

ABSTRACT

Title of Document: THE RELATIONSHIP BETWEEN EXERCISE
AND COGNITIVE FUNCTION: IS IT
ALTERED BY APOE GENOTYPE?

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The risk of minor cognitive decline and dementia increases with advancing age. Thus, as the average lifespan of humans continues to rise the number of people that are affected by dementia will rapidly increase. Dementia is described as multiple cognitive deficits that adversely impact activities of daily living. Lifestyle behaviors may prove critical in delaying or preventing the onset of cognitive decline and dementia. Specifically, exercise has been shown to decrease reaction time, improve executive function, and maintain performance on gross measures of cognitive ability in an aging population. Further, physical activity becomes even more important when the genetic susceptibility for dementia rises. Apolipoprotein (APOE) $\epsilon 4$ is one such risk factor and is associated with the development of Alzheimer's disease (AD). Severe memory loss is one defining symptom of AD and greatly reduces quality of life for afflicted individuals. The purpose of this investigation is to determine the specific behavioral impact of physical activity on those who are genetically at risk for

AD compared to those who are not. Sixty cognitively normal individuals between 50 – 70 years old were assessed on medical history, gross cognitive function, physical activity, memory performance (Sternberg memory task), executive control function (Eriksen flanker task), and finally APOE genotype. Using hierarchical regression techniques, memory and executive function scores were regressed on age, education, genotype, physical activity, and the interaction between genotype and physical activity. Analysis revealed that on the more difficult conditions of the memory task as physical activity level increased, reaction time significantly decreased for APOE $\epsilon 4$ carriers. No such relationship existed for noncarriers. These results imply, compared with other cognitive challenges, physical activity serves a protective role for maintaining memory, particularly in those who are at a genetic risk for developing dementia.

THE RELATIONSHIP BETWEEN EXERCISE AND COGNITIVE FUNCTION: IS
IT ALTERED BY APOE GENOTYPE?

By

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Dedication

In loving memory of David Joseph Magoon (1981 – 2006)

13,109,541 Minutes Well Lived

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Chapter 1

Introduction

By the year 2050, an estimated 14 million Americans will be affected by dementia (Bookheimer et al., 2000). Characterized by significant memory loss, poor judgment, and decreased reasoning ability, dementia poses a major threat to one's health and wellbeing. Alzheimer's disease (AD), the most common form of dementia, requires extensive patient care and significantly compromises interpersonal relationships. In fact, because of the growing elderly population, AD is rapidly becoming a serious public health concern. In order to attenuate the vast impact of AD, intervention and treatment options need to be optimized. Pharmacological treatments can reduce the severity of AD symptoms but do not provide a cure. Simple intervention, such as proper diet, frequent exercise, and cognitive stimulation may prove critical in delaying the onset of cognitive decline, especially for individuals who are more susceptible to the development of dementia (Fritsch et al., 2005).

Most individuals experience some cognitive decline as they age. Cross-sectional and longitudinal studies of cognitive aging consistently demonstrate decreased performance in a variety of different perceptual and cognitive processes throughout the adult life span (Kramer et al., 2004). Certain cognitive abilities tend to decline before others. Executive control, characterized by planning, scheduling, inhibition, and working memory, is likely to decline before any signs of memory impairment (Kramer et al., 1999). The specific cause of these behavioral symptoms

is unknown; however, a likely candidate is the natural deterioration of specific brain regions. For example, Head (2004) and colleagues showed age-dependent volume differences in the corpus callosum, an area of the brain supporting executive control. Additional neuroimaging studies revealed marked volume differences in the tissue density of the frontal, parietal, and temporal cortices as early as the third decade of life (Colcombe et al., 2003; Salat et al., 2004). The rate and severity of neurodegeneration and cognitive decline are not universal for all individuals. Various mitigating factors, including socioeconomic status, level of education, a history of head trauma, genetic predisposition, and lifestyle, influence the development of cognitive dysfunction (Kempler, 2005).

One important lifestyle characteristic recently associated with enhanced cognitive performance is aerobic exercise. As few as 6 months of cardiovascular training improved executive control function in humans (Colcombe et al., 2004). Further research shows that tissue density loss in the frontal, parietal, and temporal cortices is ameliorated by cardiovascular fitness. Strikingly, the areas of the brain that benefit most from exercise are also the areas that show the greatest decline early in life (Colcombe et al., 2003). Based on these results, the benefits of exercise appear to have a measurable biological basis.

Animal research further illuminates the possible mechanisms underlying the protective nature of exercise. Specific growth factors in the brain, neurotrophic factors, protect neurons, increase neural plasticity, enhance learning, and assist in the overall maintenance of the brain (Cotman & Engesser-Cesar, 2002). Voluntary exercise has been shown to significantly increase brain derived neurotrophic factor

(BDNF) in the rat brain. Following wheel running, BDNF activity is most prominent in the hippocampus, a structure central to learning and memory and also the area most affected by AD (Johnson, et al., 2003; Cotman & Berchtold, 2002; Neeper et al., 1996). Several studies indicate that BDNF production and expression are positively correlated with physical activity level, thus, more aerobic exercise leads to greater brain protection (Johnson et al.; Cotman & Berchtold). In addition to BDNF, physical activity also promotes angiogenesis in the rat brain. In this regard prolonged exercise (i.e., wheel running) has been found to increase blood perfusion and blood vessel density in the primary motor cortex (Swain et al., 2003; Black et al., 1990). Similar findings have also appeared in human studies. In a longitudinal investigation comparing physically active and sedentary retirees, those who were sedentary exhibited significant declines in cerebral blood flow (CBF) over four years of follow-up. Active retirees, however, showed greater CBF and performed significantly better on a test of cognitive function than their sedentary counterparts (Rogers et al., 1990). Greater blood supply enables greater oxygenation of the brain that enhances learning and promotes neuronal health.

Factors promoting brain health become even more important when genetic risk for dementia accelerates the rate of neurobiological and cognitive decline. The apolipoprotein E (APOE) ϵ 4 allele is recognized as a common Alzheimer's susceptibility gene. Using positron emission tomography (PET), ϵ 4 carriers show hypoactivation in the same areas of the brain that exhibit remarkable deterioration in AD, namely the hippocampus (Reiman et al., 2001). APOE ϵ 4 carriers lack the ability to repair or maintain minor abnormalities in the brain. It is likely that as these

insults accrue, brain function becomes significantly compromised, possibly to the point of dementia. The risk for dementia is significantly higher for $\epsilon 4$ carriers than noncarriers and even greater yet for those expressing the homozygous $\epsilon 4$ genotype (Reiman et al., 2005; Strittmatter et al., 1994). Despite their increased risk, not all $\epsilon 4$ carriers will develop dementia.

In this regard a recent investigation comparing APOE $\epsilon 4$ carriers and noncarriers demonstrated the protective role of physical activity in humans. The relationship between the amount of physical activity and the risk of cognitive decline in $\epsilon 4$ carriers and noncarriers was assessed in a cohort of 347 elderly Dutch men with a mean age of 74.6 ± 4.3 yr. In this study, participants were grouped by exercise behavior (*high-active* > 1 hour a day or *low-active* < 1 hour a day) and genotype ($\epsilon 4$ carriers and noncarriers). Cognitive function was measured using the Mini Mental State Examination (MMSE), a gross assessment of mental ability. Cognitive decline was defined as a drop of 3 or more points on the MMSE over a 3 year period. As the results indicated, the risk of cognitive decline was significantly reduced in *high-active* $\epsilon 4$ carriers compared to *low-active* carriers. Risk of cognitive decline was similar in all noncarriers. Thus, exercise seems to be an important factor allowing $\epsilon 4$ carriers to decrease the risk of accelerated cognitive decline (Schuit, et al., 2001).

Although the neurobiological effects of APOE $\epsilon 4$ are vast, the hippocampus, more than the frontal region, may show earlier deterioration as a result of $\epsilon 4$ (Reiman et al., 2001). Because the hippocampus is associated with memory function, $\epsilon 4$ carriers are likely to exhibit compromised memory performance. Therefore, the

biological benefits of exercise are likely to be most apparent in tasks involving the hippocampus (memory tasks).

The purpose of the current study is to determine what specific areas of cognition are most affected by physical activity in those with an increased risk for cognitive decline. Specifically, the two areas of cognition that will be measured are executive control function and memory. Kempler (2005) describes executive control as the cognitive abilities that direct and organize behavior, including anticipation, goal selection, planning, initiation of activity, self-monitoring, and use of feedback. Executive function is governed by the frontal lobe. Because the frontal region declines with age, physical activity is expected to show a positive relationship with performance on executive tasks for all participants. Memory is simply the ability to recall previous events or knowledge in a timely manner. The hippocampus plays a significant role in memory and is greatly compromised by APOE ϵ 4. Because brain function is different in ϵ 4 carriers and noncarriers, physical activity is more likely to positively influence memory function in those genetically at-risk for cognitive decline. (i.e., APOE ϵ 4 carriers).

Hypotheses

Each of the dependent measures derived from the Eriksen flanker task and those derived from the Sternberg letter-memory task will be subjected to the following hypotheses.

- 1) Physical activity will be positively associated with executive functioning, regardless of genotype.

- 2) Physical activity will be positively associated with memory performance, regardless of genotype.
- 3) When considering the APOE ϵ 4 allele, the carriers are expected to show a more positive relationship with physical activity on the memory task than the noncarriers.

Chapter 2

Review of Literature

Introduction

The review of literature in chapter II is subdivided into six sections. The first section summarizes the historical context of physical activity and cognition. Starting with early reaction time studies in the 1970s and moving to current epidemiological research, section one establishes the relationship between physical activity and the central nervous system. In section two, dementia and mild cognitive impairment (MCI) are defined and compared to normal aging. Debate persists on whether normal aging leads to dementia or if dementia is a unique entity that is independent of the normal aging process. Section three discusses the genetic influence of apolipoprotein (APOE) $\epsilon 4$ on the development of dementia. APOE $\epsilon 4$ is commonly referred to as a susceptibility gene for Alzheimer's disease (AD) and, therefore, highly related to memory function. Section four provides an in-depth analysis of the relationship between physical activity and the neurobiological mechanisms associated with Central Nervous System (CNS) integrity. In many different ways, physical activity is thought to ameliorate cognitive decline by directly impacting the biology of the brain. The focus of section five is to assess the impact of physical activity on cognitive decline in at-risk populations, namely APOE $\epsilon 4$ carriers. Physical activity may prove more important for those with a greater risk for cognitive impairment. Finally, section six summarizes the major points from each of the previous topics and reiterates the relationship between physical activity and risk of cognitive decline.

Historical Context of Physical Activity and the Aging Brain

Physical activity is a defining characteristic of a healthy lifestyle. It has been well established that regular exercise maintains the structural and functional capacity of many bodily systems including muscular, skeletal, cardiac, and respiratory. However, the relationship between physical activity and the CNS is less established. In 1975, Spirduso assessed reaction and movement time as a function of age and level of physical activity. Participants included young and older men who were either physically active or sedentary. In this cohort, physical activity was defined as the participation in racket sports 3 or more times per week. Results indicated that physical activity was a better predictor than age of reaction and movement times. In a later investigation, Spirduso and Clifford (1978) extended these results with the addition of a running group. Again, older participants who ran or played racket sports reacted and moved faster than their sedentary peers. In addition, older active participants displayed comparable reaction and movement times with sedentary participants 40 years younger. Since reaction time is related to CNS integrity, these results implicate physical activity as a plausible method for maintaining CNS functioning as one ages.

Expanding on the relationship between physical activity and reaction time, Dustman et al. (1984) assessed the impact of aerobic training on cognitive function. A sedentary cohort of 55-70 year old participants was evaluated on neuropsychological tests, depression indices, sensory thresholds, and visual acuity. Following the initial screening process, participants were assigned to either an aerobic training group or one of two control groups. Those who were assigned to the control

groups experienced either strength and flexibility training or had no organized exercise program. Following four months of training, participants in the exercise group performed significantly better on cognitive tests than both control groups. This finding is important because exercise is identified as a primary candidate for improving cognitive function in a cohort of older adults, and further strengthening the link between physical activity and CNS health.

Although behavioral differences in those with varying fitness levels had been observed, the underlying neural differences had not been investigated. Using electroencephalography (EEG), a psychophysiological measure of brain function, Dustman et al. (1990) showed that high-fit older men demonstrated more efficient brain function, better neurocognitive performance, and enhanced visual sensitivity compared with low-fit older adults. This study is one of the first to show neurobiological differences in those with varying fitness levels. It is reasonable to assume that these neurobiological differences underlie the variability in cognitive function seen in older adults.

Subsequent research revealed the specific behavioral impact of physical activity on aging. In Chodzko-Zajko and Moore's (1994) review paper, they supported the hypothesis that physical fitness is associated with more efficient cognitive processing in older adults when compared with less-fit individuals of the same ages. The relationship, however, is highly task specific. Chodzko-Zajko and Moore identified a continuum of cognitive processing moving from effortful to automatic saying that, "Effortful cognitive processes are conceived of as those requiring the allocation of considerable attentional resources for their successful

performance, whereas automatic cognitive processes are thought to be only minimally dependent upon attentional resources” (p. 197). Because of the inherent variability present in effortful tasks, the impact of physical activity is stronger among more challenging behaviors. Automatic processes however require little effort and therefore have less of an opportunity to benefit from physical activity.

Further considering the specific impact of physical activity on effortful cognitive tasks, Kramer et al. (1999) assessed the relationship between ageing, fitness and executive control processes. Executive function is mediated by prefrontal and frontal brain regions and involves tasks related to planning, scheduling, inhibition, and working memory. Furthermore, the frontal lobe has been identified as the first brain region to experience neural and cognitive changes as one grows older (West, 1996). Results indicated a substantial improvement in executive tasks over six months of aerobic fitness training. This finding is very important because it is the first to highlight the relationship between exercise and performance on a specific cognitive task. Again, the positive relationship between executive task performance and cardiovascular fitness training reiterates the role of physical activity in preserving or improving brain function in an aging population. A recent meta-analysis by Colcombe and Kramer (2003) supported the finding from above. They found that with exercise, executive function benefited more than other cognitive tasks, which again suggests a specificity affect of physical activity on mental function.

As people continue to live longer and longer the risk of serious health problems, including incident dementia, rises considerably. Therefore, beyond task specificity, there appears to be a need to consider the impact of physical activity on

specific populations, namely the aging population. In large epidemiological studies, physical activity has been shown to protect against cognitive decline and dementia in elderly persons (Laurin et al., 2001; Friedland et al., 2001). Because the elderly cohort is growing rapidly, the need to understand how lifestyle behaviors interact with aging is very important.

Laurin (2001) and colleagues conducted a study in order to explore the relationship between physical activity and cognitive decline. The initial pool of participants included 9008 randomly selected men and women over the age of 65 who were all involved with the Canadian Study of Health and Aging (CSHA). Participants underwent health history screening and were assessed on ability to complete activities of daily living. The Modified Mini-Mental State (3MS) Examination was used to evaluate cognitive function and was the main screening tool to assess dementia. All participants with a 3MS examination score ≤ 77 and a random sample of those who scored ≥ 78 were asked to take part in additional clinical evaluation. Three possible diagnoses were given including no cognitive impairment, cognitive impairment – no dementia (CIND), and dementia (including Alzheimer's disease, vascular dementia, and unclassifiable dementia). Following the initial screening process all subjects without dementia were asked to complete a questionnaire with questions about demographic characteristics, occupational and environmental exposure, lifestyle, and medical and family histories. Exercise data were included as part of the self-administered survey regarding frequency and intensity of exercise. Accordingly, physical activity level was classified as low, moderate, or high. Follow-up evaluation was conducted an average of five years after

the initial investigation. Participants experienced the same screening and clinical assessment as in the initial stage of the project. Through screening, personal choice, death, or other 4,615 participants were involved through the end of the analysis. In the final group 3,894 were still unimpaired (controls) and 436 were diagnosed as having CIND, 194 AD, 61 vascular dementia, and 30 other specific or unclassifiable dementia. Results indicate that regular exercise was more frequent for controls than for subjects with CIND or dementia. Further, after controlling for age, sex, and education all levels of physical activity were related to lower risks for CIND compared with no physical activity. Moreover, moderate and high levels of physical activity were associated with lower risks for AD and any other form of dementia. In summary and most importantly, individuals who experienced abnormal cognitive decline during the follow-up period were significantly less physically active than others.

For most people, participation in regular physical activity is a conscience decision. Regardless of the reason for exercise, this large-scale study provided evidence that regular physical activity plays a protective role against the risk of cognitive decline and dementia, especially AD. In a similar investigation, Friedland et al. (2001) reported on AD susceptibility as related to participation in “nonoccupational” activities. The 551 participants were separated into 2 groups based on dementia status. The case group consisted of 193 AD patients and the control group was comprised of 358 cognitively intact men and women. Participants answered questions about intellectual, passive, and physical activities. These questions were classified in terms of the total number of activities, hours per month,

and percentage of total activity hours devoted to each activity category. Results indicated that control subjects were more active during early (20-39) and middle (40-60) adulthood in all activities than case-group members. These results held true after accounting for year of birth, sex, education, and income adequacy. Intellectual activities yielded the greatest differences between case and control groups, yet passive and physical activities were also significantly different. Collectively, these studies demonstrated the importance of physical activity in reducing the risk of cognitive decline and/or dementia.

A more recent investigation expands on the findings from above and considers the specific relationship between physical activity and dementia. Larson (2006) and colleagues assessed whether regular exercise was associated with a reduced risk for dementia and AD. This large-scale longitudinal study consisted of 1740 persons older than 65. Exercise frequency, cognitive function, physical function, depression, health conditions, lifestyle characteristics, and APOE genotype were recorded at baseline. With an average of 6.2 years of follow-up, results indicated a reduced incidence rate of dementia for person who exercised three or more times per week compared with those who exercised fewer than three times a week (*Figure 1*). When potential confounders were adjusted for, those who exercised three or more days per week had a 32% reduction in risk for dementia. This finding is important because it was one of the first to report on specific amounts of exercise and the related risk for dementia, not simply cognitive decline.

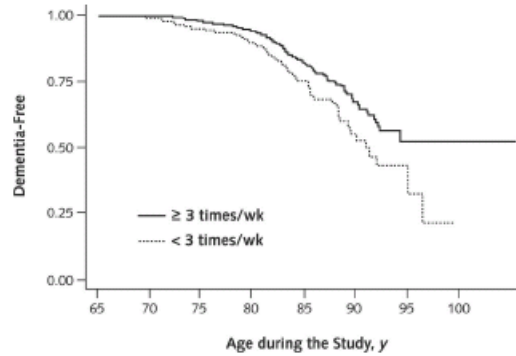


Figure 1 (Larson et al., 2006) Exercising 3 or more times per week is associated with a reduced incidence rate of dementia

Normal Aging vs. Dementia

Dementia is a disorder that impairs normal cognitive function. As defined by Kempler (2005) “Dementia is characterized by persistent, multiple cognitive deficits in at least three spheres of mental function, including memory, language, visuospatial skills, abstraction, calculation, judgment, and emotional state/personality” (p. 180). These deficits must be severe enough to compromise normal social function or interfere with work. In most cases, dementia progresses slowly, yet it can start suddenly and advance rapidly. Dementia comes in many forms such as AD, vascular dementia, and frontotemporal dementias, with AD being the most common. Age associated changes in cognitive function do not necessarily signify or predict the onset of dementia. A common way of classifying these changes in cognitive function is called MCI. Debate exists on what criteria must be present for a clinical diagnosis of MCI. Again, a critical factor in the diagnosis of MCI or dementia is assessing the extent to which the cognitive decline impacts daily living.

Not all individuals develop dementia as they age. In fact, some experience little to no cognitive decline late into life. The question is whether or not the minor cognitive decline consistent with normal aging will eventually lead to dementia or is dementia a unique entity with a specific pathology. It has been established that AD pathology is first prominent in the medial temporal lobe structures then spreading to adjacent temporal, parietal and frontal neocortex (Braak and Braak, 1991). Head (2004) and colleagues attempted to show a neurobiological difference between Alzheimer's disease and normal aging using neuroimaging. Magnetic resonance imaging (MRI) was used to gain volume measurements of the hippocampal and callosal regions of 150 participants aged 18-93 years. All participants were classified as either young, nondemented old, or early-stage AD. The brain regions of interest were divided into subgroups to enhance specificity of the comparisons between subjects. The corpus callosum was divided into five sections, each representing 20% of the rostral-caudal length, and the hippocampus was sectioned as anterior, middle, and posterior. The results indicated a significant volume reduction in the anterior callosal region in nondemented older adults compared to young adults. Moreover, no significant differences were present in callosal volume between early-stage AD and nondemented adults. Meaning that all adults, regardless of dementia, show similar age associated deterioration in the corpus callosum. In contrast, hippocampal volume was greatly reduced in early-stage AD compared to both nondemented adults and young adults. Further, no differences were found in hippocampal volume between nondemented adults and young adults. Because the hippocampus plays a key role in memory function, and memory loss is prominent in Alzheimer's disease, the volume

reduction found in this region is not unexpected. The structural differences illustrated by this investigation further support the dichotomous view of aging and AD.

Albert (1997) provides additional behavioral evidence by showing the differences between normal and abnormal memory loss. Age-related changes in memory are common and not necessarily indicative of pathology. For example, delayed recall appears to decline steadily with advancing age. In one study, Albert asked participants to listen to a lengthy passage then recall as much as possible 20 minutes later. Between the ages of 30 and 80 a consistent decline was reported. Later investigation revealed that when given more time to learn a certain passage older individuals performed just as well as younger participants. AD patients, on the other hand, have difficulty acquiring new information, no matter how much time is spent on a particular topic. Both immediate and delayed recall are significantly impaired. Therefore, the specific behavioral impact of hippocampal deterioration is exposed through significant memory impairment in AD patients.

In contrast, Buckner (2004) offers a possible explanation for changes in memory associated with normal aging. As previously discussed, both demented and nondemented adults show volume reduction in the anterior corpus callosum, which is found in the frontal lobe. Executive tasks such as planning, scheduling, abstract thought, elaboration, and inhibition are mediated by the frontal lobe and therefore impacted by depleted neuronal volume. “Reduced executive function influences memory because acts of remembering often rely on controlled processing, such as strategic elaboration during memorization and guiding search at retrieval” (p. 196). Again, not everyone with minor memory problems will develop AD or other forms of

dementia. The pathology of AD is unique and much different than age related changes in brain structure.

Apolipoprotein and Cognitive Decline

APOE plays an important role in the transport of lipids and the maintenance and repair of neurons. The $\epsilon 4$ variant of APOE retards the transportation and maintenance properties of the protein (Mahley & Huang, 2006). It has been established that the presence of APOE $\epsilon 4$ allele is highly associated with AD (Strittmatter et al., 1993; Corder et al., 1993). Corder and colleagues suggest “A total of 80% of familial and 64% of sporadic AD late onset cases have at least one $\epsilon 4$ allele compared to 31% of control subjects” (p. 921). Furthermore, Strittmatter et al. showed that the risk of AD significantly increases as the number of $\epsilon 4$ alleles increases from one to two. The specific behavioral impact of $\epsilon 4$ however, is not known. A potential explanation is that the presence of $\epsilon 4$ impacts memory function in seemingly normal individuals by affecting the hippocampus. Small changes in memory may go unnoticed for several years, but continue to worsen and eventually lead to MCI or a more severe form of dementia. In order to develop treatment and prevention options, it is important to understand when and how APOE $\epsilon 4$ impacts the brain.

Caselli et al. (2004) assessed whether memory loss was measurable before clinical diagnosis of MCI in those expressing a greater genetic susceptibility for AD based upon presence or absence of APOE $\epsilon 4$. Participants were recruited through local newspaper ads requesting cognitively normal individuals who have a first-

degree relative with AD. After screening, a total of 180 individuals including 93 $\epsilon 4$ noncarriers and 87 $\epsilon 4$ carriers (42 $\epsilon 3/\epsilon 4$ heterozygotes and 45 $\epsilon 4/\epsilon 4$ homozygotes) were enrolled in this longitudinal investigation. Participants had a mean age of 60 (± 6.2) years and included 127 women and 53 men. At the onset of participation, subjects underwent genetic testing to determine their APOE genotype. Additional demographic information, medical history (general, cardiovascular, and neurological), and education were recorded for all individuals. The Mini Mental State exam (MMSE) and Hamilton Depression Rating Scale (Ham-D) were used to ensure normal cognitive function. Any participants showing signs of cognitive impairment (< 27 on MMSE) or depression (10 or less on Ham-D) were eliminated from the study. Memory performance, language ability, spatial skills, and executive function were measured with a series of neuropsychological tests annually over a 6-year period. Verbal memory was tested using the Auditory Verbal Learning Test (AVLT) and Free and Cued Selective Reminding Test (SRT). The Ray-Osterrieth Complex Figure Test (CFT) and Benton Visual Retention Test (VRT) were used to measure visual memory. Because tests of general intelligence, language ability, spatial skills, and executive function showed no significant changes over follow-up or differences between genetic subgroups the specific tests will not be mentioned.

Results indicated that APOE $\epsilon 4$ carriers over the age of 50 demonstrate a moderate longitudinal decline in memory skills over a 33-month period, but before the symptomatic onset of MCI. Remember that, at the commencement of this investigation, all participants were deemed cognitively normal based on a MMSE score of ≥ 27 and a Ham-D score > 10 . These participants also denied any previous

memory deficiencies. Thus, the presence of $\epsilon 4$ alone seems to predict cognitive decline at a relatively young age. It should be noted that these findings suggest cognitive decline in $\epsilon 4$ carriers, not incident dementia. Further investigation needs to be done to determine if those experiencing memory loss associated with presence of $\epsilon 4$ actually develop dementia.

These findings have been corroborated by similar studies investigating cognitive decline in APOE $\epsilon 4$ carriers and noncarriers. An earlier cross-sectional investigation by Caselli et al. (1999) on whether age-related memory decline is influenced by APOE $\epsilon 4$ found similar results. Delayed and immediate recall were measured in three distinct groups; homozygous $\epsilon 4/\epsilon 4$, heterozygous $\epsilon 3/\epsilon 4$ and $\epsilon 4$ noncarriers. Results indicated that, for the homozygous group, as age increased memory performance declined, and for the heterozygotes and noncarriers no association was found. These results suggest that age-related memory decline happens earlier in cognitively normal $\epsilon 4$ homozygotes than in $\epsilon 4$ heterozygotes and noncarriers. Again, the findings of this study further support the notion of a dose response relationship between number of $\epsilon 4$ alleles and risk of dementia.

Feskens et al. (1994) asked whether the $\epsilon 4$ polymorphism predicts cognitive deterioration in a cohort of elderly men with a mean age of 74.7 years. The MMSE was used to assess cognitive function at baseline and again three years later at the conclusion of the study. Results indicate a higher prevalence of impaired cognitive function at baseline among $\epsilon 4$ carriers when compared to noncarriers. Further, $\epsilon 4$ homozygotes showed the greatest decline in cognitive function over the three-year follow-up. Likewise, heterozygous $\epsilon 4$ carriers showed moderate cognitive decline

and noncarriers exhibited the least amount of cognitive decline. Again, these results suggest a link between the APOE ϵ 4 allele and impaired cognitive function.

Research has shown similar results in cohort of women. Yaffe et al. (1997) attempted to determine whether APOE ϵ 4 was associated with cognitive decline in community-dwelling elderly women with a mean age of 71 years. A modified version of the MMSE was administered during the initial visit and then again 6 years later. Two additional cognitive tests (Trails B and Digit Symbol) were administered in conjunction with the MMSE. Again, an association between APOE ϵ 4 and cognitive decline was detected. Women with 1 or more ϵ 4 allele had worse performance on all 3 repeated cognitive test scores than those without the presence of ϵ 4. Cognitive decline was greatest among ϵ 4 homozygotes. A significant portion of most cognitive tests involves the assessment of memory function. Therefore, when performance declines on these tests it is a direct result of declining performance on memory tasks. The previous investigations equated the ϵ 4 allele with cognitive decline and therefore established the relationship between depleted memory capacity and APOE ϵ 4.

Neurobiological Mechanisms of Exercise Induced Effects on the Central Nervous System

In order to better understand how physical activity protects against cognitive decline, neuroimaging studies have proposed 2 major possibilities. First, using magnetic resonance imaging (MRI), Colcombe et al. (2003) compared brain tissue volume and aerobic fitness level in older adults. Starting in the third decade of life

brain tissue naturally deteriorates and continues until death. “Average losses are estimated at roughly 15% of cerebral cortex and 25% of the cerebral white matter between ages 30 and 90” (p. 176). The rate and severity of loss is dependent on genetic makeup, presence of pathological abnormalities, and lifestyle behaviors.

To explore the relationship between brain tissue loss and aerobic fitness level, Colcombe (2003) and colleagues recruited 55 participants with a mean age of 66.5 years. The primary outcome measures were based on gray and white density maps, created with high-resolution MRI. The Rockport 1-mile walk was used to estimate $\dot{V}O_2$ max, a gross measure of cardiovascular fitness. Considerable deterioration was observed in gray and white tissue density as a function of age. The prefrontal, superior parietal and middle/inferior cortices showed age-related declines in white matter density while the motor and occipital regions were spared. The regions showing the greatest age-related declines also exhibited the greatest amelioration by fitness (prefrontal, superior parietal and middle/inferior cortices). Furthermore, within the white matter, the anterior and transverse tracts running between the frontal and the posterior parietal lobes showed the largest beneficial effects of cardiovascular fitness. Other potential confounding variables including alcohol and caffeine consumption, hormone replacement therapy, years of education, and hypertension did not affect the relationship between cardiovascular fitness and neural tissue density. Thus, cardiovascular fitness proved to slow or prevent neural tissue loss and therefore protect the structure of the brain.

Slowing neural degeneration is one possible explanation for the positive effects of physical activity on cognitive function. Another common explanation is

that physical activity improves task-specific neural activation in the cortex. Colcombe et al. (2004) explored the impact of cardiovascular fitness on a test of executive function and assessed cortical activation using functional magnetic resonance imaging (fMRI). Executive function was measured by the Eriksen flanker task (see methods). As in the previous investigation, the Rockport 1-mile walk test was used to assess cardiovascular fitness. Based on fitness level, participants were placed in either high-fit (n=41), cardiovascular fitness training (n=15), or control (n=14) groups. All participants underwent fMRI scanning at the onset of the investigation. The high-fit group was separated by a median split on an estimate of their VO_2 max. The two groups were statistically similar in measures of age, education, hypertension, and IQ. The flanker task was performed with a low error rate for both groups. The high-fit group was consistently more efficient in dealing with the conflicting cues than the low-fit participants. In addition, the high-fit group showed greater cortical activation in areas associated with successful attentional control, and less activity in conflicting areas of the cortex.

The cardiovascular fitness training and control groups were part of a 6-month longitudinal investigation on the effectiveness of training intervention on cognitive performance and cortical activation. Following the initial fMRI and flanker assessment, participants began a supervised training regimen. The fitness training group participated in aerobic training while the control group underwent stretching and toning exercises. Following the training period, participants repeated the fMRI and flanker assessment. The aerobically trained group showed an 11% reduction in behavioral conflict from time one to time two while the control group revealed no

change in behavioral conflict over the same period. fMRI results showed greater task-related cortical activation and reduced conflict in the aerobically trained group compared with control participants. These results suggest that a period as brief as 6 months of aerobic training can improve cortical efficiency and overall brain function.

Through increased task-specific cortical activation and reduced neuronal volume loss, physical activity slows the aging process in the brain. It is important to remember that participants in both of these studies were cognitively normal and showed no signs of dementia. The protective effects of aerobic fitness may differ when certain pathology is present.

Animal studies have investigated additional neurobiological mechanisms that promote brain health through physical activity. For example, exercise is thought to cause the formation of new blood vessels in the rat brain. A process called angiogenesis; blood perfusion provides additional nourishment throughout the cortex. Black et al. (1990) tried to determine what activities promote the most angiogenesis in the rat brain. Rats were assigned to an acrobatic condition, voluntary exercise condition, forced exercise condition or inactive condition. For 30 days, rats in the acrobatic condition were given rope bridges, balance beams, tunnels, see-saws, and other obstacles. As the days moved on, acrobatic trials became progressively longer and more difficult. During the forced exercise condition, rats walked on a treadmill progressively longer each day until they were walking for one hour daily. The voluntary group had free access to a running wheel attached to their cage, with the number of wheel rotations recorded each day. The inactive group was housed in standard laboratory cages with minimal opportunities for learning or exercise.

Results indicated that the voluntary exercise group ran an average of 19 ± 4 km over the 30 day period while those in the forced exercise group only ran 10.8 km. Acrobatic and inactive rats traveled 0.9 km and 0 km respectively. Both the forced and voluntary exercisers showed greater blood vessel density in the paramedian lobules of the cerebellum than either acrobatic or inactive rats. Despite showing no angiogenesis, the acrobatic rats benefited through synaptogenesis, a process of increased connections between neuronal cells. Through learning and problem solving, the acrobatic rats stimulated neuronal cells and thus improved networking in the brain. Both angiogenesis and synaptogenesis are biological processes that support brain health and integrity. In a similar investigation, Swain (2003) and colleagues reported capillary growth in motor areas of the cerebral cortex as a result of prolonged exercise. Using the rat brain as a model, it is likely that aerobic fitness training also causes angiogenesis in humans. Greater blood vessel density allows for maintenance and nourishment of the cerebral cortex.

Another neurobiological mechanism studied in rats is brain-derived neurotrophic factor (BDNF). BDNF serves to increase neuronal survival, promote synaptic development and plasticity, enhance neurogenesis, and improves learning. Several recent investigations have suggested that exercise plays a key role in the production and secretion of BDNF in the rat brain (Cotman & Engesser-Cesar 2002; Cotman & Berchtold 2002; Johnson et al., 2003; Neeper et al., 1996).

In one report, Neeper et al. (1996) conclude that after 2, 4, or 7 nights of running BDNF mRNA was significantly increased in the hippocampus and the caudal third of the cerebral cortex of the rat brain. This is important because, as mentioned

earlier, the hippocampus is a major structure associated with memory loss in conjunction with AD. Hippocampal BDNF may prove critical in delaying or preventing to onset of memory impairment in patients at-risk for dementia. In another report, Cotman and Engesser-Cesar (2002) showed that exercise promotes BDNF expression in the rat brain when compared to sedentary rats of the same strain. Expanding on this finding, Cotman and Berchtold (2002) reported that BDNF expression increased as a product of distance ran (*figure 2*). Meaning, with more exercise, a greater amount of BDNF was found. BDNF is known to exist in humans as well. Through exercise or other mechanism, production and expression of BDNF should be optimized to protect and maintain the continuity of the brain. Again, the hippocampus is a major structure impacted by AD and also exhibits the most significant benefits from exercise through upregulation of BDNF in the rat brain.

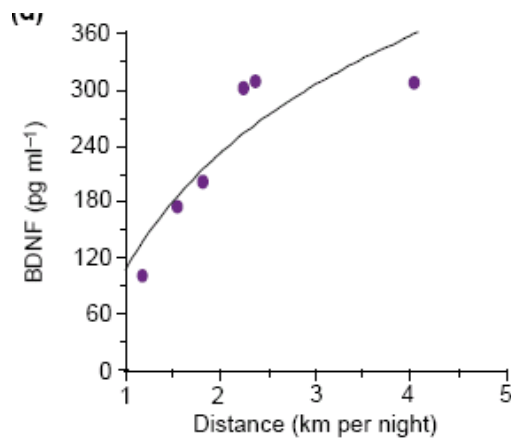


Figure 2 (Cotman and Berchtold, 2002) Both rats and mice exhibited a strong positive correlation between distance ran and amount of BDNF in the brain.

Impact of Physical Activity on Cognition in Populations At-Risk

As previously discussed, the APOE $\epsilon 4$ allele is associated with an increased risk for cognitive impairment. More specifically, APOE $\epsilon 4$ is referred to as a susceptibility gene for AD. More than 40% of those with AD carry the $\epsilon 4$ variant of

APOE. Simple intervention, such as exercise, might decrease the cognitive impact for those carrying the APOE ϵ 4 allele.

Schuit et al. (2001) examined the relationship between physical activity and risk of cognitive decline in older ϵ 4 carriers and noncarriers. All participants were previously enrolled in the Zutphen Elderly Study, a longitudinal investigation of risk factors leading to chronic disease in men. The overall analysis included 347 elderly Dutch men with a mean age of 74.6 ± 4.3 years. The Mini Mental State Examination (MMSE) was used to assess overall cognitive function. Questions on the MMSE focus on the following areas: Orientation to place and time, registration, attention and calculation, recall, language, and visual construction. A perfect score on the MMSE is 30, while a score of 25 or less represents impaired cognitive function. Each participant was assessed on the MMSE twice spanning a three year period, and cognitive decline was defined as a drop of 3 or more points over that time. A self-administered questionnaire was used to assess physical activity. Designed for retired men, this questionnaire asked about frequency and duration of walking and bicycling in the previous week, the average amount of time spent weekly on hobbies and gardening in both summer and winter; and the average amount of time spent monthly on odd jobs and sport. Each activity was converted to minutes per week and summed to estimate total weekly physical activity expenditure. Two distinct groups emerged from the inventory and were described as; *high-active* > 1 hour a day or *low-active* < 1 hour a day. APOE genotype was determined using a blood sample for each participant. Their ϵ 4 status was classified as present or absent. Despite having homozygous (2.5%) and heterozygous (20.7%) ϵ 4 carriers, no distinction was made

during the analysis. When combining genotype with physical activity, four separate groups became apparent: High active $\epsilon 4$ carriers, high active noncarriers, low active $\epsilon 4$ carriers, and low active noncarriers.

Results indicate that inactive participants were statistically more likely to experience impaired cognitive function when compared with those more active. When considering genotype, the *risk* of cognitive decline was nearly four times more likely among low-active $\epsilon 4$ carriers than high-active $\epsilon 4$ carriers. Noncarriers exhibited the smallest risk of cognitive decline (*figure 3*). This investigation shows that exercise plays an important role in reducing the risk of cognitive decline among APOE $\epsilon 4$ carriers.

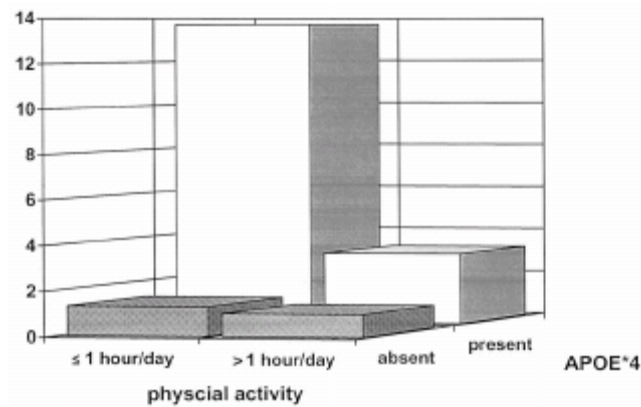


Figure 3 (Schuit et al., 2001) Low-active $\epsilon 4$ carriers have the greatest risk for cognitive decline

Another investigation on the relationship between physical activity, APOE genotype, and cognitive function yielded different results. The purpose of this study was to consider the link between physical activity and incident dementia in APOE $\epsilon 4$ carriers and noncarriers (Podewils et al., 2005). The key difference between these

two studies is that Schuit et al. (2001) assessed “risk of cognitive decline” while Podewils and colleagues measured actual cases of incident dementia.

The 3,660 participants were recruited to take part in the Cardiovascular Health Cognition Study (CHCS), a population based longitudinal study (1992-2000) investigating the risk factors for incident dementia. Participants were screened on cognitive function, physical activity, APOE genotype, and other covariates (age, gender, education, cardiovascular health, mental health, and social networking). Based on the established exclusion criteria, 233 participants were ruled ineligible and thus 3,375 remained for final analysis. Physical activity was measured using a modified version on the Minnesota Leisure Time Activity Questionnaire. Quartiles of leisure-time energy expenditure were established by estimating each participant’s weekly kilocalorie usage. An activity index was also recorded to determine the number and diversity of activities among participants. As in the previous study, all APOE $\epsilon 4$ carriers ($\epsilon 2/\epsilon 4$, $\epsilon 3/\epsilon 4$, $\epsilon 4/\epsilon 4$) and noncarriers ($\epsilon 2/\epsilon 2$, $\epsilon 2/\epsilon 3$, $\epsilon 3/\epsilon 3$) were grouped together for analysis. Baseline cognitive function was measured using the Modified Mini-Mental State examination. Diagnosis of Alzheimer’s disease was based on National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) criteria.

A total of 480 subjects developed incident dementia over 5.4 years of follow-up. When compared with those who did not, those who developed dementia had a lower education level, were more likely to carry the APOE $\epsilon 4$ allele, and had poorer cognitive performance at baseline. The results indicate an inverse association

between physical activity and Alzheimer's disease for APOE ϵ 4 noncarriers but found no association for APOE ϵ 4 carriers. Despite having different dependent measures, these results seemingly contradict those from Schuit et al. (2001), but comparisons should be made with caution. Again, Schuit and colleagues only assessed the risk for cognitive decline, not actual cases of dementia. Because of the associated risk for cognitive decline, APOE ϵ 4 carriers are good candidates to measure the impact of physical activity on an array of cognitive tasks. The apparent discrepancy found in these studies demonstrates the need for further investigation in the area of APOE ϵ 4, physical activity, and cognitive decline.

Summary

The preceding review of literature highlighted the relationship between physical activity and CNS integrity. Through measurements of reaction time, general cognitive function, and specific mental challenges physical activity level was highly associated with greater performance. In addition, these observations were made among an aging population suggesting that the benefits of exercise could be population specific. While age-related changes in cognitive function are expected, exercise may prove more critical for those with a greater susceptibility for cognitive decline, namely APOE ϵ 4 carriers. The ϵ 4 allele is related to AD and predicts cognitive decline in carriers. Using a gross measure of cognitive function, the MMSE, Schuit et al. (2001) showed that physical activity slows or reduces cognitive decline in high-active ϵ 4 carriers compared to low-active carriers. Exercise directly impacts the brain through neurobiological mechanisms such as, angiogenesis and BDNF both promoting brain health. Discrepancies in current literature on the

relationship between exercise and $\epsilon 4$ carriers demonstrate the need to continue research in this area. Delaying or preventing AD or other forms of dementia will ultimately prove critical in reducing the impact of aging on the public health system and more importantly, improve quality of life for older adults.

Chapter 3

Methods

Participants

Participants included 62 healthy men and women between the ages of 50 and 70 (*Table 1*). The participants were initially recruited for a magnetoencephalography (MEG) study investigating physical activity, genotype, and the aging brain. Local running events, health clubs, newspaper ads, and the campus community were the primary recruitment sources. Participants were assessed on medical history, cognitive function, level of physical activity, and APOE genotype.

Screening of Participants

Health problems were assessed for each participant by using a medical history questionnaire (Appendix A). Participants experiencing psychiatric or neurological disorders or those taking psychotropic medication were excluded from data collection.

Participants were screened for cognitive impairments with the Cambridge Cognitive Examination (CAMCOG, *Appendix B*). The CAMCOG is a subsection of the Cambridge Examination for Mental Disorders of the Elderly – Revised (CAMDEX-R). 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.). 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

The APOE genotype has three major isoforms; $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$, $\epsilon 3$ being the most common and associated with normal function of the gene. In that regard, the most common genotype of APOE is $\epsilon 3/\epsilon 3$. As previously discussed, the $\epsilon 4$ allele retards the normal function of APOE and negatively impacts cognitive function. In contrast, $\epsilon 2$ is associated with enhanced or improved cognitive function. Genotypes were grouped based on risk of cognitive decline. Therefore, $\epsilon 2/\epsilon 2$, $\epsilon 2/\epsilon 3$, and $\epsilon 3/\epsilon 3$ were classified as noncarriers or low risk and $\epsilon 3/\epsilon 4$ and $\epsilon 4/\epsilon 4$ were classified as

carriers or at-risk for cognitive decline. Two $\epsilon 2/\epsilon 4$ genotypes were excluded from analysis because of the competing role of each allele.

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, Gentra, 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 (Name brand) 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 pb **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.

Yale Physical Activity Survey

The Yale Physical Activity Survey (YPAS, *appendix C*) was administered to study participants during their initial visit as part of the study on physical activity, the aging brain, and genotype. This survey assesses the physical activity level of each person. Physical activity in this survey encompasses deliberate exercise as well as daily activity of people, 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. Using physical activity as a continuous variable allowed for the assessment of a dose response relationship between physical activity and cognitive function.

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.).

Eriksen Flanker Task

A modified version of the Eriksen flanker paradigm was chosen to assess executive control function (Cohen, et al., 2000). Participants were required to ignore misleading information in order to make a correct response. The Eriksen flanker paradigm measures executive control function. Participants looked at a computer screen and were given a cue “+” followed by 5 arrows “<<<<<.” Participants were instructed to indicate the direction of the center arrow (right or left) by pressing a corresponding key on the keyboard. The arrows were oriented in a congruent or incongruent fashion and can be seen in *figure 4*. Participants were encouraged to respond as quickly and accurately as possible for each of the 200 trials. Response latency and accuracy were measured during the Eriksen task. Each participant saw the following directions prior to completion of the Eriksen Flanker Task: *For each trial you will see a white cross to orient you visually “+”, followed by a row of five arrows, “>>>>>” or “>><>>”. Your task is to focus on the middle of the five arrows and press a button with your right or left index finger, corresponding to the*

direction of the middle arrow. Please respond as quickly and accurately as possible. We are interested in both your accuracy and reaction time.

| | |
|-----------------------|-------------------------|
| CONGRUENT “+” “<<<<<” | INCONGRUENT “+” “<<><<” |
|-----------------------|-------------------------|

Figure 4 Congruent and incongruent conditions for the Eriksen flanker paradigm

Sternberg Memory Task

Memory performance was measured by the Sternberg working memory task *figure 5*. Participants were given a cue followed by a string of 4, 6, or 8 letters. Each letter string size was represented equally over 100 total trials. Following the presentation of the letter string, a probe letter was presented on the screen and participants were to determine if this letter was part of the initial string by pressing a corresponding button on the keyboard. After the probe letter was given, a new trial began. Again, speed and accuracy were emphasized because they are the measures of interest. Prior to completing the Sternberg task, each participant read the following instructions: *Each trial consists of a red square as an orienting cue, a card with some letters, and a single yellow probe. Press the right “ctrl” key if the probe was among the letters. Press the left “ctrl” if the probe was not among the letters. Try to fixate the red square before each trial and respond as quickly and accurately as possible.*

| | | |
|--------------------|--|-------------------------|
| CUE: “■” 250 ms | Letter string: “T R S F K H” 300 ms | Probe: “H” YES or NO |
|--------------------|--|-------------------------|

Figure 5 A six letter string followed by the probe letter “H.”

Data Analysis

All statistical analysis was done using SPSS version 12.0. Mean and variability was reported for age, education, kcal expenditure and the MMSE score. 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 genotype, age, years of education, physical activity (i.e., Yale Index, Kcal expenditure, and Yale exercise), and each of the 16 cognitive performance scores (i.e., response accuracy and average latency for 4, 6, & 8 letter strings for both matching and mismatching conditions of the Sternberg memory task and response accuracy and average latency for both congruent and incongruent conditions of the Eriksen flanker task). Two-tailed probability was reported and in select cases where directionality was expected, 1-tailed probability was parenthetically indicated.

The relationship between physical activity and mental performance was examined using hierarchical regression analysis. Each of the 16 performance scores (i.e., response accuracy and average latency for 4, 6, & 8 letter strings for both matching and mismatching conditions of the Sternberg memory task and response accuracy and average latency for both congruent and incongruent conditions of the Eriksen flanker task) were separately regressed on age, education, genotype (i.e., presence or absence of APOE $\epsilon 4$), physical activity (Yale kcal), and the interaction between genotype and physical activity.

Chapter 4

Results

Descriptive Statistics

The mean and variability for age, education, genotype and MMSE can be seen in *table 1*. Statistical analysis revealed no differences between $\epsilon 4$ carriers and noncarriers in age, education, physical activity or MMSE.

| | Group | $\epsilon 4$ Carriers | Noncarriers | T (2-tailed p) |
|--------------------|----------------------|-----------------------|----------------------|---------------------------|
| N | 62 | 18 | 42 | - |
| Male/Female | 35/27 | 13/5 | 21/21 | - |
| Age | 60.26 (4.74) | 59.17 (5.25) | 60.74 (4.61) | $t(58) = 1.161, p = .250$ |
| Education | 17.58 (2.45) | 17.72 (2.31) | 17.52 (2.58) | $t(58) = -.280, p = .780$ |
| Ykcal | 8056.74 (4393.80) | 8698.5 (4193.84) | 7925.04 (4559.38) | $t(58) = -.616, p = .540$ |
| MMSE | 28.06 (1.2) | 27.89 (1.45) | 28.21 (1) | $t(58) = 1.003, p = .320$ |

Table 1 The mean and (standard deviation) reported for the entire group then separately for $\epsilon 4$ carriers, and noncarriers.

Correlation Analyses

Only significant correlations are reported here. The entire correlation matrix can be seen in appendix D.

Eriksen Flanker Task

Results indicated a positive correlation between age and reaction time on the congruent ($r = .307, p = .016$)(1-tailed $p = .008$) and incongruent ($r = .325, p = .011$)(1-tailed $p = .006$) conditions of the Eriksen flanker task. Age was also positively correlated with percent correct on the Eriksen incongruent condition ($r = .240, p =$

.062) (1-tailed $p = .031$). Both kcal expenditure ($r = .262$, $p = .041$)(1-tailed $p = .021$) and Yale exercise ($r = .251$, $p = .051$) (1-tailed $p = .026$) were positively related to percent correct on the Eriksen incongruent condition.

Sternberg Memory Task

Education was negatively correlated with reaction time for the six-letter string of the non-matching Sternberg task ($r = -.276$, $p = .039$)(1-tailed $p = .019$). The Presence of APOE $\epsilon 4$ was positively related to reaction time for the eight-letter string of the matching Sternberg task ($r = .336$, $p = .013$) (1-tailed $p = .007$). The number of APOE $\epsilon 4$ alleles present was positively correlated with reaction time for the eight-letter string of the non-matching condition ($r = .283$, $p = .038$)(1-tailed $p = .019$). The reported amount of exercise was positively correlated to percent correct on the Sternberg eight-letter string of the non-matching condition ($r = .336$, $p = .011$) (1-tailed $p = .006$). The YALE index was positively related to percent correct on the Sternberg six- ($r = .267$, $p = .047$)(1-tailed $p = .024$) and eight- ($r = .273$, $p = .042$) (1-tailed $p = .021$) letter strings of the non-matching condition. Finally, the YALE index was positively related to reaction time on the Sternberg six-letter string ($r = .315$, $p = .018$)(1-tailed $p = .009$) of the matching condition. All other correlations were not significant.

Hierarchical Regression

Sternberg 4-letter Condition

No significant predictors were found for any of the 4-letter conditions (i.e., match, non-match, congruent, incongruent) of the Sternberg memory task.

Sternberg 6-letter Condition

For the six-letter string of the Sternberg matching condition regression analysis revealed that increased physical activity caused a decrease in reaction time for APOE $\epsilon 4$ carriers ($F_{\text{change}}(1,48) = 7.182, p = .010, \beta = -.464$). No such relationship was shown for non-carriers (*Figure 6*). This indicates a significant interaction between physical activity and genotype on the medium level memory task. For the six-letter non-matching condition of the Sternberg task, regression analysis revealed that education was negatively related to reaction time ($F_{\text{change}}(1,51) = 4.591, p = .037$), meaning that as formal years of educations increased, reaction time decreased.

Sternberg 8-Letter Condition

An interaction was found on the hard memory task between genotype and physical activity. For the eight-letter string of the Sternberg matching condition regression analysis revealed that as physical activity increased reaction time for APOE $\epsilon 4$ carriers decreased ($F_{\text{change}}(1,48) = 4.114, p = .047, \beta = -.441$). Again, no such relationship was shown for non-carriers (*Figure 7*).

Additionally, for the eight-letter non-matching condition of the Sternberg task, regression analysis revealed that genotype was positively related to reaction time ($F_{\text{change}}(1,50) = 6.027, p = .018$). This says that the presence of APOE $\epsilon 4$ slows reaction time. Complete R^2 change and F change results can be found in appendix e.

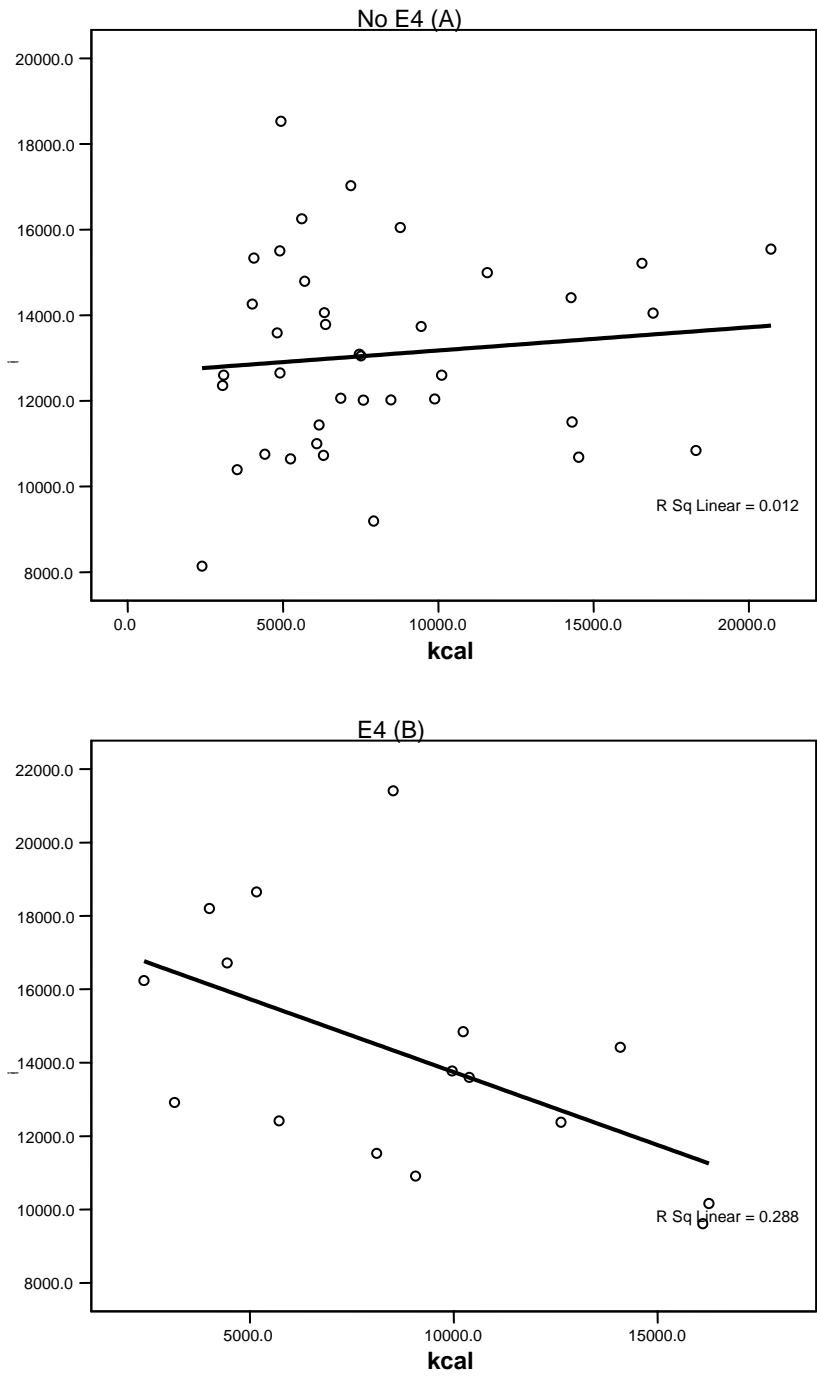


Figure 6 – Scatter plot of reaction time scores on the 6-letter matching Sternberg task and kcal expenditure for noncarriers (A) and carriers (B) of the ε4 allele.

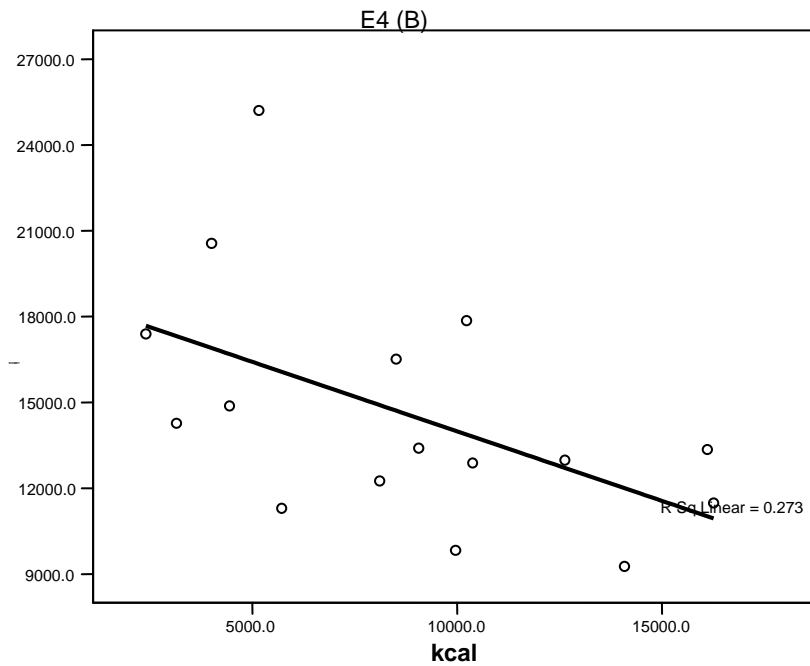
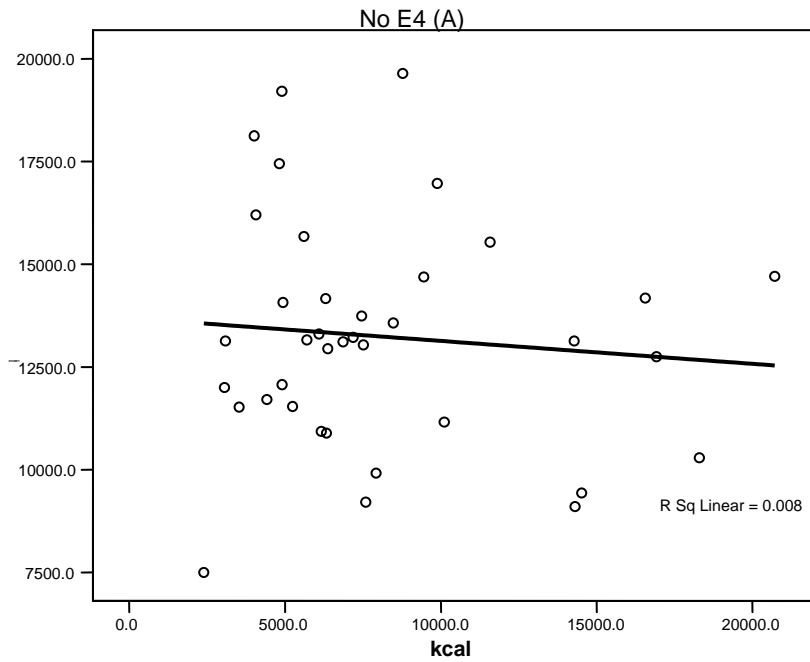


Figure 7 – Scatter plot of reaction time scores on the 8-letter matching Sternberg task and kcal expenditure for noncarriers (A) and carriers (B) of the $\epsilon 4$ allele.

Chapter 5

Discussion

Hypothesis 1

Increased physical activity will be positively associated with executive functioning, regardless of genotype.

Hierarchical regression revealed no relationship between physical activity and executive function. However, percent correct and physical activity were positively correlated on the incongruent condition of the Eriksen flanker task, meaning that participants became more accurate with greater amounts of physical activity. Because of the conflicting information, which requires executive processing for resolution, the incongruent trials were more likely to show improvement with physical activity than the congruent trials. However, both conditions of the Eriksen task require simple discrimination, leading to a high accuracy rate. As such, there was little variability in the performance of this task so the findings should be interpreted tenuously. Although Kramer et al. (1999) found significant improvements in executive function with exercise using neuroimaging; the simplistic nature of the present task may limit the ability to detect a relationship between behavioral performance and physical activity. As noted, the Eriksen flanker task has been successfully employed in neuroimaging studies (revealed a relationship between brain activation and physical activity) probably due to the greater measurement specificity of neuroimaging. Furthermore, it should be mentioned that all participants were highly educated with an average of 17.6 years of education and lacked any signs of

cognitive impairment based on an average of 28.1 on the MMSE. Both of these factors are associated with improved performance on cognitive tasks and, as such, this sample of participants provided a conservative test of the relationship between simple executive function and physical activity.

Hypothesis 2

Increased physical activity will be positively associated with memory performance, regardless of genotype.

Although an interaction between genotype and physical activity was revealed (see hypothesis 3 below) the hierarchical regression did not show unique variance accounted for in memory performance on the Sternberg task by the consideration of physical activity alone. However, positive correlations were revealed between physical activity and percent correct on the six and eight-letter non-matching trials of this task, showing that increased physical activity was associated with greater accuracy on these conditions. Because of its simplicity, no differences were expected or found for the four-letter string of the Sternberg task. Again, a possible explanation for the lack of significance found for physical activity in the hierarchical regression is that participants were both highly educated and cognitively normal during testing. The risk for dementia and cognitive decline decreases as years of education increases. In this regard, unique variance in reaction time on the medium non-matching condition was accounted for by consideration of education alone, thus demonstrating that highly educated participants responded faster than those with less education. Another possible explanation is that certain components of memory function are likely to remain stable late into life. Devoid of pathology in the brain such as

neurofibrillary tangles and amyloid plaques, only minor changes in long-term memory function are associated with aging. The Sternberg task however requires working memory and is more sensitive to declines in general memory function. That being said, performance on the Sternberg task was significantly more variable than the Eriksen flanker task because of the difficulty imposed by the six and eight-letter string conditions. As seen in figures 6 and 7, no relationship was found between memory performance and physical activity for noncarriers of $\epsilon 4$, probably because participants were high functioning to begin with. Therefore, physical activity had little opportunity to positively impact memory performance in this group.

Hypothesis 3

When considering the APOE $\epsilon 4$ allele, the carriers are expected to show a more positive relationship with physical activity on the memory task than the noncarriers.

Consistent with the predictions, APOE $\epsilon 4$ carriers showed faster reaction times for the Sternberg memory task with greater physical activity. In contrast, as discussed above, noncarriers demonstrated no relationship between physical activity and memory performance. Specifically, high-active $\epsilon 4$ carriers exhibited significantly faster reaction times on both the 6 and 8-letter matching conditions of the Sternberg memory task than low-active $\epsilon 4$ carriers. This interaction demonstrates the protective nature of physical activity in those genetically susceptible to dementia. Without any consideration of physical activity participation (i.e., model 3 of hierarchical regression), the liability of APOE $\epsilon 4$ was confirmed by the positive relationship found between genotype and reaction time for the 8-letter non-matching

Sternberg task. In other words, the presence of APOE $\epsilon 4$ alone predicts slower reaction times for carriers, but the positive impact of physical activity was clearly shown by the significant interaction between genotype and physical activity.

As previously discussed, the lack of relationship found between the predictor variables (i.e., age, education, genotype, physical activity, and physical activity genotype interaction) and the four dependent measures derived from the Eriksen flanker task (i.e. reaction time and percent correct for congruent in incongruent conditions) and four of the twelve dependent measure derived from the Sternberg memory task (i.e., reaction time and percent correct for the 4-letter match and no match conditions) was not unexpected. The simplicity of these tasks and the high cognitive ability of the participants led to little variability in performance scores. The eight remaining dependent measures corresponded with percent correct and reaction time for the six and eight-letter match and no match conditions of the Sternberg task. Although these conditions were considerably more difficult than the four-letter string, participants performed similarly on accuracy for both six and eight-letter conditions. As such, the greatest performance variability was seen with respect to reaction time. Because of the established relationship between CNS integrity and reaction time (Spirduso 1975) participants at-risk for cognitive decline (i.e., $\epsilon 4$ carriers) were expected to respond slower than those without the same risk. Therefore, the dependent measures of primary interest were reaction time scores for the six and eight-letter conditions of the Sternberg task. Likewise, out of the four possible reaction time scores, two significant interactions were found.

General Discussion

Liability of APOE $\epsilon 4$

Using neuroimaging, Head and colleagues (2004) showed anterior-to-posterior deterioration in the corpus callosum, a brain structure that mediates executive function and is compromised by age-related neuronal volume loss. When comparing AD patients with normal aging, no differences were found in the callosal region. However, when comparing the hippocampus in AD patients to normal aging, it showed significant deterioration and was behaviorally accompanied by noticeable memory impairment. One major predictor for hippocampal deterioration in humans is the presence of the APOE $\epsilon 4$ allele. In a study of cognitively normal participants, similar in makeup to the current investigation, Reiman et al. (2005) showed that $\epsilon 4$ carriers demonstrated hypoactivation in memory structures before the onset of dementia or mild cognitive impairment. However, it is likely that the neurobiological mechanisms related to physical activity are potent enough to counteract the neurodegeneration observed by Reiman. Several studies also indicated that the phenotypic expression of $\epsilon 4$ is revealed through memory dysfunction (Caselli et al., 2004; Caselli et al., 1999; Feskens et al., 1994; Yaffe et al., 1997). In the current investigation, low-active $\epsilon 4$ carriers performed noticeably worse on the Sternberg memory task than noncarriers, showing that behavioral deficits are detectible in middle-aged, cognitively normal carriers of APOE $\epsilon 4$. With the addition of physical activity, $\epsilon 4$ carriers exhibited similar performance on the Sternberg task as

noncarriers; suggesting that physical activity compensated for the cognitive deficits associated with the presence of APOE ϵ 4.

Neurobiological benefits of Physical Activity: A possible explanation for the interactive effect between genotype and physical activity

Because APOE ϵ 4 carriers have been isolated as prime candidates for cognitive decline, an understanding of the gene environment interaction between ϵ 4 and physical activity will help to slow or prevent its phenotypic expression. Through neurobiological mechanism, physical activity directly impacts the biology of the brain. As previously discussed, BDNF or brain-derived neurotrophic factor serves to increase neuronal survival, promote synaptic development and plasticity, enhance neurogenesis, and improve learning. It has been shown that exercise plays a key role in the production and secretion of BDNF in the rat brain (Cotman & Engesser-Cesar 2002; Cotman & Berchtold 2002; Johnson et al., 2003; Neeper et al., 1996). Furthermore, following exercise, the expression of BDNF is most prominent in the hippocampus (Neeper et al.). Thus, because of the association between cognitive decline in ϵ 4 carriers and deterioration of the hippocampus, BDNF likely contributes to the behavioral differences seen in the Sternberg memory task by protecting the hippocampus in high active participants.

Angiogenesis is another protective mechanism resultant from high levels of physical activity. More diffuse blood flow leads to greater nourishment and protection of the brain. Acting in accord with BDNF, angiogenesis serves to protect high-active ϵ 4 carriers against dementia. Greater circulation in the brain not only provides greater oxygenation, but also serves to remove unnecessary waste products.

Specificity

Reaction time has been described as a key predictor of central nervous system integrity. Spirduso and Clifford (1978) showed that the participation in racket sports and/or running lead to decreased reaction and movement times. Thus, in this example, the benefit of physical activity is task specific. Considering a specific population, Schuit et al. (2001) demonstrated that high-active $\epsilon 4$ carriers showed a significant reduction in the risk for cognitive decline. The findings from the current investigation combined task and population specificity by describing the relationship between physical activity and memory function (task) in those genetically at-risk (population) for dementia. Because no relationship was found between physical activity and genotype on the Eriksen task (i.e., executive function), this further suggests that the APOE $\epsilon 4$ genotype targets the hippocampus and memory function specifically.

Future Directions

Neuroimaging investigation would further illustrate the relationship between APOE $\epsilon 4$ and hippocampal deterioration. In addition, the measurement specificity afforded by neuroimaging allows for the in-depth analysis of the underlying neural pathology associated with this genotype. To combat the impact of APOE $\epsilon 4$, an exercise intervention study would help determine the specific relationship between physical activity and cognitive function. A study that employs both neuroimaging and exercise intervention would provide the strongest evidence for the unique interaction between physical activity and APOE $\epsilon 4$ genotype.

Appendix A

Medical History

Name _____ Telephone _____

Address _____

Date of Birth _____ Age _____ Gender M _____ F _____

Race, ethnicity: _____Caucasian _____Black _____Hispanic _____Asian
_____Other

Color Blind Yes _____ No _____

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

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

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

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

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 _____ |

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 B

Cambridge Cognitive Examination (CAMCOG)

The CAMDEX-R Schedule

25

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*

| 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**

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 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 |

Expression: Naming

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).

In the case of approximate answers, you should say 'Can you think of another word for it?'

Tick each item correctly named in questions 156 and 157 and enter number correct under Total

| | | | |
|-------------------------|--------------|-------|----------|
| 156. Show pencil | | | |
| What is this called? | Pencil | — | |
| Show wristwatch | | | |
| What is this called? | Wristwatch | — | |
| | Total | [...] | 9 |

| | | | |
|---|-----------------------|-------|----------|
| 157. I am going to show you some objects. | Shoe, sandal | — | |
| Please tell me the name of each one. | Typewriter | — | |
| Show 'Pictures for naming' in booklet. | Scales | — | |
| | Suitcase, Portmanteau | — | |
| | Barometer. | — | |
| | Table lamp, lamp | — | |
| | Total | [...] | 9 |

Expression: Fluency

158. Name as many different animals as you can think of. You will have one minute to do this.

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)

List all items

| | |
|----------------------|-----------|
| Number correct | [...] |
| Note: Recode: | 0 = 0 |
| For CAMCOG | 1-4 = 1 |
| score | 5-9 = 2 |
| | 10-14 = 3 |
| | 15-19 = 4 |
| | 20-24 = 5 |
| | 25+ = 6 |
| | [...] |
| | 9 |

Expression: Definitions

For questions 159-162, acceptable answers may depend on local usage

| | | | |
|------------------------------------|-----------------|---|----------|
| 159. What do you do with a hammer? | Incorrect | 0 | |
| | Any correct use | 1 | 9 |

Hit is not enough. Some other detail should be given without prompting.

| | | | |
|--|-----------------------------|---|----------|
| 160. Where do people usually go to buy medicine? | Shop (if unable to specify) | 0 | |
| | CVS, pharmacy | 1 | 9 |

In questions 161-162 a general (abstract) definition scores 2 and a specific or limited definition scores 1. Examples are given beside each score

| | | | |
|------------------------|-------------------------|---|----------|
| 161. What is a bridge? | Incorrect | 0 | |
| | Cross the bridge | 1 | |
| | Goes across a river etc | 2 | 9 |

| | | | |
|--------------------------|--|---|---|
| 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? | Shoe, sandal | — | |
| | Typewriter | — | |
| | Scales | — | |
| | Suitcase | — | |
| | Barometer | — | |
| | Table lamp, lamp | — | |
| | Total | [...] | 9 |

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

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

NA

NA

| | | | |
|--|---|--------|---|
| 169. Who was the leader of the Russians in the Second World War? | Incorrect Stalin | 0 1 | 9 |
| 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 |

Questions 166a-171a to be asked if subject was born after 1940

| | | | |
|---|---|--------|---|
| 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 <i>president of the United States?</i> | Incorrect Correct | 0 1 | 9 |
| 173. Who is <i>the vice president</i> | Incorrect Correct | 0 1 | 9 |
| 174. What is the name of the Prime Minister <i>of England?</i> <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> <i>Write down answer</i> | Incorrect Correct | 0 1 | 9 |

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: apple, table, penny.
Tick which are correct on the first 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 |

| | | | |
|--|------------|---|---|
| 182. If you are older than 50 put your hands behind your head. | Incorrect | 0 | |
| | Correct | 1 | |
| | Illiterate | 7 | 9 |

Praxis

Copying and Drawing

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'?

| | | | |
|---|-----------|---|---|
| 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 | 0 | |
| | Correct | 1 | 9 |

| | | | |
|--|-----------|---|---|
| 184. Copy this design (spiral). <i>Three connected loops are required in the correct orientation.</i> | Incorrect | 0 | |
| | Correct | 1 | 9 |

| | | | |
|--|-----------|---|---|
| 185. Copy this design (3D house). <i>Requires windows, door and chimney in correct position and in 3-dimensional representation</i> | Incorrect | 0 | |
| | Correct | 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 | [...] | 9 |

Do not draw the hands yet

Tick each component correctly completed and enter number under Total

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 | 0 | |
| | Correct | 1 | |
| | Illiterate | 7 | 9 |

Praxis: Ideational

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.

| | | | |
|--|--------------|-------|---|
| 188. I am going to give you a piece of paper. When I do, take the paper in your <i>right</i> hand. Fold the paper in half with both hands, and put the paper down on your lap. <i>Do not repeat instructions or coach</i> | Right hand | — | |
| | Folds | — | |
| | On lap | — | |
| | Total | [...] | 9 |

Score a move as correct only if it takes place in the correct sequence.
Tick each correct move and enter number correct under Total

Hand an envelope to the subject.

| | | | |
|---|-----------|---|---|
| 189. Put the paper in the envelope and seal the envelope. | Incorrect | 0 | |
| | Correct | 1 | 9 |

Writing to dictation

190. Write this name and address on the envelope:

Mr. John Brown
42 West Street, Bedford

→ give the whole string at once.

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

| | | |
|---------------------|---|---|
| Incorrect | 0 | |
| Poor but acceptable | 1 | |
| Correct | 2 | |
| Illiterate | 7 | 9 |

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 |

Record amount and response

195. If somebody went shopping and was given 15 *cents* as change from \$1, how much did they spend?

| | | |
|-----------|---|---|
| Incorrect | 0 | |
| Correct | 1 | 9 |

Record response

Memory: Recall

196. What was the name and address you wrote on the envelope a short time ago?

Tick each item answered correctly and enter number correct under Total

| | |
|--------------|--------|
| John | — |
| Brown | — |
| 42 | — |
| West Street | — |
| Bedford | — |
| Total | 1... 9 |

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? | Round, have calories | 0 | |
| | Food, grow, have peel | 1 | |
| | Fruit | 2 | 9 |

Record answer

For this question only, if score is less than 2 say 'They are also alike because they are both fruit.'

| | | | |
|---|---------------------------------------|---|---|
| 198. In what way are a shirt and a dress alike? | Have buttons | 0 | |
| | To wear, made of cloth, keep you warm | 1 | |
| | Clothing or garments | 2 | 9 |

Record answer

| | | | |
|---|-----------------------------------|---|---|
| 199. In what way are a table and a chair alike? | Wooden, have 4 legs | 0 | |
| | Household objects, used for meals | 1 | |
| | Furniture | 2 | 9 |

Record answer

| | | | |
|---|----------------------------|---|---|
| 200. In what way are a plant and an animal alike? | Useful to man, carry germs | 0 | |
| | Grow, need food, natural | 1 | |
| | Living things | 2 | 9 |

Record answer

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.

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.

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.

Number correct | | 9

Note:
Recode: >8 = 8 | .. | 9
Enter 0-8 as above

Number of perseverations | | 9

Visual reasoning200b. *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 |

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
NA Correct 1 9

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

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.

Appendix C

The YALE PHYSICAL ACTIVITY SURVEY FOR OLDER ADULTS

INTERVIEWER: PLEASE MARK TIME: _____ HR MN SEC

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

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

| <u>Work</u> | Intensity Time Code * (hrs/wk) (Kcal/min) |
|---|---|
| Shopping (e.g., grocery, clothes) | 3.5 |
| Stair climbing while carrying a load | 8.5 |
| Laundry (time loading, unloading, hanging, folding only) | 3.0 |
| Light housework: tidying, dusting, sweeping, collecting trash in home, polishing, indoor gardening, ironing | 3.0 |
| Heavy housework: vacuuming, mopping, scrubbing floors and walls, moving furniture, boxes, or garbage cans | 4.5 |
| Food preparation (10+ minutes in duration): chopping, stirring, moving about to get food items, pans | 2.5 |
| Food service (10+ minutes in duration): setting table, carrying food, serving food | 2.5 |
| Dish washing (10+ minutes in duration): clearing table, washing/drying dishes, putting dishes away | 2.5 |
| Light home repair: small appliance repair, light home maintenance/repair | 3.0 |
| Heavy home repair: painting, carpentry, washing/polishing car | 5.5 |

Other: _____

* Taylor, et al. 1978 or McArdle et al. 1981

Determined by the specific activity

| | Time (hrs/wk) | Intensity Code * |
|--|------------------|---------------------|
| <u>Yardwork</u> | | |
| (Kcal/min) | | |
| 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.

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

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

Frequency score = _____

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

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

Duration score = _____

weight = 5

VIGOROUS ACTIVITY INDEX SCORE:

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

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

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

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

8 = don't know Frequency score

= _____

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

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

Duration score = _____

weight = 4

LEISURELY WALKING INDEX SCORE:

FREQ SCORE _____ x DUR SCORE _____ x

WEIGHT _____ = _____

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

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

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

Moving score = _____

weight = 3

MOVING INDEX SCORE:

FREQ SCORE _____ x DUR SCORE _____ x

WEIGHT _____ = _____

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

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

- Score: 0 = Not at all
 1 = less than 1 hr per day
 2 = 1 to less than 3 hrs per day
 3 = 3 to less than 5 hrs per day

- 4 = 5 to less than 7 hrs per day
- 5 = 7+ hrs per day
- 7 = refused
- 8 = don't know

Standing score = _____

weight = 2

STANDING INDEX SCORE:

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

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

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

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

Sitting score = _____

Weight = 1

SITTING INDEX SCORE:

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

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

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

| | Age | | Education | | Genotype | |
|------------------------|-----------------------|----------|-----------------------|----------|-----------------------|----------|
| | R ² Change | F Change | R ² Change | F Change | R ² Change | F Change |
| Eriksen Congruent % | 0 | 0 | 0.007 | 0.421 | 0.018 | 1.025 |
| Eriksen Congruent RT | 0.095 | 5.993 | 0.001 | 0.061 | 0.016 | 0.967 |
| Eriksen incongruent % | 0.061 | 3.7 | 0 | 0.01 | 0 | 0.002 |
| Eriksen incongruent RT | 0.106 | 6.778 | 0.006 | 0.404 | 0.006 | 0.344 |
| Stern 4 Match % | 0.001 | 0.039 | 0.002 | 0.089 | 0.005 | 0.255 |
| Stern 4 Match RT | 0.001 | 0.07 | 0.005 | 0.244 | 0.034 | 1.746 |
| Stern 4 Nomatch % | 0.001 | 0.04 | 0.007 | 0.374 | 0.009 | 0.438 |
| Stern 4 Nomatch RT | 0.003 | 0.179 | 0.005 | 0.278 | 0.035 | 1.82 |
| Stern 6 Match % | 0.001 | 0.038 | 0.008 | 0.413 | 0.008 | 0.413 |
| Stern 6 Match RT | 0.001 | 0.077 | 0.002 | 0.114 | 0.041 | 2.148 |
| Stern 6 Nomatch % | 0.013 | 0.7 | 0.001 | 0.054 | 0.022 | 1.15 |
| Stern 6 Nomatch RT | 0.004 | 0.193 | 0.082 | 4.591 | 0.025 | 1.401 |
| Stern 8 Match % | 0.001 | 0.032 | 0.009 | 0.456 | 0.008 | 0.391 |
| Stern 8 Match RT | 0.001 | 0.062 | 0 | 0.005 | 0.036 | 1.858 |
| Stern 8 Nomatch % | 0.01 | 0.529 | 0.002 | 0.092 | 0.003 | 0.128 |
| Stern 8 Nomatch RT | 0.016 | 0.839 | 0.011 | 0.575 | 0.105 | 6.027 |

| Physical Activity | | PA X GENOTYPE | | Total Change | |
|--------------------------|----------|-----------------------|----------|-----------------------|----------|
| R ² Change | F Change | R ² Change | F Change | R ² Change | F Change |
| 0 | 0.02 | 0.089 | 5.313 | 0.114 | 6.779 |
| 0 | 0.024 | 0 | 0.002 | 0.112 | 7.047 |
| 0.064 | 3.939 | 0.021 | 1.314 | 0.146 | 8.965 |
| 0.003 | 0.165 | 0.002 | 0.092 | 0.123 | 7.783 |
| 0.01 | 0.496 | 0.005 | 0.23 | 0.023 | 1.109 |
| 0.055 | 2.973 | 0.036 | 2.006 | 0.131 | 7.039 |
| 0.002 | 0.097 | 0 | 0.018 | 0.019 | 0.967 |
| 0.014 | 0.714 | 0.019 | 0.985 | 0.076 | 3.976 |

| | | | | | |
|-------|-------|-------|-------|-------|--------|
| 0.002 | 0.096 | 0 | 0.016 | 0.019 | 0.976 |
| 0.015 | 0.797 | 0.122 | 7.182 | 0.181 | 10.318 |
| 0.03 | 1.569 | 0.019 | 1.018 | 0.085 | 4.491 |
| 0.028 | 1.566 | 0 | 0.001 | 0.139 | 7.752 |
| 0.002 | 0.084 | 0 | 0.016 | 0.02 | 0.979 |
| 0.059 | 3.18 | 0.072 | 4.144 | 0.168 | 9.249 |
| 0.023 | 1.168 | 0.048 | 2.544 | 0.086 | 4.461 |
| 0.006 | 0.331 | 0.001 | 0.04 | 0.139 | 7.812 |

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