However, the interaction of these two variables did account for a significant degree of explained variance in executive performance. More specifically, and based on the hierarchical regression analyses, age accounted for approximately 7% to 15% of the variance for the seven WCST measures, while the interaction of genotype and physical activity uniquely accounted for approximately 5% to 12% of

the variance for the seven measures. Follow-up analyses that examined the relationship between cognitive performance and physical activity, separately for each genotype, revealed that as much as 32% of variance in cognition was accounted for by knowledge of physical activity in the $\epsilon 4$ carriers while only 4% was accounted for in the non-carriers. The interaction of genotype and physical activity revealed that both number and percentage of perseverative errors (as well as all other WCST non-executive measures) decreased in the carriers as physical activity level increased. No significant relationships between physical activity and cognitive performance were observed in the non-carriers although there were some similar directional trends as observed in the carriers.

These results are consistent with the epidemiological findings of Schuit et al. (2001) who examined the rate of cognitive decline in high- and low-active carriers and non-carriers of APOE $\epsilon 4$ over a three-year period. She and her colleagues found that the magnitude of cognitive decline was greatest in $\epsilon 4$ carriers, but it was remarkably attenuated by physical activity, while no such effect was noted in non-carriers. It is important to note that Schuit et al. (2001) examined a global index of cognitive functioning (i.e., MMSE), while the current study specifically examined the relationship of physical activity with executive control functioning. As such, the attenuation of executive decline, as found in the present study, may largely account for the findings reported by Schuit et al.

Physical activity was assessed in the current study using the Yale Physical Activity Survey. The employment of the Yale index score in the series of regression analyses was empirically based. That is, the obtained correlations between the four

measures derived from the YPAS (i.e., (1) kilocalories, (2) exercise, (3) vigorous activity, and (4) index) and the seven WCST variables (as well as the cognitive screening tools) were highest for the index. Since the Yale index score is relatively sensitive to intensity of physical activity, while this is not the case for the other variables, there may be a critical intensity-based threshold of physical activity for its benefits to be realized.

As stated above, genotype and physical activity, when considered alone, were not related to cognitive performance. The interaction of these two variables was significant and displays the benefits that physical activity has on the WCST performance of the high-active APOE ϵ 4 carriers. The presence of the APOE ϵ 4 allele leads to a build-up of amyloid plaques and neurofibrillary tangles in the brain that decreases blood flow and increases cortical atrophy (Saunders, 2001), while some investigators have reported hypometabolism or a decline in brain activity in ϵ 4 carriers, particularly in brain regions that are affected by Alzheimer's disease (Reiman et al., 2001). Due to the increased age-related cognitive decline that the presence of the ϵ 4 allele imposes, carriers stand to benefit more from physical activity than non-carriers who maintain relative integrity of neural structures and processes.

The focus on frontally mediated executive function was based on the work of West (1996) who originated the frontal lobe hypothesis of normal aging. This hypothesis states that the frontal lobe is the region of the brain that declines the fastest with age. The prefrontal cortex, which is largely involved with executive control functioning, begins to lose its ability to inhibit unwanted responses and working memory begins to decline. This decline in frontal lobe functioning may be

accelerated by the APOE ϵ 4 allele because of the plaques and tangles that form in the brain as a result of the alleles presence (Nathoo et al., 2003, Wasco, 2001). Along with a decrease in blood flow, the brain is unable to repair neurons and maintain structural integrity so ϵ 4 carriers would be expected to show more benefit than non-carriers.

Importantly, the Wisconsin Card Sorting Test (WCST) has proven to be an effective tool for measuring executive control functioning (Dywan et al., 1992; Hartman et al., 2001; Konishi et al, 1999; Royall et al., 2002). It is a test that is highly sensitive to age and education (Heaton et al., 1993; Plumet et al., 2005). Hierarchical regression, as used in the current study, revealed that age accounted for the largest percent of the variance on all seven of the WCST variables. The population was a high functioning group in that the average number of years of education was approximately 17 years and there was no evidence of cognitive impairment. As such, the detection of exercise-related benefits in such a group is remarkable as they provide a conservative test of the link between physical activity and cognitive function.

In the present study, the non-carriers characterized by low levels of physical activity did not differ significantly from those characterized by high activity in terms of cognitive performance. It is possible that low-active non-carriers may have been able to compensate due to their high level of education. The use of behavioral analysis did not reveal any difference in cognitive performance between low-active and high-active non-carriers due to physical activity. Though not significant, the results were in favor of the high-active non-carriers, which is more than likely due to

the benefits from being more physically active. However, significant differences may be revealed at a different level of measurement. For example, neuroimaging, as compared to behavioral analyses as employed in the present study, may reveal that high-active non-carriers are more efficient in terms of the magnitude of cerebral cortical activation when completing the task, while low-active non-carriers may require more activation and, therefore, less efficient cerebral cortical processes. This kind of benefit to the non-carriers would not be revealed at the behavioral level of analysis.

With the use of structural neuroimaging, Colcombe et al. (2003^b) were able to observe age-related decline in the frontal lobe. However, their study also revealed that aerobic fitness helped to preserve tissue density in the same region of the brain. This effect is likely pronounced in APOE ϵ 4 carriers, but has yet to be determined.

Since the low-active non-carriers do not have the additional effect of APOE ϵ 4 to go along with age-related decline, they may be able to compensate for their lack of benefits from physical activity with cognitive reserve developed from education. As mentioned above, neuroimaging could reveal if the task was more effortful for low-active relative to high-active non-carriers.

Benefits of Physical Activity on the Brain

The current study reinforces the results of previous research, which has revealed the positive effects that physical activity has on the brain. The increase in blood flow and oxygen to the brain help to keep the brain healthy while the increase in synapses preserve the brains neural networks (Black et al., 1990). The neurotrophic factor expression from physical activity improves the functioning of

neurotransmitters throughout the brain, helping to maintain cognitive functioning (Neeper et al, 1996; Cotman & Engesser-Cesar, 2002; Van Hoomissen, 2005). In the process of normal aging in older adults, these cognitive benefits help to decrease the rate of cognitive decline, especially in the frontal lobe and prefrontal cortex, areas responsible for executive control functioning (Colcombe & Kramer, 2003). With these regions of the brain being the fastest to decline with age, they benefit the most from physical activity (Hall et al., 2001). These benefits are even more important for individuals who are heterozygous or homozygous for APOE ϵ 4 because of the detrimental effect this gene can have on the overall health and functioning of the brain. The enhanced expression of BDNF mRNA in the hippocampus and cerebral cortex directly benefit the regions of the brain that are most effected by APOE ϵ 4 (Cotman & Engesser-Cesar, 2002; Neeper et al., 1996; Reiman et al., 2001).

In addition, Dywan et al. (1992) reported that participants without any reported health problems or medications performed significantly better on the WCST (i.e., exhibited a lower percentage of perseverative errors) than participants with cardiovascular problems such as hypertension, coronary heart disease, transient ischemic attacks, or use of medications for these problems. Because participation in physical activity is associated with cardiovascular health, the present findings in the ϵ 4 carriers may be explained by improved circulation and lowering of systemic blood pressure, which would also affect cerebrovascular integrity.

Limitations and Future Studies

The current investigation is a cross-sectional design, which does not allow one to examine the participants' physical activity over the life-span. While the

participants' reports of physical activity was stable for the five years prior to the study, it does not tell us if cognitive performance in our middle-aged population is effected by low or high levels of physical activity during young adulthood and earlier. An intervention study would provide a more direct examination of the cause-effect relationship between physical activity and cognitive performance, while a longitudinal design would provide follow-up data on how the participants are progressing through older adulthood. The use of neuroimaging would yield stronger evidence of the condition of the frontal lobe and hippocampus, and reveal the areas of the brain that are activated during the executive control task. Furthermore, such a measurement approach would reveal how effortful it is for the participant, and provide stronger evidence on the interaction between physical activity and the APOE ϵ 4 genotype.

Implications for Public Health

These results are relevant to public health concerns pertaining to cognitive impairment and the development of dementia, more specifically Alzheimer's Disease, in the older population (Alzheimer's Association, 2004^a; Alzheimer's Association, 2004^b). A longitudinal study conducted by Rovio et al. (2005) reported that participation in leisure-time physical activity at least twice a week during midlife decreased the risk of dementia. Similar to the findings in the current study, their results were more pronounced in APOE ϵ 4 carriers. Physical activity provides us with a supplement or alternative to medication as a way of decreasing the rate of cognitive decline, and preventing or at least delaying the onset of dementia.

Appendix A



UNIVERSITY OF MARYLAND

INSTITUTIONAL REVIEW BOARD

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College Park, Maryland 20742-5121
301.405.4212 TEL 301.314.1475 FAX
irb@deans.umd.edu
www.umresearch.umd.edu/IRB

November 10, 2006

MEMORANDUM

Renewal Application Approval Notification

To: Dr. Brad Hatfield
Dr. Stephen Roth
Linzi Jones
Michelle Costanzo
Andy Ludlow
Joanne Zimmerman
Ming-Jung Woo
Joe Hearn
Ryan Conery
Department of Kinesiology

From: Roslyn Edson, M.S., CIP, *RAE*
IRB Manager
University of Maryland, College Park

Re: **IRB Application Number:** 05-0011
Project Title: "Age, Physical Activity, Genotype, and Cognitive Function"

Approval Date: October 27, 2006

Expiration Date: October 27, 2007

Type of Application: Renewal

Type of Research: Non-exempt

**Type of Review
For Application:** Expedited

The University of Maryland, College Park Institutional Review Board (IRB) approved your IRB application. The research was approved in accordance with 45 CFR 46, the Federal Policy for the Protection of Human Subjects, and the University's IRB policies and procedures. Please reference the above-cited IRB application number in any future communications with our office regarding this research.

Recruitment/Consent: For research requiring written informed consent, the IRB-approved and stamped informed consent document is enclosed. The IRB approval expiration date has been stamped on the informed consent document. Please keep copies of the consent forms used for this research for three years after the completion of the research.

Continuing Review: If you want to continue to collect data from human subjects or to analyze private, identifiable data collected from human subjects after the approval expiration date indicated above, you must submit a renewal application to the IRB Office . (Continued)

Appendix A (continued)

at least 30 days before the approval expiration date.

Modifications: Any changes to the approved protocol must be approved by the IRB before the change is implemented, except when a change is necessary to eliminate apparent immediate hazards to the subjects. If you would like to modify the approved protocol, please submit an addendum request to the IRB Office. The instructions for submitting an addendum request are posted on the IRB website at: http://www.umresearch.umd.edu/IRB/irb_Addendum%20Protocol.htm.

Unanticipated Problems Involving Risks: You must promptly report any unanticipated problems involving risks to subjects or others to the IRB Manager at 301-405-0678 or redson@umresearch.umd.edu.

Student Researchers: Unless otherwise requested, this IRB approval document was sent to the Principal Investigator (PI). The PI should pass on the approval document or a copy to the student researchers. This IRB approval document may be a requirement for student researchers applying for graduation. The IRB may not be able to provide copies of the approval documents if several years have passed since the date of the original approval.

Additional Information: Please contact the IRB Office at 301-405-4212 if you have any IRB-related questions or concerns.

Appendix B

Initials _____ Date _____
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CONSENT FORM

| | |
|---|---|
| Project Title | Age, Physical Activity, Genotype, and Cognitive Function (Revised October 12, 2006) |
| | IRB Project # 05 - 0011 |
| Why is this research being done? | <p>This is a research project being conducted by Dr. Bradley Hatfield and his co-investigators at the University of Maryland, College Park. We are inviting you to participate in this research project because you belong to one of our target groups of healthy men and women between the age of 50 and 70. Some groups have a high level of regular physical activity while others have a high level of social or intellectual activity. The purpose of this research project is to examine the effects of activity on brain performance while considering genetic predictors of cognitive decline. We hope to strengthen the developing case that even before any behavioral changes occur there may be more subtle changes in the brain only measurable by neuroimaging. The age group in this study may represent a window of opportunity to detect these changes and offer appropriate interventions to those at increased risk.</p> |
| What will I be asked to do? | <p>The procedures involve 3 phases, including 2 to 3 visits to the University of Maryland College Park campus, each for about 2 hours, and possibly 1 visit to Johns Hopkins Medical Institution or Georgetown University. All participants will complete 2 local visits, while a smaller group of participants will complete 3 local visits and 1 visit to Johns Hopkins or Georgetown. The planned schedule follows this section.</p> <p>Phase 1 will take place in the Health and Human Performance building and the Campus Recreation Center on the University of Maryland campus. Your participation requires filling out brief physical activity surveys, a screening survey for depression, a health history and family history of Alzheimer's disease survey, and surveys to estimate your psychological stress levels. You will be asked to provide a small blood sample (approximately 4 tablespoons) from an arm vein in sterile laboratory conditions for DNA testing. During phase 1 you will also complete an interview to assess your memory. This will involve questions such as: asking you to identify pictures of common objects, asking you to remember words or letters, and asking you about your recall of historical events that occurred during your lifetime. You will be administered a questionnaire to assess the amount of physical activity that you engage in, as well as two questionnaires assessing hobbies and daily mental stimulation. You will also have your height, weight, blood pressure, and skinfold body fat measured. If you are physically able to do so, you will be asked to complete a 1-mile timed walk test to measure your physical fitness. This first session should take about one to two hours.</p> <p>Following phase 1 you will be asked to participate in phase 2, also in the Health and Human Performance building on the University of Maryland campus. Upon your return, you will complete cognitive tasks in a computerized format to assess verbal memory, working memory, and inhibition. The verbal memory task involves trying to remember strings of letters presented on a screen in front of you, and that the working memory task involves matching cards presented on the screen in front of you. The inhibition task involves selecting a target arrow from distracting arrows shown along side or reading a list of words printed in distracting colors. You will respond during the tasks by pressing buttons placed in front of you or by reading aloud. The phase 2 session should take about one to two hours, and you will not be asked to do anything that requires physical activity.</p> <p>You will be asked to give permission to the research team to take photos during your participation. These photos will be used in scholarly and professional presentations. If you give permission for photos, you will not be identified in the case that your photos are used.</p> <p><input type="checkbox"/> YES I give permission to the research team to take and use photos of my participation. <input type="checkbox"/> NO I do not give permission for any photos of my participation.</p> |

Appendix B (continued)

Initials _____ Date _____
Page 2 of 4

DNA: Your DNA will be isolated from your blood cells and analyzed for the Apolipoprotein E (ApoE), BDNF, and CYP46 genes, which are related to memory decline in aging. A separate analysis will examine the ends of the DNA strands in an area called telomeres, to measure their length. The length of the telomere is affected (shortened) by long term high levels of psychological stress. Your DNA samples will be kept for a period of 15 years before being destroyed since there may be new genes of interest discovered in the near future. If in the future investigators want to examine other sites on your DNA, they can only do so with your written permission. If information regarding the significance of these genetic tests becomes established in the future, every attempt will be made to inform you of the new findings. **Your DNA information will not be disclosed to you, but you may be referred to a clinical facility if you wish to seek further information regarding your own risk for cognitive impairment.**

You now have the right to refuse permission for your DNA to be used in future studies and still participate in the current project. By checking the first option, the investigators have permission to contact you for consent to use additional DNA information, and that by checking the second option you are refusing the right for investigators to use your DNA for future studies:

YES Investigators may contact me regarding the use of my DNA for future studies.

NO Investigators may not contact me to ask permission to use my DNA in future studies.

MEG: Following phase 2 you may or may not qualify for phase 3. If you are contacted for phase 3 you will visit the Cognitive Neuroscience Linguistics Laboratory to complete two cognitive tasks assessing your verbal memory and your ability to shift strategy. The verbal memory task involves trying to remember strings of letters presented on a screen in front of you, and that the strategy shifting task involves identifying odd shapes and letters presented on the screen in front of you. You will respond during the tasks by pressing buttons placed in each hand. If you are selected to visit the Cognitive Neuroscience Linguistics Laboratory, you will perform these cognitive tasks during a non-invasive neuroimaging procedure called a magnetoencephalogram (MEG). The phase 3 session should take about one to two hours, and you will not be asked to do anything that requires physical activity.

MRI: If you qualify for phase 3 you will have a magnetic resonance image (MRI) exam at the Johns Hopkins Medical Institution in Baltimore, MD or at Georgetown University in Washington, DC. The MRI exam will take approximately 45 minutes. Prior to your exam, you will be asked to complete a standard questionnaire. The purpose of this questionnaire is to ensure that you are able to safely enter the MRI area. If you have a history of metal in your head or eyes, you cannot take part in this phase of the study. To start your MRI test, you will lie on a padded table. A Head/Neck Coil will be placed around your head, face, and neck. The coil is necessary to help the MRI machine take pictures. The table on which you are lying will be moved to the center of an MRI magnet, which looks like a long narrow tube. Even though the tube is open, some people feel confined in small places. If this bothers you, please notify the MRI staff. You may end your participation in this study at any time by telling the MRI staff. When MRI pictures are taken, radio-signals and magnetic fields are used. When this happens, it is normal for the MRI machine to make loud, banging, and clicking noises. You will be asked to wear earplugs or headphones for your comfort during the exam.

During the exam, the MRI staff is able to see and hear you. You will be able to hear the MRI staff. The MRI staff will be talking to you throughout your MRI exam and may issue simple instructions regarding holding your breath, maintaining position, etc. You will generally be requested to lie perfectly still throughout the exam.

Appendix B (continued)

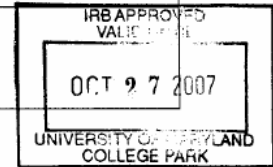
Initials _____ Date _____
Page 3 of 4

| | <table border="1"> <thead> <tr> <th data-bbox="521 338 816 373">Phase 1 1-2 hours</th> <th data-bbox="816 338 1039 373">Phase 2 1-2 hours</th> <th data-bbox="1039 338 1334 373">Phase 3 2-3 hours total</th> </tr> </thead> <tbody> <tr> <td data-bbox="521 373 816 520">UMD campus, HHP building</td> <td data-bbox="816 373 1039 520">UMD campus, HHP building</td> <td data-bbox="1039 373 1334 520">UMD campus, CNL lab Johns Hopkins, Baltimore or Georgetown University, Washington</td> </tr> <tr> <td data-bbox="521 520 816 785"> Consent, blood sample, surveys of demographics, family history of Alzheimer's, Memory tests Depression survey Physical activity survey Cognitive activity surveys Stress surveys Blood pressure, height, weight, & skinfold body fat testing Rockport 1-mile walk test </td> <td data-bbox="816 520 1039 785"> Verbal memory test Inhibition test Working memory test </td> <td data-bbox="1039 520 1334 785"> MEG testing Verbal memory test Strategy shifting test MRI testing </td> </tr> </tbody> </table> | Phase 1 1-2 hours | Phase 2 1-2 hours | Phase 3 2-3 hours total | UMD campus, HHP building | UMD campus, HHP building | UMD campus, CNL lab Johns Hopkins, Baltimore or Georgetown University, Washington | Consent, blood sample, surveys of demographics, family history of Alzheimer's, Memory tests Depression survey Physical activity survey Cognitive activity surveys Stress surveys Blood pressure, height, weight, & skinfold body fat testing Rockport 1-mile walk test | Verbal memory test Inhibition test Working memory test | MEG testing Verbal memory test Strategy shifting test MRI testing |
|--|---|---|-------------------|-------------------------|--------------------------|--------------------------|---|--|--|--|
| Phase 1 1-2 hours | Phase 2 1-2 hours | Phase 3 2-3 hours total | | | | | | | | |
| UMD campus, HHP building | UMD campus, HHP building | UMD campus, CNL lab Johns Hopkins, Baltimore or Georgetown University, Washington | | | | | | | | |
| Consent, blood sample, surveys of demographics, family history of Alzheimer's, Memory tests Depression survey Physical activity survey Cognitive activity surveys Stress surveys Blood pressure, height, weight, & skinfold body fat testing Rockport 1-mile walk test | Verbal memory test Inhibition test Working memory test | MEG testing Verbal memory test Strategy shifting test MRI testing | | | | | | | | |
| <p>What about confidentiality?</p> | <p>To help protect your confidentiality, this consent document and your health history form will be kept in a locked cabinet, separate from all the other information you provide. All other information collected in this study is numerically coded, and your name will not be identified at any time. The information collected on the questionnaires and memory tests will be kept in a different locked cabinet that can be accessed only by the research team. Your DNA samples will be stored in a locked refrigerator, which can be accessed only by the research team in the Functional Genomics Laboratory in the Health and Human Performance building at the University of Maryland. All information collected will be kept for a period of 15 years, at which point it will be destroyed. When we write a report or article about this research project, we will present grouped results only; your identity will be protected to the maximum extent possible.</p> | | | | | | | | | |
| <p>What are the risks of this research?</p> | <p>There may be some risks from participating in this research study. There is risk of bruising and infection associated with blood drawing. The risk will be minimized by using sterile techniques and by having experienced personnel draw all blood samples. There are no known risks associated with the MEG testing. The procedure measures magnetic fields generated by your own brain activity, and the machine itself emits no magnetic fields and poses no discomfort.</p> <p>The effects of magnetic fields in an MRI scanner have been extensively studied, and there are no known significant risks with an MRI exam. You may, however, be bothered by feelings of confinement (claustrophobia), and by the noise made by the magnet during the procedure. You will be asked to wear earplugs or earphones while in the magnet. You may not participate in this study if you have a pacemaker, an implanted defibrillator or certain other implanted electronic or metallic devices. It is important for you to advise the MRI staff if you have had brain surgery for a cerebral aneurysm, or if you have implanted medical or metallic devices, shrapnel, or other metal, such as metal in your eye. There are no known risks associated with having MRI imaging without contrast during pregnancy. There may be risks that are unknown.</p> | | | | | | | | | |

Appendix B (continued)

Initials _____ Date _____
Page 4 of 4

| | | | | | | | |
|---|--|------------------------|--|-----------------------------|--|----------------------------|--|
| <p>What are the benefits of this research?</p> | <p>This research is not designed to help you personally, but the results may help the investigators learn more about aging, genes, physical activity, and memory. The results from this study will be used to plan future projects based on the most important and relevant findings.</p> <p>The research team will provide short reports of the findings from the project as they become available. These reports will not include details about individuals, but may provide information and perspective for discussion with your health care practitioner. You may subscribe to this communication by email list serv. Your contact information will be kept private within the context of the research project, and will not be otherwise shared or sold. If you decline to join this list, you may receive the reports by U.S. mail.</p> <p><input type="checkbox"/> YES You may add my email to the group contact list. <input type="checkbox"/> NO You may not add my email to the group contact list.</p> | | | | | | |
| <p>Do I have to be in this research? May I stop participating at any time?</p> | <p>Your participation in this research is completely voluntary. You may choose not to take part at all. If you decide to participate in this research, you may stop participating at any time. If you decide not to participate in this study or if you stop participating at any time, you will not be penalized. You are able to ask questions or to withdraw from participation at any time without penalty. You may refuse to answer any questions on the surveys that make you uncomfortable. You must be given a copy of this consent form for your records.</p> | | | | | | |
| <p>Is any medical treatment available if I am injured?</p> | <p>The University of Maryland does not provide any medical, hospitalization or other insurance for participants in this research study, nor will the University of Maryland provide any medical treatment or compensation for any injury sustained as a result of participation in this research study, except as required by law.</p> | | | | | | |
| <p>What if I have questions?</p> | <p>This research is being conducted by Dr. Bradley Hatfield, in the Department of Kinesiology, at the University of Maryland, College Park. If you have any questions about the research study itself, please contact: Dr. Bradley Hatfield at: 2134C HHP Bldg. Dept. of Kinesiology, College Park, MD 20742; office (301) 405-2485; email bhafiel@umd.edu .</p> <p>You may also contact: Institutional Review Board Office, University of Maryland, College Park, Maryland, 20742; (e-mail) irb@deans.umd.edu; (telephone) 301-405-0678</p> <p>This research has been reviewed according to the University of Maryland, College Park IRB procedures for research involving human subjects.</p> | | | | | | |
| <p>Statement of Age of Subject and Consent</p> | <p>Your signature indicates that:</p> <ul style="list-style-type: none"> you are at least 18 years of age; the research has been explained to you; your questions have been fully answered; and you freely and voluntarily choose to participate in this research project. | | | | | | |
| <p>Signature and Date</p> | <table border="1" style="width: 100%;"> <tr> <td style="width: 10%;">NAME OF SUBJECT</td> <td style="width: 90%;"></td> </tr> <tr> <td>SIGNATURE OF SUBJECT</td> <td></td> </tr> <tr> <td>D A T E</td> <td></td> </tr> </table> | NAME OF SUBJECT | | SIGNATURE OF SUBJECT | | D A T E | |
| NAME OF SUBJECT | | | | | | | |
| SIGNATURE OF SUBJECT | | | | | | | |
| D A T E | | | | | | | |



Appendix C

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

Blood pressure pills

Cortisone

Cough medicine

Digitalis

Hormones

Insulin or diabetic pills

Iron or blood medications

Laxatives

Sleeping pills

Estrogen

Other medications not listed _____

Tranquilizers

Weight reducing pills

Blood thinning pills

Dilantin

Allergy shots

Water pills

Antibiotics

Barbituates

Phenobarbital

Thyroid medicine

Vitamin E

Have you ever had any conditions or injuries which required brain surgery? Yes _____ No _____

If so, please explain _____

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 _____

Appendix C (continued)

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 previous five decades.

____ Using the scale below, 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

- 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

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 you answered yes to any of these questions, please answer the following 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 how many. Do not give names.

Parents Yes ____ No ____ How many _____

Siblings Yes ____ No ____ How many _____

Grandparents Yes ____ No ____ How many _____

Appendix D

Cambridge Cognitive Examination (CAMCOG)

25

The CAMDEX-R Schedule

Section B Cognitive examination – CAMCOG

Before commencing, make sure you have the following items:

| | | |
|----------------------------------|-----------------|---|
| Booklet | Pencil | Wristwatch (with a second hand for timing) |
| Blank sheet of paper (A4) | Envelope | Coins: two coins of different value |

Ensure that calendars and clocks are not available to assist subjects in answering questions about date and time.

This section contains all 19 items of the Mini-Mental State Examination of Folstein et al. (1975). Some, but not all of these items are used in scoring the more comprehensive Cambridge Cognitive Examination (CAMCOG). A list of the items comprising each of these examinations is set out on pp. 65–66

It is important that you speak slowly and clearly. If the subject appears not to have heard or understood, repeat the question (unless the item specifically prohibits repetition).

Do not give correct answer if a wrong answer or no answer is given.

Make a note of any unusual responses including extra memory items recalled.

Coding: This section differs from other sections of the CAMDEX in that subjects who don't know, refuse to answer or give a silly answer are given a score of 0 (not 8), which is equivalent to giving an incorrect answer. Where a score of 9 or 99 is recorded, indicate why the question was not asked.

Write something on every question.

I am going to ask you some questions now which have to do with your memory and concentration. Some of them may seem rather easy, others may be difficult, but we need to ask everyone the same questions.

Orientation *Note the time at beginning: _____*

Time

| | | | |
|----------------------------------|-----------|---|---|
| 139. What day of the week is it? | Incorrect | 0 | |
| | Correct | 1 | 9 |

What is the date today?

| | | | |
|-----------|-----------|---|---|
| 140. Date | Incorrect | 0 | |
| | Correct | 1 | 9 |

| | | | |
|------------|-----------|---|---|
| 141. Month | Incorrect | 0 | |
| | Correct | 1 | 9 |

| | | | |
|-----------|-----------|---|---|
| 142. Year | Incorrect | 0 | |
| | Correct | 1 | 9 |

| | | | |
|--------------------------|-----------|---|---|
| 143. What is the season? | Incorrect | 0 | |
| | Correct | 1 | 9 |

*Allow flexibility when season changes, e.g. for northern hemisphere:
 March = winter/spring: June = spring/summer
 September = summer/autumn: December = autumn/winter*

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Appendix D (continued)

| Place | | | |
|-----------------|--|----------------------|----------------|
| 144. | Can you tell me where we are now? For instance, what county (state) are we in? | Incorrect | 0 |
| | | Correct | 1 9 |
| 145. | What is the name of this town (city)? | Incorrect | 0 |
| | | Correct | 1 9 |
| 146. | What are two main streets nearby (or near your home)? | Incorrect | 0 |
| | | Correct | 1 9 |
| 147. | What floor of the building are we on? | Incorrect | 0 |
| | NA | Correct | 1 9 |
| 148. | What is the name of this University? | Incorrect | 0 |
| | | Correct | 1 9 |

If tested at home, the address must include enough information for mail to arrive

| Language | | | |
|---|--|-----------------|-----|
| Comprehension: Motor response | | | |
| <i>If the subject does not complete the full sequence then the whole instruction may be repeated, without change in tone or tempo, to ensure that it has been heard and understood. Prompting and coaching stage by stage are not allowed</i> | | | |
| I am going to ask you to carry out some actions, so please listen carefully | | | |
| 149. | Please nod your head. | Incorrect | 0 |
| | | Correct | 1 9 |
| 150. | Touch your right ear with your left hand. | Incorrect | 0 |
| | | Correct | 1 9 |
| 151. | Before looking at the ceiling please look at the floor. | Incorrect | 0 |
| | | Correct | 1 9 |
| 152. | Tap each shoulder twice with two fingers keeping your eyes shut. | Incorrect | 0 |
| | | Correct | 1 9 |
| Comprehension: Verbal response | | | |
| I am going to ask you some questions and would like you to answer 'yes' or 'no' | | | |
| 153. | Is this place a hotel? | Incorrect | 0 |
| | | Correct ('no') | 1 9 |
| 154. | Are villages larger than towns? | Incorrect | 0 |
| | | Correct ('no') | 1 9 |
| 155. | Was there wireless/radio in this country before television was invented? | Incorrect | 0 |
| | | Correct ('yes') | 1 9 |

Appendix D (continued)

| The CAMDEX-R Schedule | | 27 |
|---|--|-----------|
| Expression: Naming | | |
| <p><i>In questions 156 and 157 accurate naming is needed. Descriptions of function or approximate answers are not acceptable. Acceptable answers may depend on local usage. Some items may have more than one correct name, as has been indicated. Errors include description of function (e.g. 'used for telling the time' for watch) and approximate answers (e.g. 'weighing machine' for scales; 'bag' or 'carrier' for suitcase; 'light' for lamp).</i></p> <p><i>In the case of approximate answers, you should say 'Can you think of another word for it?'</i></p> <p><i>Tick each item correctly named in questions 156 and 157 and enter number correct under Total</i></p> | | |
| 156. Show pencil | Pencil | — |
| What is this called? | | |
| Show wristwatch | Wristwatch | — |
| What is this called? | | |
| | Total | [] 9 |
| <hr/> | | |
| 157. I am going to show you some objects. Please tell me the name of each one. Show 'Pictures for naming' in booklet. | Shoe, sandal | — |
| | Typewriter | — |
| | Scales | — |
| | Suitcase, Portmanteau | — |
| | Barometer. | — |
| | Table lamp, lamp | — |
| | Total | [] 9 |
| <hr/> | | |
| Expression: Fluency | | |
| 158. Name as many different animals as you can think of. You will have one minute to do this. | Number correct | [][][] |
| <p><i>Only if subject asks for clarification, explain that animals include birds, fish, insects, humans, etc. If subject gets stuck, encourage him/her with 'Can you think of any more?' Record number correct in one minute (repetitions not to be counted but age and sexual variants should be counted e.g. calf, cow, bull)</i></p> <p><i>List all items</i></p> | <p>Note: Recode:</p> <p>For CAMCOG score</p> <p>0 = 0</p> <p>1-4 = 1</p> <p>5-9 = 2</p> <p>10-14 = 3</p> <p>15-19 = 4</p> <p>20-24 = 5</p> <p>25+ = 6</p> | [] 9 |
| <hr/> | | |
| Expression: Definitions | | |
| <i>For questions 159-162, acceptable answers may depend on local usage</i> | | |
| 159. What do you do with a hammer? | Incorrect | 0 |
| | Any correct use | 1 9 |
| | <i>Hit is not enough. Some other detail should be given <u>without prompting.</u></i> | |
| <hr/> | | |
| 160. Where do people usually go to buy medicine? | Shop (if unable to specify) | 0 |
| | CVS, pharmacy | 1 9 |
| <hr/> | | |
| <i>In questions 161-162 a general (abstract) definition scores 2 and a specific or limited definition scores 1. Examples are given beside each score</i> | | |
| 161. What is a bridge? | Incorrect | 0 |
| | Cross the bridge | 1 |
| | Goes across a river etc | 2 9 |

Appendix D (continued)

| | | | |
|--------------------------|--|---|---|
| 162. What is an opinion? | Incorrect | 0 | |
| | A good opinion of someone | 1 | |
| | A person's ideas about something; what you think | 2 | 9 |

Expression: Repetition

Only one presentation is allowed so it is essential that you read the phrase clearly and slowly, enunciating all the S's.

| | | | |
|--|-----------|---|---|
| 163. I am going to say something and I would like you to repeat it after me: 'No ifs, ands or buts'. | Incorrect | 0 | |
| | Correct | 1 | 9 |

Code 1 only if entire phrase is correct

Memory

Recall

| | | | |
|---|------------------|-------|---|
| 164. Can you tell me what were the objects in the coloured pictures I showed you a little while ago? <i>Either descriptions or names are acceptable. Tick each item correctly recalled and enter number correct under Total. If subject previously gave an incorrect name in question 157 but recalls it at this stage, score as correct</i> | Shoe, sandal | — | |
| | Typewriter | — | |
| | Scales | — | |
| | Suitcase | — | |
| | Barometer | — | |
| | Table lamp, lamp | — | |
| | Total | [...] | 9 |

Recognition

Show: 'Pictures for recognition' in booklet
Tick each item correctly recognised and enter number correct under Total

| | | | |
|--|------------------|-------|---|
| 165. Which of these did I show you before? | Shoe, sandal | — | |
| | Typewriter | — | |
| | Scales | — | |
| | Suitcase | — | |
| | Barometer | — | |
| | Table lamp, lamp | — | |
| | Total | [...] | 9 |

Retrieval of remote information

Note: Questions 166–171 should be asked if the subject was born before 1940. Questions 166a–171a should be asked if the subject was born after 1940.

Now I am going to ask you some questions about the past

| | | | |
|---|------------------|---|---|
| 166. When did the First World War begin? (Within 1 year) | Incorrect | 0 | |
| | 1914 (in Europe) | 1 | 9 |

| | | | |
|--|------------------|---|---|
| 167. When did the Second World War begin? (Within 1 year) | Incorrect | 0 | |
| | 1939 (in Europe) | 1 | 9 |

NA

| | | | |
|---|-----------|---|---|
| 168. Who was the leader of the Germans in the Second World War? | Incorrect | 0 | |
| | Hitler | 1 | 9 |

Appendix D (continued)

| The CAMDEX-R Schedule | | 29 | |
|---|---|--------|---|
| 169. Who was the leader of the Russians in the Second World War? | Incorrect Stalin | 0 1 | 9 |
| NA | | | |
| 170. What was Mae West famous for? <i>Any appropriate verbal or non-verbal answer which indicates memory</i> | Incorrect Entertainer, Film Star, Life jacket | 0 1 | 9 |
| 171. Who was the famous flyer whose son was kidnapped? <i>Close approximations to the name are acceptable</i> | Incorrect Lindbergh | 0 1 | 9 |
| <i>Questions 166a-171a to be asked if subject was born after 1940</i> | | | |
| 166a. Who was the US President who was shot in Texas? | Incorrect John F. Kennedy | 0 1 | 9 |
| 167a. What is Yoko Ono famous for? | Incorrect Wife of Beatle, John Lennon | 0 1 | 9 |
| 168a. Who was the first man to set foot on the moon? | Incorrect Neil Armstrong | 0 1 | 9 |
| 169a. What was Edmund Hillary famous for? | Incorrect First to reach summit of Mt Everest | 0 1 | 9 |
| 170a. Who was the first woman Prime Minister of India? | Incorrect Indira Ghandhi | 0 1 | 9 |
| 171a. Who was the famous cinema actress who married Prince Rainier of Monaco? <i>Close approximations to the name are acceptable</i> | Incorrect Grace Kelly | 0 1 | 9 |
| Retrieval of recent information | | | |
| 172. What is the name of the president of the United States? | Incorrect Correct | 0 1 | 9 |
| 173. Who is the vice president? | Incorrect Correct | 0 1 | 9 |
| 174. What is the name of the Prime Minister of England? <i>For one month after an election, if the name of the former PM is given, ask 'Is he/she still Prime Minister?'</i> | Incorrect Correct | 0 1 | 9 |
| 175. What has been in the news in the past week or two? <i>If a general answer is given, e.g. 'war' ask for details</i> Write down answer | Incorrect Correct | 0 1 | 9 |

Appendix D (continued)

Registration

I am going to name three objects. After I have finished saying all three, I want you to repeat them. Remember what they are because I am going to ask you to name them again in a few minutes.

| | | | |
|---|--------------|-------|----------|
| 176. Name the following three objects taking one second to say each: <i>apple, table, penny</i> . Tick which are correct on the <i>first</i> attempt and enter number correct under total. | Apple | — | |
| | Table | — | |
| | Penny | — | |
| | Total | [...] | 9 |

| | | | |
|---|-------------------|-------|----------|
| 177. If any errors or omissions are made on the first attempt, repeat all the names until subject learns all three (maximum of five repeats). Record number of repeats (record 0 if all correct on first attempt) | Number of repeats | [...] | 9 |
|---|-------------------|-------|----------|

Attention/concentration

| | | | |
|---|--------------------|----------|----------|
| 178. Now I would like you to count backwards from 20. | Two or more errors | 0 | |
| | One error | 1 | |
| | Correct | 2 | 9 |

| | | | |
|--|--------------|-------|----------|
| 179. Now I would like you to take 7 away from 100. Now take 7 away from the number you get. Now keep subtracting 7 until I tell you to stop. | 93 | — | |
| | 86 | — | |
| | 79 | — | |
| | 72 | — | |
| | 65 | — | |
| | Total | [...] | 9 |

Record answers. Score 1 point each time the difference is 7, even if a previous answer was incorrect. Maximum score = 5 points

Memory: Recall

| | | | |
|--|--------------|-------|----------|
| 180. What were the three objects I asked you to repeat a little while ago? | Apple | — | |
| | Table | — | |
| | Penny | — | |
| | Total | [...] | 9 |

Tick each item answered correctly and enter number correct under Total

Language: Reading comprehension

Show 'Reading comprehension' in booklet.
I would like you to read this and do what it says
It is not necessary for the subject to read aloud. If subject reads instruction but fails to carry out action, say 'now do what it says'

If failure appears to be due to illiteracy, enquire whether subject learned to read. If illiterate code 7

| | | | |
|-----------------------|------------|----------|----------|
| 181. Close your eyes. | Incorrect | 0 | |
| | Correct | 1 | |
| | Illiterate | 7 | 9 |

Appendix D (continued)

| The CAMDEX-R Schedule | | 31 | |
|--|--|------------------|---|
| 182. If you are older than 50 put your hands behind your head. | Incorrect Correct Illiterate | 0 1 7 | 9 |
| Praxis | | | |
| Copying and Drawing | | | |
| <i>The subject should draw and write on the sheet of paper provided, see p. 56 Make sure the subject has finished before moving on to the next picture, e.g. by saying 'have you finished that one'?</i> | | | |
| 183. Copy this design (pentagon). <i>Each pentagon should have 5 sides and 5 clear corners and the overlap should form a diamond</i> | Incorrect Correct | 0 1 | 9 |
| 184. Copy this design (spiral). <i>Three connected loops are required in the correct orientation.</i> | Incorrect Correct | 0 1 | 9 |
| 185. Copy this design (3D house). <i>Requires windows, door and chimney in correct position and in 3-dimensional representation</i> | Incorrect Correct | 0 1 | 9 |
| 186. Draw a large clock face and put all the numbers in. <i>When the subject has done this say, 'Now set the hands to 10 past 11 (11.10)'.</i> | Circle (or square) All numbers in correct position Correct time Total | — — — 1 | 9 |
| <i>Do not draw the hands yet</i> | | | |
| <i>Tick each component correctly completed and enter number under Total</i> | | | |
| Writing: Spontaneous | | | |
| 187. Write a complete sentence on this sheet of paper. <i>Indicate bottom of drawing sheet. Ask the subject what he/she has written and transcribe it onto the drawing sheet. Spelling and grammar are not important, but the sentence must have a subject (real or implied) and a verb. 'Help!' or 'Go away' are acceptable.</i> | Incorrect Correct Illiterate | 0 1 7 | 9 |
| Praxis: Ideational | | | |
| <i>Read the following statement and then hand a sheet of paper to the subject. Make a point of handing to the subject's midline. No repetition of this question is allowed. Speak clearly and slowly having first made sure you have the subject's full attention.</i> | | | |
| 188. I am going to give you a piece of paper. When I do, take the paper in your right hand. Fold the paper in half with both hands, and put the paper down on your lap. | Right hand Folds On lap Total | — — — 1 | 9 |
| <i>Do not repeat instructions or coach</i> | | | |
| <i>Score a move as correct only if it takes place in the correct sequence. Tick each correct move and enter number correct under Total</i> | | | |
| <i>Hand an envelope to the subject.</i> | | | |
| 189. Put the paper in the envelope and seal the envelope. | Incorrect Correct | 0 1 | 9 |

Appendix D (continued)

Writing to dictation

| | | | | | | | |
|--|------------|----------------|-------------------------|----------------------------------|---------------------|---|--|
| 190. Write this name and address on the envelope: | Incorrect | 0 | | | | | |
| <table border="0"> <tr> <td rowspan="3" style="font-size: 2em; vertical-align: middle;">}</td> <td>Mr. John Brown</td> </tr> <tr> <td>42 West Street, Bedford</td> </tr> <tr> <td>→ give the whole string at once.</td> </tr> </table> | } | Mr. John Brown | 42 West Street, Bedford | → give the whole string at once. | Poor but acceptable | 1 | |
| | | } | Mr. John Brown | | | | |
| | | | 42 West Street, Bedford | | | | |
| → give the whole string at once. | | | | | | | |
| Correct | 2 | | | | | | |
| | Illiterate | 7 | 9 | | | | |

Spelling and neatness are not important. Criterion is whether letter is likely to reach exact destination, e.g. 'Jon Brwn' is acceptable; '24' and 'Burford' are incorrect

Then say: Please try to remember this name and address as I shall be asking you about them later on

If the subject is unable to write, code 7 and say the address slowly, twice, and ask him/her to remember it

Praxis: Ideomotor

In questions 191-193 a correct MIME is needed. If the subject uses fingers to represent scissors or brush, say e.g. 'Pretend you are holding a toothbrush.' Score 1 if the subject makes a brushing movement but not as though holding a toothbrush

| | | | |
|--|-------------------|---|---|
| 191. Show me how you wave goodbye. | Incorrect | 0 | |
| | Correct | 1 | 9 |
| 192. Show me how you would cut with scissors. | Incorrect | 0 | |
| | Partially correct | 1 | |
| | Correct | 2 | 9 |
| 193. Show me how you would brush your teeth with a toothbrush. | Incorrect | 0 | |
| | Partially correct | 1 | |
| | Correct | 2 | 9 |

Calculation

Mental calculation is required. Paper and pencil are not allowed.

Show the subject two different commonly used coins or notes of different value.

| | | | |
|--|-----------|---|---|
| 194. How much money does this make? | Incorrect | 0 | |
| | Correct | 1 | 9 |
| <i>Record amount and response</i> | | | |
| 195. If somebody went shopping and was given 15 cents as change from \$1, how much did they spend? | Incorrect | 0 | |
| | Correct | 1 | 9 |
| <i>Record response</i> | | | |

Memory: Recall

| | | | |
|--|--------------|---|---|
| 196. What was the name and address you wrote on the envelope a short time ago? | John | — | |
| | Brown | — | |
| | 42 | — | |
| | West Street | — | |
| | Bedford | — | |
| | Total | 1 | 9 |

Appendix D (continued)

The CAMDEX-R Schedule 33

Executive function

Abstract thinking

These questions investigate the capacity to work out the general relationships between objects. Fully correct answers score 2, partially correct answers score 1.

Examples are given beside each score. If the subject says 'They are not alike', say 'They are alike in some way. Can you tell me in which way they are alike?'

I am going to name two things and I would like you to tell me in what way they are alike. For example, a dog and a monkey are alike because they are both animals.

| | | | | | | | | | | |
|---|--|----------------------------|---|--|---------------------------------------|---|--|----------------------|---|---|
| 197. In what way are an apple and a banana alike? | <table border="0" style="width: 100%;"> <tr> <td>Round, have calories</td> <td style="text-align: right;">0</td> <td></td> </tr> <tr> <td>Food, grow, have peel</td> <td style="text-align: right;">1</td> <td></td> </tr> <tr> <td>Fruit</td> <td style="text-align: right;">2</td> <td style="text-align: right;">9</td> </tr> </table> | Round, have calories | 0 | | Food, grow, have peel | 1 | | Fruit | 2 | 9 |
| Round, have calories | 0 | | | | | | | | | |
| Food, grow, have peel | 1 | | | | | | | | | |
| Fruit | 2 | 9 | | | | | | | | |
| <i>Record answer</i> | | | | | | | | | | |
| <i>For this question only, if score is less than 2 say 'They are also alike because they are both fruit.'</i> | | | | | | | | | | |
| 198. In what way are a shirt and a dress alike? | <table border="0" style="width: 100%;"> <tr> <td>Have buttons</td> <td style="text-align: right;">0</td> <td></td> </tr> <tr> <td>To wear, made of cloth, keep you warm</td> <td style="text-align: right;">1</td> <td></td> </tr> <tr> <td>Clothing or garments</td> <td style="text-align: right;">2</td> <td style="text-align: right;">9</td> </tr> </table> | Have buttons | 0 | | To wear, made of cloth, keep you warm | 1 | | Clothing or garments | 2 | 9 |
| Have buttons | 0 | | | | | | | | | |
| To wear, made of cloth, keep you warm | 1 | | | | | | | | | |
| Clothing or garments | 2 | 9 | | | | | | | | |
| <i>Record answer</i> | | | | | | | | | | |
| 199. In what way are a table and a chair alike? | <table border="0" style="width: 100%;"> <tr> <td>Wooden, have 4 legs</td> <td style="text-align: right;">0</td> <td></td> </tr> <tr> <td>Household objects, used for meals</td> <td style="text-align: right;">1</td> <td></td> </tr> <tr> <td>Furniture</td> <td style="text-align: right;">2</td> <td style="text-align: right;">9</td> </tr> </table> | Wooden, have 4 legs | 0 | | Household objects, used for meals | 1 | | Furniture | 2 | 9 |
| Wooden, have 4 legs | 0 | | | | | | | | | |
| Household objects, used for meals | 1 | | | | | | | | | |
| Furniture | 2 | 9 | | | | | | | | |
| <i>Record answer</i> | | | | | | | | | | |
| 200. In what way are a plant and an animal alike? | <table border="0" style="width: 100%;"> <tr> <td>Useful to man, carry germs</td> <td style="text-align: right;">0</td> <td></td> </tr> <tr> <td>Grow, need food, natural</td> <td style="text-align: right;">1</td> <td></td> </tr> <tr> <td>Living things</td> <td style="text-align: right;">2</td> <td style="text-align: right;">9</td> </tr> </table> | Useful to man, carry germs | 0 | | Grow, need food, natural | 1 | | Living things | 2 | 9 |
| Useful to man, carry germs | 0 | | | | | | | | | |
| Grow, need food, natural | 1 | | | | | | | | | |
| Living things | 2 | 9 | | | | | | | | |
| <i>Record answer</i> | | | | | | | | | | |

Ideational Fluency

200a. I am going to give you the name of a common object and I would like you to tell me as many uses for it as you can. For example, if the object was a SHEET OF PAPER it could be used to write on, to make a fan or it could be used to make a paper plane. The uses don't have to be serious – they can be ridiculous or humorous as well – so let your imagination have a free rein. The important thing is to try and think of as many uses as you possibly can in the time given. Try to make the uses as different from each other as possible.

Begin when I say the object and continue until I tell you to stop.

How many different uses can you think of for a BOTTLE?

Start timing and continue for 90 seconds, then say STOP.

Record all responses.

| | | | | | | | | | | | | | | | | |
|--|---|----------------|-----|---|--------------|--|--|----------------|----|---|--------------------|--|--|--------------------------|-----|---|
| <p><i>A correct response is any possible use of a single bottle, pieces of a bottle or numerous bottles, e.g. for strong liquid, as a weapon, as an instrument, smashed into pieces and used for art work, for juggling. Correct responses must specify a use; 'to smash', 'to stand on' are incorrect.</i></p> <p><i>A response is considered a perseveration if it is repeated verbatim or if the same idea is repeated with different examples, e.g. to store water, beer, cordial, orange juice, wine.</i></p> | <table border="0" style="width: 100%;"> <tr> <td>Number correct</td> <td style="text-align: right;"> ... </td> <td style="text-align: right;">9</td> </tr> <tr> <td>Note:</td> <td></td> <td></td> </tr> <tr> <td>Recode: >8 = 8</td> <td style="text-align: right;"> .. </td> <td style="text-align: right;">9</td> </tr> <tr> <td>Enter 0–8 as above</td> <td></td> <td></td> </tr> <tr> <td>Number of perseverations</td> <td style="text-align: right;"> ... </td> <td style="text-align: right;">9</td> </tr> </table> | Number correct | ... | 9 | Note: | | | Recode: >8 = 8 | .. | 9 | Enter 0–8 as above | | | Number of perseverations | ... | 9 |
| Number correct | ... | 9 | | | | | | | | | | | | | | |
| Note: | | | | | | | | | | | | | | | | |
| Recode: >8 = 8 | .. | 9 | | | | | | | | | | | | | | |
| Enter 0–8 as above | | | | | | | | | | | | | | | | |
| Number of perseverations | ... | 9 | | | | | | | | | | | | | | |

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Appendix D (continued)

Visual reasoning

200b. *Show 'Visual reasoning test' in booklet*

Show first item

Here are four boxes. Three of them have an object inside and this one is empty. Which of these objects below should go in the empty box? *Encourage subject to point to the correct response*

If subject makes an error on any of the first two items, point to the correct response and explain why it is correct.

Item 1:

The top row has a big yellow circle with a big blue circle beside it, so the bottom row needs a big blue circle.

Item 2:

The top row is blue; it has a little square beside the big circle. The bottom row is yellow, so it needs a little yellow square beside the yellow circle.

Do not make any further corrections.

If subject made an error, record which item (A to F) was chosen.

| | |
|--------------|----------------|
| C | — |
| A | — |
| E | — |
| D | — |
| F | — |
| B | — |
| Total | [...] 9 |

Perception: Visual

Famous people

Show 'Recognition of famous people' in booklet

201. Who is this?

*Score as correct if picture is recognised
Correct name is not required, but record any answer
which does not correspond exactly to the examples given*

| | |
|--------------------------|----------------|
| Queen | — |
| Pope, Archbishop, Bishop | — |
| Total | [...] 9 |

Object constancy

Show 'Recognition of objects' in booklet

202. These are pictures of objects taken from unusual angles.
Can you tell me what they are?

*Criterion is whether the object is recognised, not that it is named correctly, therefore descriptions of function are acceptable.
Tick each item answered correctly and enter number correct under Total*

| | |
|-----------------|----------------|
| Spectacles | — |
| Shoe | — |
| Purse, suitcase | — |
| Cup and saucer | — |
| Telephone | — |
| Pipe | — |
| Total | [...] 9 |

Appendix D (continued)

The CAMDEX-R Schedule 35

Recognition of person/function
Indicate any two people available, e.g. cleaner, doctor, nurse, patient, relative
If none available, score 9

203. Can you tell me who this is, or what he/she does? Incorrect 0
Correct 1 9

NA

Passage of time

204. Without looking at your watch, can you tell me what the time is now (to the nearest hour)? Incorrect 0
Correct 1 9

205. Without looking at your watch, can you tell me how long you think we have been sitting in this room? Time in minutes 999

Sitting in this room?

206. Record finishing time of interview with subject.

Actual duration of interview (minutes) Time in minutes 999
Check against starting time recorded at beginning of Section A.

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Appendix E (continued)

| | Time (hrs/wk) | Intensity Code * (Kcal/min) |
|--|------------------|-----------------------------------|
| <u>Yardwork</u> | | |
| Gardening: planting, weeding, digging, hoeing | _____ | 4.5 |
| Lawn mowing (walking only) | _____ | 4.5 |
| Clearing walks!driveway: sweeping, shoveling, raking | _____ | 5.0 |
| Other: _____ | _____ | ____# |
| <u>Caretaking</u> | | |
| Older or disabled person (lifting, pushing wheelchair) | _____ | 5.5 |
| Childcare (lifting, carrying, pushing stroller) | _____ | 4.0 |
| <u>Exercise</u> | | |
| Brisk walking (10+ minutes in duration) | _____ | 6.0 |
| Pool exercises, stretching, yoga | _____ | 3.0 |
| <u>Vigorous</u> calisthenics, aerobics | _____ | 6.0 |
| Cycling, Exercycle | _____ | 6.0 |
| Swimming (laps only) | _____ | 6.0 |
| Other: _____ | _____ | ____# |
| <u>Recreational Activities</u> | | |
| 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, sifting, standing, and some other things that you usually do.

Appendix E (continued)

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 = 3 1-60 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 = 3 1-60 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.)

Appendix E (continued)

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 = ito 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 _____
 xWEIGHT _____ = _____

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

Appendix E (continued)

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 = flight.) _____

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 <u>More</u> | Little <u>More</u> | <u>Same</u> | Little Less | Lot Less | <u>Don't know</u> |
|--------|--------------------|-----------------------|-------------|----------------|-------------|-------------------|
| 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 F

Wisconsin Card Sorting Test

Sample Scoring Sheet

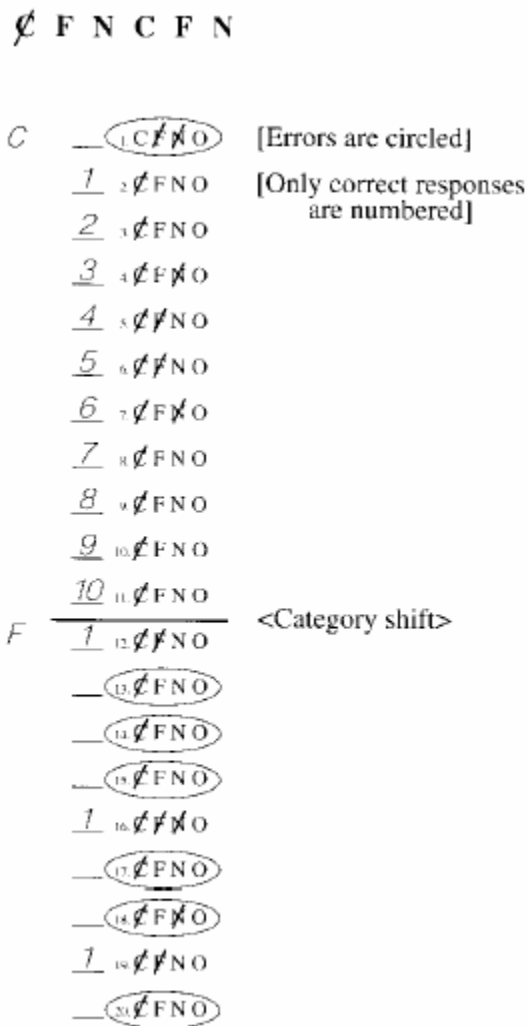


Figure 3. Illustration of scoring correct responses and errors.

C = color
 F = form
 N = number
 O = other

Appendix F (continued)

| (a) | (b) | (c) | (d) |
|--|--|--|-------------------------|
| C — <u>1</u> C F X O | C — <u>1</u> C F X O | C — <u>1</u> C F X O | C <u>1</u> C F N O |
| — <u>2</u> C F N O [unambiguous error] | — <u>2</u> C F N O [unambiguous error] | — <u>2</u> C F N O [unambiguous error] | <u>2</u> C F N O |
| — <u>3</u> C F N O p | <u>1</u> C F N O | — <u>3</u> C F N O p | <u>3</u> C F N O |
| — <u>4</u> C F N O p | <u>2</u> C F X O | — <u>4</u> C F N O p | <u>4</u> C F X O |
| — <u>5</u> C F N O | <u>3</u> C F N O | <u>1</u> C F N O p | <u>5</u> C F N O |
| — <u>6</u> C F X O | <u>4</u> C F N O | <u>2</u> C F N O p | <u>6</u> C F N O |
| <u>1</u> C F X O | — <u>5</u> C F N O p | — <u>7</u> C F N O p | <u>7</u> C F X O |
| <u>2</u> C F N O | <u>1</u> C F N O | — <u>8</u> C F X O | <u>8</u> C F N O |
| <u>3</u> C F N O | <u>2</u> C F N O | — <u>9</u> C F N O p | <u>9</u> C F N O |
| <u>4</u> C F N O | <u>3</u> C F N O | — <u>10</u> C F N O p | <u>10</u> C F N O |
| <u>5</u> C F N O | <u>4</u> C F N O | — <u>11</u> C F N O p | F — <u>11</u> C F N O p |
| <u>6</u> C F N O | <u>5</u> C F N O | — <u>12</u> C F X O | <u>1</u> C F N O p |
| <u>7</u> C F N O | <u>6</u> C F N O | — <u>13</u> C F N O p | — <u>11</u> C F N O p |
| <u>8</u> C F N O | <u>7</u> C F N O | — <u>14</u> C F N O p | — <u>14</u> C F N O p |
| <u>9</u> C F N O | <u>8</u> C F N O | — <u>15</u> C F X O | — <u>15</u> C F N O p |
| <u>10</u> C F X O | <u>9</u> C F X O | — <u>16</u> C F N O | <u>1</u> C F X O p |
| F — <u>17</u> C F N O p | <u>10</u> C F N O | — <u>17</u> C F X O | — <u>17</u> C F N O p |
| — <u>18</u> C F X O | F — <u>18</u> C F X O | <u>1</u> C F X O | — <u>18</u> C F X O p |
| — <u>19</u> C F X O | <u>1</u> C F N O | — <u>19</u> C F X O | <u>1</u> C F N O p |
| — <u>20</u> C F N O p | — <u>21</u> C F N O p | — <u>20</u> C F X O | — <u>20</u> C F N O p |

Figure 4. Illustration of scoring perseverative responses.

p = perseveration

C = color

F = form

N = number

O = other

Appendix F (continued)

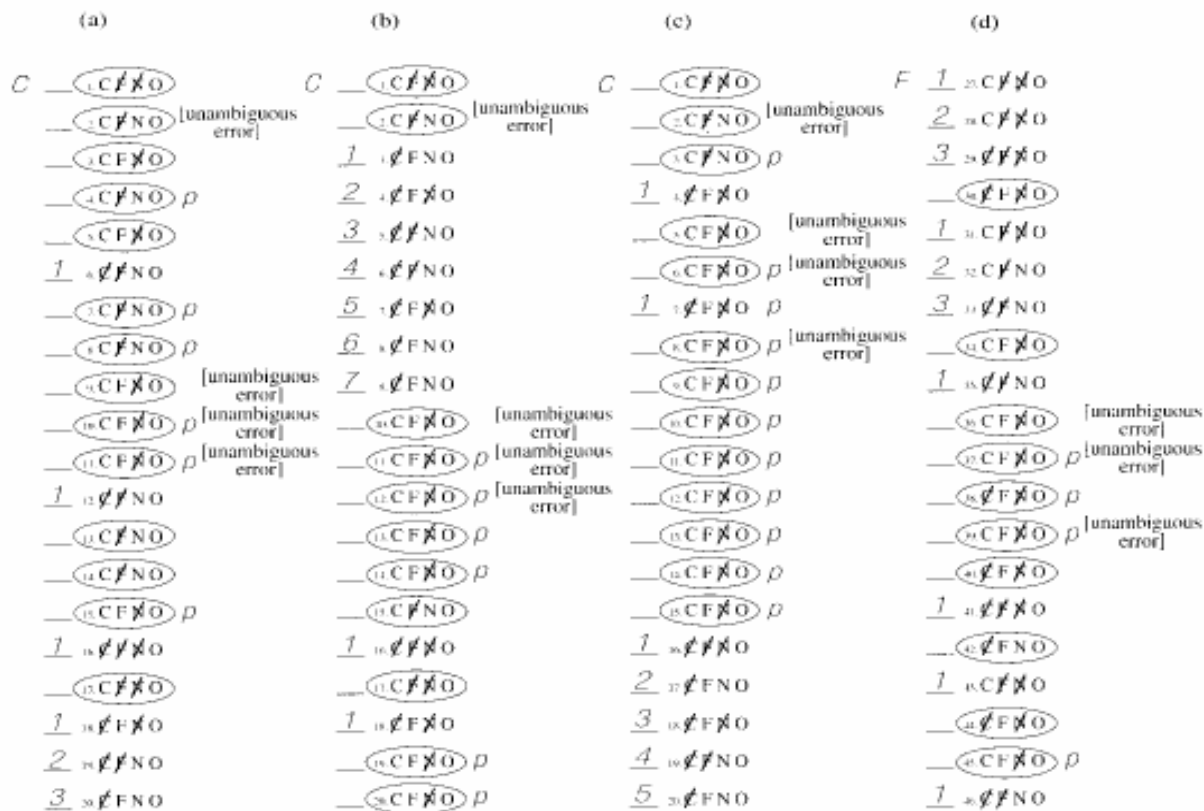


Figure 5. Illustration of the perseverated-to-principle changing within a category.

p = perseveration

C = color
 F = form
 N = number
 O = other

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