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ACUTE EFFECTS OF DIET AND EXERCISE ON COGNITIVE FUNCTION AND BRAIN ACTIVATION IN AN AGING POPULATION

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ACUTE EFFECTS OF DIET AND EXERCISE ON COGNATIVE FUNCTION AND BRAIN ACTIVATION IN AN AGING POPULATION

By

Natalie Stein

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Abstract

ACUTE EFFECTS OF DIET AND EXERCISE ON COGNITIVE FUNCTION AND BRAIN ACTIVATION IN AN AGING POPULATION

By

Natalie Stein

Background: Aging and lifestyle factors have been associated with age-related cognitive decline, including executive function. Epidemiological aging studies suggest a role of diet and exercise in cognition but less is known about acute effects in an experimental setting. *Objective*: Compare the effects of a high saturated fat, low nutrient-dense standard breakfast (SB), nutrient dense breakfast (NB), and NB with aerobic exercise (30 min at 50-65% heart rate reserve, AE) on cognitive function and brain activation in older adults. *Methods*: A three arm, randomized, cross-over design was used in healthy adults (n=19, 69.7 ± 4.9 y). Cognitive function was assessed with CogState® tasks. Evaluation of brain activation was with the brain blood oxygen level-dependent response during functional MRI with a flanker arrow task requiring inhibition. *Results*: Overall, NB with or without AE did not improve cognition in healthy older adults. In the CogState®, accuracy improved on prediction (executive function) in NB over NB + AE, and speed declined for monitoring (attention) in NB compared to SB, $p<0.05$. No significant treatment effects were found in the flanker arrow task or for brain activation in the inferior and middle frontal gyrus. *Discussion and Implications*: This study tested SB, NB, and NB + AE on cognition in healthy older adults. Although longer interventions of diet and exercise may affect cognitive function in older adults, our results suggest these lifestyle factors do not have acute effects.

Dedication

Patri meo

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Key to abbreviations

A anterior

AD Alzheimer's disease

AE aerobic exercise

BDNF brain-derived neurotrophic factor

BOLD blood oxygenation level-dependent

CBF cerebral blood flow

EEG electroencephalography

fMRI functional magnetic resonance imaging

HRR heart rate reserve

I inferior

IFG inferior frontal gyrus

L left

MCI mild cognitive impairment

MEG magnetoencephalography

MFG middle frontal gyrus

MMSE Mini-Mental State Examination

NB nutrient dense breakfast

P posterior

PET positron emission tomography

PCG pre-central gyrus

R right

S superior

SB standard breakfast

Chapter I: Introduction, Background, and Specific Aims

Introduction

Overall, the percentage of older adults is increasing in the United States. By increasing at the rate of 1.2% per year, the American population aged 65 years and over is growing faster than any other segment of the population (NCHS 2009). Within the next 20 years, adults aged 65-74 years old are expected to comprise 10% of the population (Day 2001). Aging is associated with many chronic health conditions, and there has been much focus on these age-related conditions. Cognitive decline, especially in executive function, is a normal part of aging (Mitchell 2009). Executive function is required for higher order cognitive processing tasks such as decision making, attention, and memory (Alan, Clemens et al. 2006) (Berkman, Seeman et al. 1993), and performance on these tasks can decrease with age (West, Schwarb et al. 2009). Interest in understanding cognition during aging has prompted numerous studies investigating factors that may influence the brain during the aging process.

A wide variety of components combine to affect age-related cognitive function and decline. Some of these components, such as age, gender, and genetics are unalterable. However, other factors that likely affect brain health are modifiable through lifestyle choices. Diet and physical activity (PA) are two such factors that may affect cognition during the aging process. Numerous studies have suggested associations between habitual diet and physical activity and cognitive function or decline in older adults (Vaynman and Gomez-Pinilla 2005; Lichtenstein, Appel et al. 2006). In addition, some dietary factors and some forms of exercise have the

potential to acutely affect cognition (Hindmarch, Quinlan et al. 1998; Tomporowski 2003; Chui and Greenwood 2008).

Dietary factors refer to a wide range of components including dietary patterns and individual foods, as well as isolated or specific nutrients. Both foods and food components have been studied for their possible effects on the brain. Various studies investigating the effects of diet on the brain have found that different components can positively or negatively influence cognitive function (Gillette Guyonnet, Abellan Van Kan et al. 2007). For example, some epidemiological studies have found positive correlations between cognitive function and fish intake (Nurk, Drevon et al. 2007), or between cognitive function and vitamin E intake (Masaki, Losonczy et al. 2000). Other factors that may be beneficial for cognition include consumption of vitamin C, total antioxidants, certain polyunsaturated fatty acids, and folic acid. Negative factors include saturated fat intake and simple sugars (Molteni, Barnard et al. 2002).

Physical activity is another modifiable lifestyle factor that may greatly affect cognitive health. Physical activity and exercise has been associated with higher cognitive performance (Weuve, Kang et al. 2004) or slower cognitive decline during aging (van Gelder, Tijhuis et al. 2004). Various epidemiological studies have looked at both physical fitness and habitual exercise. Results have ranged from higher cognitive performance or slower cognitive decline with increased habitual physical or fitness to no correlations with cognition. In contrast to these long-term studies, other studies have investigated the acute effects of a single bout of exercise on cognitive performance. Some have shown that a bout of exercise can improve

performance on certain cognitive tasks (Hillman, Snook et al. 2003; Kashihara, Maruyama et al. 2009). These studies have typically been conducted in healthy younger adults.

Multiple cognitive tests can be used to detect cognitive impairment or assess cognitive function (Wild, Howieson et al. 2008; de Jager, Schrijnemaekers et al. 2009). One such tool of cognitive tests is CogState® (CogState© Limited, Melbourne, Australia). The CogState® tests for research are a battery of computerized tests, with each short test designed to test specific cognition domains. The research investigator can choose which individual tests to administer based on the cognitive function that is to be evaluated in the study.

Aside from cognitive performance, another aspect of cognitive function is brain processing during cognitive tasks. While the CogState® exam can evaluate cognitive performance, brain imaging, particularly functional magnetic resonance imaging (fMRI) may provide insight into pathways that are used during cognitive tasks. Also, these techniques help assess processing speed. This technique depends on local blood oxygenation levels in the brain that change in conjunction with neural processing. The basis of fMRI is a change in net magnetization of specific brain regions. Neuronal firing, such as in response to a task, leads to changes in local blood flow and oxygenation. The use of fMRI allows determination of which specific brain regions are being used to complete cognitive tasks and the degree of activation by evaluating the magnitude of the MRI signal.

Established cognitive tasks can be used to intentionally activate specific brain regions. This allows the investigation of differences in brain activity due to

different treatments such as a meal or exercise. Different treatment groups might show different magnitudes of change in activation, or show differences in relative activation of different parts of the brain. For example, correct performance of the Eriksen flanker task requires decision making, conflict resolution, and inhibition skills (Ochsner, Hughes et al. 2009) and therefore can activate brain regions responsible for these different processes. Diet or exercise could potentially affect these skills. Using altered brain pathways or requiring more or less mental effort could be detectable if these alterations cause differences in fMRI signal location or magnitude.

It appears that diet and exercise are important elements in influencing brain health. Current evidence suggests that habitual diet and exercise patterns affect cognitive function long term in older adults. In addition, certain dietary components consumed in one session (Chui and Greenwood 2008) or single bouts of exercise (Netz, Tomer et al. 2007; Pontifex, Hillman et al. 2009) have been found to acutely improve cognitive function in healthy younger adults. However, there have been no studies on the acute effects of a single meal and bout of exercise in an aging population. Determining their effects on cognitive function and brain activation would help increase understanding of how diet and exercise affect the brain.

The overall objective of the study was to assess the effects of a standard breakfast (SB), a nutrient dense breakfast (NB), and a nutrient dense breakfast plus aerobic exercise (AE) on cognitive function and brain activation in an aging population.

We compared the acute effects of a single meal: a standard breakfast (SB), modeled after a realistic American breakfast, and a nutrient dense breakfast (NB). The SB diet included components thought to have negative effects on the brain, including high amounts of saturated fat and sugar. The NB included dietary components associated with improved cognition or endothelial function, including whole-grain bread and cereals, antioxidants, fruit and vegetables, and omega-3 fatty acids. Another condition (NB + AE) included a session of aerobic exercise (AE) at an intensity between 50% and 65% of their heart rate reserve (HRR) after consuming the NB meal. After the meal and exercise bout or control condition, cognitive function was evaluated based on performance on the CogState® tests. Brain activation was assessed using fMRI to determine the brain blood oxygen level-dependent (BOLD) response (Buxton, Uludag et al. 2004) during functional magnetic resonance imaging (fMRI) to determine activation in interference regions of the brain during an Eriksen flanker test with congruent and incongruent conditions.

Specific Aims and Hypotheses

Aim 1: Assess the acute effects of a standard breakfast (SB) and nutrient dense breakfast (NB) on cognitive function and brain activation.

Hypothesis 1:

a. Compared to SB, NB will improve performance on a battery of cognitive tasks.

b. Compared to SB, NB will increase brain activation during executive function processing in the inferior frontal gyrus (IFG) and middle frontal gyrus (MFG).

Aim 2: Assess the acute effects of a bout of moderate aerobic exercise (AE) on cognitive function and brain activation.

Hypothesis 2:

a. Compared to SB or NB alone, NB + AE will improve performance on a battery of cognitive tasks.
b. Compared to SB or NB alone, NB + AE will increase brain activation during executive function processing in the inferior frontal gyrus (IFG) and middle frontal gyrus (MFG).

Review of the Literature

Aging and the brain

The population of the United States is aging, with adults over 65 years old composing 12.4% of the population according to the 2000 Census. Older adults are also the fastest growing segment of the population and are projected to make up 19.7% of the nation's population by the year 2030 (Census 2001). The rapid growth of this population segment is associated with age-related health conditions (CDC 2009). These conditions include increased risk for cardiovascular disease and osteoporosis, and changes in vision or hearing (CDC 2009). The brain is also commonly affected in aging, leading to conditions ranging from mild cognitive impairment (MCI) to Alzheimer's disease (AD). Cognitive dysfunction can also occur during normal aging (Thomas, Darvesh et al. 2001), and age-related cognitive

impairment is a significant contributor to disability in aging (Desai, Grossberg et al. 2004). Cognitive decline is associated with increased mortality and decreased quality of life (McGuire, Ford et al. 2006).

Changes in the brain that occur during aging are evident as changes in physiology and in cognitive performance, which may be associated with each other (Charlton, Barrick et al. 2009). Age-related changes in brain anatomy include decreases in gray matter volume, in the superior, middle, and medial frontal brain regions, and superior parietal brain regions (Driscoll, Davatzikos et al. 2009). Another age-related change in brain physiology is blood flow. During the progression of AD, increased vasoconstriction impairs cerebral blood flow (CBF) and likely promotes the cognitive impairment evident in AD (Farkas and Luiten 2001). In fact, decreased CBF was subsequently associated with increased areas of white matter hyperintensities, which are associated with aging and may result from reduced local perfusion (Brickman, Zahra et al. 2009).

During aging, changes in cognitive function, especially executive function, are widely recognized (West, Schwarb et al. 2009). Executive function can be defined as "computational processes involved in the selection, scheduling and coordination of complex cognitive functions" (Hillman, Erickson et al. 2008), and it is likely to be impaired during normal aging (Jones, Nyberg et al. 2006). Age-related declines in cognitive function are evidenced through decreased performance in tasks such as working memory (Charlton, Schiavone et al. 2009), inhibition and executive function (Henry, von Hippel et al. 2009), word generation (Heuer, Janczyk et al. 2009), episodic memory (Charlton, Barrick et al. 2009), attention

(Silver, Goodman et al. 2009), and cognitive processing speed (Kennedy and Raz 2009; Zanto, Toy et al. 2009).

Although some regional changes in brain volume are normal, changes may be linked to impaired cognition. For example, one study showed that individuals with smaller hippocampus and frontal lobe volumes also had lower executive function. As this cohort was followed over 15 years, these individuals displayed more rapid decline in executive function than individuals with larger hippocampus and frontal lobe volumes at baseline (Cardenas, Chao et al. 2009). Results of the aforementioned Driscoll study were similar. Accelerated changes were measured in individuals diagnosed with MCI compared to controls in whole brain volume, orbitofrontal cortex (OFC) volume and temporal gray matter (Driscoll, Davatzikos et al. 2009). Further links between brain anatomy and cognitive function are apparent with the association between neuroanatomical degradation and impaired performance on executive function tasks including processing speed, working memory, inhibition, task switching, and episodic memory (Kennedy and Raz 2009). Older adults (74 years) have a smaller increase in frontal lobe CBF than younger adults (30 years old) in response to executive function (word stem completion and visual search) tasks measured by transcranial Doppler ultrasound (Sorond, Schnyer et al. 2008). Diffusion tensor imaging techniques have shown associations between white matter integrity and processing speed, working memory, inhibition, task switching, and episodic memory (Kennedy and Raz 2009).

Age-related changes in the brain, reviewed by Baquer et al. (2009), include metabolism, structure, and function (Baquer, Taha et al. 2009). The nature of these

changes suggests that they are not necessarily inevitable. Theories of causes of aging, such as oxidative stress, imply that age-related cognitive changes might be modifiable through lifestyle factors. In fact, predictors of cognitive decline or maintaining cognitive function during aging include modifiable lifestyle factors such as exercise or smoking habits (Yaffe, Fiocco et al. 2009). Evidence supports the hypothesis that some age-related cognitive changes are influenced by modifiable lifestyle factors, including nutrition and physical activity.

Diet and the brain

Issues in conducting dietary studies

This section describes some of the many challenges in studying effects of diet on brain function. The above section describes mechanisms that may contribute to age-related changes in the brain. The routes of these potential mechanisms suggest that factors affecting aging in the brain may be modifiable, and these may encompass lifestyle factors including diet and exercise. Various dietary patterns and food components have been studied for their potential influence on brain health, but their acute effects in aging adults are not fully understood. Likely beneficial dietary factors include fruits and vegetables (Polidori, Pratico et al. 2009), fish and other sources of long chain polyunsaturated fatty acids (Nurk, Drevon et al. 2007), vitamins such as folate and vitamin B12 as well as the antioxidant vitamins either from the diet or from supplements, and other dietary factors such as flavanols and polyphenols from plant-based food sources (Fisher, Sorond et al. 2006). In addition, saturated fat and sugars have been investigated as having harmful effects (Morris, Evans et al. 2004).

The acute effects of dietary components on cognition during aging have not been extensively studied. Instead, studies in aging adults have been long-term observational studies. The benefits of observational studies such cohort or case-control studies include lower cost, and greater feasibility. However, cause and effect relationships cannot be determined from these kinds of studies. Intervention studies or clinical trials can test hypotheses about cause and effect, but they are more expensive and time-consuming than observational studies. As a result, much of the existing literature on humans is focused on long-term associations between diet and exercise and cognition in aging adults, or on acute cause and effect relationships of diet and exercise on cognition in younger populations.

Because of the difficulties in conducting controlled experimental studies in humans, efforts to elucidate the potential effects and mechanisms of diet on cognition during aging have led to animal studies. These have a variety of economic and logistical advantages. Unlike human studies, which are limited by practical considerations like palatability, subject compliance, and cost, researchers can determine dietary composition in animal studies, and can therefore focus on the component of interest by manipulating the amount present in the diet. Animal feeding studies also include the opportunity to accurately measure consumption, which is difficult in humans due to misreporting. This is a particular challenge when studying older adults (McNeill, Winter et al. 2009). In addition to controlling dietary factors, researchers can control living and testing conditions in animals, and minimize the potential confounding effect of differing individual responses to treatment by using littermates. Finally, the short life span of animals compared to

humans means faster aging and therefore the ability to determine age-related changes more quickly than in humans.

Fruit and Vegetables

A number of studies have evaluated the effect of fruits or vegetables on cognition during aging. For example, vegetable intake has been examined as a possible factor in cognitive health during aging. In one study, cruciferous and green leafy vegetables had an apparent protective effect against cognitive decline using global assessment in women over 70 years old, and higher consumption of green leafy vegetables was associated with higher scores in episodic memory tests. However, consumption of other vegetables was not associated with higher test scores (Kang, Ascherio et al. 2005). A study by Morris et al. found that higher consumption of vegetables but not fruit was associated with slower cognitive decline in men and women over age 65 (Morris, Evans et al. 2006). In addition to these epidemiological human studies, some investigative animal studies have shown a relationship between fruit and vegetables and cognition (Joseph, Shukitt-Hale et al. 2005). In aged rats, eight week supplementation with strawberry, spinach, or blueberry extracts led to improvements in spatial memory compared to a control group (Joseph, Shukitt-Hale et al. 1999). Furthermore, blueberry supplementation restored long term potentiation and synaptic strength (measured by the excitatory post-synaptic potential), which decrease in normal aging, back to the level of young rats (Coultrap, Bickford et al. 2008).

Dietary Fat

In addition to fruit and vegetables, dietary fat and sugar have long been under consideration as important factors in cognitive function and brain health during aging. As reviewed by Youdim et al., dietary lipids likely affect brain physiology and consequently affect brain function (Youdim, Martin et al. 2000). In the aging brain, membrane concentration of docosahexaeneoic acid can decline, leading to impaired cognition. This long chain n-3 essential fatty acid may protect against age-related cognitive impairment because it stimulates antioxidant defenses (Wu, Ying et al. 2004), counteracts impairment of spatial memory induced by production and accumulation of beta amyloid, a peptide toxin, (Hashimoto, Tanabe et al. 2005), normalizes metabolism (Tsukada, Kakiuchi et al. 2000), and improves synaptosomal membrane fluidity. Furthermore, docosahexaeneoic acid concentrations are inversely correlated with diabetes and cardiovascular disease (Cole, Ma et al. 2009).

Because of these mechanisms, intake of fatty acids has been hypothesized to impact cognitive status during aging. The effect of n-3 fatty acids is reasonably expected to be beneficial, and the effect of saturated fatty acids negative. As in other areas of health, such as cardiovascular, the potential effects of n-6 and monounsaturated fatty acids are not clear. Surprisingly, evidence is mixed regarding the possible protective effects of n-3 polyunsaturated fatty acids on brain health. These fatty acids appear protective against AD (Cole, Ma et al. 2009), likely through incorporation into phospholipid membranes over time as shown in rats (Petursdottir, Farr et al. 2008). In a human cohort study, n-3 polyunsaturated fatty

acid intake was not associated with incidence of dementia over an average follow-up of six years among participants aged 55 years at baseline (Engelhart, Geerlings et al. 2002). In addition, a study showing inverse associations of fish consumption with cognitive impairment ruled out the n-3 polyunsaturated fatty acid found in fish by controlling for overall n-3 polyunsaturated fatty acid intake as the potential reason for the observed relationship (Morris, Evans et al. 2005).

Studies have also been conducted to investigate dietary fats other than n-3 polyunsaturated fatty acid, and most show neutral or negative effects on cognition. In a prospective longitudinal study among adults with an average baseline age of 68 years, linoleic acid, an n-6 polyunsaturated fatty acid, was weakly associated with cognitive decline (Kalmijn, Janssen et al. 2000). However, in the same cohort mentioned above, neither n-6 polyunsaturated fatty acid nor total polyunsaturated fatty acid or monounsaturated fatty acid intake were associated with incidence of dementia (Engelhart, Geerlings et al. 2002). A different cohort study increased the evidence for the role of dietary fat with its findings that consumption of monounsaturated fatty acid and the ratio of polyunsaturated:saturated fatty acid intake were each inversely associated with cognitive decline over 6 year follow-up period of participants with a baseline age of at least 65 years. Saturated fat and trans fat were associated with cognitive decline in this study (Morris, Evans et al. 2004), but not in the Rotterdam study, which also found no associated cognitive decline with total fat or cholesterol intake.

Dietary sugar

Substantial evidence supports the significance of blood sugar levels in brain health. It is apparent that chronic conditions associated with impairment of glycemic regulation in the blood are also associated with increased risk for a variety of cognitive disorders. In an excellent review, Roriz-Filho et al. discuss cognitive effects of diabetes and impaired glucose tolerance during aging, including impairments in cerebral vasculature function. Over time, these conditions are associated with decreases in cognitive performance and differences in brain anatomy compared to healthy adults (J, Sa-Roriz et al. 2009).

In humans, there has been much focus on the cognitive effects of altered glycemic control occurring during insulin resistance and type 2 diabetes (T2D). Insulin resistance and T2D are each risk factors for developing AD and vascular dementia (Yaffe, Blackwell et al. 2004; J, Sa-Roriz et al. 2009). Both T2D and pre-diabetes are associated with impaired cognitive performance and the development of impaired cognitive performance among post-menopausal women (Yaffe, Blackwell et al. 2004), and hyperglycemia is associated with other neuropsychiatric disorders (Bruce, Harrington et al. 2009). Imaging studies have substantiated these negative effects of dysregulation of blood glucose; for example, an MRI study found that atrophy of the hippocampus and amygdala was associated with T2DM (den Heijer, Vermeer et al. 2003)

Aside from the cognitive effects of impaired glucose metabolism associated with hyperglycemia, dietary intake of simple sugars may also have negative effects on cognition and the brain through direct and indirect mechanisms. Excess sucrose

exposure and intake can lead to obesity (Cohen 2008), and obesity in middle age and later in life has been associated with increased risk of AD development (Mrak 2009), possibly due to changes in cerebral vasculature. More direct evidence of the negative impact of sucrose on cognition is apparent in a study on diet-induced obese rats. Rats given access to a sucrose solution or a high fat diet became obese, but only the sucrose group displayed impaired spatial learning and memory, while the fat-exposed group did not show impaired cognition (Jurdak, Lichtenstein et al. 2008). A different study, in otherwise healthy rats, found that recovery after traumatic brain injury was impaired in rats on a high sugar diet compared to rats on a normal chow diet. In addition, levels of BDNF were lower in the high sugar group, which implies that dietary sugar could decrease synaptic plasticity and impair learning ability (Molteni, Barnard et al. 2002; Molteni, Wu et al. 2004). These studies together imply that dietary sugar may be a significant factor in cognitive function, but further acute studies need to be conducted to determine effects on cognitive performance and brain activation.

Antioxidants (vitamins C and E)

Because cognitive decline has been linked to lipid peroxidation in the brain, dietary antioxidants are likely to positively influence cognitive status. Particular emphasis has been on vitamins E and C. Results have been mixed, with some studies finding a beneficial effect of vitamins E and C, and other studies finding no association with cognitive performance or cognitive decline. In a two year clinical trial, vitamin E supplementation ameliorated cognitive decline in AD (Sano, Ernesto et al. 1997). In the Honolulu Aging Study, initial data analysis showed a

dramatically reduced odds ratio (0.12) of developing vascular dementia in men aged 71-94 who took vitamin E and C supplements compared to those who did not supplement (Masaki, Losonczy et al. 2000). Other studies have found either weak or no associations between vitamins E and C intake or status and the risk of cognitive decline or AD incidence (Riviere, Birlouez-Aragon et al. 1998; Foy, Passmore et al. 1999). Conclusions are further complicated by misalignment of what would be expected to be adequate dietary intake and the finding that AD and Parkinson disease patients may have lower plasma antioxidant capacity than in controls despite nutritional adequacy, suggesting differential utilization of these antioxidant vitamins in cognitive impairment.

Folic acid and Vitamin B12

Folic acid and vitamin B12 are two other vitamins that have been implicated as possible factors in brain health during aging. Older adults are at particular risk of vitamin B12 deficiency because of age-related impairments in the production of intrinsic factor, which is required for vitamin B12 metabolism. Vitamin B12 and folate are known to be important in overall neurological health, since folic acid deficiency is linked to neural tube defects in fetuses, and vitamin B12 deficiency causes neurological symptoms related to nerve damage (Black 2008). In addition, both of these vitamins are necessary coenzymes in the cycle that produces methionine during the metabolism of homocysteine, and higher homocysteine levels are associated with impaired cognition (Lehmann, Gottfries et al. 1999) and more atrophy of the hippocampal and cortical regions of the brain in healthy aging adults (den Heijer, Vermeer et al. 2003). It is not yet certain whether supplemental or

pharmaceutical doses of folic acid and vitamin B12, above the RDIs, might have positive effects on cognition. Instead, consuming adequate amounts of these vitamins might prevent the neurological symptoms associated with deficiency, with excess intake of these nutrients leading to no further improvements in cognitive function (Vogel, Dali-Youcef et al. 2009). The potential cognitive effects of each nutrient are difficult to independently determine because of their close relationship to each other regarding metabolism, function, consequences of deficiency, and potential effects of supplementation.

The suggested effects of these vitamins on cognition during aging has generated considerable interest and led to numerous studies. Investigations have focused on dietary intake (Kang, Ascherio et al. 2005; Devore, Grodstein et al. 2009) as well as serum status (Morris, Jacques et al. 2007) of these nutrients in subjects ranging from healthy participants (Plotnick, Corretti et al. 1997) to those with AD (Aisen, Schneider et al. 2008). Long term epidemiological studies have had mixed results, and may depend on factors such as nutrient status. For example, a high serum folate level (top quintile) appeared be protective against cognitive impairment among participants with normal serum B12 levels, but was associated with faster cognitive decline in participants whose serum levels of vitamin B12 were deficient (Morris, Jacques et al. 2007). Similar studies have shown mixed results, ranging from promising suggestions that folic acid or vitamin B12 are associated with cognition (Balk, Raman et al. 2007), to no association of dietary intake with AD (Morris, Evans et al. 2006), to increased rate of cognitive decline with higher serum folate levels (Morris, Evans et al. 2005). In an experimental study among

participants aged 50-70 years old, supplementation for three years of 800 micrograms daily of folic acid led to slower declines in selected cognitive domains compared to a placebo group (Durga, van Boxtel et al. 2007).

Other nutrients

In addition to the dietary factors discussed above, a variety of other nutritional factors may also affect cognitive performance and brain activation. They are too numerous to be discussed individually in great detail, but include vitamins, supplements, herbals, botanicals, and non-nutrient factors including phytochemicals. Much of the existing data about these nutrients in humans is from cross-sectional or epidemiological studies rather than experimental interventions. For example, a higher vitamin D intake was associated with higher cognitive functioning in age 65-99 black and white elders (Buell, Scott et al. 2009). Other cross-sectional studies using self reported dietary intake found that curcumin (Ng, Chiam et al. 2006) and lignans (Kreijkamp-Kaspers, Kok et al. 2007) were associated with less cognitive impairment among an older population. It is difficult to draw firm conclusions; for example, lignans are found in foods associated with health and potential dietary factors improving cognition, so the results found in the aforementioned study may not be due solely to lignan intake. Other factors potentially associated with cognition include garlic (Borek 2006) and soy isoflavones (Lee, Lee et al. 2005). However, it is impossible to determine cause and effect from observational studies. Some intervention studies have suggested the efficacy of ginkgo biloba (Kanowski, Herrmann et al. 1996), ginseng (Petkov, Kehayov et al. 1993; Wesnes, Ward et al.

2000), and guarana (Kennedy, Haskell et al. 2004; Kennedy, Haskell et al. 2008) extracts.

Instead of focusing on single nutrients or components, some studies have investigated the effects of dietary patterns, groups of nutrients, or whole foods. Fruits and vegetables are a common focus in these studies, and polyphenols from fruit may be beneficial for cognition, according to a review (Lau, Shukitt-Hale et al. 2005). Adherence to a Mediterranean dietary pattern has been associated with a lower risk of AD. This dietary pattern is high in fruit and vegetables, legumes, cereals, and monounsaturated fats mainly from olive oil, low in meat and poultry and saturated fat, and moderate in low fat dairy and red wine (Scarmeas, Luchsinger et al. 2009). Studies have found that strawberry and blueberry extract decrease oxidative stress in aging rats. Also, spinach, strawberry and blueberry increase vitamin E concentrations in brain, which could also lead to decreased detrimental oxidative stress. Spinach, strawberry, and blueberry dietary supplementation in these rats also improved memory compared to control groups (Joseph, Shukitt-Hale et al. 1999). Antioxidants are another broad group of nutrients that may decrease cognitive impairment. One type of antioxidants, flavanols, such as those found in cocoa, may decrease onset of AD and MCI (Patel, Rogers et al. 2008).

Exercise and the brain

Effects of chronic exercise and physical fitness on cognition

Physical activity is a lifestyle factor with a multitude of health benefits. Regular exercise decreases the risk of many conditions such as type 2 diabetes, metabolic syndrome, obesity (Brown, Avenell et al. 2009), stroke (Hooker, Sui et al.

2008), and hypertension (Brown, Avenell et al. 2009). Other benefits of exercise include promoting wound healing in low-risk punch biopsy (Emery, Kiecolt-Glaser et al. 2005) and after brain injury (Devine and Zafonte 2009), improving sleep quality (Cintra, Poyares et al. 2009), and improving mental health (Williams and Lord 1997). Another likely benefit of exercise is improved cognitive function. Positive effects of exercise on cognition have been noted throughout the human lifespan, from fetal brain development to cognitive performance in late adulthood (Hillman, Erickson et al. 2008). Exercise may affect cognitive function and the brain long term and acutely.

Chronic exercise may have beneficial effects on cognition during aging through a variety of mechanisms. Individuals with habitually higher levels of exercise or better physical fitness may have enhanced cognitive performance or decreased rate of cognitive decline compared to sedentary individuals (Colcombe, Kramer et al. 2004). Many possible mechanisms could explain these potential advantages of exercise. Effects of exercise related to cognition include increased neuroplasticity and neurogenesis, changes in endothelial function, and increased brain volume. Exercise stimulates the hippocampus to produce brain-derived neurotrophic factor (BDNF), which is a neurotrophic factor that promotes neurogenesis and is also associated with learning and memory (Minichiello, Korte et al. 1999). Another explanation for the proposed effects of exercise on cognition is the cardiovascular fitness hypothesis, which is the link between physical fitness and cerebral blood flow (CBF) (Swain, Harris et al. 2003; Ainslie, Cotter et al. 2008), cerebral structure (Colcombe, Erickson et al. 2003), and BDNF levels (Vaynman

and Gomez-Pinilla 2005). Exercise can improve vascular function by increasing vascular elasticity (Yung, Laher et al. 2009). Taken together, these physiological effects of exercise could conceivably improve cognition through their actions on the brain. However, studies have not directly tested whether these mechanisms explain the role of exercise on cognition in aging.

Some experimental studies have tested the effects of exercise on the brain. In one study among healthy older adults (average age 66 years), a six month aerobic training regimen consisting of walking for three times a week for 30 minutes found improved interference processing in healthy older adults compared to a stretching and toning control group (Colcombe, Kramer et al. 2004). A separate study among slightly younger (average age 57 years) clinically depressed adults tested the effects of a four month exercise intervention, and found improvements in executive function related to exercise compared to antidepressant treatment (Khatri, Blumenthal et al. 2001).

So far, a number of epidemiological studies have investigated the associations between physical activity and cognition during aging. Evidence is not sufficient to conclude a causal effect of exercise on cognition during aging, but many studies investigating the effects of exercise or physical fitness have found associations with cognition. These measures include cognitive performance (Bixby, Spalding et al. 2007) and slower rate of cognitive decline (Morris, Evans et al. 2005) during aging.

A meta-analysis on the effect of physical fitness on cognitive health in older adults concluded that there is an association between fitness and cognitive

performance (Colcombe and Kramer 2003). Another meta-analysis concluded that exercise training programs in elderly subjects with cognitive impairment or dementia increase fitness, physical and cognitive function, and positive behavior (Heyn, Abreu et al. 2004). Because of the implied link between fitness or training and cardiovascular adaptations, both of these studies support the cardiovascular fitness hypothesis that links physical fitness to improved cognition. However, in a separate study, a meta-regression was conducted to determine the effect of changes in fitness on cognition. While exercise apparently played a role in cognition, it was unclear whether fitness was even a positive or a negative factor. Factors such as age and health showed a bigger effect size than physical fitness, and in fact, increases in physical fitness were negatively associated with cognitive performance changes (Etnier, Nowell et al. 2006). As with studies on dietary factors, published evidence is not yet sufficient for making definitive statements on associations between exercise and cognition.

Acute effects of exercise on cognition

Observed effects of physical fitness and regular exercise on cognition are likely related to adaptations that result from regular exercise. There are also several acute physiological changes with acute exercise that may improve cognitive function. One study found that acute exercise led to an increase in brain-derived neurotrophic factor (BDNF) as well as improved cognitive performance on a stroop task (Ferris, Williams et al. 2007). Other acute effects of exercise include exercise-induced changes in blood flow and endothelial function. A normal response to exercise includes increased blood flow to peripheral tissues through vasodilation,

possibly through induction of endothelial nitric oxide (Endres, Gertz et al. 2003). Peripheral blood flow increases via increased systolic blood pressure and decreased diastolic blood pressure. A review of the literature shows that cerebral blood flow (CBF) may also increase during exercise, although to a lesser extent than peripheral blood flow (Querido and Sheel 2007). Heightened CBF may parallel increases in arterial blood pressure and vascular resistance (Kulikov, Doronina et al. 2009).

These studies did not directly assess measurements of brain function such as cognitive performance or brain activity, but the documented physiological effects of exercise may be conducive to cognition. In fact, some studies investigating the acute effects of exercise on cognition have found promising results for the acute role of exercise in executive function (Cordova, Silva et al. 2009). However, the effects are not certain, since not every study has found changes in cognition after exercise (Hillman, Snook et al. 2003; Audiffren, Tomporowski et al. 2009). Furthermore, experimental design has not been consistent between studies. Populations have varied widely, including studies in young healthy adults (Audiffren, Tomporowski et al. 2009; Pontifex, Hillman et al. 2009) and studies in older adults with chronic obstructive pulmonary disease (Emery, Honn et al. 2001). Another inconsistency between studies is the exercise bout, which varies in length, type, and intensity. Duration of exercise varies, ranging from 20 (Cordova, Silva et al. 2009) to 60 or more minutes (Hogervorst, Riedel et al. 1996) for the session. Acute bouts of exercise described in the literature include cycle ergometry (Emery, Honn et al. 2001; Cordova, Silva et al. 2009), maximal resistance exercise, and treadmill exercise (Pontifex, Hillman et al. 2009). Effort ranges from aerobic to maximal

effort (Hogervorst, Riedel et al. 1996; Emery, Honn et al. 2001). Taken together, these variations in study design and results have prevented the ability to draw conclusions about the effects of exercise.

Methods of measuring brain function

Numerous tests have been developed to evaluate cognitive function for a variety of purposes such as determining cognitive impairment or measuring cognitive performance. Assessing cognitive status is critical in studies related to brain function to ensure that study participants are at the appropriate cognitive condition for the requirements of the study design.

A common test used to indicate cognitive impairment, such as that associated with MCI or AD, is the mini-mental state examination (MMSE). This diagnostic test was developed as a clinical tool for physicians to evaluate cognitive status of patients (Folstein, Folstein et al. 1975), and is an excellent tool for identifying mild cognitive impairment and dementia in community and primary care settings (Mitchell 2009). Since its inception, the MMSE has also been used for research purposes. For example, a study among healthy participants might use the MMSE as a screening tool to ensure that participants are not cognitively impaired (de Jager, Schrijnemaekers et al. 2009). Another example of the utility of the MMSE is to monitor changes in cognition over time (Deschaintre, Richard et al. 2009). The MMSE has excellent sensitivity for detecting cognitive impairment, with one study showing 100% sensitivity in determining cognitive impairment in determining cognitive impairment compared to DSM-III guidelines among nearly three thousand participants aged over 65 years (Gagnon, Letenneur et al. 1990).

Furthermore, the MMSE has a low rate of false negatives (Anthony, LeResche et al. 1982).

The MMSE targets various cognitive domains relating to executive function, and these include mental tracking, expressive language, visual constructive, immediate free verbal recall, and delayed verbal free recall (Cullen, O'Neill et al. 2007). The test is administered in person by an interviewer. Questions are asked regarding orientation (time and date), registration (such as repeating objects in a list), attention and calculation (e.g., spelling "world" backward), recall (recalling objects in a list), and language (including following directions and writing a sentence). To see a sample MMSE test, please see Appendix 1. Each correct answer is worth one point, and the maximum possible score is 30 points. A score over 26 is usually considered normal among individuals with a high school education or more, and a score over 23 is considered normal among individuals who did not complete high school. Scores from 20 to 26 indicate mild cognitive impairment (MCI), 10 to 19 show moderate to severe cognitive impairment, and below ten indicates severe cognitive impairment (Folstein and Whitehouse 1983).

The St. Louis University Mental Status (SLUMS) examination is another method of assessing cognitive function. This assessment is a more recent development than the MMSE, and was designed as an alternative to the MMSE in evaluating mild neurocognitive impairment (Tariq, Tumosa et al. 2006). Like the MMSE, the SLUMS examination is administered in person by an interviewer, and it includes written and oral elements. Questions also include orientation (date and location), memory (recall of objects in a list), and attention (answering questions

about an audio story). A perfect score is 30 points. For a high school graduate, a score of 27-30 is considered normal, a score of 21-26 indicates mild neurocognitive impairment, and 1-20 is considered dementia. For a sample test, please see Appendix 2.

Beyond initial screening for dementia, more specialized tests can be used as study outcome measures in order to evaluate the effects of different treatments. The CogState® test (CogState© Limited, Melbourne, Australia) is an example of a novel method for measuring cognitive function. It is a recently developed battery of computerized tasks, and can be used for screening for dementia (Darby, Maruff et al. 2002) or for measuring cognitive performance in various domains (de Jager, Schrijnemaekers et al. 2009). Individual researchers can customize the battery to their specific studies by choosing which tasks to present to participants. Each task targets specific cognitive functions or domains, such as executive function, attention, spatial memory and delayed recall, learning, and memory (Pietrzak, Olver et al. 2009). The CogState® as chosen for this study takes about 20 minutes to complete. It is a repeatable test that has been shown not to have practice effects (Collie, Maruff et al. 2003; Falleti, Maruff et al. 2006). As a relatively new development, CogState® shows promise for evaluating cognitive performance in middle aged and older populations (Wild, Howieson et al. 2008; Padmanabhan, Leslie et al. 2009). One study found that compared to the well-established Hopkins Verbal Learning Test, the CogState® may have enhanced ability to detect cognitive deficits aside from memory (de Jager, Schrijnemaekers et al. 2009). Other studies have also used this battery in older populations to test cognitive function (Cargin,

Maruff et al. 2007; Paile-Hyvarinen, Raikkonen et al. 2009). The tests are scored for accuracy and for speed.

Another useful function of cognitive tasks in research studies is to activate specific areas of the brain so that brain imaging techniques can determine which pathways are being used for processing. The flanker interference task is an example of a task used to measure conflict monitoring skills (Eriksen and Schultz 1979). Conflict monitoring enables goal-oriented behavior, which contributes to decision making used in executive function tasks (Botvinick, Braver et al. 2001). There are multiple variations of the flanker inhibition task that can be used. In the flanker task, reaction time and accuracy of responses are measured. The flanker task can be composed of letters or arrowheads. For the arrowhead version of the flanker, participants must indicate whether the center arrow is pointing to the left or the right. Each prompt to the participant is either for a congruent or incongruent condition. In the congruent condition, all of the arrows are pointing in the same direction; in the incongruent condition, the center arrow is pointing toward the opposite direction of the other arrows. The congruent and incongruent conditions of the flanker task use different pathways in the brain (Ochsner, Hughes et al. 2009)

Methods of measuring brain activation

Measuring brain activation can yield valuable information about processes that are occurring in the brain during cognitive processes. Measuring brain activation while subjects are performing a particular task can reveal such information as processing speed, which brain regions are used for specific purposes, and neurocognitive pathways that connect different brain regions. Brain activation

can be studied noninvasively using a variety of methods that are based on neurovascular coupling, which is the principle that neuronal activity and cerebral blood flow (CBF) are related. Event-related potentials are measured using magnetoencephalography (MEG) and electroencephalography (EEG). Other techniques include positron emission tomography (PET), and functional magnetic resonance imaging (fMRI). These methods are discussed in greater detail in review papers (Wintermark, Sesay et al. 2005; Shibasaki 2008), and have been used to demonstrate age-related changes in brain function (Prichep 2007; Small, Bookheimer et al. 2008).

Both MEG and EEG are based on electrophysiology in the brain. MEG measures the magnetic fields produced from brain activity, and EEG measures their associated electric potentials. These methods have excellent temporal resolution, on the order of milliseconds. However, spatial resolution is as large as a centimeter, which is a limitation for using MEG and EEG.

Because of their superior spatial resolution within 4-6 mm, both PET and fMRI have been used to measure regional brain activation. Positron emission tomography is used to measure regional cerebral blood flow (rCBF), which increases with neuronal firing, and regional cerebral blood volume, which decreases with neuronal firing. A radioactive isotope with a short half-life is injected into the bloodstream. The isotope is then integrated into metabolic pathways so that metabolism can be measured. One commonly used isotope is ^{18}fluorodeoxyglucose (FDG). As FDG gets metabolized, the gamma radiation measured can be used to estimate accumulation of glucose consumption in specific regions. One example of

the use of PET is in the characterization of the brains of senescence-accelerated mice (SAM), which age rapidly. One study found that compared to normal mice, SAM exhibited increased oxidative stress and lower performance on behavioral tests. Using PET allowed the association of these characteristics with decreased brain glucose consumption and metabolism (Borras, Stvolinsky et al. 2009).

Functional magnetic resonance imaging is another technique used to measure brain activation in response to stimuli. Magnetic resonance imaging is based on differences in magnetic properties. One brain fMRI technique is the brain blood oxygenation level-dependent (BOLD) response (Buxton, Uludag et al. 2004). The BOLD response depends on changes in blood deoxyhemoglobin, which is paramagnetic. In response to neuronal firing, local blood flow increases to restore oxygen to active neurons. This increase in local blood flow is greater than local oxygen uptake by firing neurons, leading to a net decrease in deoxyhemoglobin concentration. Diamagnetic properties increase, leading to increased signal intensity. Advantages of fMRI include a shorter scanning time (since it is not necessary to wait for the uptake of radioactive isotopes), no need for exogenous contrast agents, and the ability to map the functional images to high-quality anatomical images gathered by the same scanner.

Functional MRI has been used to map regional changes in brain activation in response to simple tasks such as tapping a finger, solving arithmetic problems, or watching visual stimuli. This method has been used to determine which areas of the brain are active during various tasks. For example, fMRI experiments have confirmed that the anterior cingulate cortex (ACC) is active during conflict

monitoring and resolution, such as tasks requiring inhibition (Pochon, Riis et al. 2008). Furthermore, fMRI has shown a link between activity in the ACC and prefrontal cortex (Kerns, Cohen et al. 2004), both of which demonstrate the brain BOLD response during performance of Eriksen flanker tasks (MacDonald, Cohen et al. 2000; Botvinick, Braver et al. 2001). In the current study, regions of particular interest are based on a previous fMRI study measuring brain activation in older adults during a flanker arrow task. Right inferior frontal gyrus (IFG) / middle frontal gyrus (MFG) / precentral gyrus (PCG), as well as the right MFG / Brodmann Area 6 (BA6), showed activation during a flanker arrow task (Zhu 2008).

Various studies investigating the effects of diet and exercise on the brain have used fMRI to measure brain activation. A previously mentioned study assessed the effects of aerobic training, consisting of 30 minutes of walking three times weekly for six weeks, on cognition and brain activation in older adults (average age 66 years old). Compared to the control group, which met three times weekly for stretching and toning, the aerobically trained group showed increased activation in the prefrontal and parietal cortices and the ACC during a flanker arrow task (Colcombe, Kramer et al. 2004). There is also evidence that dietary factors can also affect the brain BOLD response. For example, a pilot study found that single dose of flavanol-rich cocoa led to increased cerebral blood flow. A consequent study found that five days of cocoa ingestion over five days led to an increase in the brain BOLD response during a task-switching paradigm (Francis, Head et al. 2006). A study investigating the acute effects of diet on the brain BOLD response compared the effects of a effects of a single control (350 kcal, 57% carbohydrates,

28% fat) or high-fat (765 kcal, 26% carbohydrates, 67% fat) meal on brain activation during a motor task. Reported results included a decrease in the brain BOLD response after ingestion of the high fat meal (Noseworthy, Alfonsi et al. 2003). However, a similar study looked at the acute effects of the same meals on the brain BOLD response during similar motor tasks, plus visual and integrative/cognitive tasks in healthy young adults. This study did not find a direct effect of postprandial lipemia on the brain BOLD response (Slade, Carlson et al. 2009). These studies still leave many gaps in the area of the brain BOLD response to dietary and exercise factors.

Study rationale

Gaps in literature

Despite the significance of the topic and the amount of interest, many aspects of the link between lifestyle and cognitive function during aging remain unknown (Van Dyk and Sano 2007). Many studies have looked at the relationship between long-term dietary intake of nutrients or foods and cognitive decline in aging humans. Epidemiological studies have suggested associations between dietary intake and brain health during aging, but evidence is inconclusive. Selected dietary factors appear to be associated with enhanced cognition (dietary fat, apple juice, vegetables, and B vitamins, for example) (Morris, Evans et al. 2004; Chan, Graves et al. 2006; Polidori, Pratico et al. 2009), some appear to be associated with impaired cognitive performance or accelerated cognitive decline (saturated fat, for example) (Kaplan and Greenwood 1998; Morris, Evans et al. 2004), and some have still undetermined effects on brain health (for example, total fat intake) (Kaplan and

Greenwood 1998; Ariogul, Cankurtaran et al. 2005). Similar to dietary factors, exercise is likely to impact cognitive function during aging, but here, too, the link is unclear. Over time, habitual exercise habits or physical fitness level may be correlated with improved cognitive function or slower cognitive decline (Cotman and Berchtold 2002; Colcombe, Erickson et al. 2006), but the possible effects of exercise on cognition are still unclear (Colcombe and Kramer 2003).

The possible acute effects of diet and PA on cognitive function and brain activation are also unclear, and less research has been conducted on acute effects than on long-term epidemiological studies to determine possible associations or correlations with habitual lifestyle factors. In an aging population especially, research on the acute effects on cognition is sparse, and the potential acute effects of various lifestyle factors is largely undetermined. To our knowledge, no studies have combined a single mixed meal plus a bout of exercise within the recommendations (non vigorous) in this population of healthy older adults. One study has investigated the effects of a 14 day lifestyle longevity program of diet, exercise, relaxation exercises, mental exercises, on cognitive function and brain activation (Small, Silverman et al. 2006). The intervention group showed improvements in word fluency compared to the control group. Findings from this study are promising, since the two-week intervention period is far less than the time periods measured in prospective epidemiological studies, and suggest the need to determine whether a single meal or exercise bout can show effects on the brain.

Justification

The acute effect of diet and exercise on cognition in an aging population is an exciting and important area of study. The American population includes an increasing number of older adults. Aging is associated with cognitive impairment or decline, but it may be possible to slow or decrease these negative effects through the modifiable lifestyle factors of diet and exercise. It is currently unknown whether a single meal and bout of moderate intensity exercise can acutely affect executive function and brain activation in healthy older adults. Results of this study are an important addition to our knowledge of cognition in the aging brain. Determining whether either a single mixed meal or a bout of exercise is effective in altering cognitive performance or brain activation will increase our understanding of the potential ways in which lifestyle impacts cognitive health during aging.

Findings from this study will help elucidate the role of lifestyle factors on cognition. Any changes or lack of change in cognitive performance or brain activation between treatments (SB, NB, or NB + AE) will help uncover the potential connections between these lifestyle factors and cognition. In addition, changes that are found would imply certain modes of action for how diet or physical activity would influence cognition. Eventually, knowing this could help to guide development of recommendations for the most effective diet and exercise regimens for cognition in an aging population so that individuals can have greater control over their brain health.

This study is truly a novel experiment in many regards. The study design is unique for its combination of population and treatments. Participants in this study,

unlike in other acute cognitive studies, are representative of a healthy aging population (Pfeiffer, Ludwig et al. 2005; Ferris, Williams et al. 2007; Chui and Greenwood 2008). Furthermore, compared to many published acute studies on lifestyle factors and brain activation, the treatments in this study could conceivably be more representative of what an individual might choose in real life regarding diet and exercise. The SB meal is representative of American dietary patterns in its macronutrient composition, and it is also composed of palatable, standard foods in the American diet. While components of the NB diet are by design different from the SB diet, it is still conceivable that individuals would be willing to choose a breakfast like this one. This is in contrast to the majority of previous acute experimental studies whose treatments have instead been a concentrated amount of a specific nutrient or food, or combination of nutrients or food that are given in doses unlikely to be consumed in a typical meal. Similarly, the bout of exercise in this study may be a more accurate representation of reality for most individuals. The majority of published studies have looked at the acute effects on cognition following a bout of more intense exercise (Hogervorst, Riedel et al. 1996; Kashihara and Nakahara 2005; Cordova, Silva et al. 2009). In contrast, the exercise intensity in this study is only moderate, and may be a more likely portrayal of what individuals might be willing and able to do in a free-living setting.

Aside from its novelty regarding the specific diet and exercise treatments, this study is innovative because of its outcome measures, which include assessment both of cognitive performance and of brain activation. While multiple diet or exercise studies have focused on cognitive performance (Netz, Tomer et al. 2007;

Chui and Greenwood 2008; Cordova, Silva et al. 2009; Kashihara, Maruyama et al. 2009; Nilsson, Radeborg et al. 2009) or brain activation using fMRI (Francis, Head et al. 2006) or other techniques (Kamijo, Hayashi et al. 2009) to measure brain activity, this study investigates both of these. Executive function will be assessed using the CogState battery of tests, and changes in brain activation in the middle frontal gyrus and superior frontal gyrus after treatment will be assessed using fMRI to measure the brain oxygen level-dependent (BOLD) response (Buxton, Uludag et al. 2004) during a Flanker arrow paradigm.

The purpose of this study was to assess acute effects of a breakfast and bout of aerobic exercise on the cognitive function and the brain BOLD response in a healthy aging population, using two different diets and a bout of moderate aerobic exercise. We compared the acute effects of a single meal: a standard breakfast (SB), modeled after a realistic American breakfast, and a nutrient dense breakfast (NB). The SB diet included components thought to have negative effects on the brain, including high amounts of saturated fat and sugar. The NB included dietary components associated with improved cognition or endothelial function, including antioxidants, fruit and vegetables, and omega-3 fatty acids. To check whether exercise might have additional effects on cognition, the third branch of the study (NB + AE) included the NB breakfast plus a bout of moderate exercise within the American College of Sports Medicine (ACSM) and American Heart Association (AHA) joint recommendations for older adults (Nelson, Rejeski et al. 2007). We hypothesized that compared to SB, NB would improve executive function and brain

activation in the inferior frontal gyrus and middle frontal gyrus (regions associated with inhibition), and that AE would further enhance these effects.

Chapter II. Acute effects of diet and exercise on cognitive function and brain activation in an aging population

Abstract

Aging and lifestyle factors have been associated with cognitive decline. Certain diet components or patterns, or exercise regimens may help increase cognition or slow age-related cognitive decline. Epidemiological aging studies suggest a role of diet and exercise in cognition but less is known about acute effects. This study's objective was to compare the effects of a high saturated fat, low nutrient dense standard breakfast (SB), nutrient dense breakfast (NB), and NB combined with aerobic exercise (30 minutes at 50-65% estimated heart rate reserve, AE), on cognitive function and brain activation in aging adults. This was a three arm, randomized, cross-over design among healthy adults (n=19, 69.7 ± 4.9 y). Participants ate a SB or NB (NB, NB + AE treatments) breakfast and walked (NB + AE condition) for 30 minutes at 50-65% estimated heart rate reserve. Cognitive function was assessed with CogState® battery of tasks. Brain activation was evaluated through the brain blood oxygen level-dependent response during functional MRI with a flanker arrow task requiring inhibition control. Compared to SB, NB with or without AE did not improve cognition in healthy older adults. There was a significant improvement in accuracy on the prediction task (executive function) in the CogState® battery between in the NB compared to the NB + AE condition ($p<0.05$). In addition, there was a significant increase in response time in

NB compared to SB ($p<0.05$) in the monitoring task (testing attention). No significant treatment effects were seen in the flanker arrow task. Brain activation (percent signal change) was not significantly different between treatments in the regions of interest in the right inferior frontal gyrus, middle frontal gyrus, precentral gyrus (centroid at R39, A3, S32), and in the right middle frontal gyrus, Brodmann Area 6 (centroid at R29, P1, S54). This study was designed to test the effects of palatable meals and a bout of moderate exercise on cognition in healthy older adults. Although longer interventions of diet and exercise may affect cognitive function and/or brain activation in older adults, our results suggest these lifestyle factors do not have acute effects.

Introduction

Nutrient intake and physical activity patterns throughout the lifespan can influence cognition during older adulthood, a time when cognitive function tends to decline and is of widespread concern (Connell, Scott Roberts et al. 2007; Gillette Guyonnet, Abellan Van Kan et al. 2007; Hillman, Erickson et al. 2008; Wilcox, Sharkey et al. 2009). In particular, executive function may be impaired, often decreasing performance on tasks involving memory or interference (Jones, Nyberg et al. 2006). Dietary patterns associated with a Mediterranean diet may be protective against development of AD (Scarmeas, Luchsinger et al. 2009). Foods such as vegetables and fish, and nutrients such as antioxidants and omega-3 fatty acids, may ameliorate age-related decline (Denny 2008). Herbal supplements may also be effective, as demonstrated in a trial that found improvements in cognitive symptoms with 52 weeks of ginkgo supplementation in patients with mild AD (Le

Bars, Katz et al. 1997). In contrast, long term consumption of diets high in saturated fat and refined sugar are associated with impaired learning and decreased neuronal plasticity in rats (Molteni, Barnard et al. 2002). In humans as well, selected studies have shown associations between consumption of saturated fat, trans fat, and sugars, and development of impaired cognitive function and accelerated cognitive decline (Morris, Evans et al. 2004).

Studies also suggest the beneficial effects of exercise on cognition. Hillman, Motl et al. found that among individuals aged 15-71 years, higher physical activity levels were associated with faster reaction time in a flanker task, which tests interference control. In addition, increased physical activity was positively associated with accuracy in the older adults (40-71 years) (Hillman, Motl et al. 2006). Other studies also correlate increased fitness or physical activity levels with less cognitive decline over time (Berkman, Seeman et al. 1993; Kramer, Colcombe et al. 2003; Sturman, Morris et al. 2005) or with improved cognitive function (Colcombe, Kramer et al. 2004; Lindwall, Rennemark et al. 2008). These studies investigate associations rather than causal relationships, and do not combine the effects of both diet and exercise. One experimental study looked at the effects of diet and exercise over two weeks. Small et al. (2006) reported improved executive function (word fluency) following a lifestyle longevity regime including mental and physical exercise, a "longevity diet" (high in fruit and vegetables and low in saturated fat), and relaxation, in a small sample of 35-69 year old adults. Furthermore, the intervention group displayed a decrease in resting activity in the left dorsolateral prefrontal cortex. This suggests that lifestyle factors may cause

changes in cognition and brain function within weeks (Small, Silverman et al. 2006).

In addition to influences of chronic intake of certain foods and physical exercise on cognition in humans, dietary components and exercise may also have acute effects on cognitive function. For example, a single meal may impair cognitive among individuals with impaired glycemic control, and these effects are attenuated with simultaneous ingestion of antioxidant vitamins (Chui and Greenwood 2008). Phytochemicals or supplements may be effective as well (Youdim and Joseph 2001). For example, ginseng improved serial sevens subtraction performance and decreased subjective fatigue (VAS) one hour after dose (Reay, Kennedy et al. 2005). However, research in this area is limited. The effects of a single bout of exercise have been studied somewhat more extensively than effects of a single meal, and exercise may improve cognitive function acutely (Kashihara and Nakahara 2005; Audiffren, Tomporowski et al. 2009; Cordova, Silva et al. 2009).

Although diet and exercise are evidently important in cognitive function, no studies to our knowledge have tested the acute effects of a single meal and bout of exercise on executive function and brain activation in older adults. We tested the acute effects of these lifestyle factors on executive performance using a battery of computerized tests (CogState®). In addition, our study measured the brain blood oxygen level-dependent (BOLD) response (Buxton, Uludag et al. 2004) during functional magnetic resonance imaging (fMRI) during a flanker task to determine activation in interference regions of the brain. Our objective was to compare the

acute effects of diet and exercise on cognitive performance and brain activation. To test the effects of nutrition on cognitive function and brain activation, we compared two different meals. The standard breakfast (SB) included factors, such as high levels of sugar and saturated fat and low nutrient density, that may impair cognition (Molteni, Barnard et al. 2002; Wu, Molteni et al. 2003), while the nutrient dense breakfast (NB) incorporated numerous factors, such as antioxidants, n-3 fatty acids, whole grains, fruits, and vegetables, that may enhance cognition (Morris, Evans et al. 2002; Wu, Ying et al. 2004; Chui and Greenwood 2008). In addition, because of the evidence suggesting the acute benefits of exercise, we also tested whether a bout of moderate aerobic exercise (AE) would increase any observed effects of NB. We hypothesized that NB would improve cognitive function and brain activation in the inferior frontal gyrus and middle frontal gyrus compared to SB, and that AE would further enhance these effects.

Materials and Methods

Participants: All procedures were approved by the Michigan State University Institutional Review Board for human studies. Participants each gave informed written consent (Appendix 3), and also signed a compliance form for the Health Insurance Portability and Accountability Act (Appendix 4). Healthy adults over 60 years old and with no unstable disease state were recruited from the Lansing, Michigan, area.

Inclusion criteria were right handedness (assessed by the Edinburgh handedness inventory (Oldfield 1971), age greater than 60 years old, and no dementia, as assessed by initial self-report and by Mini-Mental State Examination

(MMSE) score (score < 27 among individuals with a high school education, or a score < 24 among individuals without a high school diploma). Participants had to be willing to consume each of the meals that were served. They also had to be able to complete the exercise bout of 30 minutes of treadmill walking, and were required to obtain written permission from their personal physicians (Appendix 5) to participate in the AE. Participants had to be able to undergo MRI as determined by a magnetic materials safety form (Appendix 6).

Exclusion criteria included a self-report of habitually exceeding recommendations for AE from the American College of Sports Medicine and the American Heart Association (Nelson, Rejeski et al. 2007). Based on these recommendations, potential participants were excluded if they reported exercising for 5 or more days a week for at least 30 minutes at a moderate intensity, or for 3 or more days a week for at least 30 minutes at a vigorous intensity. Potential participants were also excluded if they did not consume meat, could not walk for 30 consecutive minutes on a treadmill or could not undergo MRI due to claustrophobia, body weight > 114 kg or BMI > 35, or metallic implants that were not MRI compatible. Other exclusion criteria were the use of beta blockers, dementia or anti-psychotic medications, or insulin, history of stroke, presence of recent cardiovascular events, severe hypertension (systolic blood pressure > 200 mm Hg), diabetes, moderate to severe depression, fibromyalgia, chronic fatigue syndrome, peripheral vascular or arterial disease, or a chronic infectious disease.

Out of the 26 screened individuals who met the inclusion criteria, 19 finished all three treatment arms of the study. One individual had hyperglycemia,

with a fasting glucose level of 13.3 mmol* L^{-1}). One subject did not complete the AE session because of recent hospitalization for atrial fibrillation. Another subject was unable to complete the AE session because of an abnormal EKG as read by the physician. Of the 19 participants who completed the three treatments, 11 also completed the fMRI. The smaller subset was due to technical issues (n=3), enlarged ventricles (n=2), and excessive motion (n=3) that could not be corrected. Participants were compensated $25 for each laboratory visit, and participants received results of their participation in the study (see Appendix 12).

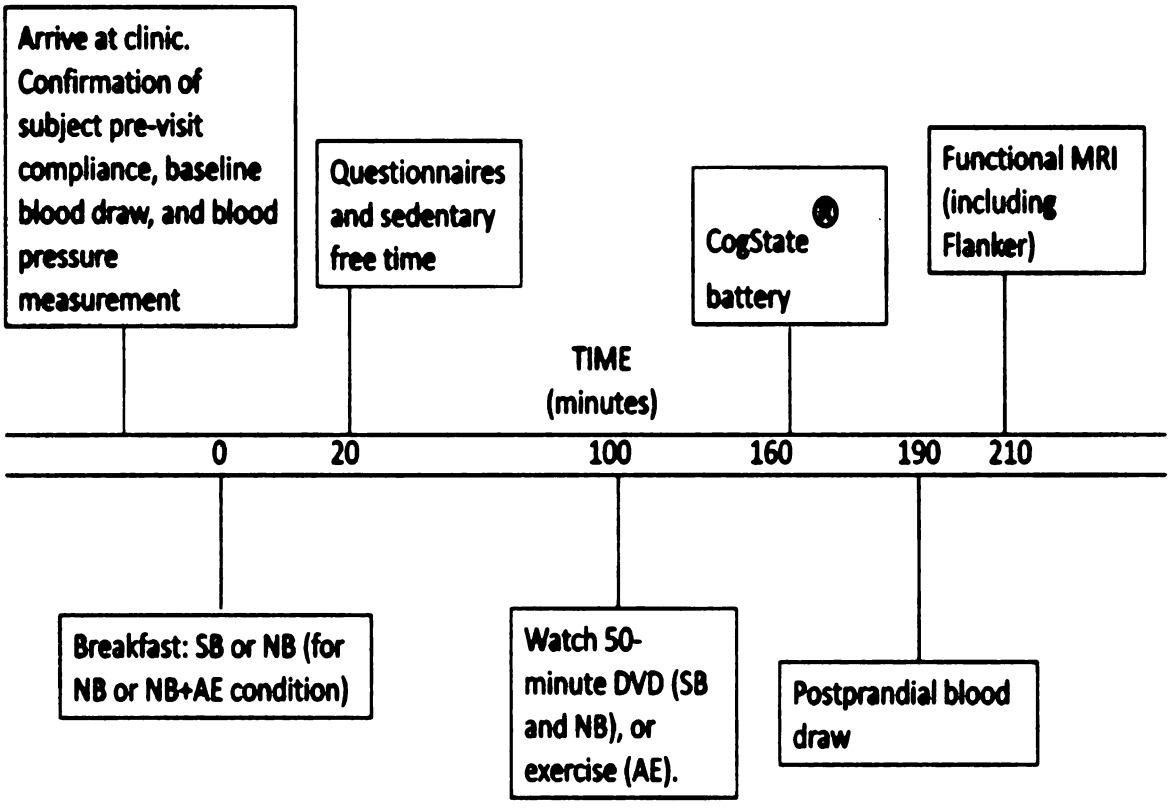
Study overview: We used a three-arm unblinded randomized crossover design. Subjects made four visits to the laboratory. Visit one was an introductory visit. Visits two through four were treatments administered in random order, separated by at least three days.

Previsit instructions for treatment visits included maintaining their habitual dietary pattern for the duration of the study, and drinking plenty of fluids and refraining from exercise the day before the visit. Participants arrived at the clinic after a ten hour fast, with no caffeine consumption or aspirin use on the day of the visit.

See Figure 1 for the protocol for visits 2-4. Participants arrived at 9:00 a.m. Blood pressure was taken manually with a cuff sphygmanomometer and blood was drawn. Breakfast was served at 9:20, and participants had 20 minutes to consume the meal. Next, subjects completed one of the remaining questionnaires (SLUMS or geriatric depression scale (GDS)), or reviewed their food records and PA logs for clarity. Subjects then had 30-60 minutes to complete perform a sedentary activity

such as reading, and they repeated this activity each visit. At 11:00, they began to watch a DVD or exercise (AE). At 11:50, subjects took the CogState© exam. The postprandial blood draw was at 12:30, immediately followed by the MRI exam, which lasted about 45 minutes.

Figure 1: Schematic of protocol.



SB = standard breakfast, NB = nutrient dense breakfast, AE = aerobic exercise.

Treatments

Diets: The standard breakfast (SB) was low in nutrient density and high in saturated fat and simple carbohydrates; it included components that plausibly could impair cognition and/or vascular function based on previous studies (Kaplan and

Greenwood 1998; Molteni, Barnard et al. 2002; Bourre 2006). The nutrient dense cognitive diet (NB) breakfast included components believed to enhance cognition and/or vascular function (Gillette Guyonnet, Abellan Van Kan et al. 2007). The meal provided 400, 550, or 700 calories, or approximately 25% of subjects' daily caloric needs based on the Harris-Benedict equation (Harris 1919) and appropriate activity factors based on self-reported habitual physical activity levels. Breakfast portions were measured using an Ohaus Scout® Pro Balance electronic scale (Ohaus Corporation, Pine Brook, New Jersey). Table 1 and Table 2 show the specific breakfast foods and nutrients profile, respectively. The macro-composition as a percent of total kilocalories was 55% fat, 27% carbohydrate, 16% protein, and 25% saturated fat, and it contained < 1 g dietary fiber. The macro-composition as a percent of total kcal was 30% fat, 54% carbohydrate, 7% protein, and less than 1% saturated fat, and it included 26 g fiber. The NB breakfast was also high in antioxidants with the 700 kcal breakfast containing an oxidative radical antioxidant capacity value of approximately 21217 based on calculations from the USDA database (USDA 2007). None of the components in the SB breakfast were included in the USDA database, implying an oxidative radical antioxidant capacity value of zero. Subjects consumed each meal within 20 minutes.

Table 1: Nutrients in the 700 kilocalorie breakfasts

Nutrient	Standard breakfast	Nutrient dense breakfast
% kilocalories from fat	55	30
% kilocalories from saturated fat	25	<1
n-3 fatty acids, g	0.3	2.2
% kilocalories from protein	16	17
% kilocalories from carbohydrate	27	54
% kilocalories from sugars	25	13
dietary fiber, g	1	26
servings of fruit and vegetables	0	3
vitamin C, mg	1.3	49
vitamin E, mg	0.9	3.8
potassium, mg	402	1097
folate, dietary folate equivalents, μg	77	199
vitamin B12, μg	0.41	4.9
kilocalories	700	700

Table 2: Composition of the 700 kilocalorie breakfasts

Standard breakfast	
Food	Amount
white bread	25 g
butter	5 g
jelly (regular sugar)	10 g
fruit drink	177 ml
whole milk	267 ml
2 scrambled eggs	2 large
sausage, breakfast pork	56 g
decaffeinated tea/coffee	177 ml

Table 2 (continued)

Nutrient dense breakfast	
Food	Amount
cereal, Kashi go lean crunch	53 g
soy milk, vanilla	177 ml
blueberries, unsweetened, frozen	155 g
vegetarian sausage, breakfast patties	76 g
bread, whole wheat, 100%	28 g
almond butter	10 g
fruit spread, blueberry, 100% fruit	15 g
juice, vegetable, canned	177 ml
nuts, walnuts, English, dried	14 g
tea, green, authentic, brewed	240 ml

Exercise: The AE bout was supervised by an American Cardiac Life Support (ACLS)-certified physician. The exercise session included a 5 min warm-up at a self-selected walking pace, 30 min of walking at goal intensity, and 5 min of a slow cool-down. The goal intensity was 50-65% of estimated heart rate reserve, calculated as RHR+0.5(MHR-RHR), where RHR is resting heart rate and MHR is estimated maximal heart rate based on 220-age (Fox, Naughton et al. 1971). Participants maintained the treadmill speed, and the percent incline on the treadmill was adjusted to achieve the target heart rate. Data were recorded on an exercise

documentation form (Appendix 8). Electrocardiograms were monitored throughout the warm-up, exercise, cool-down, and short recovery period, and recorded using the Nasiff Interpretive PC ECG/PC EKG (Cardiocard) program (Nassiff Associates, Brewerton, New York). Every 5 minutes, blood pressure was taken manually according to AHA scientific guidelines (Pickering, Hall et al. 2005) to ensure an appropriate response to exercise. In addition, participants were asked to use the Borg Scale for ratings of perceived exertion (RPE) (Borg, Hassmen et al. 1987). For the SB and NB visits, subjects viewed a neutral 50 min documentary video prior to the CogState© and fMRI. Participants' personal physicians received a letter summarizing the exercise session (Appendix 13) and the EKG.

Measurements: Clinic visit 1 familiarized participants with parts of the study including walking on the treadmill and using the Borg Scale for rating of perceived exertion, practicing the cognitive battery exam twice, and having a mock MRI exam. Height and weight, ankle brachial index, and resting heart rate were measured during this visit, and the Mini-Mental State Examination (Folstein and Whitehouse 1983) was administered.

Dietary assessment: Participants were asked to complete a three day food record for assessment of usual intake. The three days consisted of two days during the week (non-holiday Monday through Friday) and a weekend day (Saturday or Sunday), and participants were asked to record days that were representative of their usual intake. Food records were reviewed with participants to clarify items and portion sizes. Food record data were analyzed using Food Processor (ESHA Research, Salem, Oregon). Average intake of select nutrients is shown in Table 5.

Participant dietary intake was compared both to national recommendations and to national average intakes.

Physical activity assessment: Habitual physical activity was estimated using GT1M Activity Monitors (Actigraph, Pensacola, Florida). Participants were asked to wear an accelerometer for 7 consecutive days during which they kept activity levels at their normal levels. During those 7 days, participants recorded their sleep, long distance travel, and activities in a physical activity log, to help interpret the accelerometer data, which was used to estimate usual physical activity levels of participants. Participants were asked to place the accelerometers on either hip using a provided belt hook, and to remove the accelerometer for water activities and sleeping. Data were downloaded to a computer. Output was expressed in counts per 1-minute epoch. For each individual, total daily counts were converted to daily kilocalories of expenditure. Activity was classified by counts per 1-minute epoch using the cut points ≤ 1951 (light), 1952-5724 (moderate), 5725-9498 (hard), or 9499 (very hard) counts per minute (Freedson, Melanson et al. 1998). Complete accelerometer data were obtained for 16 participants. The accelerometers of two study participants did not download properly, and the final participant did not wear an accelerometer.

Other cognitive assessment: During subsequent visits, participants filled out the short form-36, cognitive failures questionnaire (Broadbent, Cooper et al. 1982) (Appendix 9), and the Saint Louis University Mental Status Examination (Tariq, Tumosa et al. 2006) (Appendix 2). At the end of the visit, participants were given instructions for preparation for future visits (Appendix 10).

Blood analyses: Blood samples were obtained through routine venipuncture of the median cubital vein by a trained phlebotomist. For each of the three treatment visits, blood samples were taken both fasting and postprandial (180 minutes). Samples clotted for 30 minutes, and were centrifuged. Serum was frozen at -20°C for later analysis by Sparrow Hospital laboratories. Samples were analyzed for glucose and insulin to assess glycemic control and tolerance, which can influence post-prandial cognitive function (Nilsson, Radeborg et al. 2009). Timing of cognitive testing and fMRI were based on the postprandial rise in triglycerides, which have been shown to peak within 2-3 hours postprandial (Cortes, Nunez et al. 2006). Total cholesterol, HDL cholesterol and LDL cholesterol were also measured. For each serum measure, a repeated measures analysis of variance was used to compare fasting concentrations between the three visits. The gains scores between fasting and postprandial draws were compared using repeated measures analysis of variance to test the effects of treatment (SB, NB, and NB + AE) on changes in concentrations. Analysis was conducted using SPSS software 17.0 (SPSS, Chicago, IL), and significance was set at $p < 0.05$.

Cognitive assessment:

The computerized CogState© battery (CogState© Limited, Melbourne, Australia) included nine tasks, each targeting a certain domain of cognition. For each of the 9 different tests, Table 3 shows the name of the test, the specific cognition, and the question to which participants were responding.

Table 3: CogState© battery of tests

Individual Test	Abbreviation	Cognitive Domain Tested	Test Question
Continuous Paired Associate Learning	CPAL	Memory and Spatial Memory	In what locations do these pictures belong?
One Word Learn	OWL	Verbal Memory	Have you seen this word repeatedly before?
Identification	IDN	Visual Attention	Is the card red?
One Back	ONB	Attention/Working Memory	Is the previous card the same?
One Card Learn	OCL	Visual Learning and Memory	Have you seen this card before in this task?
Monitoring	MON	Attention	Has a card touched a white line?
Prediction	PRD	Executive Function	Is the next card red?
Continuous Paired Associate Learning-Delayed Recall	CPAR	Memory and Spatial Memory-Delayed Recall	In what locations did these pictures belong?
One Word Learn Delayed Recall	OWLR	Long Term Memory	Have you seen this word repeatedly before?

Each participant practiced the entire battery twice during their initial introductory visit, and these practice tests were not scored. Each testing session included task instructions and a non-scored short pre-test for each task to remind participants of how to complete that particular task. During the testing, a researcher was in the room to give any necessary assistance with instructions. Each task was scored for accuracy and for reaction time. To help avoid skewness, accuracy scores were computed as the inverse sine of the fraction correct, while reaction times were computed as the logarithm of the response time in milliseconds.

The study protocol required each participant to take the CogState battery a total of five times: the first two times, on the introductory visit, were unscored, while the three times during the treatment visits were scored and used as outcome measures. A repeated measures analysis of variance was used to evaluate possible effects of which breakfast (SB or NB) was consumed first (n=19). To test effects of condition (SB, NB, or NB + AE) and time (visit one, two or three) on accuracy and response speed, a repeated measures general linear model analysis of variance with Bonferroni–adjusted pairwise comparison was performed using SPSS software 17.0 (SPSS, Chicago, IL). Significance was set at $p < 0.05$.

Flanker paradigm: An Erikson Flanker arrow task was used during the functional scans of the MRI. There were three functional runs of 7 minutes each, and it was a rapid event-related paradigm. Stimuli were rows of 7 arrows. The center arrow pointed either in the same (congruent (C)) ("<<<<<<<" or ">>>>>>>") or the opposite (incongruent (IC)) ("<<< > <<<" or "<<< > <<<") direction as the flanking arrows. Arrows pointed either to the right or left. Text was white, presented on a black background.

Each of the stimuli conditions (C or IC) was presented for 2500 ms 48 times every run, with each condition presented an equal number of times in each direction. Stimuli were randomized using an "RSFgen" program from AFNI software (Cox 1996). Also, baseline data were gathered by randomly presenting a white fixation cross at the center of the black viewing screen for 2500ms 72 times within the run, so that the ratio of stimuli presentation to baseline for each run was 96:72. During the Flanker stimuli, participants were to indicate as quickly as possible whether the

center arrow was pointing to the right or to the left by pressing a button. During the fixation crosses, participants were instructed to continue viewing the screen but not to press a response button. A repeated measures general linear model analysis of variance was used to test effects of condition on accuracy (percent correct) and response speed (milliseconds). Analysis was performed using SPSS software 17.0 (SPSS, Chicago, IL). Significance was set at $p < 0.05$.

fMRI:

Set-up: The instructions and stimuli were back-projected on a 32 inch LCD screen behind the magnet bore. Participants viewed the stimuli through a mirror attached to the top of the head coil. The LCD screen subtended 10° x 13° of visual angle. Responses of whether the center arrow was pointing left or right and response times were recorded using a pair of 5-button keypads. The functional paradigm was controlled by IFIS-SA (Invivo, Gainesville, Florida), and subjects responded to cues using their right or left index fingers.

Acquisition: Images were collected using a GE 3T Signa® HDx MR scanner (GE Healthcare, Waukesha, WI) with an 8-channel head coil. Subjects were supine, and motion was limited by foam padding. During each scanning session, images were acquired for localization, and then first- and higher-order shimming was done to improve magnetic field homogeneity. Functional echo planar images (three runs) were acquired with 34 axial slices with TE = 27 ms, TR = 2500 ms, flip angle = 80°, field of view = 22 cm, matrix size = 64 x 64. The first four data points of each run were discarded. Each set of slices was acquired 168 times during each

functional run. After the functional data acquisition, high-resolution volumetric T1-weighted spoiled gradient-recalled images with cerebrospinal fluid suppressed were obtained to cover the whole brain with 120 1.5 mm sagittal slices, 500 ms time of inversion, 24 cm FOV and 8° flip angle.

Data analysis:

All fMRI data pre-processing and analyses were conducted with AFNI software (Cox 1996). For each subject, the acquisition timing difference was first corrected for different slice locations. With the first functional image as the reference, rigid-body motion correction was done in three translational and three rotational directions. The amount of motion in these directions was estimated and then the estimations were used in data analysis. For each subject, spatial blurring with a full width half maximum of 4 mm was used to reduce random noise (Parrish, Gitelman et al. 2000), and also to reduce the issue of inter-subject anatomical variation and Talairach transformation variation during group analysis. For the group analysis, all images were converted to Talairach coordinate space (Rey, Dellatolas et al. 1988) with an interpolation to 1 mm^3 voxels. Throughout the paper, the coordinates of brain activity are presented in Talairach space in the format of (RL, AP, IS) in mm, where R = Right, L = Left, A = Anterior, P = Posterior, I = Inferior, and S = Superior.

For the data analysis of each individual subject, the impulse response function (IRF) at each voxel with respect to each stimulus condition was resolved with multiple linear regressions using the "3dDeconvolve" software in AFNI (Ward, Shum et al. 2002). The IRFs were resolved to seven points from zero to 15 sec at the resolution of 2.5 sec. The BOLD signal change was calculated based on the area under the IRF curve.

The equivalent BOLD percent signal change relative to the baseline state was then calculated for each flanker type (congruent and incongruent). The MRI signal modeling also included the subject motion estimations in the three translational and the three rotational directions, and the constant, linear and quadratic trends for each of the three functional runs.

A region of interest analysis was used to compare the BOLD response between conditions. After deconvolution of the impulse response function, the BOLD activation was extracted from two regions in the frontal cortex previously shown to be differentially active during a similar rapid-event related flanker paradigm in older adults (Zhu 2008). These regions were a 849 mm^3 cluster at the right inferior frontal gyrus, middle frontal gyrus, precentral gyrus (centroid at R39,A3,S32) and a 437 mm^3 cluster at the right middle frontal gyrus, Brodmann Area 6 (centroid at R29, P1, S54). The BOLD activation from the incongruent condition compared to fixation was examined. Peak BOLD signal intensity (SI) was compared across conditions with repeated measures ANOVA. Significance was set at $p < 0.05$.

Results

Table 4: Participant characteristics

Characteristic (n = 19 unless otherwise indicated)	Value
Age (years)	69.7 ± 4.9
Number female/male	14/5
body mass index (kg/m^2)	24.7 ± 3.2
years of education	16 ± 3
systolic blood pressure (mmHg)	124 ± 14
diastolic blood pressure (mmHg)	74 ± 8
ankle brachial index [a]	1.2 ± 0.1
resting heart rate (beats/min)	63 ± 7
physical activity (kilocalories/day) (n=16)	254 ± 114
physical activity (bouts per week of moderate or more intense physical activity) (n=16)	1.6 ± 1.9
Fasting triglycerides (mg/dl)	101 ± 16
Total cholesterol (mg/dl)	205 ± 12
HDL cholesterol (mg/dl)	70 ± 9
LDL cholesterol (mg/dl)	118 ± 10
Fasting glucose (mmol/L)	5.0 ± 0.2
Fasting insulin (µmol/L)	0.2 ± 0.1
mini-mental state examination score [b]	29.1 ± 1
St. Louis University mental status score [c]	28 ± 2.5
geriatric depression scale score [d]	0.1 ± 0.4

Table 4 (continued)

Values are mean ± standard deviation.

Abbreviations: HDL = high density lipoprotein, LDL = low density lipoprotein.

[a] average of right and left. Ankle brachial index was calculated as the ratio of the blood pressure in the ankle (average of pressure of posterior and anterior tibial arteries) to the blood pressure in the brachial artery.

[b] score out of 30 on MMSE (Folstein and Whitehouse 1983); cognitive impairment may be indicated by a score < 27 among individuals with a high school education, or a score < 24 among individuals without a high school diploma.

[c] score on SLUMS out of 30; a score < 27 may indicate cognitive impairment.

[d] score on the short form of the geriatric depression scale (Almeida and Almeida 1999) out of a possible 15 points. A score > 5 indicates possible depression and the need for medical follow-up.

Table 5: Average habitual daily intake of study participants.

Nutrient	Intake	Range
kilocalories	1778	1214 – 2579
% kilocalories from fat	33 ± 4	25 – 38
% kilocalories from saturated fat	10 ± 2	6 – 13
n-3 fatty acids, g	0.5 ± 0.5	0.1 – 2.5
% kilocalories from protein	16 ± 5	11 – 32
% kilocalories from carbohydrate	52 ± 6	34 – 58
dietary fiber, g	22 ± 6	11 – 35
servings of fruit and vegetables	4.3 ± 2.3	2.0 – 9.3
vitamin C, mg	122 ± 68	55 – 297
vitamin E, mg	9.7 ± 8.5	0.7 – 33.5
potassium, mg	2259 ± 559	1517 - 3710
folate, dietary folate equivalents, µg	446 ± 249	145 – 871
vitamin B12, µg	5.5 ± 4.1	2.1 – 16.8

Values are based on three day food records of usual intake and presented as mean ± standard deviation and range; n=19.

Table 6 shows the timing of data collection for the subjects.

Table 6: Timing of data collection

	SB	NB	NB + AE
completion of breakfast	16 ± 5	19 ± 6	19 ± 6
video or aerobic exercise	98 ± 9	93 ± 12	111 ± 15
completion of aerobic exercise	N/A	N/A	161 ± 17
start of CogState®	156 ± 8	152 ± 14	172 ± 16
postprandial blood draw	189 ± 11	176 ± 46	204 ± 18
MRI and flanker task (midpoint)	204 ± 15	201 ± 20	220 ± 16

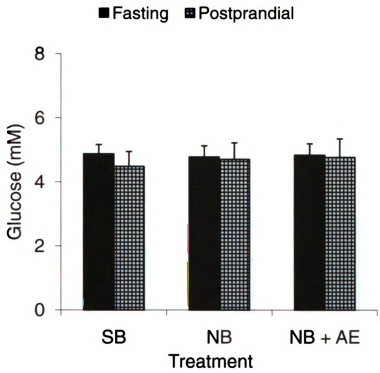
Values are presented as mean ± standard deviation in minutes after being served breakfast (n= 19).

Breakfast: A total of eight participants ate the 400 kcal breakfasts, ten ate the 550 kcal breakfasts, and one ate the 700 kcal breakfasts. Compliance for breakfast consumption among the nineteen participants was nearly complete. All but one consumed the entire SB, with the remaining participant refusing to drink the decaffeinated coffee because of the taste. Two participants, one assigned to the 400 kcal breakfast and one assigned to the 550 kcal breakfast, each reported being too full to finish the NB breakfast. The participant assigned to the 400 kcal breakfast left uneaten half of the toast with almond butter and fruit spread (80 kcal), while the other left uneaten half of the cereal with soy milk (100 kcal). Study data were included for these subjects.

Exercise: The average exercise intensity during the 30 minute bout was 56 ± 6 % HRR. Post-exercise systolic blood pressure tended to decrease from a resting average of 127 ± 15 mmHg pre-exercise to 119 ± 13 mmHg post exercise (p=0.09), and diastolic blood pressure significantly decreased from 73 ± 9 to 65 ± 6 mmHg (p=0.004). Systolic blood pressure at the end of exercise was 147 ± 17 mmHg, and diastolic was 69 ± 9 mmHg. All 19 subjects completed the entire exercise bout.

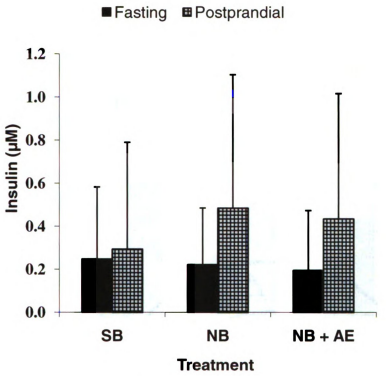
Serum glucose, insulin, and lipid levels: Blood was drawn at an average of 190 minutes after the meal was served. Serum levels of glucose, insulin, and lipids are shown in Figure 2, Figure 3, and Figure 4, respectively, for n=19 participants for glucose, insulin, and triglycerides in SB and NB conditions, and n=18 participants for NB + AE triglycerides (the laboratory did not report results for triglycerides for one subject's postprandial triglyceride levels in the NB + AE condition). There were no differences in fasting values between the three visits with treatment. The magnitude of change between fasting and postprandial serum glucose levels was significantly different in SB compared to NB + AE ($p = 0.026$), with a trend toward a significant difference in SB compared to NB ($p = 0.052$). For insulin, the magnitude of the change from fasting levels was significantly different in SB compared to NB ($p = 0.001$) and to NB + AE ($p = 0.013$). For triglycerides, the magnitude of the change from fasting to postprandial measurements was significantly different in SB compared to NB + AE ($p < 0.001$) with a trend toward significance for SB compared to NB ($p = 0.055$). For each of the three treatments, total cholesterol, HDL cholesterol, and LDL cholesterol did not change significantly between the fasting state and the postprandial blood draw (data not shown).

Figure 2: Fasting and postprandial serum concentrations of glucose.



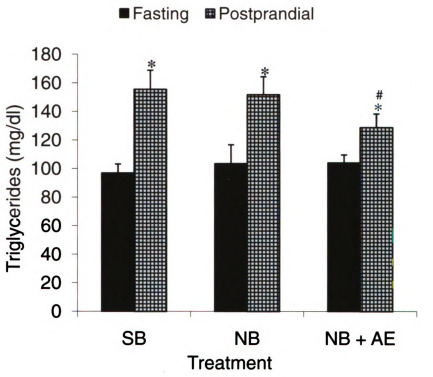
Fasting and postprandial serum glucose concentrations for n=19 participants. SB = standard breakfast, NB = nutrient dense breakfast, AE = aerobic exercise. Values are mean ± SD.

Figure 3: Fasting and postprandial serum concentrations of insulin



Fasting and postprandial serum insulin concentrations for n=19 participants. SB = standard breakfast, NB = nutrient dense breakfast, AE = aerobic exercise. Values are mean ± SD.

Figure 4: Fasting and postprandial serum concentrations of triglycerides



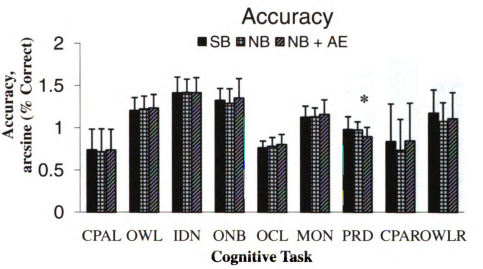
Fasting and postprandial serum concentrations for n=19 participants for SB and NB, and n=18 participants for NB + AE. SB = standard breakfast, NB = nutrient dense breakfast, AE = aerobic exercise. * significantly different from fasting, # significantly smaller postprandial increase compared to SB, $p < 0.05$. Values are mean ± SD.

CogState Results

Results for accuracy on the CogState® battery are shown in Figure 5 and expressed as arcsine (% correct) for each task in the battery. Overall, ND and ND + AE did not improve cognitive performance compared to SB. Repeated measures analysis using a general linear model showed that for the prediction task,

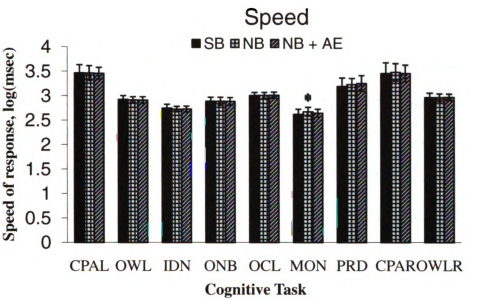
performance was significantly better during the NB condition compared to the NB + AE condition ($p = 0.031$). For the other tasks, there was no effect of treatment or time on accuracy. Results for response time are shown in Figure 6 and expressed as log-transformation of time, in milliseconds, to answer the question. Repeated measures analysis using a general linear model showed that for the monitoring task, performance was significantly faster during the NB condition compared to the SB condition for response time ($p = 0.048$). There were no significant effects of treatment on accuracy or response time for the other cognitive tasks. In addition, there was no significant effect of which breakfast was served first (data not shown).

Figure 5: CogState® battery results for response accuracy



Data are shown as mean arcsine (percent correct) ± standard deviation; n=19. CPAL=continuous paired associated learning, OWL=one word learn, IDN=identification, ONB=one back, OCL=one card learn, MON=monitoring, PRD=prediction, CPAR=continuous paired associate learning recall, OWLR=one word learn recall. * significantly different from SB condition, $p<0.05$.

Figure 6: CogState® battery results for response speed



Data are shown as mean log (response time, msec) ± standard deviation; n=19. CPAL=continuous paired associated learning, OWL=one word learn, IDN=identification, ONB=one back, OCL=one card learn, MON=monitoring, PRD=prediction, CPAR=continuous paired associate learning recall, OWLR=one word learn recall. * significantly different from SB condition, $p<0.05$

Flanker results

Flanker results are summarized in Table 1Table 7. Overall, performance was highly accurate, with a 99% accuracy rate in C and 98% correct in IC over the three runs and for each treatment condition. There was no significant effect of treatment on accuracy. As expected, the response times for IC and C were significantly different, with the overall average for IC 880 ± 24 msec and C 762 ± 37 msec ($p<0.001$). There were no significant effects of time or treatment on the percent difference in response time between IC and C.

Table 7: Flanker results

	Acc C	Time C	Acc IC	Time IC	Time (IC – C)	IC-C*100% C
SB	99%	753 msec	99%	866 msec	112 ± 60 msec	15.0%
NB	98%	766 msec	98%	888 msec	121 ± 57 msec	16.1%
NB + AE	99%	766 msec	98%	888 msec	121 ± 63 msec	16.2%
Average	98%	762 msec	98%	880 msec	118 msec	15.5%

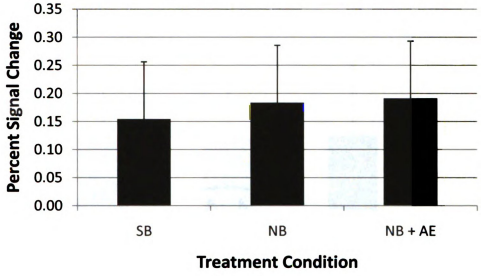
Results for the Flanker test (n=16). SB = standard breakfast. ND = nutrient dense breakfast. AE = aerobic exercise. C = congruent condition. IC = incongruent condition.

fMRI results

Brain activation was extracted from two distinct regions of interest: a 849 mm^3 cluster at the right IFG, MFG, PFG (centroid at R39,A3,S32), and a 437 mm^3 cluster at the right MFG, BA 6 (centroid at R29, P1, S54), shown in Figure 9 and Figure 10. The brain BOLD response between incongruent flanker and baseline (fixation cross) conditions was similar between treatment conditions. Neither region showed a significant effect of treatment on peak BOLD response between any of the conditions (Figure 7 and Figure 8). The peak percent signal change from baseline for each condition averaged between 0.16% to 0.19% in the IFG / MFG / PFG cluster (Figure 7), and 0.17% to 0.19% in the MFG / BA6 cluster (Figure 8). When averaging over all treatments, the range of peak BOLD was 0.079-0.0359 % in the IFG / MFG /PCG and 0.048 – 0.291 % in the MFG / BA6 cluster. The

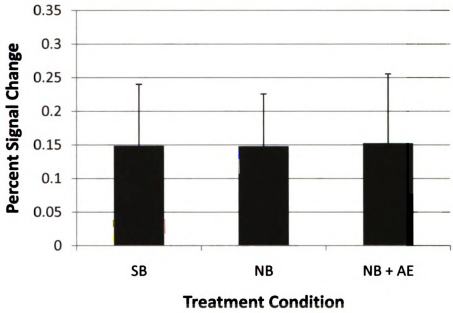
average hemodynamic IRFs are shown for each condition in Figure 9 and Figure 10 for each region. Although there are subtle visual differences in the response curves, there were no significant differences between the conditions.

Figure 7: fMRI percent signal change in IFG / MFG / PCG



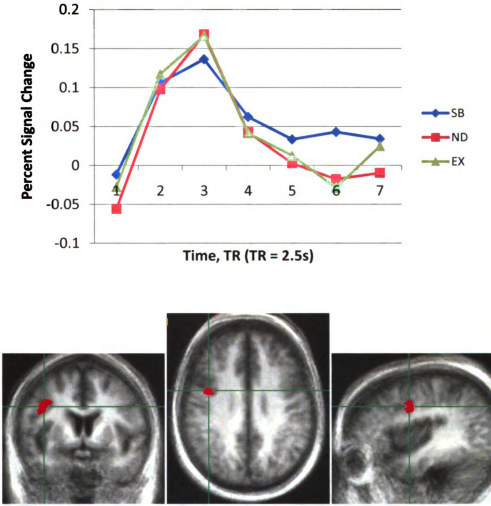
Values are mean ± standard deviation of percent signal change in the brain BOLD response for the incongruent condition compared to baseline in a 849 mm^3 cluster at the right inferior frontal gyrus (IFG), middle frontal gyrus (MFG), precentral gyrus (PCG)(centroid at R39,A3,S32) (n=11). SB = standard breakfast, NB = nutrient dense breakfast, NB + AE = nutrient dense breakfast plus aerobic exercise, R = right, A = anterior, S = superior.

Figure 8: fMRI percent signal change in MFG / BA6



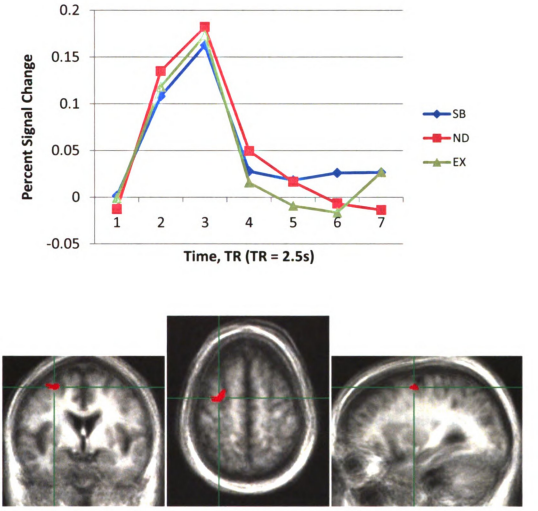
Values are mean ± standard deviation of percent signal change in the brain BOLD response for the incongruent condition compared to baseline in a 437 mm^3 cluster at the right middle frontal gyrus (MFG), Brodmann Area 6 (BA6) (centroid at R29, P1, S54) (n=11). SB = standard breakfast, NB = nutrient dense breakfast, NB + AE = nutrient dense breakfast plus aerobic exercise, R = right, A = anterior, S = superior.

Figure 9: Group BOLD response in IFG / MFG / PCG



Group-averaged ROI analysis of the brain BOLD response in the IFG/MFG/PCG region (n = 11). The graph shows the average impulse response function in response to incongruent flanker stimulus presentation. Images are of a 849 mm^3 cluster located at the right inferior frontal gyrus (IFG), middle frontal gyrus (MFG), precentral gyrus (PCG) (centroid at R39,A3,S32). SB = standard breakfast, NB = nutrient dense breakfast, NB + AE = nutrient dense breakfast plus aerobic exercise, R = right, A = anterior, S = superior.

Figure 10: Group BOLD response in MFG / BA6



Group-averaged ROI analysis of the brain BOLD response in the MFG/BA6 region (n = 11). The graph shows the average impulse response function in response to incongruent flanker stimulus presentation. Images are of a 437 mm^3 cluster at the right middle frontal gyrus (MFG), Brodmann Area 6 (BA6) (centroid at R29, P1, S54). SB = standard breakfast, NB = nutrient dense breakfast, NB + AE = nutrient dense breakfast plus aerobic exercise, R = right, A = anterior, S = superior.

Discussion

The objective of this study was to evaluate the acute effects of a meal and aerobic exercise on cognitive function and brain activation. Our study is an important addition to current knowledge about the effect of lifestyle factors in this population. In contrast to our hypotheses, we did not find large overall effects of treatment, with significant differences found only in accuracy on the prediction task (Figure 5) and in response speed in monitoring (Figure 6) in the CogState® battery.

To our knowledge, this study was the first to compare the acute effects on cognitive function and brain activation in a healthy aging population of a high saturated fat, high sugar, low nutrient density meal with a nutrient-dense mixed meal, comprised of nutrients such as antioxidants, n-3 fatty acids, and folic acid, in combination with a bout of exercise. Much of the current data on healthy brain aging comes from epidemiological studies demonstrating correlations rather than causation. Participants in previous studies of acute effects have been younger adults (Nappo, Esposito et al. 2002; Kashihara and Nakahara 2005). Furthermore, existing studies on the acute effects of diet and exercise on cognition have only investigated specific nutrients, such as cocoa flavanols (Francis, Head et al. 2006) or a sole bout of exercise rather than an entire meal in addition to exercise. Our study was also novel in its inclusion of fMRI as well as the CogState® test battery to measure brain activation in addition to cognitive performance in executive tasks.

Participant baseline characteristics categorized them as a healthy aging population (Table 1). There was no cognitive impairment as measured by the MMSE assessment, which is a widely used method of detecting cognitive

impairment (Mitchell 2009). The SLUMS assessment was developed in order to improve diagnosis of mild neurocognitive disorder (Tariq, Tumosa et al. 2006). Our study resulted in three subjects achieving normal MMSE scores of 30, 29, and 28, and scores on the SLUMS (23, 24, and 25) that indicate possible cognitive impairment. In general, lipid profiles were low risk, serum insulin and glucose were within the healthy range, and the average blood pressure was normal. Analysis of three-day food records showed that participants had adequate intake of key nutrients, which may have impacted response to treatment. As an example, the average intake for fiber of study participants reported in their three-day food records was above the national average intake (Appendix 14); it is possible that participants with a lower average fiber intake at baseline may have shown a greater effect of the NB breakfast.

The American Heart Association and American College of Sports Medicine recommends that older adults complete 30 minutes of moderate physical activity, five or more days a week (Nelson, Rejeski et al. 2007). Out of the 16 participants who had complete accelerometer data over seven days, two met those criteria according to the accelerometer classifications of exercise intensity based on counts per minute. This information was validated with subjective assessment of activity in the corresponding logs.

Other tests have documented declines in executive function with age (Zimmerman, DelBello et al. 2006), and the CogState® test also shows potential for use in aging populations, as in our study. Another study that used this battery resulted in similar scores on the identification (attention) and one-back (visual

attention and working memory) tasks, which are the two specific tasks in common with our study. Participants included healthy adults who were 69 years old on average (Cargin, Maruff et al. 2007).

We had hypothesized a beneficial effect of NB and a further increase in performance with the addition of AE, but found no difference from the SB treatment. The frontal lobe hypothesis of aging partially attributes decline to slow changes in neuroanatomy during aging (Park, Smith et al. 1996). Therefore, measurable changes in executive function would require time for interventions to show effects. Changes in cognitive performance would not be detectable in an acute study such as ours. The novelty of the CogState® battery and its customizable nature make comparison between studies difficult, but participants in our study showed no signs of cognitive impairment based on their CogState® results when compared to published data on healthy younger (age 46 ± 10 years) participants (Maruff, Thomas et al. 2009).

We did randomize the study treatment order, but it is unlikely that this study was affected by potential practice effects in the CogState® battery. In one study, no practice effects were shown with repeated testing over a period of one month. The tasks tested in that study included identification, monitoring, and one-back tests (Falleti, Maruff et al. 2006). Additional testing investigated the practice effects of taking the identification and one-back tasks four times within three hours, and found a maximum of 90 msec improvement in reaction time and 15% improvement in accuracy between test-taking occasions (Collie, Maruff et al. 2003).

The Flanker arrow task tests inhibition abilities, which decline with age due to decreased executive function (McCabe, Robertson et al. 2005) and decreased ability to ignore proactive interference during memory tasks (Emery, Hale et al. 2008). Further potential differences between processing in younger and older adults are revealed by the finding that aging is associated with slower reaction times in flanker tests both in congruent and incongruent conditions (Hillman, Motl et al. 2006; Zhu 2008). A study using a similar arrow flanker paradigm found similar results to our study. The study by Kamijo et al. did not find significant effects of light and moderate exercise on flanker inhibition in older adults aged 60-74 years old (Kamijo, Hayashi et al. 2009). Reaction time improved only slightly in both congruent and incongruent conditions. Therefore, our data are not inconsistent with these recently published findings which do not show improved cognitive performance during inhibition in older adults following acute aerobic exercise.

We had hypothesized that the difference in reaction time between C and IC conditions would decrease in NB and even further with the addition of AE, demonstrating enhanced ability to perform inhibition and decision making tasks. However, the analysis of percent change in reaction time in the IC condition compared to the C condition did not show an effect of treatment on any task. A possible explanation for our findings could be that the SB, NB, and NB + AE treatment conditions did not affect the particular functions tested by the Eriksen flanker arrow task at a detectable magnitude.

Another novel aspect of this study is the inclusion of fMRI to determine the acute effects of diet and exercise on brain activation. We had hypothesized that NB

and AE would increase activation in inhibitory regions of the brain such as IFG and MFG. We had expected an increase in BOLD response indicating increased neuronal firing during NB and AE treatments due to an improved cognitive response during the Flanker task. However, as we did not measure behavior differences, lack of differences in activation are expected, and we did not see differences between treatments in the BOLD response. It is plausible that different factors in our study may have had opposing effects on cerebral blood flow, which may be correlated with the endothelial function, or the brain BOLD response. Treatment factors in our study that likely increased blood flow or endothelial function included AE and certain components of the NB breakfast such as monounsaturated fat (Karatzi, Papamichael et al. 2008), and the antioxidant vitamins C and E (Plotnick, Corretti et al. 1997). However, these factors may have been negated by a potential decrease in the brain BOLD response in our target brain regions after NB and AE due to decreased effort used to complete the Flanker task. In addition, the fMRI exam was completed on average approximately 90 minutes after AE, which may have been too long after AE for increased blood flow to continue. As our study also found (data not shown), blood pressure drops below pre-exercise levels within minutes after completion of AE but recovers 90 minutes post-exercise (Kenney and Seals 1993; Kulics, Collins et al. 1999).

The results of our study imply that the beneficial effects of diet and exercise do not occur immediately, and may only occur after longer exposure to a specific treatment. For example, a cross sectional study among healthy older adults found an association between vitamin B6 and B12 intake and greater grey matter volume,

and this is likely a long term effect of diet (Erickson, Suever et al. 2008). This conclusion is consistent with longer term studies of both diet and exercise effects. Certain dietary patterns are associated with maintenance of cognitive function during aging (Kang, Ascherio et al. 2005) and (Masaki, Losonczy et al. 2000), while others are associated with accelerated cognitive decline (Morris, Evans et al. 2004). Physical fitness, which is a likely result of habitual exercise, is associated with increased cortical capillary supply, synaptic connections, and neuron development among older adults (Kramer, Bherer et al. 2004). In addition, increased habitual levels of physical activity may be associated with higher cognitive performance and less cognitive decline (Weuve, Kang et al. 2004; Hillman, Motl et al. 2006), although the reduction in relative risk of developing cognitive impairment may be small (Podewils, Guallar et al. 2005).

The acute effects of diet and exercise on cognitive performance and brain activation in an aging population have not been thoroughly investigated. Our study adds to the knowledge in this area. Future acute studies may help elucidate the mechanism behind the effects of diet and exercise. For example, future studies could measure brain-derived neurotrophic factor (BDNF), which has been shown to be important in cognition. The neurotrophic factor BDNF is associated with less cognitive impairment in adults and is associated with increased synaptic and neuronal plasticity (Gunstad, Benitez et al. 2008) which typically decline with age (Burke and Barnes 2006). Since BDNF decreases with saturated fat intake (Molteni, Wu et al. 2004) and increases with exercise (Gold, Schulz et al. 2003), our study treatments likely affected BDNF levels.

Additional future directions could include more intervention studies. Some studies should investigate effects of long-term dietary and exercise interventions on cognition in older populations. Other studies might evaluate acute effects of isolated nutrition components to determine specific effects, since our study only looked at mixed meals. Additionally, studies could compare results in younger and older adults.

Future studies are needed to determine if longer term diet and exercise regimens, such as for weeks or months, can improve cognition in older adults. An effective method of determining the required time to achieve results would be to implement a diet and exercise regimen and monitor subjects regularly over time until changes in cognitive performance or brain activation can be detected. In addition, the particular dietary components and exercise that may acutely affect cognition should be further investigated in this population. This could be done by including separate and combined treatments to unravel specific effects. In addition, there is a need to determine the specific frequency, duration, and intensity of exercise needed to achieve results.

Chapter III: Conclusions

This study was the first we know of to investigate the acute effects of a nutrient dense mixed meal in combination with a bout of exercise on cognitive function and brain activation in healthy older adults without dementia. Many previous studies on determinants of healthy brain aging have been epidemiological, allowing them to demonstrate only correlations rather than causative relationships between lifestyle factors and cognitive performance or decline. For example, a Mediterranean diet and PA were associated with a lower risk of developing AD according to the results of a prospective cohort study (Scarmeas, Luchsinger et al. 2009). Acute studies have shown positive effects of exercise on cognitive performance, but subjects in these studies have mainly been animals (Soya, Nakamura et al. 2007) or younger adults (Chui and Greenwood 2008; Audiffren, Tomporowski et al. 2009). Older adults may respond differently than young adults to a meal or a bout of physical activity.

Furthermore, existing studies investigating acute effects of diet and exercise have looked only at isolated meal components or a bout of exercise rather than an entire meal in addition to exercise (Hillman, Snook et al. 2003; Francis, Head et al. 2006). The present study looked at the effects of a full meal in addition to a bout of exercise. Compared to a specific food or nutritional supplement, a mixed meal, such as the NB breakfast that was included in this study, is more representative of what individuals might choose to improve their cognitive and overall health during aging. Our study did not find acute effects of a single meal on cognitive function, underscoring the importance of the need to systematically evaluate long-term

dietary patterns in brain health during aging. Long-term intervention studies could support data from observational studies that show associations between diet and cognitive function.

Population

The relative uniqueness of our study population compared to populations studied in the published literature may help to explain our study results. Cognitive status, typical dietary intake and nutritional status, and physical activity habits may all influence the effect of diet or exercise interventions such as those in our study. Previous studies have mainly been conducted in populations that may be different from in the current study in their ages (Francis, Head et al. 2006) or health condition, such as cognitive or nutritional status (Malouf, Grimley et al. 2003). For example, one of the few fMRI studies investigating the effects of a dietary component found that cocoa flavanol ingestion led to an increase in the brain BOLD response (Francis, Head et al. 2006). However, this study was conducted in younger adults, who may have a greater BOLD response than older adults (Ances, Liang et al. 2008).

Cognitive health is another important factor for study results. Some experimental studies finding clear implications about the role of diet in cognitive health focus on populations with cognitive impairment at baseline. For example, studies have examined the progression of cognitive decline during cognitive disorders such as AD (Aisen, Schneider et al. 2008) or MCI or dementia (Malouf, Grimley et al. 2003). One such investigation found that increased intake of vitamins C and E from supplements or food sources like oils may slow cognitive decline during AD (Engelhart, Geerlings et al. 2002); this may be because of certain altered

metabolism displayed by AD patients compared to healthy individuals. Patients with AD have decreased vitamin C and E antioxidant capacity (Foy, Passmore et al. 1999), as well as increased oxidative stress in brain tissue and an associated lower vitamin C status (Riviere, Birlouez-Aragon et al. 1998) than healthy controls. This may explain the efficacy of antioxidant supplementation in AD, and suggests that supplementation does not necessarily improve cognition function in healthy individuals. Healthy individuals may respond to specific lifestyle regimens differently than AD or otherwise cognitively impaired individuals. This is illustrated by a set of data from the Honolulu Aging Study also focusing on the effects of vitamin C and E supplement use on cognitive function and decline during aging. Initial analysis suggested a protective effect of vitamin C and E supplementation against vascular dementia and cognitive decline (Masaki, Losonczy et al. 2000). However, later analysis to exclude those with dementia at the start of the study found that there was no association between supplementation use and risk of dementia (Laurin, Foley et al. 2002). Our study, which was conducted among individuals with no known cognitive impairment, may have different results than studies among cognitively impaired individuals. Our study population was also highly educated, with an average of 16 years of formal education.

Nutritional status, typical intake, and exercise habits are other important considerations when interpreting the results of studies on nutrition and cognition because they can determine how certain nutrients affect cognition. For example, data from NHANES show varying relationships between folate intake and cognitive

function depending on nutritional status. In participants with adequate vitamin B12 status, higher folate intake was associated with decreased relative risk (0.4) of cognitive impairment; conversely, higher folate intake along with vitamin B12 deficiency was associated with a higher relative risk (2.6) of cognitive impairment (Morris, Jacques et al. 2007). These results demonstrate the significance of nutrient status when evaluating the effects of dietary interventions on cognitive function. For our study, participants were likely nutritionally adequate based on their general health and three-day food record of usual intake (Table 5). Furthermore, compared to national averages, study participants on average had higher intakes of nutrients such as fiber (22 grams compared to 14) that indicate overall dietary quality. Participants were near national intakes for folate, vitamin B12, and potassium (USDA 2008).

Study Meals: Standard Breakfast and Nutrient Dense Breakfast

Formulation of the SB and NB breakfasts was based on available studies regarding the relationship between nutrition and exercise. According to the literature, certain dietary patterns are associated with improved cognition and slower cognitive decline over time (Masaki, Losonczy et al. 2000; Kang, Ascherio et al. 2005), while others are associated with accelerated cognitive decline (Morris, Evans et al. 2004). The SB meal was reflective of a common American breakfast, including pork sausage, scrambled eggs and cheese, toast and jelly, decaffeinated coffee, and a sugar-based fruit drink. The SB meal included dietary factors that may be detrimental to cognitive health over time. As shown in Table 1, 25% of the calories in SB were from saturated fat, and another 25% of the calories were from

sugar. Each of these nutrients has been linked to impaired cognition or accelerated cognitive decline (Molteni, Barnard et al. 2002; Morris, Evans et al. 2004).

In contrast to the SB breakfast, the NB breakfast was formulated to benefit cognitive function. It minimized saturated fat (< 1% total energy), and was extremely low in added sugars, both of which may impair cognition. This breakfast was designed to improve cognitive performance by incorporating foods and nutrients such as vegetables, n-3 fatty acids, soy products, and blueberries, which have been linked to improved cognition according to the results of previous studies (Denny 2008). Overall, there were minimal effects of diet on cognitive function; most tasks showed no difference between treatments.

Response time during a monitoring task involving attention was slightly faster for NB compared to SB. The outcome of minimal differences in the main cognitive outcomes in this study may partially be attributed to the dietary factors used in our study. For example, the NB breakfast incorporated a generous amount of fruits and vegetables (2.5 servings per 700 kcal) because of evidence suggesting that fruit and vegetable intake may be a positive factor in brain health during aging (Polidori, Pratico et al. 2009). One particularly convincing cross-sectional study compared healthy subjects aged 45-102 years classified as having high intake or low intake according to responses on food frequency questionnaires. After accounting for age, nearly every individual in the higher intake group scored higher than nearly every individual in the low intake group. Similar results were found with plasma antioxidant status and cognitive scores (Polidori, Pratico et al. 2009). A separate study found a slower rate of cognitive decline among aging women with the highest

cruciferous vegetable and green leafy vegetable intakes (Kang, Ascherio et al. 2005).

The fat content of the SB and NB breakfasts was another interesting dietary factor in our study. Studies have published conflicting results about the associations between dietary fats and cognition. For instance, the incidence of dementia in adults over 55 years old was found to have no association with dietary intake of polyunsaturated fat, monounsaturated fat, n-3 or n-6 fatty acids, trans fats, saturated fat, total fat, or cholesterol (Engelhart, Ruitenberg et al. 2005). However, other studies have found that fatty acid composition can impact cognition during aging. Morris et al found that saturated and trans fat intakes were associated with greater score decreases over a 6 year follow-up of African-American and white males over 65 years old in the Chicago Health and Aging Project (Morris, Evans et al. 2004). Two studies reported conflicting results when searching for a link between fish intake, which is associated with omega-3 FAs, and cognitive decline (Morris, Evans et al. 2005; Nurk, Drevon et al. 2007). To add to the assortment of results, another study among 50-70 year old adults found no cross-sectional differences between those with higher n-3 versus lower n-3 intakes, but a slower decline over three years in sensorimotor and complex speed (Dullemeijer, Durga et al. 2007). We chose to include saturated fat in the SB meal because of its possible actions to decrease cognitive function (Solfrizzi, Panza et al. 2003), and to include n-3 fatty acids in the NB diet for their potential to improve cognitive function (Kalmijn, Feskens et al. 1997).

Another explanation for our results is that despite basing our SB and NB breakfasts on available information about cognition, it is true that currently, little is definitive regarding the effects of nutrients on cognition. In addition to individual variation combined with differences in measurement techniques attributed to study design, many personal factors such as health and nutritional status could potentially influence the brain directly, or interact with nutrients to change the magnitude or even direction of cognitive effects. For instance, numerous cognitive studies have focused on folic acid and B12, which are likely to be significant factors in brain health. These vitamins have been studied somewhat extensively compared to some other nutrients. They are a good example of complex interactions between nutrients and personal factors, since conclusions have varied between studies and differences may be attributable to population characteristics. One study found that folate and vitamin B12 supplementation were associated with slowed decline in AD patients (Remington, Chan et al. 2009), while another found that supplementation with a combination of folic acid, vitamin B6, and vitamin B12 in subjects sufficient in those nutrients had no effect on progression of AD (Aisen, Schneider et al. 2008). In non-AD subjects, results from studies on the effects of folic acid and vitamin B12 on cognition also vary. In a biracial longitudinal study, dietary intakes of neither folic acid nor vitamin B12 were associated with development of AD (Morris, Evans et al. 2006). In this same study, analysis of data from non-AD aging adults determined a protective effect of folate against cognitive impairment among those with normal vitamin B12 status. However, folate was associated with increased impaired in those with low vitamin B12 status (Morris, Jacques et al. 2007). And,

in another study, daily supplementation with a mixed supplement including folic acid and vitamin B12 for eighteen months showed no effect compared to the placebo group on tests of cognitive function (van Uffelen, Chinapaw et al. 2008).

These studies have drawn different conclusions regarding the efficacy of dietary factors such as folic acid and vitamin B12 in cognition. These conflicting results suggest that we do not yet definitively know the effects of dietary factors on cognition during aging. Furthermore, our study design had some differences from much of the published literature. It is possible that if our study participants had a lower habitual dietary quality, such as fewer fruits and vegetables, they might have been more responsive to the study treatments. Based on analysis of usual dietary intake of food records, our subjects were likely sufficient in key nutrients including folic acid and vitamin B12. In addition, subjects were cognitively healthy according to MMSE and SLUMS evaluations. These and related factors, such as lower saturated fat intake of our subjects compared to national averages, may have affected the potential results of the different breakfasts in our study and explain differences in results between our study and published studies.

This study was acute, investigating the effects of one single meal on cognitive function and brain activation within hours of consumption. Since the published literature is sparse regarding the acute effects of specific diet components on cognition, dietary components in this study were largely chosen based on studies correlating chronic diet with age-related changes in cognition. Other components were chosen based on their short term effects on endothelial function. It is possible that long term consumption of these diets could result in either accelerated cognitive

decline (SB) or in maintenance of cognitive function (NB) over longer time periods, even though we found that acute differences were unremarkable.

While chronic dietary intervention could conceivably be required before the emergence of measurable differences in the cognitive outcomes we measured, there are other changes that may have taken place with the acute breakfasts in this study. For example, this study did not measure endothelial function or blood flow, but these may have been affected by the diet treatments. Many dietary components can also either acutely increase or decrease endothelial function and blood flow. Consuming a high fat meal impairs endothelial function about 2-4 hours postprandial compared to a lower fat meal (Vogel, Corretti et al. 1997). Saturated and trans fatty acids may be especially potent in decreasing vasoreactivity. The postprandial decrease in flow-mediated vasodilation can be attenuated by consuming walnuts, a source of n-3 polyunsaturated fatty acids, or salad (romaine lettuce, carrot, and tomato) along with the meal, or consuming the antioxidant vitamins C and E with the high fat meal (Plotnick, Corretti et al. 1997; Cortes, Nunez et al. 2006). In one study, cocoa flavanols increased vasodilation and also the brain BOLD response during an fMRI task (Francis, Head et al. 2006). Together, these observations demonstrate nutrition's role in acute physiological effects, some of which could conceivably affect cognition.

Exercise

Our study investigated the acute effects of a bout of moderate AE, i.e., walking on a treadmill at 50-65% HRR, on cognitive performance and brain activation in an aging population. The methods and results lead to interesting

comparisons with previous studies. Studies investigating the acute effects of exercise on cognition are varied in their participants, study design, and results. Many of the previous studies on acute effects of exercise were conducted in a younger adult population (Ferris, Williams et al. 2007; Coles and Tomporowski 2008; Pontifex, Hillman et al. 2009) or in animals (Huang, Jen et al. 2006; Soya, Nakamura et al. 2007). In addition, the bout of exercise in these studies varies in their mode, intensity, and duration. Our study adds to the body of knowledge about the effects of a specified dose of exercise performed at these specifications.

Taken together with previous findings from long term studies, the findings of our study suggest that AE may be more effective in long term rather than acute cognition. Some intervention studies have been conducted to investigate the effects of exercise on cognitive function. Some have found positive cognitive effects of exercise programs (Cotman and Berchtold 2002). In one study, 70-80 year old men and women diagnosed with MCI walked twice weekly in a group setting for a year. Compared to a low-intensity exercise placebo control group, men who were assigned to group walks improved memory (auditory verbal learning), and women in the exercise group improved attention (stroop speed) and memory (auditory verbal learning) (van Uffelen, Chinapaw et al. 2008). A six-month clinical trial in healthy but sedentary adults aged 60-79 years compared the effects of three times weekly 60 minute sessions of aerobic training to stretching and toning controls. This study found increases in gray and white matter brain regions in the training group (Colcombe, Erickson et al. 2006).

The significance of routine exercise in brain health is consistent with the overall trend found in a meta-analysis of epidemiological studies that found associations between fitness and cognitive function in older adults (Berkman, Seeman et al. 1993; Colcombe and Kramer 2003). Other reviews have also suggested an overall effect of exercise or fitness in reducing cognitive impairment or maintaining cognitive function with aging (Hillman, Erickson et al. 2008; Deslandes, Moraes et al. 2009). However, one meta-regression was unable to make definitive conclusions regarding the effects of fitness, finding that effects varied based on age and health status (Etnier, Nowell et al. 2006). Similarly, another study included participants aged 65 or older at baseline and found a only a non-significant relative risk of 0.85 for developing dementia over the next 5.4 for those in the highest quartile of physical activity compared to the lowest quartile (Podewils, Guallar et al. 2005).

As mentioned earlier, a separate study looked at the effects of a 14-day "longevity" lifestyle intervention on cognitive function and brain activation. The exercise component of the intervention included 3 bouts of walking per week. (Small, Silverman et al. 2006). Interestingly, the intervention showed positive effects on cognition despite the exercise program falling short of national guidelines. It is important to note, though, that the exercise was only a portion of the intervention and may not have affected results. These results show promise for positive effects of exercise even without meeting the recommendations for at least 5 days per week of moderate intensity (Nelson, Rejeski et al. 2007). Exercise regimes less rigorous than national guidelines may be more realistic for older adults, since

only a self-reported 32% of Americans meet national guidelines for physical activity (1996), and over half of adults over age 65 report no leisure time physical activity (2008). Our study population was consistent with these national figures, averaging1.6 bouts per week (Table 4). Only 13% (2 of 16 subjects with complete physical activity data) met the recommended five bouts per week, and 25% (4 out of 16 subjects) achieved at least three bouts per week.

Improvements in, maintenance of, or slower declines in cognitive parameters are consistent with what we know about the adaptations that occur with habitual exercise. The cardiovascular fitness hypothesis relates physical fitness to the adaptations that occur over time that reduce the risk of cardiovascular disease (Hamilton, Hamilton et al. 2007). Adaptations associated with exercise that reduce risk of CVD include improved vasoelasticity, weight control, decreased blood pressure, and improved blood lipid profile (Brown, Avenell et al. 2009; Yung, Laher et al. 2009). Exercise also increases CBF (Swain, Harris et al. 2003) and increases production of brain-derived neurotrophic factor (BDNF) (Vaynman and Gomez-Pinilla 2005). In further support of the cardiovascular fitness hypothesis, a cross sectional study compared active older adults (defined as at least 180 minutes per week in sport or aerobic activity over the past ten years) to inactive (defined as less than 90 minutes per week over the past ten years) older adults. The study used MR angiography to show that the highly active group had lower tortuosity in large vessels and an increased number of small vessels than lower physically active group in cerebrovasculature (Bullitt, Rahman et al. 2009). Another observation supporting the cardiovascular fitness hypothesis is the association of faster left ventricular

expansion, which is part of the pathophysiology of coronary heart disease, with earlier development of MCI (Carlson, Moore et al. 2008).

Serum BDNF is another factor implicated in the relationship between exercise and cognitive function. Higher levels of BDNF are associated with less cognitive impairment in otherwise healthy older adults (Gunstad, Benitez et al. 2008). Higher BDNF levels lead to increased synaptic and neuronal plasticity, which is lower with aging (Burke and Barnes 2006). Serum levels of BDNF have been shown to increase with short bouts (15-30 minutes) of exercise (Gold, Schulz et al. 2003; Tang, Chu et al. 2008). However, these studies were both done in younger adult populations, and BDNF increases were transient, lasting only about 30-50 minutes. Since the present study did not measure BDNF, it is unknown whether BDNF levels were affected by the bout of exercise. Even if BDNF levels did increase, it is possible that there would have been no effect on the cognitive outcomes of the study. Exercise-induced BDNF is only transient, about 30-50 minutes, and participants finished their cognitive and fMRI testing approximately 80 minutes after exercise completion. Another reason for the longer term effects of exercise on cognition might be that BDNF increases plasticity in the brain, which aids learning by allowing the development of novel pathways.

The parameters of our bout of AE complement the existing literature and may help give insight into how exercise might impact cognition in an aging population. The AE in our study was a relatively moderate session of walking on a treadmill at an intensity of 50-65% of estimated HRR based on the age of the participant. Some studies finding rapid improvements in cognition after a single

period of exercise have used resistance exercise rather than continuous exercise as the treatment. Some have found that resistance exercise is effective (Liu-Ambrose and Donaldson 2009), while others have found AE to be more effective than resistance exercise for cognition (Pontifex, Hillman et al. 2009). Others have used cycle ergometry as the mode of exercise, and found improvements in executive function (Cordova, Silva et al. 2009). It also appears that intensity may be a factor in the efficacy of exercise in cognitive function. In the study mentioned above, physically active women aged an average of 64 years were randomly assigned to 20 minute bouts of exercise on a cycle ergometer at an intensity of 0% (no exercise), 60%, 90%, and 110% of aerobic threshold. After exercising, subjects underwent cognitive testing for domains requiring executive function. Simple response time (alertness) was improved for all exercise groups, and other test results were unchanged for the 60% and impaired for the 110% group. In the group performing exercise at 90%, the executive function tasks of verbal fluency, Tower of Hanoi (number of movements), and Trail Making Task B, were improved compared to the control group. (Cordova, Silva et al. 2009). Results of this and other studies underscore the significance of exercise intensity on cognitive function.

Aside from type and intensity of exercise, the timing of measurement of cognitive function or brain activation relative to the bout of exercise is another important variable. Our study measured cognitive function using the CogState® test battery with the testing session beginning at an average of 10 minutes after completion of AE including cool down. The fMRI exam commenced an average of 35 minutes after starting the CogState® battery, or a total of 45 minutes after

completion of AE. Previous studies have implied that small differences in timing may greatly affect results. In studies that tested cognitive function at differing time points following exercise, healthy older adults showed improvements in cognitive function after eight minutes after completing exercise (Cordova, Silva et al. 2009), and adults with chronic obstructive pulmonary disease showed some improvements in verbal fluency twenty minutes after finishing maximal exercise (and five minutes after completing cool down) (Emery, Honn et al. 2001). In contrast, younger adults showed no changes in executive function when tested 48 minutes after exercise completion (Hillman, Snook et al. 2003). Another study found improved executive function in young adults during but not after completion of an exercise bout on a cycle ergometer (Audiffren, Tomporowski et al. 2009). Because there are further differences in these studies beyond timing of testing, currently we can only speculate about the role of timing when trying to determine the acute effects of AE on cognition.

CogState®

This study was compared executive performance using CogState® tests during each of the three study treatments: SB, NB, and NB + AE. The CogState® computerized system is a recently developed method to test cognitive function in a short amount of time. To compose the CogState® battery for a particular study, the study investigator chooses specific tasks from the selection of tasks developed by the CogState® company (CogState® Limited, Melbourne, Australia). The specific tasks and cognition skills used in our study are listed in Table 3. To achieve normal distributions, accuracy was reported as the inverse sine function of the percent

correct (Figure 5), and speed was reported as the logarithm of the response time in milliseconds (Figure 6).

The only significant effects of treatment that were detected in the CogState® battery were on the prediction and monitoring tasks. For prediction, accuracy was found to be different in NB versus NB + AE ($p < 0.05$). The prediction task targets executive function, which was the focus of this study and is known to decrease during aging. The decrease in accuracy in prediction with the addition of AE to NB may plausibly be attributable to mental fatigue caused by exercise, but the difference in percent correct (83% in NB versus 78% in NB + AE) is very small despite its statistical significance. For the monitoring task, which tests attention, speed of response was significantly slower in NB than in SB ($p<0.05$).

No significant effect of treatment was found for the other tasks in the battery; nor did we detect significant effects of time. In addition, we found no significant differences between speed of response due to treatment or time. Previous data have shown a practice effect between the first and second attempts when consecutive CogState® tests were administered with a 10 minute break. These effects leveled off with repetition of the tests at one week and one month intervals (Falleti, Maruff et al. 2006). Our study design included two unscored practice tests during the introductory visit to the lab, and each task during those practice tests and the subsequent scored tests during SB, NB, and NB + AE was preceded by a practice round of tests. This study design appears to have been effective in minimizing effects of time.

The MMSE scores of our population classified them as cognitively normal, but the relative novelty of the CogState® test battery combined with its feature of customizability means that only a few previous studies are available to compare baseline results. Another factor limiting the availability of baseline data is the nature of the computerized battery. The researcher's flexibility in choosing which tests to include limits the ability to compare the battery. Instead, each CogState® test battery is composed of a unique collection of tasks, which are sequentially ordered according to the researcher's preference.

Furthermore, the company is continually updating the tasks that are offered, meaning that some tasks, available for only limited periods of time, are included in only a relatively small number or studies. However, one previous study investigating cognitive function was conducted over six years in a comparable study population of healthy adults averaging 69.2 years of age at baseline, and 64% female. Cognitive changes were tracked using a variety of cognitive tests, including two of the same CogState® tasks to assess cognitive function as in our study. These tasks were the identification (to test attention) and the one-back (to test visual attention and working memory) tasks. Among adults in the study who did not display cognitive decline during the duration of the study, scores on the identification task averaged 97% accuracy and 550 msec reaction time, compared to our average of 99% accuracy and 540 msec reaction time, and scores on the one-back task averaged 82% accuracy and 851 msec reaction time, compared to our average of 96% accuracy and 770 msec reaction time (Cargin, Maruff et al. 2007). It is difficult to compare across studies, but these appear to be minor differences. A

possible influence is the average education level attained by participants in each study. Cargin et al. reported an average of 13 years of education, while our study participants averaged 16 years.

Existing studies have largely focused on different applications than our study. The CogState® test battery has been used to detect mild cognitive impairment (Darby, Maruff et al. 2002) or memory decline over the course of months (Maruff, Collie et al. 2004). Other applications have included assessment of cognitive status following head injury during sports such as soccer (Makdissi, Collie et al. 2001). However, the battery has not previously been used to detect acute treatment effects in a healthy aging population.

Eriksen Flanker and Brain Activation

To compare acute effects of SB, NB, and NB + AE on cognition and brain activation, this study also assessed performance on an Eriksen flanker arrow task and measured brain activation using fMRI and the brain BOLD response. The Eriksen flanker arrow task presents conditions that are congruent or incongruent, with the incongruent condition requiring response inhibition. The task was designed to elicit nearly perfect responses in accuracy in both congruent and incongruent conditions, and our study's results were consistent with this intention (e.g., 98% accuracy). To assess the effects of treatment and time, we compared relative changes in response time between congruent and incongruent conditions across treatment conditions and time (visit number). This analysis yielded no significant differences.

The Eriksen flanker arrow task paradigm was also used as a stimulus to activate relevant areas of the brain for detection of the brain BOLD response during

fMRI. A recent fMRI study investigated brain activation during a similar conflict resolution paradigm to our study. That study detected activation in the IFG/MFG/SFG and MFG/BA6 regions (Zhu 2008). Other studies have shown activation in the anterior cingulate cortex (Pochon, Riis et al. 2008; Ochsner, Hughes et al. 2009), and medial frontal cortex (Ochsner, Hughes et al. 2009). These areas are known to be important in conflict resolution (Andersson, Ystad et al. 2009), and function may be impaired with age.

We had hypothesized that AE would increase blood flow to the brain, thus improving cognitive performance and increasing the brain BOLD response. Overall, the study's participants were healthy older adults, with no known peripheral arterial disease or unstable cardiovascular conditions. The healthy status of our participants may have masked possible changes in the BOLD response.

The brain BOLD response is dependent on the amount of oxygen reaching the brain, and the magnitude of the response has been shown to be dependent on baseline cerebral blood flow (CBF). Increased CBF leads to a smaller response, while decreased CBF allows for a larger BOLD response. Factors affecting vasoreactivity of vessels in the brain and brain perfusion can potentially affect the magnitude of the BOLD response. Nutrients and exercise each have the potential to influence endothelial function.

Dietary components that have been shown to improve endothelial function include antioxidants (Plotnick, Corretti et al. 1997), n-3 fatty acids (Cortes, Nunez et al. 2006), and cocoa flavanols (Fisher, Sorond et al. 2006), while saturated fats have been shown to impair endothelial function (Cortes, Nunez et al. 2006) and high

carbohydrate meals impair endothelial function in insulin-resistant individuals (West 2001). Some components of the SB and NB meals in our study were based on these effects because of the possibility of effects on the BOLD response.

Like diet, exercise also affects peripheral vasculature, leading to our hypothesis that the NB + AE condition would increase brain activation compared to the SB and NB conditions. A normal response to exercise includes increased systolic and decreased diastolic blood pressure (Singh, Larson et al. 1999). As reported in the results, blood pressure dropped below pre-exercise levels within minutes of finishing AE. This was likely due to vasodilation arising from decreased sympathetic output. These changes are consistent with previous studies showing that vascular compliance improves after moderate exercise (Kingwell, Berry et al. 1997). In addition, exercise increases cerebral blood flow through the mechanisms of increased blood pressure and decreased pH from increased CO_2 (Ide, Boushel et al. 2000). These peripheral effects of exercise could potentially eventually affect the brain BOLD response.

The incongruent flanker task condition elicited a greater BOLD response compared to baseline in the IFG/MFG/PCG (Figure 9) and MFG/BA6 (Figure 10) regions. These findings are consistent with brain imaging studies investigating executive function during aging. For example, (Small, Silverman et al. 2006) used positron emission tomography to show differential activation with a longevity lifestyle task in Brodmann Area 6. More important, a recent study was conducted using a similar Eriksen flanker arrow paradigm in the same MRI scanner (Zhu 2008). That study found activation in the inferior and middle frontal gyrus and is

consistent with our findings. In fact, our analysis was based on the ROIs defined in the study by Zhu et al. Repeated measures analysis of variance did not detect an effect of treatment among our subjects in either ROI (Figure 7 and Figure 8).

We did not find differences in the percent change in activation between the C and IC conditions during the flanker task in frontal regions. Even if the treatment conditions altered CBF as expected, this lack of treatment effects may partially be explained by the age of our participants. For example, although CBF and the brain BOLD response are typically correlated, this relationship is less clear in older adults. One study found the BOLD response to be lower in older adults than younger ones despite similar changes in CBF in response to a visual checkerboard stimulus (Ances, Liang et al. 2008). This finding could explain why we found only nominal effects of treatment on the brain BOLD response during fMRI. Another explanation is that effects might not necessarily be systemic; on the contrary, peripheral effects of treatment might not be generalizable to CBF and brain activation.

Study Strengths

This study was an important initial step in determining the role for diet and exercise in brain health during aging. A practical long term goal is to adequately understand the role of lifestyle factors to be able to make recommendations for individuals to follow in daily life to optimize brain health. To do this, it is necessary to increase our understanding of the lifestyle factors that impact cognitive function during aging. This is done using experimental studies to evaluate cause and effect versus the potential correlations or associations found in epidemiological cohort studies. This acute study directly compared the effects of different treatments in a

three arm randomized control design, so that any differences found could reasonably be attributed to treatment effects. Furthermore, this study addressed the issue of concern, which is brain function during aging, because study participants were from an aging population rather than a standard young healthy adult population as in some previous studies (Hindmarch, Quinlan et al. 1998; Coles and Tomporowski 2008; Pontifex, Hillman et al. 2009).

Another strength of this study was its design. It was a randomized, crossover design study with three arms: SB, NB, and NB plus AE. Participants were healthy residents 61-84 years of age, and were included in the study only after screening procedures. Before undergoing study treatment, participants were familiarized with the different aspects of the study to ensure accurate results and avoid difficulties on the actual days of data collection. This included an introduction to the MRI scanner using a mock brain image to ensure that claustrophobia was not a problem. Another procedure to enhance participant familiarity included walking on the treadmill, during the familiarization session, at the projected incline and pace of the bout of exercise to be performed during the NB plus AE session. Participants also practiced the CogState® battery of tests twice to avoid practice effects during the real testing periods, and were introduced to the Flanker arrow task. The study design was also strong because treatments were representative of situations that could be replicated in real life. The diets were mixed meals composed of ordinary foods, and the bout of exercise fell within the range of the intensity and amount recommended by the AHA and ACSM for older adults (Nelson, Rejeski et al. 2007). Finally, combining diet and AE, as was done

for the third treatment arm of the study (NB + AE), is practical because some individuals seeking to improve brain health may be attentive to both diet and AE.

This study was well controlled to minimize effects of potential confounders. Each participant had their laboratory visits scheduled to be separated by at least three days to avoid any possible potential for residual effects of treatment. To ensure that results were due to treatment and not to confounding recent lifestyle factors, participants were asked to continue their usual diet and exercise regimens for the duration of the study. The exception to this request was that individuals were asked to refrain from exercising the day before each treatment visit to be sure that any effects of AE or lack thereof were due to the study treatment. Because of the acute nature of the study, subject visits were carefully timed to maximize similarities in experiences between and within subjects. An ACLS-certified physician attended each bout of AE during the study. Aside from ensuring safety, this supervision increased confidence that participants were at the target intensity through careful monitoring of blood pressure, heart rate, and ECG. All of these factors combine to demonstrate the novelty, solid design, and careful control of this study.

Another strength of this study was its multiple outcome measures. We evaluated both cognitive function, using the CogState® battery, and brain activation, using fMRI. Assessing both of these measures increased the likelihood of observing potential effects of diet and PA on the brain. Beside uncovering differences due to treatment, including the CogState® and fMRI could help explain how these treatments might be effective. Understanding both cognitive

performance and brain activation could give insight into potential mechanisms for how lifestyle factors could affect the brain. For example, a change in brain activation without a change in cognitive performance with treatment could imply a compensatory effect that uses alternate pathways in the brain to process information.

Study Limitations

This study focused on the acute effects of the modifiable lifestyle factors of diet and exercise on cognition. A longer term goal would be to improve brain health during aging through altering diet and exercise. The treatments in this study did not result in dramatic differences in their effects on cognition or brain activation, and this may have been a result of being realistic rather than in supplemental doses or intense exercise. Each treatment was deliberately developed to reflect reasonable and realistic meals or exercise that an average older adult could conceivably integrate into daily life. The potentially effective ingredients, such as vegetables, omega-three fatty acids, or added sugars, might have been at quantities too small to show an acute response if one existed. The AE bout may similarly have been too moderate in intensity. To address these issues, it would be necessary to undertake studies investigating different nutrients individually, and to conduct dose-response studies both with nutrients and with quantity and intensity of exercise.

Another apparent weakness of the study is the lack of the logical fourth arm, which would have been the treatment of SB plus AE. This fourth treatment was excluded from the study for a variety of reasons, including money, time, and increased participant commitment. The study design may also have introduced selection bias into the study. Recruiting was through posted fliers at the university where the study was conducted, and potential participants chose to call and become involved

in the study. Our subjects were likely more interested in the study topic than the general population and may have been more conscious of their lifestyle choices.

Future directions and implications

This study is an early investigation of the acute effects of diet and exercise on cognition in an aging population. Future acute studies might seek to determine the individual effects of specific nutrients or foods on cognitive function and brain activation when doses are higher than in this study. Exercise duration, type, and intensity could also be investigated. In addition to altering specific diet or exercise treatments, the time course could also be modified in future studies to determine whether these treatments are effective at times other than we measured. For example, one study found an effect of exercise on cognitive function when performance was measured at 8 minutes after completion of exercise (Cordova, Silva et al. 2009), but another study found no effect at 48 minutes after exercise completion (Hillman, Snook et al. 2003). Future studies should also measure BDNF because it is increased with long term exercise and could be important in improving cognitive function because of its role in synaptic plasticity (Vaynman, Ying et al. 2004).

Unlike the results of some epidemiological studies (Donini, De Felice et al. 2007), this study showed no clear relationship between diet and AE and cognitive function or brain activation in an aging population. This implies that effects may require longer term interventions. While acute studies might provide insight to mechanisms that would explain long-term effects and acute studies might not be enough to cause the adaptations necessary at the cellular level that lead to visible

effects over time. Future studies are needed to determine the length of time necessary to achieve improvements in cognition due to diet and exercise. An effective method of determining the required time to achieve results would be to implement a diet and exercise regimen and monitor subjects regularly over time until changes in cognitive performance or brain activation can be seen. Study groups would be a control group, a group with a nutrition intervention, a group with an exercise intervention, and a group with both nutrition and exercise interventions.

Beyond determining the precise effects of certain diet and exercise treatments on acute cognitive function, it is also important to establish achievable diet and exercise guidelines to improve the cognitive health of the target population of aging adults. Currently, only a minority of Americans meet national recommendations for diet and exercise. For example, less than 25% of the population of the United States reported achieving the recommended five servings of fruit and vegetables per day (2007). Physical activity is also limited in Americans, with the Centers for Disease Control and Prevention estimating that about 74% of adults in the United States do not meet the recommendation for 30 minutes of moderate PA most days of the week (2003). With these statistics, it is important to attempt to develop realistic and feasible guidelines rather than prescribe stringent dietary constraints and difficult quantities of exercise. Developing such guidelines would require further studies whose treatments involved ordinary types and quantities of foods, and achievable exercise. For example, while it is exciting to discover that cycle ergometry exercise at 90% of anaerobic threshold led to improvements in multiple executive function tasks

(Cordova, Silva et al. 2009), it may not be realistic to expect that the general population would incorporate such sessions into their typical lifestyles. Also important is to conduct studies in this particular population of healthy aging adults because studying other populations lowers the external validity of the study.

Appendices

Appendix 1: Mini-Mental State Examination (MMSE)

For explanation and scoring, please see Table 4.

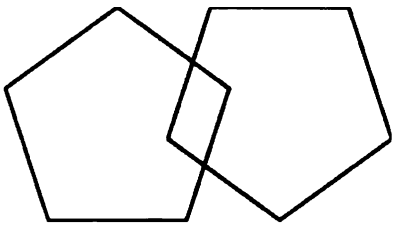
Subject_____ Examiner

_____

Date _____ MMSE SCORE _____

Maximum	Score	
		Orientation
5	( )	What is the (year) (season) (date) (day) (month)?
5	( )	Where are we (state) (country) (town) (campus) (building)?
		Registration
3	( )	Name 3 objects: 1 second to say each. Then ask the patient all 3 after you have said them. Give 1 point for each correct answer. Then repeat them until he/she learns all 3. Count trials and record. Trials _____
		Attention and Calculation
5	( )	Serial 7's. 1 point for each correct answer. Stop after 5 answers. Alternatively spell "world" backward.
		Recall
3	( )	Ask for the 3 objects repeated above. Give 1 point for each correct answer.
		Language
2	( )	Name a pencil and watch.
1	( )	Repeat the following "No ifs, ands, or buts"

3	(	)	Follow a 3-stage command: "Take a paper in your hand, fold it in half, and put it on the floor."
1	(	)	Read and obey the following: CLOSE YOUR EYES
1	(	)	Write a sentence.
1	(	)	Copy the design shown.



Appendix 2: St. Louis Mental Status Examination (SLUMS)

For explanation and scoring, please see Table 4.

VAMC

SLUMS Examination (Tariq, Tumosa et al. 2006)

Questions about this assessment tool? Email aging@slu.edu

Name _____ Age _____

Is the patient alert? _____ Level of education _____

(1) 1. What day of the week is it?

(1) 2. What is the year?

(1) 3. What state are we in?

4. Please remember these five objects. I will ask you what they are later.

Apple pen tie house car

5. You have $100 and you go to the store and buy a dozen apples for $3 and a tricycle for $20.

(1) How much did you spend?

(2) How much do you have left?

6. Please name as many animals as you can in one minute

(0) 0-4 animals (1) 5-9 animals (2)10-14 animals (3)15+ animals

7. What were the five objects I asked you to remember? 1 point for each one correct.

8. I am going to give you a series of number and I would like you to give them to me backwards. For example, if I say 42, you would say 24.

(0) 87 (1) 649 (1) 8537

9. Th

eleve

(2) H

(2)Ti

(1) I

(1) V

11. I

goin

Jill

mar

thre

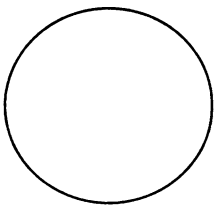
brin

Jack

(2)

(2)

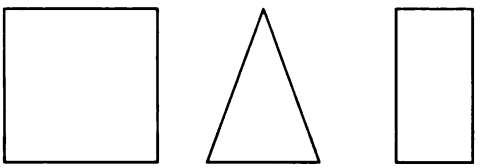
9. This is a clock face. Please put in the hour markers and the time at ten minutes to eleven o-clock.



(2) Hour markers okay

(2)Time correct

(1) 10. Please place an X in the triangle.



(1) Which of the above figures is largest?

11. I am going to tell you a story. Please listen carefully because afterwards, I'm going to ask you some questions about it.

Jill was a very successful stockbroker. She made a lot of money on the stock market. She then met Jack, a devastatingly handsome man. She married him and had three children. They lived in Chicago. She then stopped work and stayed at home to bring up her children. When they were teenagers, she went back to work. She and Jack lived happily ever after.

(2) What was the female's name? (2) What work did she do?

(2) When did she go back to work? (2) What state did she live in?

_____ TOTAL SCORE

Appendix 3: Informed Consent

INFORMED CONSENT

Effect of exercise and nutrition on cognitive function in aging

Depts. Radiology, Physiology and Osteopathic Manipulative Medicine
Michigan State University

1. You are being asked to participate in a study on the effects of exercise and nutrition on cognitive function (thinking and cognition). The purpose is to examine changes in cognition function and brain activation following one period of exercise (30 minutes) and following meals with various nutrient compositions.

2. Your participation in this study will require a minimum of 4 laboratory visits. The sessions will last between 2 and 5 hours. You will be required to walk on a treadmill for 30 minutes at a sub-maximal exercise intensity using a self-selected walking speed. You will also be required to consume a meal with various nutrient composition. You will have blood drawn for measures of cholesterol, triglycerides, lipoproteins, glucose and insulin. You will also have magnetic resonance imaging (MRI) to take pictures of your brain while performing cognitive tasks. MRI is a safe and noninvasive instrument that is often used for examining soft tissue like your organs, cartilage, ligaments and brain. You will lie supine on the MRI table and watch a computer monitor for instructions during the MRI. The MRI will take approximately 30-45 minutes. You will also perform a battery of cognitive tests on a computer in the lab. You will receive the results from your blood tests (fasting glucose and insulin, cholesterol and lipids) and the results from the cognitive performance tests. You will also be compensated $25 per visit for study participation.

3. The only known risks of MRI are the possibility that loose metallic objects might be attracted into the magnet, or that metallic prostheses or pacemakers might be affected by the magnet. Therefore, you should remove all metal objects from your person; you should not participate if you have a pacemaker or other implanted metallic device. You should not participate if you have an unstable heart, metabolic, neurological disease, or if you have peripheral arterial disease. For the MRI test, you might experience claustrophobia or discomfort from lying in the same position for 30-45 minutes. We will provide you with cushions and pillows to increase your comfort during the MRI. The machine is also equipped with mirrors and a fan which may make you feel more comfortable. In addition, you can communicate with the researchers at any time through a microphone inside the machine. However, you may not want to participate if you have extreme claustrophobia.

Although there are not known risks of MRI exams, the possibility that there might be unknown risks cannot be ruled out. Because the imaging process produces loud pinging noises, you will be provided with earplugs to wear during the experiment.

4. You are free to discontinue your participation in the study at any time, and for any reason, including feelings of claustrophobia in the MRI machine, discomfort during the test procedures, etc. You will not be charged or billed for any of the procedures or laboratory tests associated with this study.

5. Any information you provide, and all data collected, will be treated in confidence. Your privacy will be protected to the maximum extent allowable by law.

6. The results of this study will be made available to you at your request. Furthermore, on your request you can receive an additional explanation during the study, or after your participation is completed. In that case, you will contact Dr. Jill Slade, phone 355-0120, x351 or Dr. Joe Carlson, 355-0120, x346. You may also contact Jill Slade or Joe Carlson by mail (184 Radiology Building, Michigan State University, East Lansing, MI 48824) or by email (jslade@msu.edu, jjc@radiology.msu.edu). If you have questions or concerns about your rights as a research participant, please feel free to contact Peter Vasilenko, Ph.D., Director of the Human Subject Protection Programs at Michigan State University by phone: (517) 355-2180, fax: (517) 432-4503, email: ucrihs@msu.edu, or regular mail: 202 Olds Hall, East Lansing, MI 48824

7. Your participation in this study does not guarantee any beneficial result to you. If the MRI data collected suggests a need for further study, you will be referred to an appropriate physician.

8. If you are injured as a result of your participation in this research project, Michigan State University will assist you in obtaining emergency care, if necessary, for your research related injuries. If you have insurance for medical care, your insurance carrier will be billed in the ordinary manner. As with any medical insurance, any costs that are not covered or in excess of what are paid by your insurance, including deductibles, will be your responsibility. Financial compensation for lost wages, disability, pain or discomfort if not available. This does not mean that you are giving up any legal rights you may have. You may contact Jill Slade 517-355-0120, x351or Joe Carlson 355-0120, x346 with any questions.

Your signature below indicates your voluntary agreement to participate in this study.

_____	_____
Participant's Signature	Date
_____	_____
Witness' Signature	Date

Appendix 4: Patient authorization for disclosure of health information for research

Patient Name: _____

Address:_____

Date of Birth: _____

I AUTHORIZE THE DISCLOSURE OF MY HEALTH INFORMATION

FROM: _____ TO: __Jill Slade, PhD

184 Radiology

Department of Radiology, Michigan State University

East Lansing, MI 48824

(517) 355-0120, x. 351

DESCRIPTION OF INFORMATION TO BE DISCLOSED (Select one of the following):

__ALL information contained in my medical record OR

_X_ONLY disclose the following information: information related to cardiovascular, peripheral vascular, or neural conditions/disorders and information on surgeries that may have involved medical implants

RESEARCH STUDY FOR THIS DISCLOSURE:

Title of Study: Effect of Exercise and nutrition on cognitive function in aging

Name of research leader: Jill Slade, PhD.

Affiliation of Researcher: Assistant Professor, Department of Radiology

IRB# i026479#06-1080 Name of IRB: MSU BIRB

EXPIRATION: expires at the end of the research study

REVOCATION, REFUSAL, REDISCLOSURE

Appendix 5: Permission letter to physicians for exercise

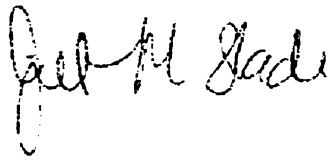
Month Day, Year
John Doe, MD
1234 Some Street
City, MI 12345
Fax: 123-456-1234
Tele: 123-456-1235

Dear Dr. Doe,

Your patient, **Jane Smith (DOB)** has volunteered to participate in a study at Michigan State University. The study focuses on the influence of nutrition and exercise on cognitive function.
This study has been approved by the Institutional Review Board at Michigan State University (please see the enclosed consent form).
For this study, the research participant will walk on a treadmill at a self-selected pace for 30 minutes at a moderate, sub-maximal exercise intensity (50% of heart rate reserve) under the supervision of an ACLS certified clinician. **Ms. Smith** needs to obtain medical clearance from you in order to participate in this research.

At your earliest convenience, please return this form via fax (517-432-2849) or mail. If you have any questions, please contact Jill Slade, PhD, at (517) 355-0120 ext. 351 or Joe Carlson, PhD, RD, at 355-0120 ext. 346.

Sincerely,



Jill M, Slade, Ph.D.

Jane Smith may participate in the research study entitled "The effect of exercise and nutrition on cognitive function in aging."

_____ Approve _____ Decline

_____ Date

_____ Physician Signature

John Doe, MD

Appendix 6: Magnetic Materials Safety Questions

Magnetic Materials Safety Questions:

Please explain to the subject that the following questions are standard precautionary questions related to MRI procedure. A MRI involves a powerful magnetic field that will cause problems for people with any metal within their bodies.

1.) Do you have a neurostimulator (nerve stimulator)? Yes No

2.) Do you have a heart Pacemaker or implanted defibrillator? Yes No

3.) Do you have an ear implant? Yes No

4.) Do you have any metal fragments in your head, eyes or skin? Yes No

5.) Do you wear any patches that deliver medications through the skin? Yes No

6.) Do you have any implants of any kind, metal joints, rods, plates, pins, screws, nails, clips, stents?Yes No

Explain:_____

7.) Have you ever worked as a machinist, metal worker or welder? Yes No

8.) Have you had any surgeries? If yes what type and when? Yes No

_____

_____

9.) Do you have problems with claustrophobia? Yes No

10.) Do you have epilepsy or seizure disorder? Yes No

Appendix 7: Geriatric Depression Scale

MOOD SCALE
(short form)

Choose the best answer for how you have felt over the past week:

1. Are you basically satisfied with your life? YES / **NO**

2. Have you dropped many of your activities and interests? **YES** / NO

3. Do you feel that your life is empty? **YES** / NO

4. Do you often get bored? **YES** / NO

5. Are you in good spirits most of the time? YES / **NO**

6. Are you afraid that something bad is going to happen to you? **YES** / NO

7. Do you feel happy most of the time? YES / **NO**

8. Do you often feel helpless? **YES** / NO

9. Do you prefer to stay at home, rather than going out and doing new things? **YES** / NO

10. Do you feel you have more problems with memory than most? **YES** / NO

11. Do you think it is wonderful to be alive now? YES / **NO**

12. Do you feel pretty worthless the way you are now? **YES** / NO

13. Do you feel full of energy? YES / **NO**

14. Do you feel that your situation is hopeless? **YES** / NO

15. Do you think that most people are better off than you are? **YES** / NO

Answers in **bold** indicate depression. Although differing sensitivities and specificities have been obtained across studies, for clinical purposes a score > 5 points is suggestive of depression and should warrant a follow-up interview. Scores > 10 are almost always depression.

Appendix 8: Exercise documentation form

Date_____ # S_____ DOB_____ Age____Gender ____

Pre-exercise protocol followed (consent, meds etc.) _____

Resting HR_____50% HRR _____65% HRR_____[(MHR-RHR) x 50%] + RHR= THR

Resting Blood Pressure, Heart Rate & ECG

	Sitting	**Standing**
Blood Pressure	**_____/_____ mm Hg**	**_____/_____mm Hg**
Heart Rate (ECG)	**_____beats/min**	**_____ beats/min**

***Exercise Warm-up (3-5 min)*- BP _____/_____ mm Hg; ECG _____ HR _____**

Exercise BP & HR & RPE *Assess every 5 min unless SSs; print ECG every 5 min*

_____ECG time____min BP _____/____ HR ____ RPE_____
MPH_____%Incline_____

_____ ECG time____min BP _____/____ HR ____ RPE_____
MPH_____%Incline_____

_____ECG time ____min BP _____/____ HR ____ RPE_____
MPH_____%Incline_____

_____ECG time ____min BP _____/____ HR ____ RPE_____
MPH_____%Incline_____

_____ECG time ____min BP _____/____ HR ____ RPE_____
MPH_____%Incline_____

_____ECG time ____min BP _____/____ HR ____ RPE_____
MPH_____%Incline_____

Exercise duration- _____minutes; Average HR _____beat/ min

***Cool down* time_____ MPH_____%Incline_____**

Post Exercise BP & HR

Immediate Post- BP_____/_____ HR_____ beat /min
ECG_____

5 min post BP_____/_____ HR_____ beat /min
ECG_____

10 min post BP_____/_____ HR_____ beat /min
ECG_____

Comments/ Summary-

Appendix 9: The Cognitive Failures Questionnaire

Please see Table 4 for explanation.

The Cognitive Failures Questionnaire

Modified from (Broadbent, Cooper, FitzGerald & Parkes, 1982)

The following has been modified from the original questionnaire:
A column has been added for the subject to decide if the question/item has gotten worse or occurs more frequently with age. The subject will answer "Yes" or "No".

Broadbent, D.E., Cooper, P.F., FitzGerald, P., & Parkes, K.R. (1982). The Cognitive Failures Questionnaire (CFQ) and its correlates. British Journal of Clinical Psychology, 21, 1-16.

The following questions are about minor mistakes which everyone makes from time to time, but some of which happen more often than others. We want to know how often these things have happened to your in the past 6 months. Please circle the appropriate number. Also, please circle whether, in your opinion, this has gotten worse or occurs more frequently with age.

Answer for each question:

Very often	Quite often	Occasionally	Very rarely	Never
4	3	2	1	0

Worse with age? Yes No

1. Do you read something and find you haven't been thinking about it and must read it again?

2. Do you find you forget why you went from one part of the house to the other?

3. Do you fail to notice signposts on the road?

4. Do you find you confuse right and left when giving directions?

5. Do you bump into people?

6. Do you find you forget whether you've turned off a light or a fire or locked the door?

7. Do you fail to listen to people's names when you are meeting them?

8. Do you say something and realize afterwards that it might be taken as insulting?

9. Do you fail to hear people speaking to you when you are doing something else?

10. Do you lose your temper and regret it?

11. Do you leave important letters unanswered for days?

12. Do you find you forget which way to turn on a road you know well but rarely use?

13. Do you fail to see what you want in a supermarket (although it's there)?

14. Do you find yourself suddenly wondering whether you've used a word correctly?

15. Do you have trouble making up your mind?

16. Do you find you forget appointments?

17. Do you forget where you put something like a newspaper or a book?

18. Do you find you accidentally throw away the thing you want and keep what you meant to throw away – as in the example of throwing away the matchbox and putting the used match in your pocket?

19. Do you daydream when you ought to be listening to something?
20. Do you find you forget people's names?

21. Do you start doing one thing at home and get distracted into doing something else (unintentionally)?
22. Do you find you can't quite remember something although it's "on the tip of your tongue"?

23. Do you find you forget what you came to the shops to buy?

24. Do you drop things?

25. Do you find you can't think of anything to say?

Appendix 10: Instructions for treatment visits

These instructions were for participants to follow before each of their three treatment visits and during the duration of the study.

Instructions for Visits 2-4.

Please come in after an overnight fast (at least 10 hours).
Do not drink any coffee, tea, or other beverages in the morning except water.
During the duration of the study, please eat what you would consider to be your normal diet.
If you regularly consume alcoholic beverages, please restrict your intake as described. Please limit your alcohol consumption the evening before your visit to no more than 1 drink for females or 2 drinks for males. 1 drink is the equivalent of a 12 oz. can of beer or a 4 oz. glass of wine.

Please try to follow a regular sleep pattern for the duration of the study.

Do not take any aspirin the morning of your visit.

Please avoid exercise the day before your visit and the morning of your visit.

Wear comfortable walking clothes and shoes for your visit.

Please do not wear eye shadow.

Please bring in your diet and/or physical activity log and monitor with you for your visit.

Feel free to bring books, crossword puzzles, or music with you; you will have about an hour of free time in the lab.

	Date	Time
Visit 2	_____	____
Visit 3	_____	____
Visit 4	_____	____

Please contact Natalie Stein at 517-355-0120, x242 with any questions about your appointment!

Appendix 11: Telephone Screening Questionnaire

Date Screened _____ Screened By _____

Status _____

1.) Name _____ Phone # _____

2.) Mailing Address / email:

3.) DOB _____ Sex M / F Height _____ Weight _____

BMI_____

4.) Are you right or left handed? RIGHT / LEFT

5.) How many years of schooling? _____

6.) Are you worried about your cognition (your ability to think, remember, make decisions?) Yes / No

7.) Current Health Status in general _____

_____

8.) Do you have any physical limitations? Yes / No If yes, list:

_____

9.) Do you use an assistive device for walking? Yes / No

10.) Do you have joint pain/arthritis? Yes / No_____

11.) Do you have any allergic reactions? Yes / No

_____

12.) Are you anemic? Yes / No

13.) Have you had a stroke? Yes / No

Have you had a mini stroke or transient ischemia attack? Yes / No

14.) Do you have **unstable/recent** cardiovascular (including unstable ischemia, heart failure, myocardial uncontrolled arrhythmia, and aortic stenosis) or unstable metabolic disease (hypertension, diabetes, thyroid disease)? Yes / No

Details: _____

15.) Do you have chronic heart failure or hypertrophic cardiomyopathy? Yes / No

16.) Do you /have you had an aneurysm? Yes / No

17.) Do you have severe arterial hypertension (systolic BP > 200mmHg, diastolic pressure >110mm Hg? Yes / No

18.) Do you have high blood pressure? Yes / No

19.) What your most recent BP? _____mmHg, Date:_____ Don't remember

20.) Do you have acute pulmonary embolism? Yes / No

21.) Do you have a chronic infections disease (AIDS, mononucleolus, hepatitis)? Yes / No

22.) Do you have cardiovascular disease? Yes / No

_____

23.) Have you had a recent heart attack? Yes / No Date:

_____

24.) Do you have peripheral arterial disease or peripheral vascular disease? Yes / No

25.) Do you have fibromyalgia? Yes / No

26.) Do you have chronic fatigue syndrome? Yes / No

27.) Have you been diagnosed with dementia? Yes / No

28.) Have you been diagnosed with moderate or severe depression? Yes / No

29.) Have you been diagnosed with schizophrenia or bipolar disorder or do you have hallucinations? Yes / No

30.) Do you have diabetes? Yes / No Type I / Type II

If yes, how long have you been diagnosed?

_____If yes, do you take insulin? Yes / No

31.) Do you have any other chronic medical conditions? Yes / No

List: _____

32.) Do you have a pacemaker? Yes / No

33.) Do you have an implanted medical stent? Yes / No

If yes, where is the stent and what kind is it (look on your medical card)?

_____

34.) Do you have any other implanted metal? E.g. neurostimulator, pins, plates, rod, screws? Yes / No If yes, where is the metal located?_____

35.) Do you smoke? Yes / No

If yes, for how long? _____

How much? _____ppw / ppd

36.) Do you chew tobacco? Yes / No

If yes, for how long? _____ How much? _____ per day

37.) Are you a past smoker? Yes / No

38.) Do you wear dentures? Yes / No

If yes, are they: removable / partial (bridge/crown) / fixed

What is the brand? _____

39.) Do you wear a hearing aid? Yes / No

40.) Do you wear corrective lenses? Yes / No

If yes, what kind of correction?

_____

41.) Are you taking a beta blocker? Yes / No If yes, circle the med:

Betapace (sotalol), Blocadren (timolol), Brevibloc (esmolol), Cartrol (carteolol), Coreg (carvedilol), Corgard (nadolol), Inderal (propranolol), Inderal-LA (propranolol), Kerlone (betaxolol), Levatol (penbutolol), Lopressor (metoprolol), Normodyne (labetalol), Sectral (acebutolol), Tenormin (atenolol), Toprol-XL (metoprolol), Trandate (labetalol), Visken (pindolol), Zebeta (bisoprolol), Alprenolol,Corgard (Naldolol), Nebilet (Nebivolol)

42.) What other medications are you taking?

_____

_____

_____

43.) Are you taking any of the following dietary supplements? (Circle those that apply, and note duration and frequency of use)

Gingko Biloba DHA (Docosahexaenoic acid, fish oils) Vitamin E

gotoKola (Centella Asia Tica) Ginseng

Notes: _____

44.) What (other) supplements/vitamins are you taking and how often?

_____

45.) Are you allergic to any foods or beverages? Yes / No

If yes, List:

_____

46.) Do you currently exercise (walking included)? Yes / No

Mode _____Duration (time/day):

_____ Frequency (days/wk): _____ Other details:

_____

47.) Has this level of physical activity been consistent over the last 3 months? Yes/No

48.) Is fatigue a problem for you? Yes / No Leg fatigue? Yes / No

49.) Can you walk continuously for 30 minutes? Yes / No / Do not know

50.) When was the last time you walked continuously for 30 minutes?

_____

51.) Do you have difficulty breathing or shortness of breath when walking? Yes / No

52.) Have you ever walked on a treadmill? Yes / No

53.) How many alcoholic drinks do you have per week? _____ Per day _____?

54.) Do you have any dietary restrictions? Yes / No. If yes, please list:

_____

55.) What is the name and phone number of your primary physician?

_____

56.) When was your last doctor's visit?

_____

57.) When was your last physical?

_____

58.) Do you have a cardiologist? Yes / No

If yes, provide contact info

_____

59.) Have you ever had an MRI? Yes / No If yes, when?

_____

[If the person clearly does not qualify at this point, ask the following:]

60.) Would you be interested in other research studies at MSU? Yes/ No

If yes, may we keep your contact information on file and contact you about future studies? Yes / No

[If the person may qualify at this point, ask the following:]

When is a good time to reach you (day/time)? _____

Appendix 12: Study summary report to participants

Month Day, Year
Jane Smith
Street Address
City, MI, zip code

Dear Jane,

Thank you for participating in our study on the effects of nutrition and exercise on cognition supported by the Michigan State University Radiology Department! We know this report is long overdue and we thank you for your patience, and more importantly for your participation. Enclosed, please find a summary of your results from our study. The first two pages show your performance on the computerized CogState battery compared to the study's average (average age 70 years). The next page of the report shows your fasting blood measures. Also included is an analysis of your regular nutrient intake based on the three days of food records that you completed.

We have selected certain key nutrients to include in this report because they are important for your health. Eating an appropriate number of calories is an integral part of maintaining an appropriate weight, which can help decrease the risk of chronic diseases like cardiovascular disease and diabetes. Diets low in saturated fat, sodium, and cholesterol, and high in fiber, unsaturated fat, potassium, and fruits and vegetables are likely to decrease the risk of chronic diseases and may slow the aging process in the brain. Vitamins A and C are healthful antioxidants that are found in many fruits and vegetables. There is also an estimate of your daily intake of the important nutrients folate, iron, and calcium, whose intakes are sometimes inadequate in our diets. The final page of the nutrient summary gives an indication of the variety of foods you ate by showing the average number of servings that you ate from each food group. All of your nutrient intakes are compared to the recommended levels.

Our main study focus was to determine if a single meal or bout of exercise influenced cognitive function in older adults. In this study that you participated in, we did not find an improvement in cognitive function with a Nutrient Dense Diet or exercise compared to a Standard American Diet. We are still analyzing the brain MRI data, but we also have not found an effect of the meal or exercise on brain activity during the task that you completed in the MRI scanner. We were particularly interested in your executive processing because aging is sometimes associated with a loss of the ability to focus on a specific task. For example, in one of the tasks you completed, you were asked to identify the direction of the center arrow while ignoring distracters (the directions of the surrounding arrows). This is

an example of the inhibitory process, which is more difficult as we age. Other research groups have shown that chronic or regular exercise does improve cognitive function and that certain nutrients can also improve cognition. Our research suggests that consistent lifestyle choices of a nutrient dense diet and exercise program are required for positive adaptations to occur. In other words, keep the fiber, fruits and vegetables, healthy fats, and daily exercise in your lifestyle - they are still important factors when it comes to brain health!

Thank you again for your participation in our study. We greatly appreciate your generous help! Please review the material enclosed and feel free to call Natalie Stein if you have any questions.

Sincerely,

The Exercise and Nutrition Laboratory
Department of Radiology
517-355-0120, x242

Jill M. Slade, PhD, Joseph J. Carlson, PhD, RD, Natalie J. Stein, BS

Name: _____

The following tables summarize the scores from the battery of cognitive tests preformed on the computer during the study. For each of the tests and treatments, your score is an average from all your visits. The last column lists the average from the entire group that completed the study. Your accuracy and speed in performing each task is listed in the tables below. There is also a description of the test.

Table 8: Participant report for accuracy

Accuracy is the proportion of correct responses given during the task. 100% would mean that you did not make any errors and 50% would mean that you made a mistake ½ the time. Of course, higher accuracy is better.

ACCURACY	Cognitive area	Task description	Your Score	Group Average
Continuous Paired Associate Learning	Memory and Spatial Memory	In what locations do these pictures belong?		67%
One Word Learn	Verbal Memory	Have you seen this word before in this task?		94%
Identification	Visual Attention	Is the card red?		99%
One Card Learn	Visual Learning and Memory	Have you seen this card before in this task?		70%
One Back	Attention/Working Memory	Is the previous card the same?		97%
Monitoring	Attention	Has a card touched a white line?		90%
Prediction	Executive Function	Is the next card red? (Then, remember the sequence of cards)		81%
Continuous Paired Associate Learning Delayed Recall	Memory and Spatial Memory-Delayed Recall	In what locations did these pictures belong? (repeat task 1)		72%
One Word Learn Delayed Recall	Long Term Memory	Have you seen this word repeatedly before? (repeat task 2)		90%

Table 9: Participant report for speed

Speed is the length of time it took to respond to each stimulus (e.g. card, picture or word). The time is reported in milliseconds (msec). The lower number means a faster or better time.

SPEED	Cognitive area	Task description	Your Score	Group Average
Continuous Paired Associate Learning	Memory and Spatial Memory	In what locations do these pictures belong?		2897 msec
One Word Learn	Verbal Memory	Have you seen this word before in this task?		827 msec
Identification	Visual Attention	Is the card red?		540 msec
One Card Learn	Visual Learning and Memory	Have you seen this card before in this task?		1016 msec
One Back	Attention/Working Memory	Is the previous card the same?		770 msec
Monitoring	Attention	Has a card touched a white line?		442 msec
Prediction	Executive Function	Is the next card red? (Then, remember the sequence of cards)		1673 msec
Continuous Paired Associate Learning Delayed Recall	Memory and Spatial Memory-Delayed Recall	In what locations did these pictures belong? (repeat task 1)		2902 msec
One Word Learn Delayed Recall	Long Term Memory	Have you seen this word repeatedly before? (repeat task 2)		921 msec

Table 10: Participant report for bloodwork

These are the values from your bloodwork. These values are from the fasting blood draw taken in the morning before you ate breakfast. For each measurement, your individual values are listed next to the normal range.

	Your Value	Normal Range		
Total cholesterol (mg/dl)		125-200		
HDL (mg/dl)		30-60		
LDL (mg/dl)		60-130		
Triglycerides (mg/dl)		10-150		
Glucose (mg/dl)		80-110		
Insulin (IU/ml)		6.0-29.0		
Total cholesterol/HDL ratio		Risk Group	Men	Women
		.5X	3.4	3.3
		Average	5	4.4
		2X	9.6	7
		3X	23	11

Appendix 13: Sample letter to physicians after exercise

Month Day, Year

John Doe, MD
1234 Some Street
City, MI 12345
Fax: 123-456-1234
Tele: 123-456-1235

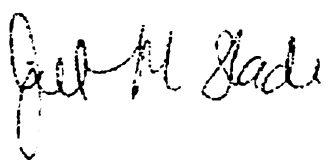
Dear Dr. Doe,

Your patient, **Jane Smith (DOB)** recently volunteered as a research participant in a study at Michigan State University. The study focused on the influence of nutrition and exercise on cognitive function. For this study, the research participant walked on a treadmill at a self-selected pace for 30 minutes at a moderate, sub-maximal exercise intensity (50% of heart rate reserve) under the supervision of an ACLS certified clinician. During the duration of the exercise, the participant's ECG and blood pressure were monitored.

Enclosed, please find the ECG and blood pressure reports from the resting state, warmup, 30 minutes of exercise, and post-exercise.

If you have any questions, please contact Jill Slade, PhD, at (517) 355-0120 ext. 351 or Joe Carlson, PhD, RD, at 355-0120 ext. 346.

Sincerely,



Jill M, Slade, Ph.D.

Resting and sub-maximal exercise EKG

Name_____

Date_____

DOB _____

Medications:_____

Participant's physician_____
Address _____
_____
_____
Phone _____
Fax _____

Supervising physician
Kiran Sarikonda, MD
Pager 517-432-3411

Description of Exercise: 30 minutes of treadmill walking at a sub-maximal intensity (50-65% heart rate reserve) plus 5 minutes warm-up and cooldown.

_____
Kiran Sarikonda, MD

Appendix 14: National recommendations compared to participant intake and national average intake.

These tables compare select nutrients that were highlighted in this study. The recommended intakes are Dietary Reference Intakes from the Institute of Medicine. Subject intake was calculated based on a three-day food record, as described in the text and reported in Table 5. Average national intake was based on NHANES (USDA 2008) and National Cancer Institute (NCI 2009) data.

Table 11: Nutrient comparisons for females

FEMALES

	Recommended intake	Subject intake	National Average
Age (years)	51-70	67.9 ± 3.5	60-69
kilocalories	1978	1669 ± 365	1598
% kilocalories from fat	20-35**	32 ± 4	36
% kilocalories from saturated fat	*	9 ± 2	12
n-3 fatty acids, g		0.9 ± 0.8	
% kilocalories from protein	10-35**	17 ± 5	16
% kilocalories from carbohydrate	45-65**	51 ± 7	49
dietary fiber, g	21	19 ± 4	14.3
servings of fruit and vegetables	2.8	4.4 ± 2.4	2.8
vitamin C, mg	75	136 ± 73	79.7
vitamin E, mg	15	11 ± 9	6.5
potassium, mg	3500	2327 ± 613	2376
folate, dietary folate equivalents, µg	200	374 ± 203	449
vitamin B12, µg	1.5	6.3 ± 4.6	4.69

* Not necessary for prevention of chronic disease, so there is no recommendation for intake.

**Amounts given in Acceptable Macronutrient Distribution Ranges.

Table 12: Nutrient comparisons for males

MALES

	Recommended intake	Subject intake	National Average
Age (years)	≥ 70	75 ± 4.6	≥ 70
kilocalories	2054	2082 ± 466	1984
% kilocalories from fat	20-35%**	33 ± 3	35
% kilocalories from saturated fat	*	11 ± 1	12
n-3 fatty acids, g		0.8 ± 0.5	
% kilocalories from protein	10-35%**	14 ± 2	16
% kilocalories from carbohydrate	45-65%**	54 ± 3	48
dietary fiber, g	30	27 ± 7	16.8
servings of fruit and vegetables	3.1	4.1 ± 2.3	1.7
vitamin C, mg	75	82 ± 29	97.4
vitamin E, mg	15	6 ± 3	7
potassium, mg	3500	2059 ± 344	2863
folate, dietary folate equivalents, µg	200	644 ± 278	590
vitamin B12, µg	1.5	3.4 ± 1.2	6.09

* Not necessary for prevention of chronic disease, so there is no recommendation for intake.
**Amounts given in Acceptable Macronutrient Distribution Ranges.

Appendix 15: Correlations between habitual physical activity and selected study outcome measures

Weekly energy expenditure was estimated using GT1M Activity Monitor accelerometers as described in the Materials and Methods section in Chapter II of the text. These figures show correlations of individual weekly physical activity per body weight in kilograms with key study outcome measures averaged across all three treatment conditions (SB, NB, and NB + AE). kcal = kilocalories, IFG = inferior frontal gyrus, MFG = middle frontal gyrus, PCG = precentral gyrus, BA6 = Brodmann's Area 6, C = congruent condition of flanker task, IC = incongruent condition of flanker task, SI = signal intensity of BOLD response, R = right, A = anterior, S = superior. R^2 = goodness of fit, calculated from Pearson's correlation coefficient.

Figure 11: Correlations between physical activity and study outcomes

A. Physical activity versus maximum percent change in signal intensity in the brain BOLD response during the incongruent condition of the flanker compared to baseline in a 849 mm^3 cluster at the right inferior frontal gyrus, middle frontal gyrus, precentral gyrus (centroid at R39,A3,S32).

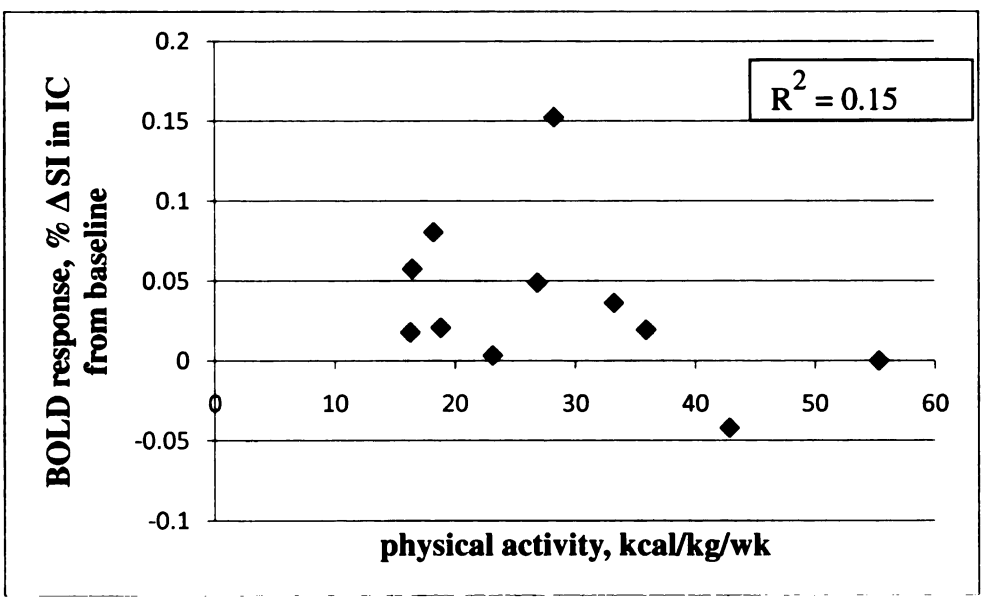


Figure 11 (Continued)

B. Physical activity versus maximum percent change in signal in the brain BOLD response during the incongruent condition of the flanker compared to baseline in a 437 mm^3 cluster at the right middle frontal gyrus, Brodmann's Area 6 (centroid at R29, P1, S54).

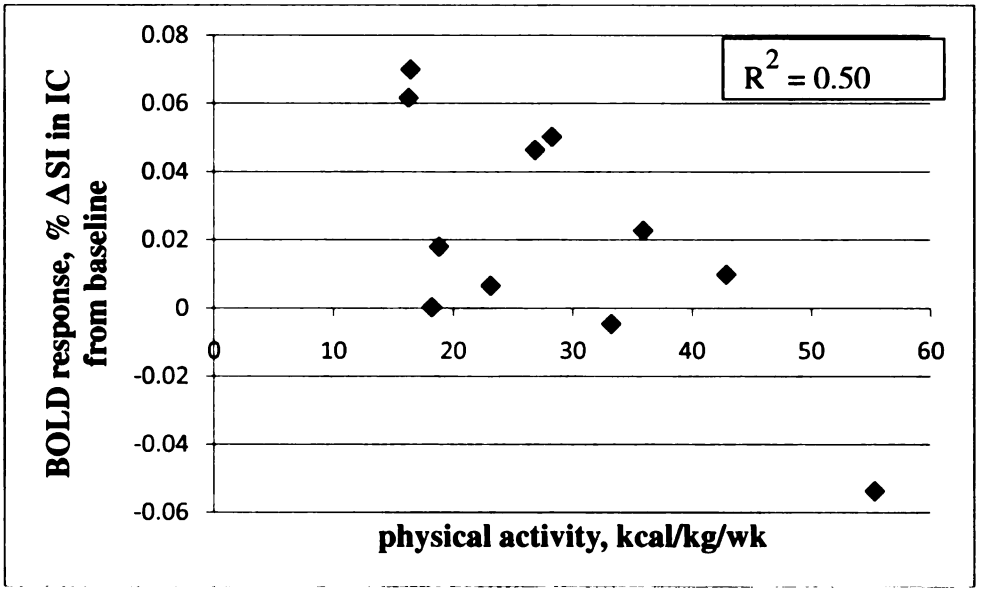
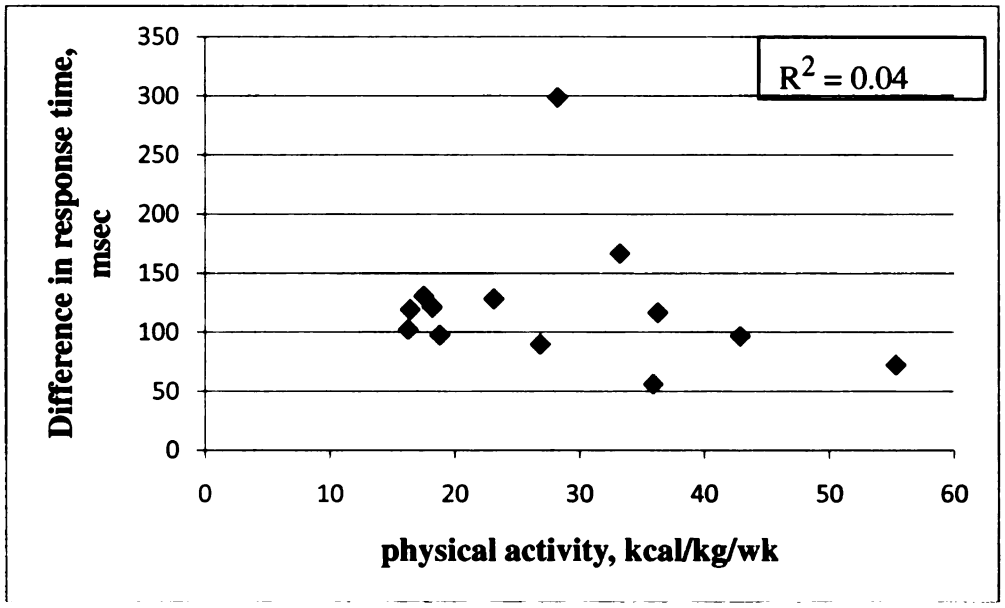
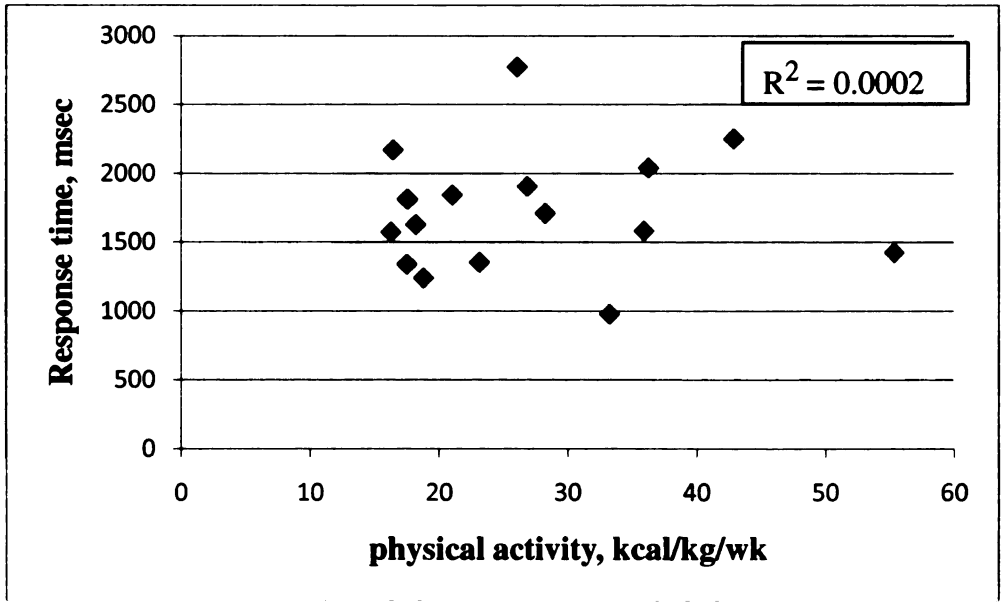


Figure 11 (Continued)

C. Physical activity versus difference in response time, in milliseconds, between the incongruent and congruent conditions in the flanker task.



D. Physical activity versus response time, in milliseconds, on the prediction task of the CogState© battery.



Appendix 16: Flanker results

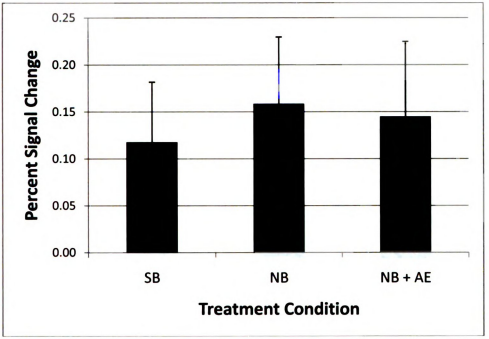
Table 13: Flanker results for participants with fMRI data

	Acc C	Time C	Acc IC	Time IC	Time (IC-C)	$\frac{IC-C}{C}*100\%$
SB	99%	751 msec	99%	860 msec	109 ± 70 msec	15%
NB	99%	771 msec	99%	890 msec	119 ± 59 msec	16%
NB + AE	99%	763 msec	99%	881 msec	119 ± 77 msec	16%
Average	99%	761 msec	99%	877 msec	115 msec	16%

Results for the Flanker test (n=11; same subjects as included in fMRI analysis). Acc = accuracy. Time = average response time. SB = standard breakfast. ND = nutrient dense breakfast. AE = aerobic exercise. C = congruent condition. IC = incongruent condition. Values are mean or mean ± SD.

Appendix 17: fMRI BOLD percent signal change in congruent flanker condition in inferior frontal gyrus / middle frontal gyrus / precentral gyrus

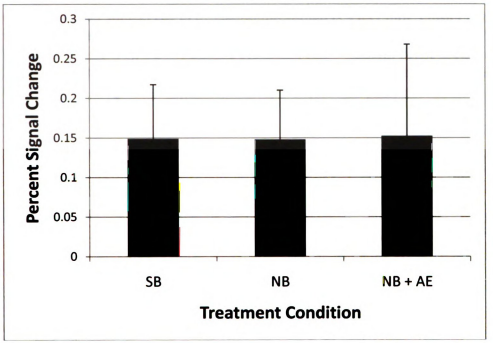
Figure 12: BOLD percent signal change in IFG / MFG / PCG



Values are mean ± standard deviation for percent signal change in the brain BOLD response for the congruent condition compared to baseline in a 849 mm^3 cluster at the right inferior frontal gyrus, middle frontal gyrus, precentral gyrus (centroid at R39,A3,S32) (n=11). SB = standard breakfast, NB = nutrient dense breakfast, NB + AE = nutrient dense breakfast plus aerobic exercise, R = right, A = anterior, S = superior.

Appendix 18: fMRI BOLD percent signal change in congruent flanker condition in middle frontal gyrus / Brodmann's Area 6

Figure 13: BOLD percent signal change in MFG / BA6



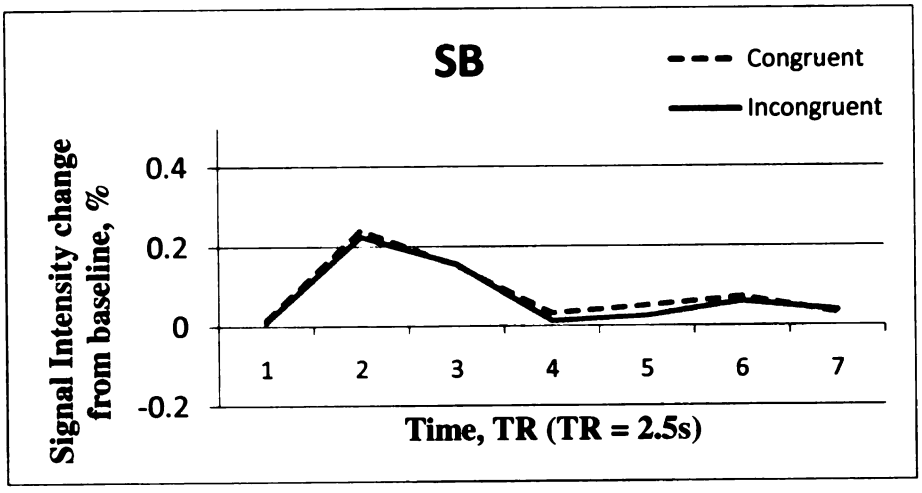
Values are mean ± standard deviation of percent signal change in the brain BOLD response for the congruent condition compared to baseline in a 437 mm^3 cluster at the right middle frontal gyrus, Brodmann's Area 6 (centroid at R29, P1, S54) (n=11). SB = standard breakfast, NB = nutrient dense breakfast, NB + AE = nutrient dense breakfast plus aerobic exercise, R = right, A = anterior, S = superior.

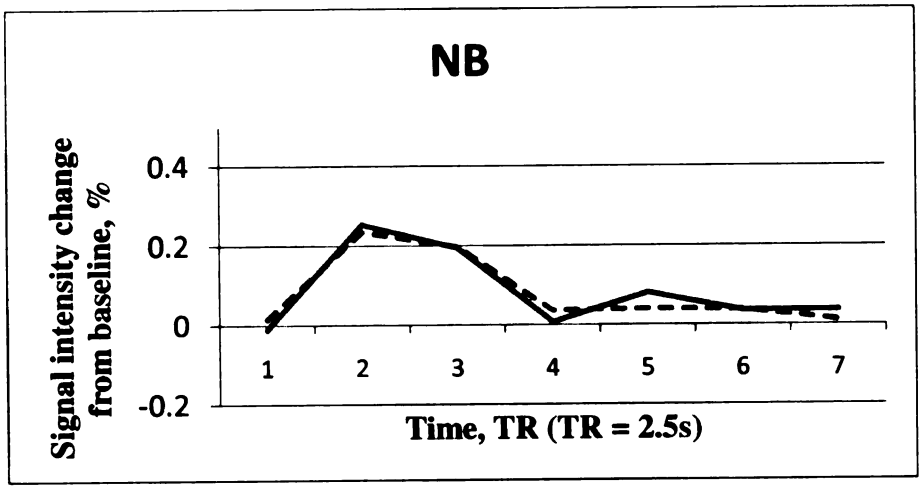
Appendix 19: Impulse-response functions for individual participants

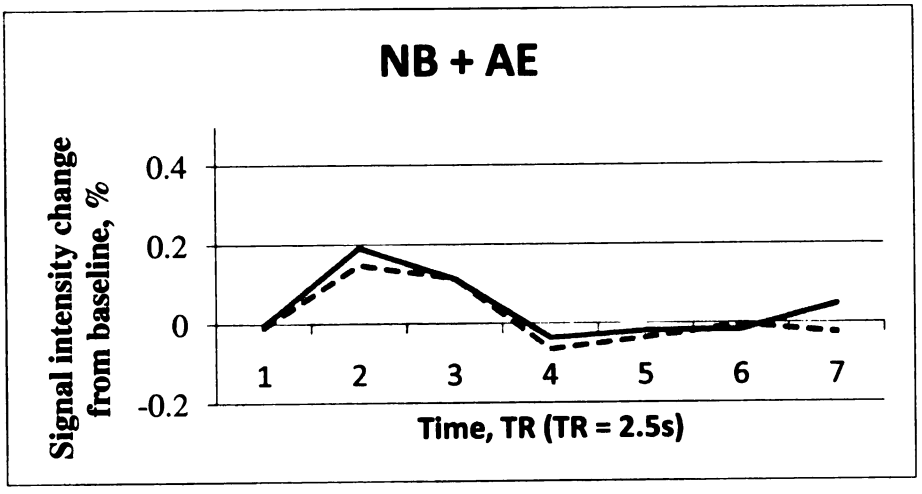
Figure 14: Individual impulse-response functions (A-K, pages 149-159)

These impulse-response functions show brain BOLD responses for each study treatment (SB, NB, and NB + AE). Brain activation is shown as the percent signal change in brain BOLD response from baseline during incongruent flanker tasks for each individual subject (n=11). The region shown is a 849 mm^3 cluster at the right inferior frontal gyrus, middle frontal gyrus, precentral gyrus (centroid at R39,A3,S32) (n=11). SB = standard breakfast, NB = nutrient dense breakfast, NB + AE = nutrient dense breakfast plus aerobic exercise, BOLD = blood oxygen level-dependent, R = right, A = anterior, S = superior, TR = repetition time.

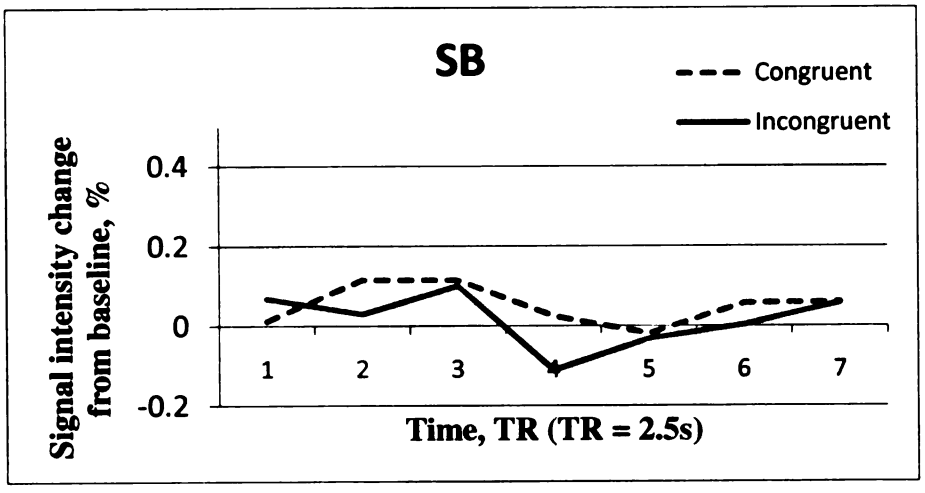
A. Subject 101

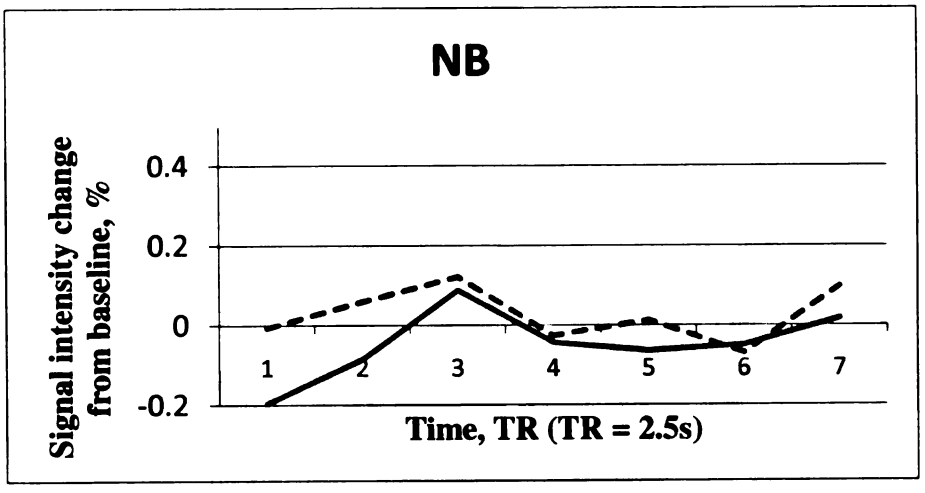


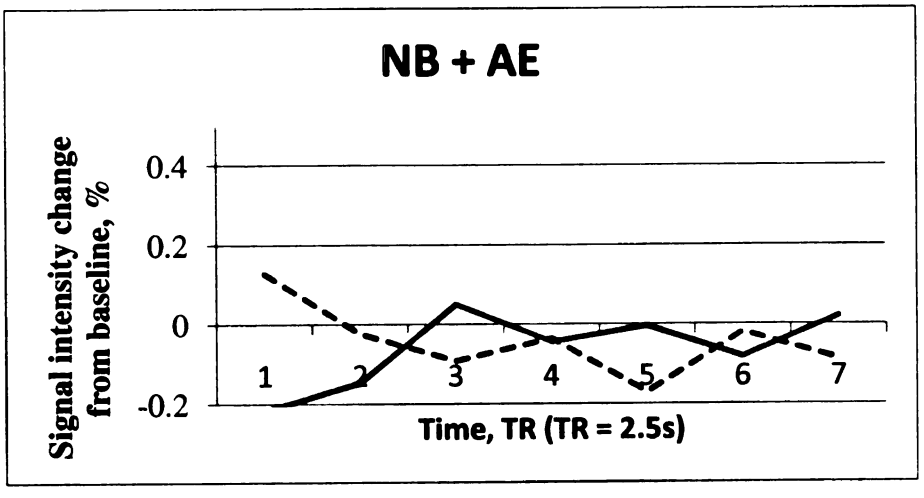




B. Subject 104







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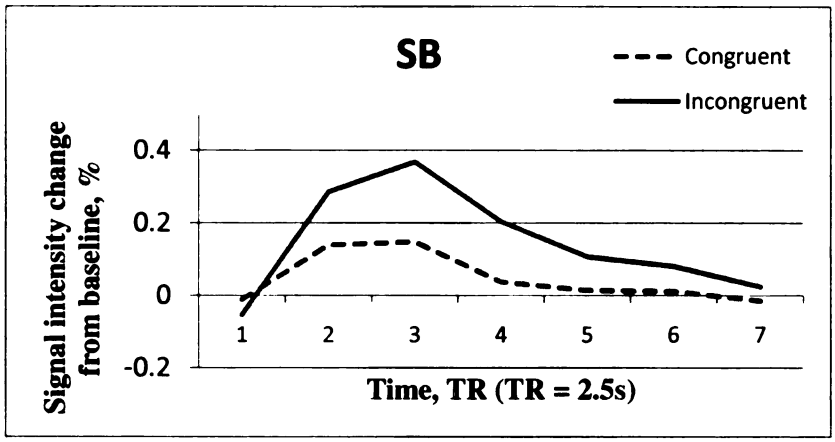

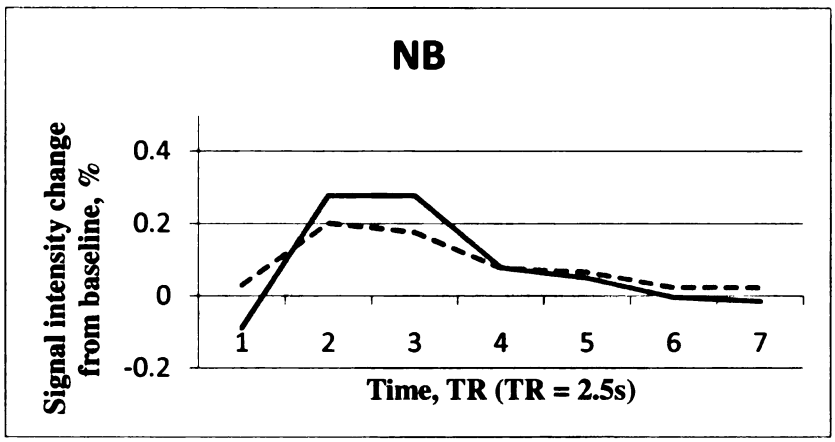

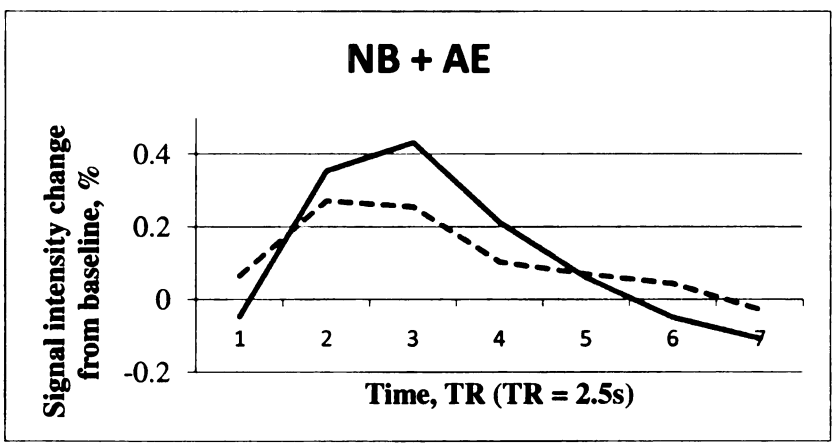

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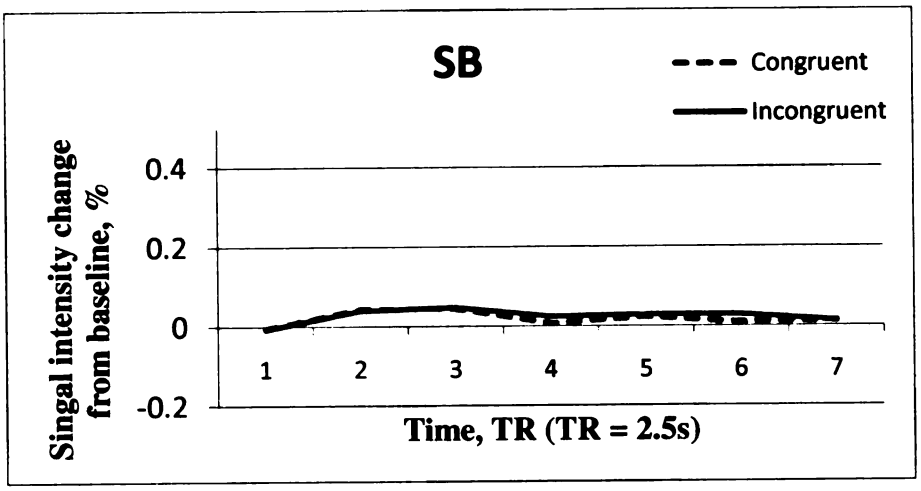

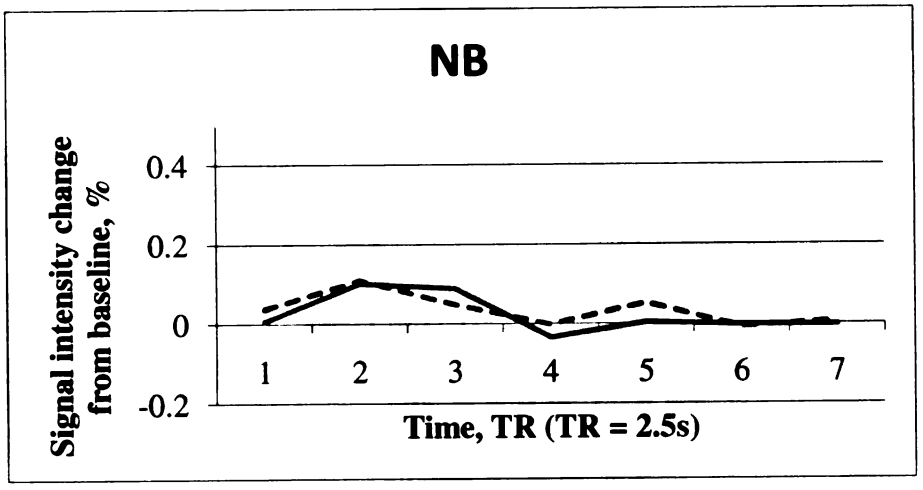

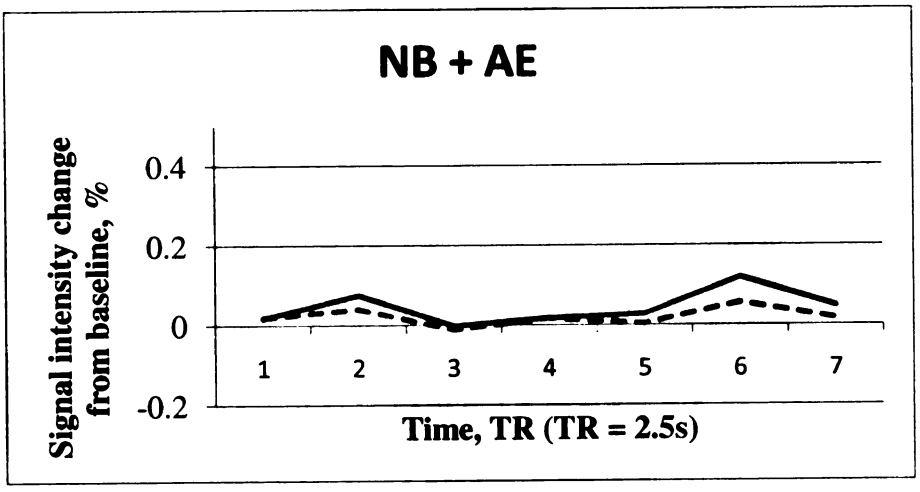

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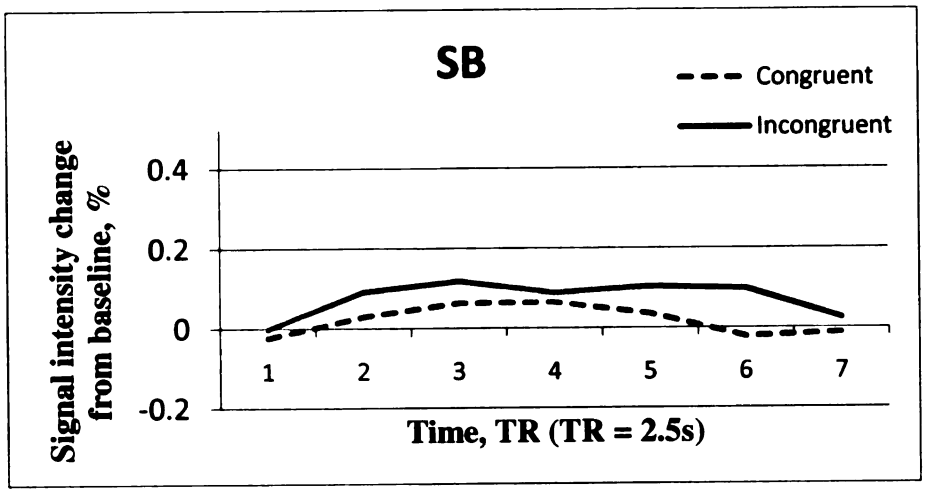

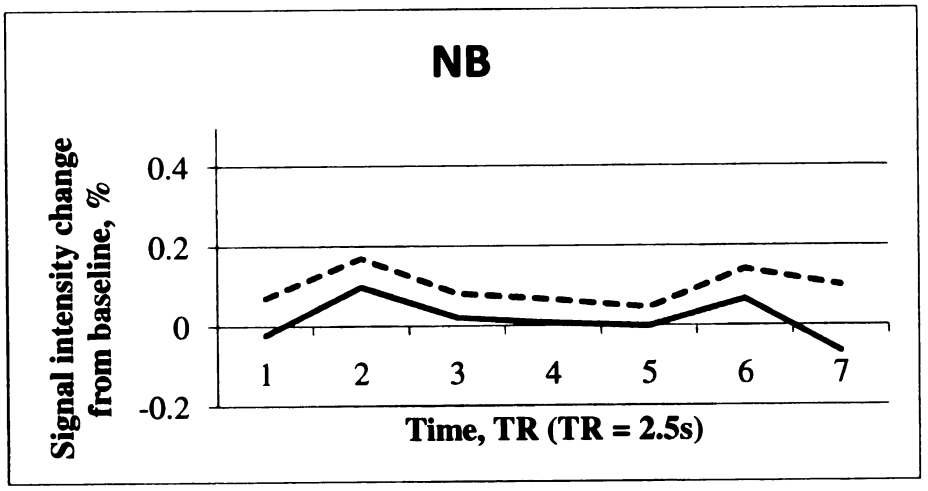

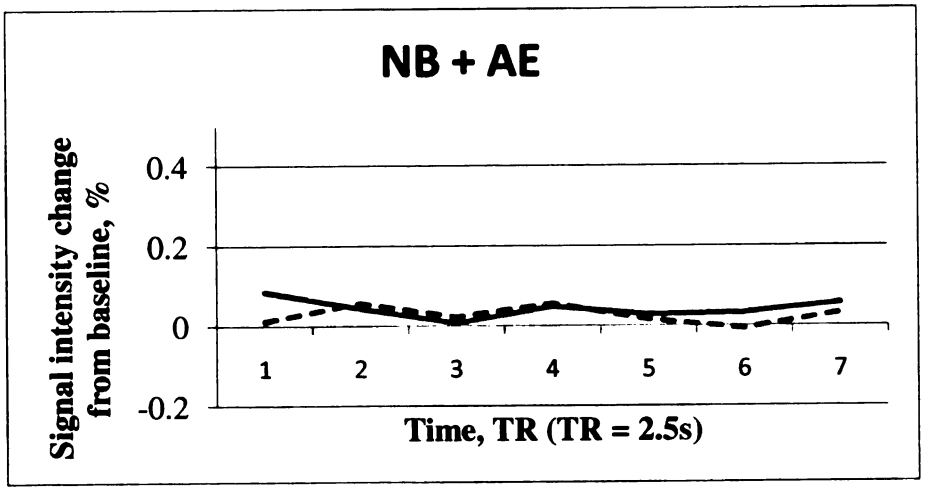

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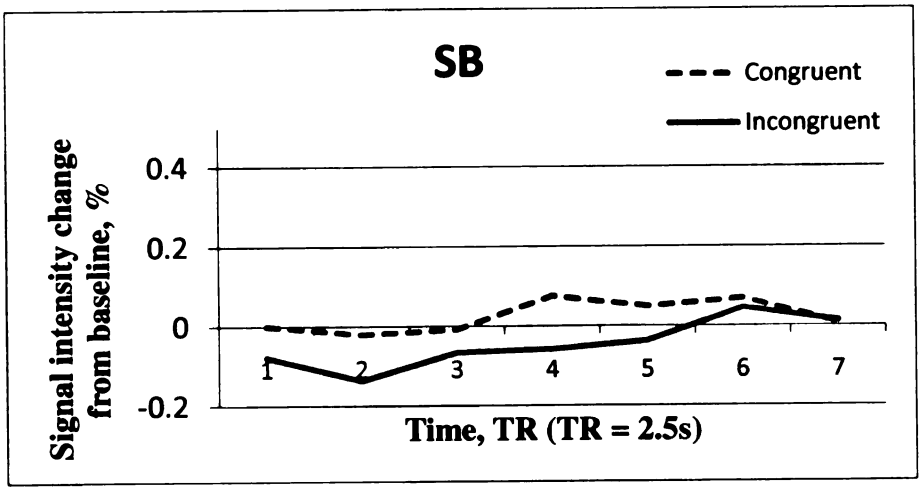

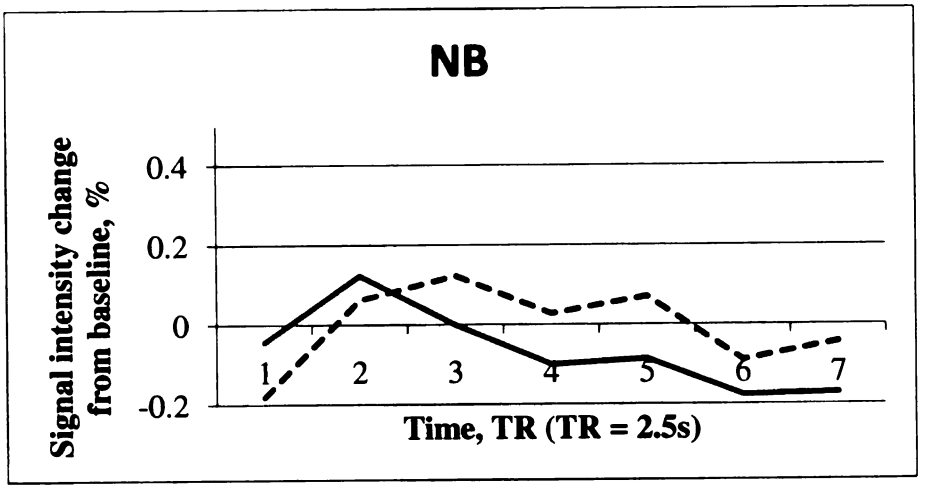

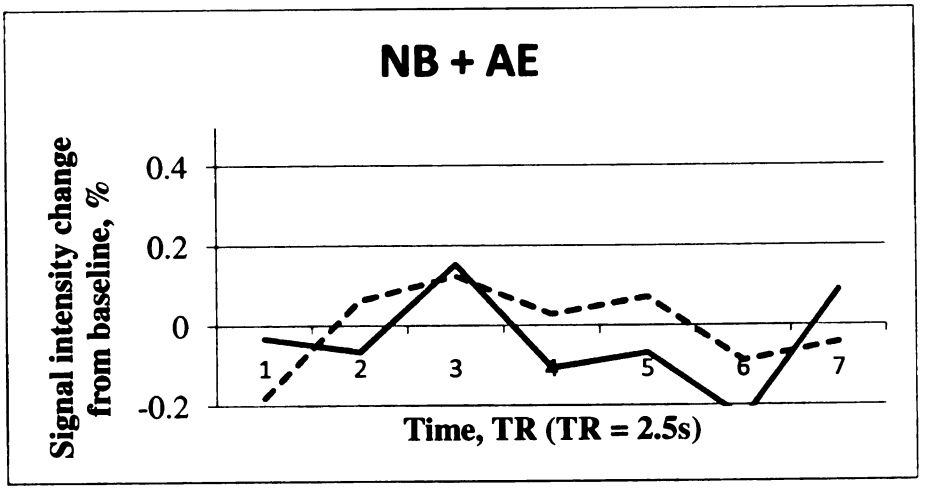

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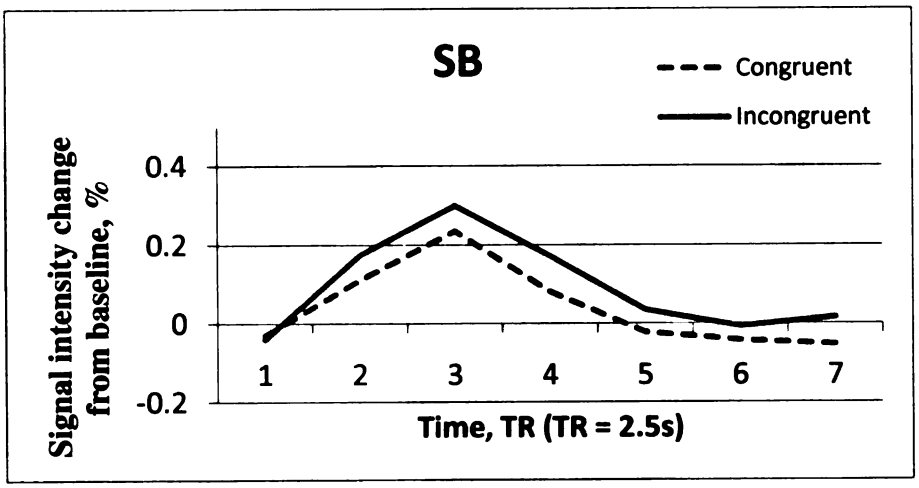

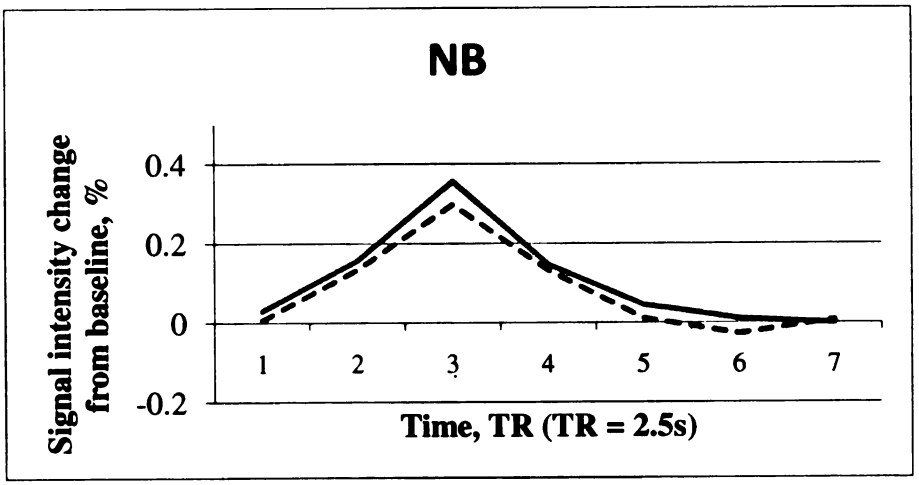

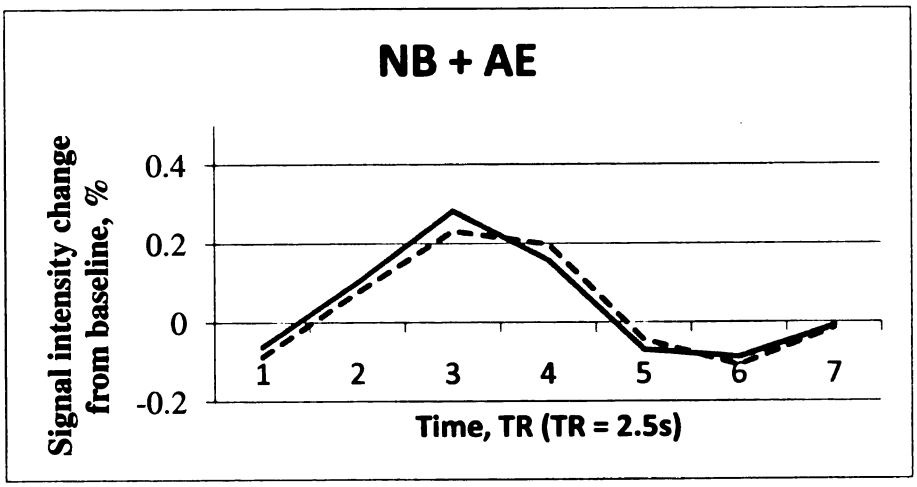

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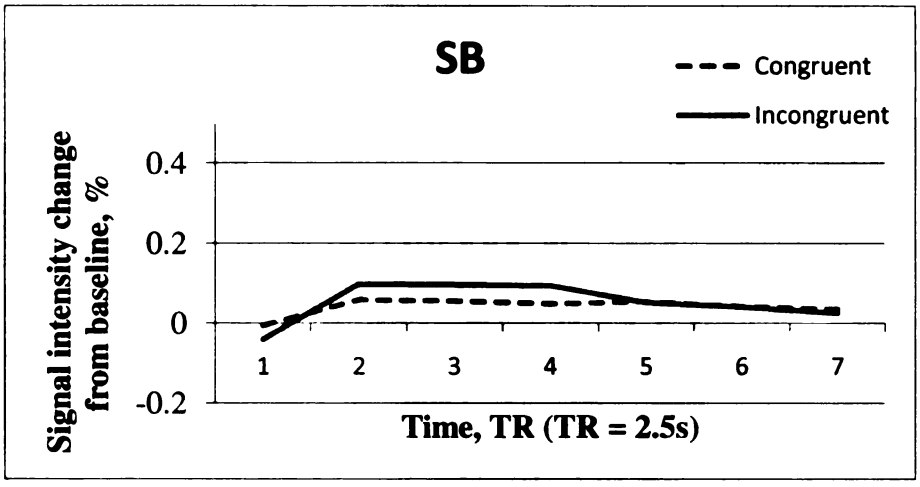

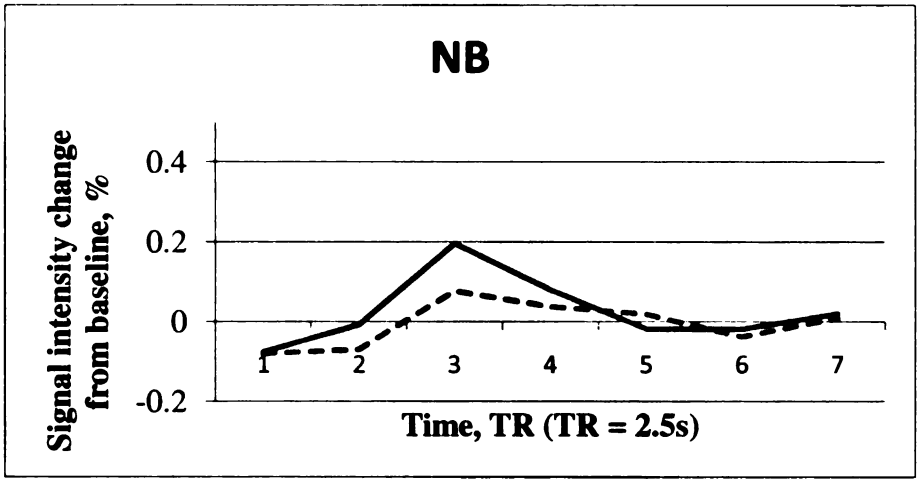

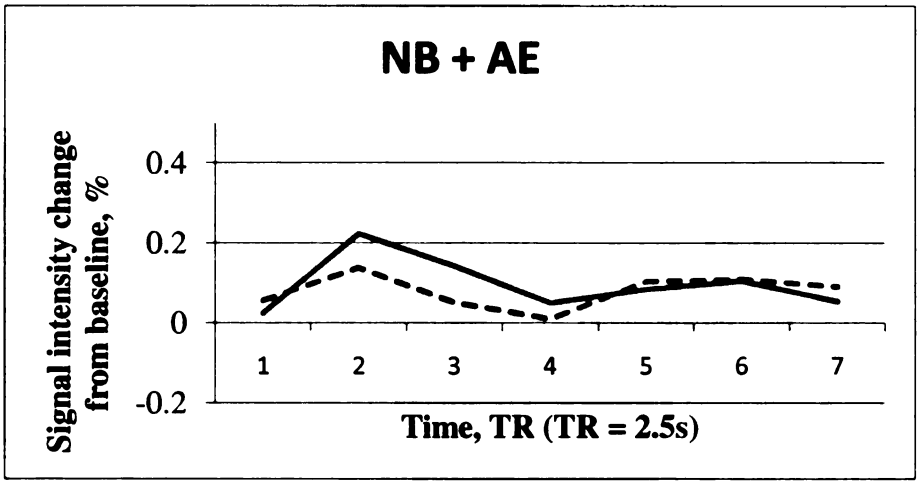

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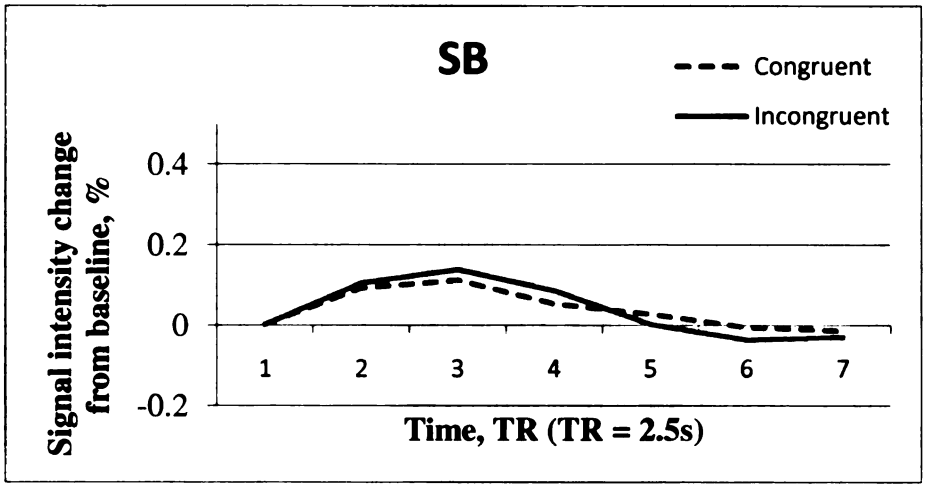
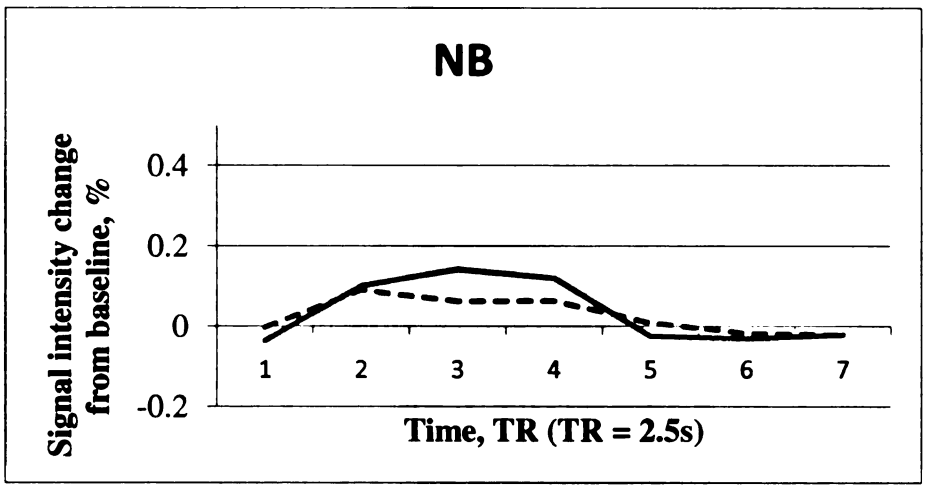
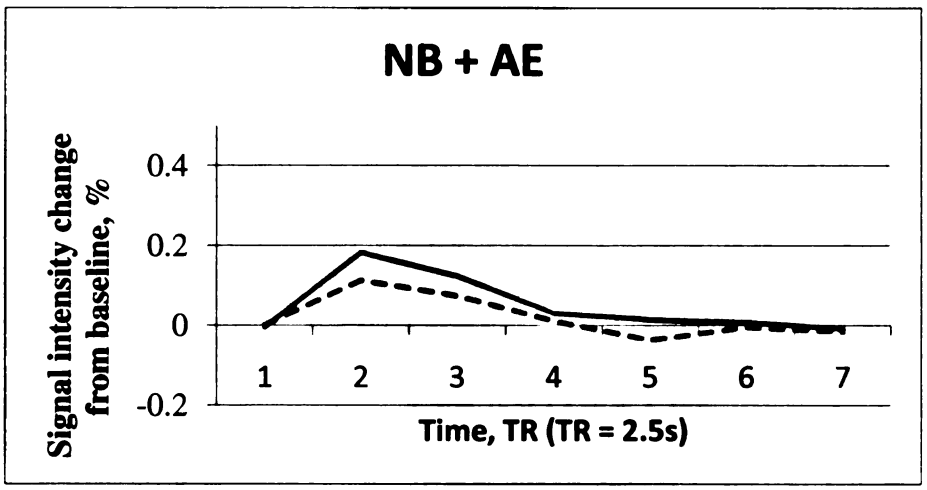
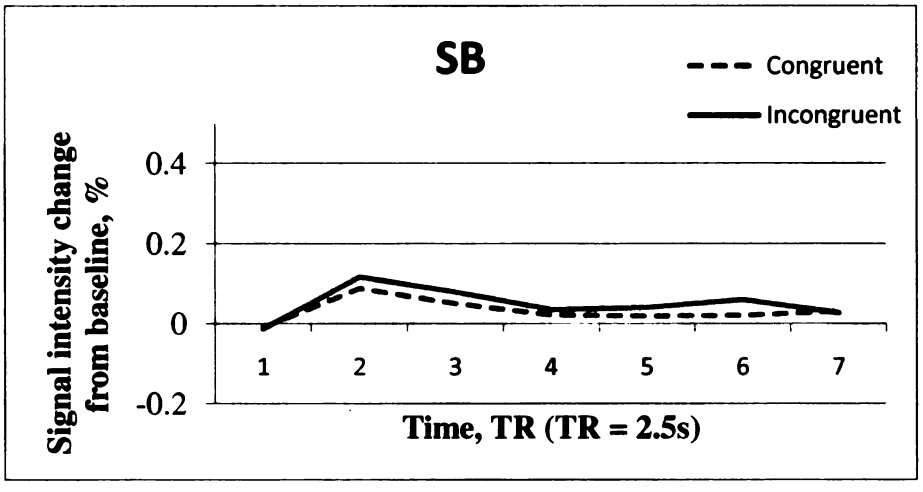
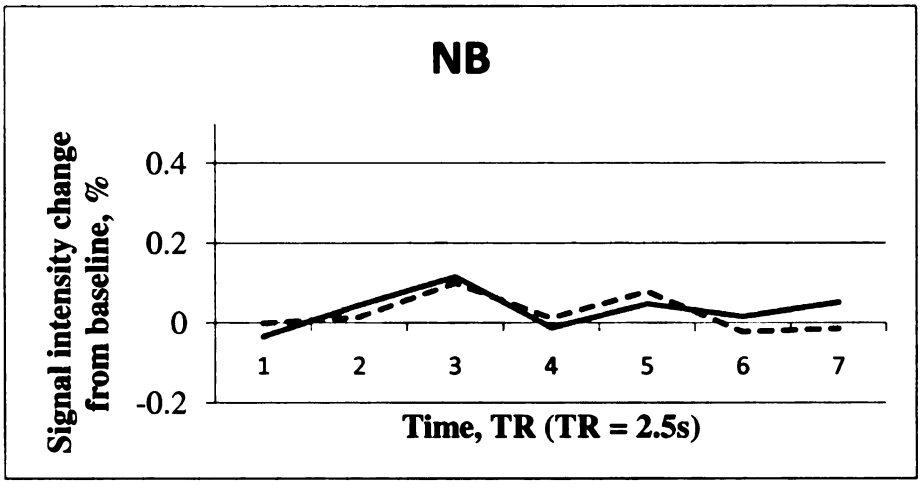


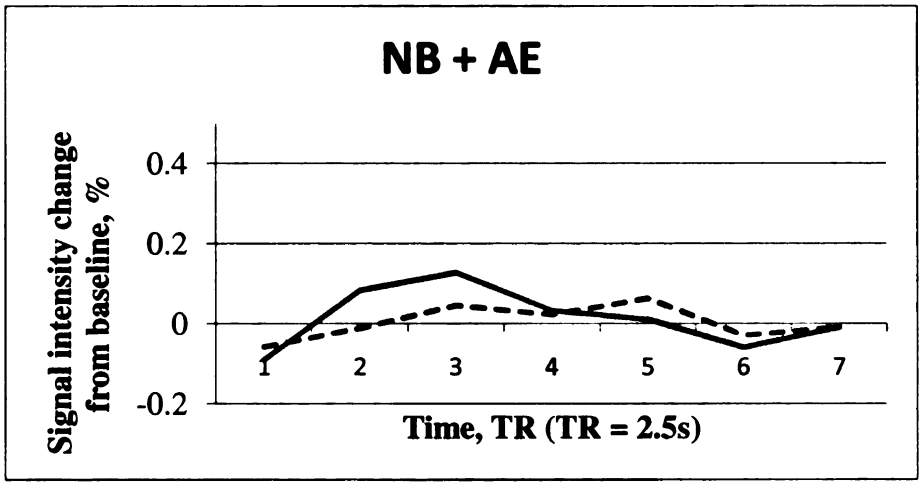




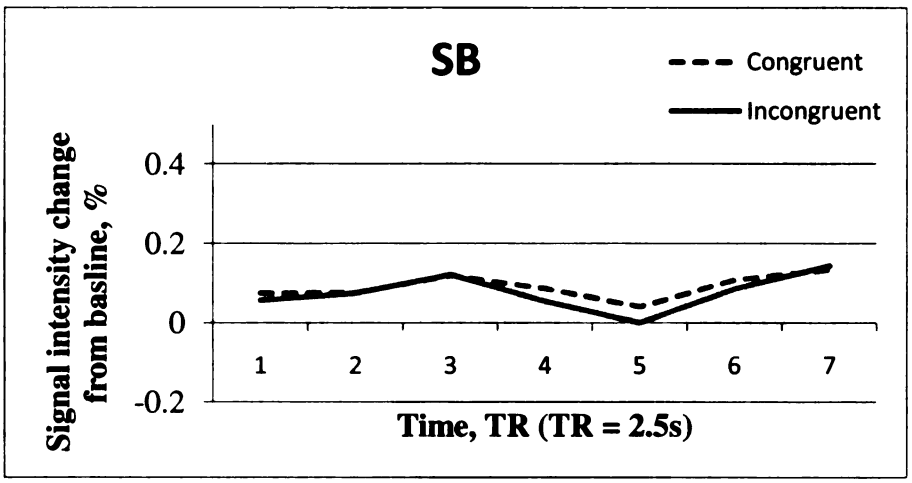
J. Subject 122

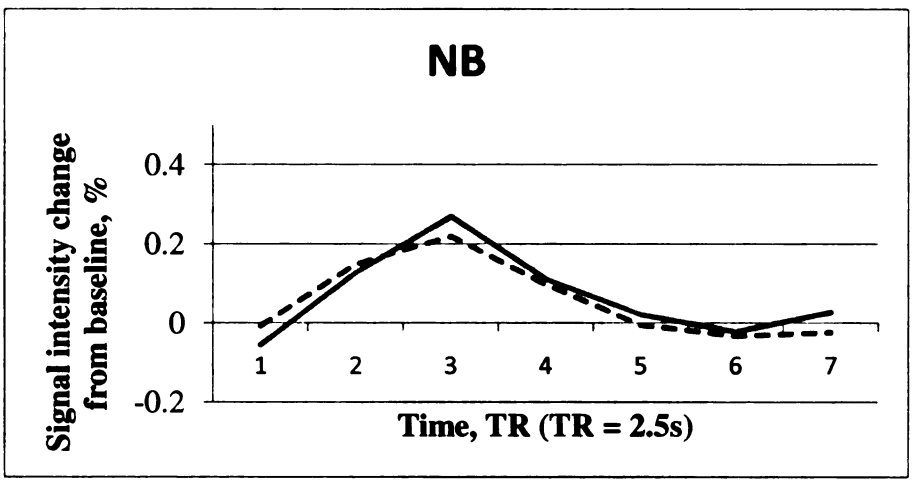


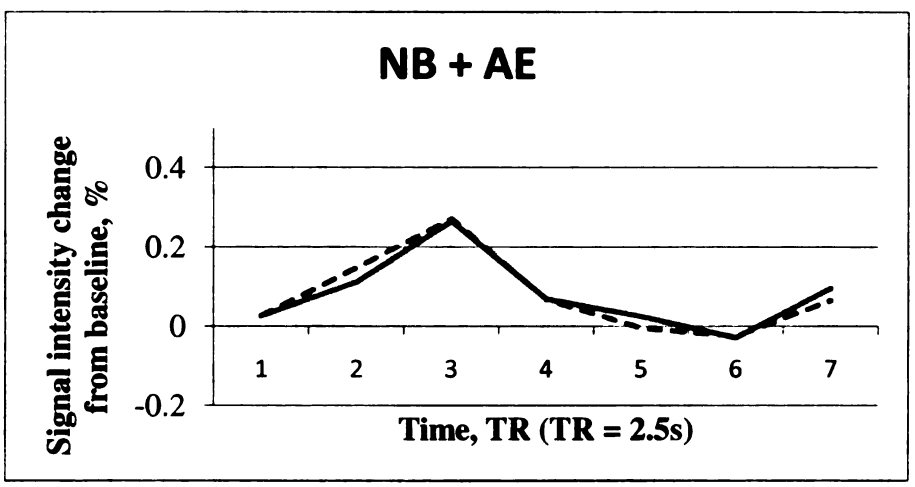




K. Subject 126







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