ABSTRACT

Title of Thesis: THE IMPACT OF ACUTE AEROBIC EXERCISE ON SEMANTIC MEMORY ACTIVATION IN HEALTHY OLDER ADULTS

Junyeon Won, Master of Arts, 2018

Thesis Directed By: J. Carson Smith, Ph.D.
Department of Kinesiology

This study investigated the effects of a single session of exercise on brain activation during recognition of Famous names and Non-Famous names compared to seated-rest in healthy older adults using fMRI. Using a within-subjects counterbalanced design, 30 participants (ages 55-85) underwent two experimental visits on separate days. During each visit, participants engaged in 30-minutes of rest or stationary cycling exercise immediately followed by the famous name discrimination task (FNT). HR and RPE were significantly higher during exercise. Acute exercise was associated with significantly greater semantic memory activation (Famous > Non-Famous) in five out of nine regions. Enhanced semantic memory processing is observed following acute exercise, characterized by greater fMRI response to Famous than Non-Famous names. These findings suggest that exercise may improve semantic memory retrieval in healthy older adults, and may lead to enhancement of cognitive function.

THE IMPACT OF ACUTE AEROBIC EXERCISE ON SEMANTIC MEMORY ACTIVATION IN HEALTHY OLDER ADULTS

By

Junyeon Won

Thesis submitted to the Faculty of the Graduate School of the
University of Maryland, College Park, in partial fulfillment
of the requirements for the degree of
Master of Arts
2018

Advisory Committee:
Professor J. Carson Smith, Ph.D., Chair
Professor Rodolphe Gentili, Ph.D.
Professor Sushant Ranadive, Ph.D.

Acknowledgements

I would like to extend all of my gratitude to those who have supported me in the completion of this thesis. Special thanks to:

· Dr. Carson Smith for serving as my advisor and providing me with constant support and guidance and opportunities to grow as a student and scientist.

· Dr. Rodolphe Gentili and Dr. Sushant Ranadive for serving on my committee and providing valuable insight into this study.

· Lauren Weiss for helping me throughout this project as well as my two years of graduate school. Thank you all for your encouragement! I wouldn't have made it through without you.

· Alfonso Alfini for taking the role of the leader of this project and dependable mentor for me. I sincerely appreciate your help.

· Harry, Dan, and Calvin for your friendship and support through the graduate school.

· My fantastic family for giving me all the love and support.

Support for this research was provided by the Department of Kinesiology and the School of Public Health of the University of Maryland.

Table of Contents

List of Tables

Supplementary Tables

List of Figures

Supplementary Figures

CHAPTER I: REVIEW OF LITERATURE

Overview

With aging comes declines in physical activity (Ahlskog, Geda, Graff-Radford, & Petersen, 2011) and cognitive ability (Raz et al., 2005). Such declines adversely effect on performing routine activity and puts independence of later life at jeopardy (Rejeski & Mihalko, 2001). It is increasingly clear that physical inactivity among older adults facilitates many different health risks encompassing cardiovascular disease, diabetes, cancer, obesity, hypertension, and osteoarthritis (Warburton, Nicol, & Bredin, 2006). Also, growing old is accompanied with neurodegeneration that is associated with impaired ability to perform tasks of daily living including comprehension of medication labels, driving, utilization of emergency telephone information, and understanding of transportation schedules (Ball, Owsley, Sloane, Roenker, & Bruni, 1993; Leirer, Morrow, Pariante, & Sheikh, 1988; Vance, Wadley, Ball, Roenker, & Rizzo, 2005).

Three aspects of successful aging or maintaining a high quality of life for older adults, suggested by Rowe and Kahn (2000), consist of freedom from disease, engagement with life, and physical and mental competence. Since the key for high quality of life lies in feeling and functioning better on a daily basis, and for most, living independently (Spirduso & Cronin, 2001), health problems due to lack of physical activity and cognitive impairment due to aging induce serious risk for older adult's quality of life. In our aging society, with an escalating proportion of people aged over 65, a growing number of people are at risk of losing their autonomy. It is imperative to find strategies to protect against the development of cognitive impairment and thereby sustaining the autonomy of elders, which is an important topic recently from public health perspective (Vance et al., 2005).

Exercise is a viable public health intervention for maintaining or increasing quality of life among older adults (Rejeski & Mihalko, 2001). It is well-established that sustained exercise participation reaps a plethora of benefits, such as cardiovascular fitness, and preventing loss of bone density and muscle mass (DiPietro, 2001; Florindo et al., 2002; Woo, 2000). In addition to the physiologically preventative role of regular physical activity, the benefits of routine exercise include improved psychological well-being through reduced stress, anxiety and depression (Blumenthal et al., 1999). Although some pharmaceutical interventions may elicit some health benefits, no other interventions have produced sustaining general health benefits (Seals, Hagberg, Hurley, Ehsani, & Holloszy, 1984).

In addition to such physiological and psychological health benefits, robust effects of exercise on enhancing and protecting brain function as well as delaying the onset of cognitive decline and improved cognitive function in elders have been demonstrated (Cotman & Engesser-Cesar, 2002). Despite the fact that the fundamental questions about how physical activity leads to beneficial impacts on cognitive function have not yet been fully answered, increased cerebral blood flow (CBF) and brain-derived neurotrophic factor (BDNF) are the most widely understood mechanisms as a result of physical activity.

Mechanisms of Improvement in Cognition after Acute Exercise

Cerebral Blood Flow (CBF)

CBF is closely associated with increase in brain metabolism. Recently, clinical reports have found significant contribution of cerebral and vascular diseases to the development of cognitive dysfunction and dementia (Esiri, Nagy, Smith, Barnetson, & Smith, 1999; Gorelick et al., 2011; T O'Brien et al., 2003). Given this evidence, it can be expected that CBF and its

regulation may play a pivotal role in altering cognitive function. In fact, the natural age-related declines in resting CBF have been associated with poor cognitive function (Ogoh et al., 2014).

Habitual physical exercise may delay the onset of age-related global cerebral atrophy and increase global CBF, therefore reduce the risk of cerebrovascular-related brain diseases caused by aging (Ide & Secher, 2000). Ainslie et al. (2008) looked at the association between physical fitness and cerebral blood flow in both young and old adults. 153 healthy sedentary and 154 endurance trained men aged between 18 and 79 years went through maximal oxygen consumption, body max index (BMI), blood pressure and middle cerebral artery blood velocity (MCAv) measurements. The relationships between age, training status, BMI and MCAv were then analyzed. Results showed that MCAv was consistently elevated in endurance-trained men compared to the sedentary group throughout the age range. This finding suggests that regular aerobic-endurance exercise is associated with higher MCAv in men aged 18-79 years.

Thomas and colleagues (1989) measured the changes in CBF in humans during submaximal dynamic exercise. 16 healthy subjects (28 years) were placed on a Krogh cycle ergometer in a semi-recumbent position during which time they were instructed to exercise for 15 min with a metronome at 60 rpm with 56% of maximal O_2 uptake. CBF was measure using the cerebrograph and ergo-oxyscreen capnography technique. CBF was also measure at rest for baseline. Results revealed that CBF increased by 31% in the initial slope index and 58% in the first compartment flow during dynamic exercise (Thomas, Schroeder, Secher, & Mitchell, 1989).

The effect of acute bout of exercise on CBF was also examined using functional magnetic resonance imaging (fMRI) technique. The study carried out by Smith and colleagues (2010) aimed to determine the optimal inversion time to detect changes in global CBF and

examine differences in CBF in the motor cortex at rest or during a finger-tapping task. Five young healthy adults completed the first fMRI scan session before the exercise session. It is followed by an exercise session where they exercised on an electronically braked cycle ergometer at rating of 13 (with the verbal anchor 'somewhat hard') on the Borg 6-20 Rating of Perceived Exertion (RPE) a subjective perception of exertion. Approximately 10 min after the exercise ended, participant underwent the second scan session. The results showed that an effective time inversion time to detect changes in CBF after a single session of exercise was 1575ms. Also, performing acute exercise was associated approximately 20% increases in global CBF. The finding suggests that changes in human CBF may be induced by 30 min of aerobic exercise (J. C. Smith, Paulson, Cook, Verber, & Tian, 2010).

Brain-Derived Neurotrophic Factor (BDNF)

BDNF is a member of the nerve growth factor family (Hohn, Leibrock, Bailey, & Barde, 1990). BDNF supports differentiation and survival of diverse neurons in the peripheral and central nervous systems during its development (Snider, 1994). Hippocampus, cerebral cortex and subcortical nuclei contain abundant amount of BDNF (Mu, Li, Yao, & Zhou, 1999). BDNF also influences the growth and survival of glial cells by activating signal transduction pathways (Soler et al., 1999). High BDNF concentrations in the brain are associated with neuronal growth and survival, as well as synaptogenesis, leading to cognitive and affective benefits (Cotman & Engesser-Cesar, 2002).

Exercise has been proposed to be a factor inducing and regulating BDNF expression (Neeper, Gomez-Pinilla, Choi, Cotman, & others, 1995; Neeper, Gómez-Pinilla, Choi, & Cotman, 1996). Upregulation of BDNF induced by physical activity may promote

neuroprotection processes in the brain and less cortical atrophy (Cotman & Engesser-Cesar, 2002). Stummer and colleagues (1994) found that rats with two weeks of exercise showed decreased mortality and brain damage following cerebral ischemia. They suggested that an increase in BDNF expression is one possible mechanism that would protect brain from damage (Stummer, Weber, Tranmer, Baethmann, & Kempski, 1994).

Other studies indicate that acute exercise facilitates BDNF expression. One looked at the effects of acute exercise on serum BDNF levels in humans and the association between exercise intensity and BDNF responses (Ferris, Williams, & Shen, 2007). 15 healthy young adults (4 female, 11 male; 25.4±1.0 years) performed a graded exercise test to determine VO_{2max} and ventilatory threshold (VT) on a cycle ergometer. The participants performed two 30-min exercise bouts that corresponded to the VT+10% (high intensity) or VT-20% (low intensity) in a counterbalanced order. A 10-mL blood withdrawal was taken before and after the GXT and exercise sessions in order to measure changes in BDNF levels. Results showed that the GXT and VT+10% resulted in significant increases in serum BDNF levels compared to baseline. VT-20% did not show significant increases in BDNF relative to baseline. The results indicate that moderate to high intensity exercise may be required to increase serum BDNF (pBDNF) (Ferris et al., 2007).

Vega et al. (2006) tested whether acute aerobic exercise has effects on the serum concentrations of BDNF. 8 recreational athletes (24.6±1.3 years) performed acute exercise that consisted of 10 min warm-up with pedal rate at 70 rpm and 2 min of cycling at 2 Watt followed by incremental exercise to exhaustion with 25 W steps every 30 s. The blood was collected at 3, 6, 10 and 15 min post exercise. Blood analysis revealed significantly increased pBDNF at the point of exhaustion while no significant differences were found between at rest and recovery.

Coelho and colleagues (2014) investigated the effects of acute exercise on BDNF levels in elderly with Alzheimer's disease (AD) and healthy controls. 21 older adults with AD (76.3±6.2 years) and 18 healthy older adults (74.6±4.7 years) underwent the submaximal-graded exercise treadmill test of moderate intensity on the treadmill. Using Balke Ware protocol, it started with a walking speed of 4km/h and grade of 3%. The speed was steady and the grade was increased in 1% every 3 minutes, until the participant reached 85% of maximum heart rate (HR) and above 16 in RPE scale. In each stage which lasted for 3 minutes, blood samples were collected from the ear lobe into lactate reagent strips. Results showed that acute aerobic exercise is associated with significant increase in BDNF plasma levels in AD patients and in the healthy controls. This finding indicates that the enhancement of BDNF levels might be facilitated by the acute aerobic exercise (Coelho et al., 2014).

In a nutshell, the vital role of increased CBF and BDNF induced by acute exercise is well supported by a body of evidence. Although these studies are well described, the mechanism underlying the benefits of exercise for cognition may not be driven by a single factor. Many investigators endorse the idea that a variety of cellular, molecular, and neurochemical mechanisms that underlie this relationship are unclear (S. Colcombe & Kramer, 2003). In thinking of how to advance this important line of research, it is critical to develop theoretical underpinnings of basic mechanism between the two variables. Future studies need to build up evidence for explaining complicated neural procedure during enhancement in cognition following acute and chronic exercise. Also, finding conclusive evidence about the relation between peripheral BDNF (pBDNF) and central BDNF is another important direction for future studies. Currently, there is a disagreement regarding the efficacy of using pBDNF as a surrogate marker of central BDNF. Peripheral measurement is endorsed by studies suggesting that pBDNF passes through the blood-brain barrier (Pan,

Banks, Fasold, Bluth, & Kastin, 1998; Poduslo & Curran, 1996) and other findings showed concentrations of central (neural) and peripheral measures of BDNF are positively correlated (Rasmussen et al., 2009; Seifert et al., 2010). In contrast, it is suggested that BDNF does not cross the blood-brain barrier (Pardridge, 2007; Pardridge, Wu, & Sakane, 1998) and correlation between pBDNF and central BDNF is not supported (Kyeremanteng, James, Mackay, & Merali, 2012). Discovering conclusive evidence regarding positive correlation between pBDNF and neural BDNF would support the efficacy of measuring pBDNF in exercise literature.

Acute Exercise and Cognitive Function

Acute Exercise and Executive Function

Executive function is the most commonly discussed cognitive domain that demonstrates positive changes after acute bout of exercise. Weng and colleagues evaluated whether different forms of acute exercise produce differential effects on executive function in healthy young adults. Using a within-subject design, 26 young adults (14 female, 12 male; 25.23±0.56) engaged in a 30-min bout of moderate intensity aerobic cycling and passive motor-driven cycling on two separate days in counterbalanced order. The N-back test, which measures working memory and inhibitory control, was used to assess executive function before and immediately following acute exercise and motor-driven cycling. The results showed a disproportionate increase in performance accuracy on the 2-back condition, compared to 1-back condition after a single session of aerobic exercise; however, passive exercise did not result in the same effect. The finding suggests the facilitating effects of the

active aerobic exercise on executive function was uniquely associated with volitional control over the bodily systems (Weng, Pierce, Darling, & Voss, 2015).

Chang et al. (2011) examined the effects of a single session of moderate to vigorous intensity aerobic exercise on executive functions of planning and problem solving. 42 participants (29 female, 21.97±1.66 years; 13 male, 22.26±1.94) were randomized into exercise and control groups. Participants in the exercise group pedaled on a cycle ergometer for 30 minutes at an intensity of 14-17 RPE for 20 min, including a 5 min warm-up and 5 min cool-down. The pedal cadence was set at 70 rpm and workload was increased by 15 W every 2 min. The control group read materials associated with aerobic exercise for 30 min. A Tower of London Task (TOL Task) was administered before and immediately after each assigned condition. The results showed that total correct score increased significantly from pretest to posttest for the exercise group, whereas no significant difference was found in the control group. This finding suggests acute exercise is associated with improvement in total correct score of TOL Task, reflecting the beneficial effects of acute exercise on the quality of planning and problem solving.

Another study investigated whether acute bout of moderate or vigorous intensity exercise yields beneficial effects on executive function in older women. 11 aerobically fit older women (65.8±3.8 years) completed 20-min exercise session on a motorized treadmill on two separate days for either moderate-intensity exercise (50% of VO_{2max}) and vigorous-intensity exercise (75% of VO_{2max}) before performing modified flanker task and d2 tests for executive function measurements. The modified flanker task measures response time and accuracy with the arrows displayed in the same direction as the middle arrow and the arrow of reference in the congruent situation and opposite direction as the middle arrow and the arrow of reference in incongruent situation. d2 test includes arbitrarily assorted letters in lines shown at a time

when one to four dashes over and under each letter appears. The participant only has to choose the letter ”d” with two dashes above or below the letter. The executive function was tested before, immediately after, and 30-min post exercise. Results revealed that enhanced performance in response times in modified flanker task immediately following both moderate and vigorous exercise. d2 tests demonstrated improvement immediately after acute exercise for both intensities. These findings indicate that an acute bout of exercise with moderate and vigorous intensities can enhance executive function performance in healthy older women (Peiffer, Darby, Fullenkamp, & Morgan, 2015).

Since executive function appears to get the greater benefit induced by aerobic exercise compared to other aspects of cognition to aerobic exercise (S. Colcombe & Kramer, 2003), executive function is the most widely discussed area of cognition in the exercise study. Many different measurements from flanker to N-back to TOL to d2 tests have been used in the experimental designs. Also, participants with different age and gender were also used in these studies, demonstrating a single session of exercise has positive effects on executive function. Taking into account that executive function is a multi-componential construct with several distinct process, exercise may not impact each component of executive function equally (Best, 2010). Future studies need to continue to build evidence regarding whether or not acute aerobic exercise is equally impactful to each component of executive function. Also, it is unclear whether all forms of aerobic exercise are comparable in their impact on executive function. Specifically, group games with the cognitive challenges (e.g., the need to act in a goal-directed and strategic fashion) may pose differential impact on executive function relative to non-group games that do not cause cognitive challenges (Budde, Voelcker-Rehage, Pietra\s syk-Kendziorra, Ribeiro, & Tidow, 2008; Pesce, Tessitore, Casella, Pirritano, & Capranica, 2007). Additionally, an interesting question for future research

concerns comparing the effect of cognitively-engaging sedentary activities and exercise on executive function enhancement. Future studies need to address these questions to advance our understanding on the association between exercise and executive function.

Acute Exercise and Attention

Not only executive function, but findings also reveal that acute exercise is related to improvement in attention. Palmer and colleagues investigated whether acute exercise has effects on preschooler's cognitive function. Using a within-subject and counterbalanced design, 16 children (3 girls, 13 boys; 49.4±5.3 years) underwent exercise and sedentary conditions on different days before performing a cognitive function test. The exercise condition lasted for 30 minutes with developmentally and instructionally promoting motor skills and exercise participation. Participants engaged in 30 min of seated rest for the sedentary condition. Within in 5 min following the participation of exercise or sedentary condition, participants completed Picture Deletion Task for Preschoolers to select answer out of many distractors to assess attention level. The findings revealed that acute exercise is associated with significant improvement in preschoolers' sustained attention. However, acute exercise did not significantly affect response inhibition. These data indicate that acute exercise that promotes motor skill may be associated with better attention in kids attending preschool (Palmer, Miller, & Robinson, 2013).

The other study tested coordinative exercise on attentional performance in adolescents. 115 healthy adolescents (aged 13-16 years) were randomized into coordinative exercise (CE) and normal sport lesson (control group). Both groups went through the d2 test to measure attention and concentration at baseline and immediately after each assigned condition. CE group performed the d2-test 10 min after completing CE and control group performed the test

after 10 min of normal sport lesson. CE consisted of bouncing a volleyball and a basketball and throwing a handball. The normal sport lesson was conducted at a moderate intensity without any specific coordinative request. Results revealed enhanced attention and concentration in both groups with a significantly higher progression in the CE group compared to control group. These data suggest that coordinative skills might reap benefit in improving attention and concentration in adolescents when it is used in educational setting (Budde, Voelcker-Rehage, Pietras syk-Kendziorra, Ribeiro, & Tidow, 2008).

The objective of the study carried out by Hsieh and colleagues was to assess the effects of resistance exercise (RE) on attention control in younger and older adults. Using a within subject design, 17 older adults (66.4±1.2 years) and 18 younger adults (23.9±2.3 years) participated in seated rest and RE with a moderate intensity for 30 mins including 5 to 10 min warm-up, two sets of 10 repetitions of each of the eight exercises at 70% of the individual's previously determined 10 RM. The rest intervals between sets and exercise were 30 and 90s, respectively. Following the RE protocol, participants were seated quietly in a dimly lit room for 10 min before performing the GO/NO-GO test which examines attentional control. For the resting condition, they read materials regarding exercise and health for 30 min and sat for 10 min without reading before completing GO/NO-GO test. Results showed a significantly shorter response time (RT) following RE relative to the rest session and the size of the reduction in RT after RE was similar for both age groups. These findings suggest that RE improves attention control in adult males and this effect is not moderated by age (Hsieh, Chang, Fang, & Hung, 2016).

All in all, results of this recent literature exploring the effects of acute bout of exercise on attention tend to support that acute exercise is associated with improved attention. Investigating the link between exercise and attention is significant for preschoolers and

adolescents, as exercise may be able to be used as an effective tool to improve academic performance. Given that schools across the United States are reducing or eliminating physical education requirements, in an effort to increase students' academic performance owing to the increasing importance placed on standardized testing (Story, Nanney, & Schwartz, 2009), these findings are timely and valuable as these may support the importance of physical activity class in education environment. Future studies need to replicate the methods to consolidate the association between acute exercise and attention.

Acute Exercise and Memory

The potential for exercise to affect memory is becoming increasingly recognized. Because of the role of exercise in enhancing neurogenesis, brain plasticity and hippocampal-dependent learning and memory, exercise serves as a potential therapeutic tool to preserving and improving memory. Indeed, converging lines of evidence in both rodents and humans have documented that increased leisure-time physical activity is associated with enhanced memory function. Findings using animal models have reported the effects of exercise on memory with behavioral and brain structure improvements as well as enhancement of neurotrophic factors in task-related brain regions including hippocampus and parahippocampus (Gómez-Pinilla, Ying, Roy, Molteni, & Edgerton, 2002; Pereira et al., 2007; Russo-Neustadt, Alejandre, Garcia, Ivy, & Chen, 2004; Vaynman, Ying, & Gomez-Pinilla, 2004). Human studies have also found that physical activity leads to increases in catecholamines and neurotrophins, positively mediating changes in memory (Erickson et al., 2011; Vaynman & Gomez-Pinilla, 2006).

In particular, acute bout of exercise is associated with enhanced short-term memory performance. The effects of a single session of exercise on memory consolidation and

underlying neural mechanisms were examined on 81 young, healthy and German university students (40 female, 40 male; 22±2.36 years). They were randomly assigned into a high-intensity exercise group (~80% HR_{max}), a low-intensity exercise (~57% HR_{max}), or a seated rest group. Participants listened to auditory stimuli to learn 20 Polish words that were not familiar to them before performing acute bout of exercises on cycle ergometer or rest. Participants then watched a silent movie for 20 minutes to decrease arousal in the exercise groups. Following the movie, participants listened to 40 Polish words and responded with the German translation thereafter. A day (24 hours) after the test, retention of the vocabulary was measured. The data revealed that comparison between exercise and rest group indicated that exercise did not enhance the absolute number of However, high-intensity exercise group forgot significantly less words compared to resting group 24 hours after learning (Hötting, Schickert, Kaiser, Röder, & Schmidt-Kassow, 2016).

Winter et al. (2007) looked at whether acute exercise effects on learning and memory. 30 healthy young adults (22.2±1.7 years) engaged in three conditions (moderate exercise, vigorous exercise, and rest) on three different days and the sequence was counterbalanced. Moderate exercise involved 40 minutes of low impact running at a fixed individual HR and vigorous exercise was consisted of two sprints (started at 8 km/h, increased by every 10s by 2km/h) of 3 minute each, separated by a 2 minute break. RPE and HR were measured prior to and after each of the conditions. Participants then went through memory test in which visually presented object pictures were shown 200ms after the onset of the auditory presentation of a pseudoword. To test for learning effects, participants were asked to transfer spoken pseudowords into German object names. A different version of the novel vocabulary was used for every condition to reduce the learning effect. Results showed that participants learned 20% faster after completing vigorous exercise relative to moderate exercise or being sedentary, but

overall learning accuracy was not different between conditions. This finding indicates that short bouts of intense exercise can be used to increase the rate of learning, but not the amount of learning.

The dose-response relationship between exercise intensity, short-term memory, and BDNF was studied on 16 young adults (7 female, 9 male; 23±2 years). Participants completed 3 exercise sessions at different intensities including VO_{2max}, 20% below ventilatory threshold (Vt), and 20% above Vt. Each condition lasted for 30 minutes including 3 minutes of warm-up and 3 minutes of cool-down. HR and RPE were measured with 3 minute interval throughout the sessions for intensity measurement. Memory test was immediately followed using Rey Auditory Verbal Learning Test (RAVLT) which measures short-term memory, learning, and long-term memory recall. Participants also completed the RAVLT recognition trial 24 hours later to examine the effect of acute exercise on long-term memory. pBDNF were collected before and after exercise. Findings revealed that memory performance 24 hour following the exercise session was significantly better after VO_{2max} relative to 20% below Vt session, indicating maximal intensity exercise resulted in the largest benefits after the 24 hour delay. However, there was no significant difference between conditions in short-term memory performance (Etnier et al., 2016).

A line of evidence indicate that exercise is also associated with improvement in long-term memory. Basso and colleagues assessed the effects of acute bout of exercise on a range of frontal and medial temporal lobe dependent cognitive functions and how long these effects last. 85 young adults were randomized into either a vigorous, acute aerobic exercise (n=42) or a video watching control group (n=43). Participants at the exercise group performed a 50-min cycling on a stationary bike at vigorous intensity with a 5-min warn up and 5-min cool down. They were instructed to pedal at 85% of HR_{max}, while participants belonged to video watching

group watched video for 60 minutes. They then underwent a series of cognitive tests including Hopkins Verbal Learning Test Revised for verbal learning and memory, Modified Benton Visual Retention Test for memory function, Stroop Color and Word Test for executive function, Symbol Digit Modalities Test for visuomotor processing, Digit Span Test for attention and working memory, Trail Making Test for cognitive flexibility and Controlled Oral Word Association Test for verbal fluency. Participants from each group performed the tests at their assigned delay periods (30 min, 60 min, 90 min, and 120 min). The result showed a single session of 50 min of vigorous-intensity aerobic exercise in healthy adults enhances prefrontal cortex but not hippocampal dependent cognition. Also, cognitive enhancements induced by acute exercise lasted longer for up to 2 hours (Basso, Shang, Elman, Karmouta, & Suzuki, 2015).

Labban and Etnier (2011) examined the association between acute aerobic exercise and long-term memory. 48 young adults (33 female, 15 male; 22.02 years) were randomly assigned to either exercise-prior, exercise-after group or control group. Exercise-prior group completed the 30-min acute exercise protocol (including 5-min warm-up and 5-min cool-down, RPE rage 13-15 during exercise), immediately followed by reading paragraphs. 30 minutes after the exposure, participants were asked to recall paragraphs. Exercise-after group were rested first and then exposed to the paragraph before completing exercise protocol and recall process. Control group did not exercise but rested quietly before and after paragraph exposure. Comparison between the recall after each condition showed that the mean number of paragraph elements correctly recalled after the 35-min delay was greatest for the exercise-prior group, followed by the exercise-after group and then the control group. This finding indicates that engaging in an acute bout of moderately intense exercise prior to exposure and consolidation may yield enhanced performance on a delayed task (Labban & Etnier, 2011).

Together with executive function, an emerging body of multidisciplinary literature has documented the beneficial impacts of acute exercise on memory. Memory is an important domain of cognition to study, as it is closely related to neurodegenerative process as well as cognitive diseases, especially for older adults (Bishop, Lu, & Yankner, 2010). Short-term and long-term memory studies indicate both of these are enhanced by effects elicited by acute exercise. With increase in cognitive impairment as well as cognitive diseases in older adults (Logsdon, Gibbons, McCurry, & Teri, 2002), a caveat to be considered is to look at the effects of exercise on memory of older adults with potential risk for cognitive impairment and patients with cognitive diseases in the future.

Semantic Memory

Memory for specific experiences is called episodic memory and it depends heavily on retrieval of conceptual knowledge (Binder & Desai, 2011). In contrast, semantic memory encompasses all acquired knowledge about the world and is the basis for nearly all human activity which is abstracted from actual experience without reference to any specific experience (Binder & Desai, 2011). The semantic system is associated with the retrieval of information that is not directly stored in it, and retrieval of information does not change its contents (Tulving, 1972).

Evidence that the impairment in semantic memory is related to AD has been well-established (Chertkow, Whatmough, Saumier, & Duong, 2008; Salmon, Butters, & Chan, 1999). Also, there is a growing importance to include semantic memory in assessing cognitive decline in cognitively intact older adults (Carter et al., 2012; Spaan, Raaijmakers, & Jonker, 2005). Importantly, semantic memory has an important advantage over episodic memory when

it comes to investigating cognitive decline in older adults. For older adults, episodic memory tasks are inherently challenging, and therefore, potential activation of brain regions are associated with increased effort rather than the memory circuits of interest. On the other hand, semantic memory tasks are typically less effortful for older adults to complete which makes it possible to improve validity in the process of data collection (Hantke et al., 2013).

The FNT is a semantic memory task in which participants are asked to undergo recognition of famous people's names from a distant time epoch (1950s), names with enduring fame (1950s – 1990s), famous names from a more recent time period (1990s) and not-familiar names (Nielson et al., 2006). Since it was invented, a series of findings have used the FNT and have demonstrated the effectiveness of FNT in detecting neural activation in brain regions related to semantic memory (Douville et al., 2005; Hantke et al., 2013; Nielson et al., 2006; Seidenberg, Guidotti, Nielson, Woodard, Durgerian, Antuono, et al., 2009; Sugarman et al., 2012; Woodard et al., 2009).

In summary, semantic memory refers to ideas and concepts that are not drawn from personal experience. Significance of studying semantic memory lies in its effectiveness in detecting cognitive impairment in older adults (Carter et al., 2012). To test semantic memory, many previous studies used the FNT which requires less effort relative to episodic memory performance, an important advantage in using the semantic memory task for older adults. Despite the fact that there has been increasing acknowledgement of the importance of studying semantic memory in recent years, there is only a handful of studies that has investigated semantic memory in general, exercise studies in particular. Findings in the future should address the remaining questions about the effect of exercise on semantic memory function.

Functional Magnetic Resonance Imaging (fMRI)

fMRI, as a non-invasive tool for imaging functionally active brain regions, is gaining popularity (Logothetis, 2008; Ogawa et al., 1992). Since its beginning more than two decades ago, fMRI has been widely used for research purpose because of its usefulness to understand human brain, with more than 40,000 published papers according to PubMed and the number of research using fMRI is growing (Eklund, Nichols, & Knutsson, 2016).

Blood-oxygen-level-dependent (BOLD) imaging is the most popular method in fMRI measurement (Arthurs & Boniface, 2002). Basically, BOLD examines neural activation using hemodynamics of the brain (Huettel, Song, & McCarthy, 2004). The process of detecting BOLD signal goes like: 1) when neurons activate, it corresponds with the increase in metabolic demands to meet energetic needs of neurons 2) increase in blood flow followed by oxygenated blood is supplied 3) oxygenation is increased which generates MR signal (Huettel et al., 2004).

Interestingly, oxygenated hemoglobin is diamagnetic with little effect on magnetic field. In contrast, deoxygenated hemoglobin is paramagnetic, being attracted to a magnetic field, though it comes with less concentration of magnetic flux than ferromagnetic objects (Ogawa, Lee, Kay, & Tank, 1990). Although it seems reasonable decrease in MR signal should appear followed by increased neuronal activity that results in increased oxygen consumption, there is an increase of local MR signal as increased blood flow displaces deoxyhemoglobin (Pauling & Coryell, 1936). BOLD contrast was found to depend upon the total amount of deoxygenated hemoglobin in a brain region, which in turn depended upon the balance between oxygen consumption and oxygen supply (Thulborn, Waterton, Matthews, & Radda, 1982).

In conclusion, functional image of MRI is based on BOLD contrast which is sensitive to oxygenation level. Since BOLD signal is treated as an index of neural activation, BOLD

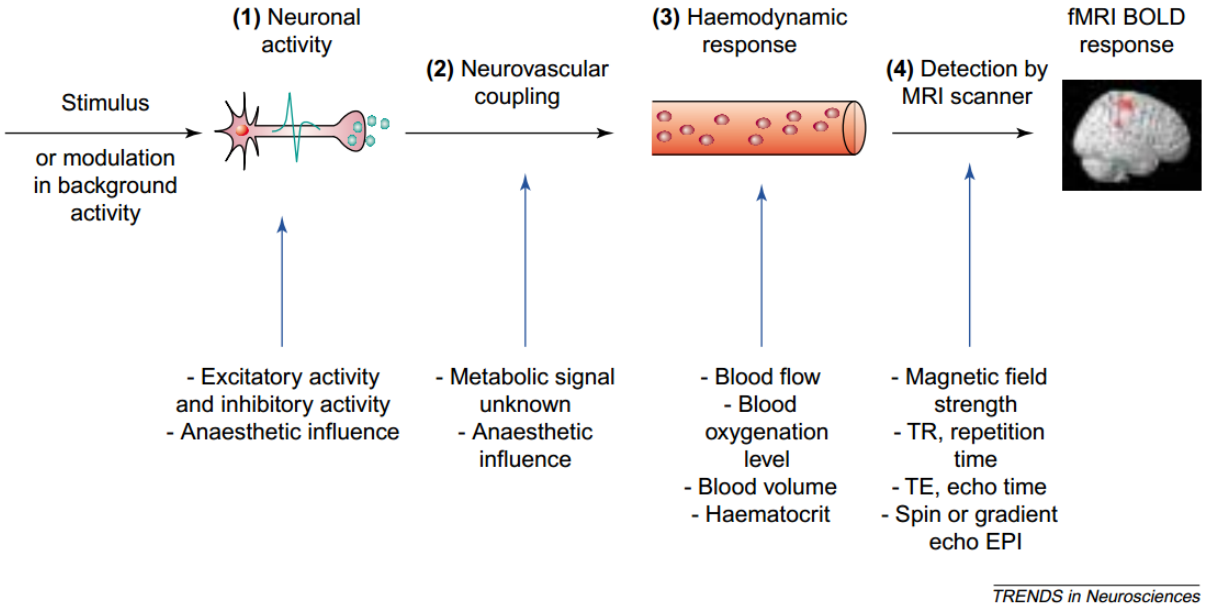


Figure 1. The hemodynamic response and fMRI BOLD signals (Arthurs & Boniface, 2002) : (1) the neural response to a stimulus (2) increase in neural activity increases metabolic demands to meet energetic needs of neurons (3) blood flow increases and oxygenated blood is supplied (4) increase in oxygenation increases local MR signal.

analysis is an effective tool to investigate the effect of exercise on brain activation during a variety of cognitive tests. Recently, the number of exercise studies using fMRI BOLD analysis grows, using many different types of exercise as well as cognitive tasks. With regards to experimental design, future research should take advantage of recent advances in brain imaging technique to systematically examine the effect of physical activity on brain activation.

Summary

Growing old comes with neurodegenerative process and cognitive impairment. Wealth of knowledge suggest that physical activity is an effective intervention to delay the onset of decline in cognition and keep cognitive diseases at bay. Accordingly, physical

activity can promote health and function in individuals, playing a pivotal role in improving quality of life among elders.

Collectively, there is considerable support for the view that a single session of exercise can facilitate enhancement in a range of cognitive domains including executive function, attention, and memory. In reviewing the extant literature with various cognitive tests and participants across ages, it is clear that a single bout of exercise is associated with improved cognition. Such consensus that exercise may promote brain functions sheds light on the importance of using physical activity as a therapeutic and protective tool to reverse cognitive ability in older adults. It has been implicated that the beneficial effects of exercise on cognition are regulated by augment in CBF and BDNF. Because there are a multitude of unanswered questions regarding complex neural, molecular, and biochemical procedures as a result of exercise, understanding of the mechanisms that underlie between exercise-cognition remains limited.

Semantic memory is related to ideas and concepts that are not from personal experience. FNT is an effortless semantic memory task which is effective in determining neurodegenerative process of older adults. Functional MRI BOLD signal has been discovered fairly recently and it relies on blood-oxygen levels to examine neural spikes of the brain. Since there are a handful of semantic memory research using fMRI signal, future studies will certainly benefit from the examination of the effects of exercise on brain activation during semantic memory performance using BOLD signal.

CHAPTER II: SIGNIFICANCE AND RESEARCH QUESTIONS

Significance of the Research

Although the exercise-memory effect is robust across the literature, most studies have focused on perceptual or short-term memory paradigms and episodic memory (Nouchi et al., 2014; Ruscheweyh et al., 2011; Weinberg et al., 2014), while the association between exercise and semantic memory performance has received little attention in the exercise neuroimaging literature. Although semantic memory plays a significant role in functions of storing information about the features and attributes that define concepts and the processes that allow us to efficiently retrieve information (Martin & Chao, 2001), insufficient numbers of exercise research studied semantic memory. Research regarding semantic memory need more spotlight and identifying the impact of exercise on semantic memory is critical, given that one of the greatest predictors of neurodegenerative procedure is the inability to remember familiar names, the most common memory complaint among older adults (Jonker, Geerlings, & Schmand, 2000). Findings suggest that the semantic memory system, in particular, is vulnerable to the earliest stages of cognitive decline (Henry, Crawford, & Phillips, 2004; Lonie et al., 2009). Reasons for this paucity of literature is that BOLD analysis is relatively new to exercise science and the majority of neuroimaging techniques being used in the exercise literature are focused on event-related brain potentials (ERP) using electroencephalogram (P. J. Smith et al., 2010). There have been relatively few fMRI studies to assess the effect of aerobic exercise on semantic memory activation.

Only a few studies have examined how fitness and long-term exercise intervention affect semantic memory activation. Our lab conducted a pilot study to examine the differential impacts of acute exercise intensity on semantic memory activation investigated BOLD

activation before and after moderate-intensity exercise (~ 60% of HR_{max}) and high-intensity exercise (~ 75% of HR_{max}), respectively. Thirteen healthy young adults (18-29 years) showed significant reduction in BOLD activation following acute moderate-intensity exercise compared to baseline. High intensity exercise also demonstrated reduced brain activation, but its effect was not as significant as moderate-intensity exercise. Smith and colleagues (2013) have also showed that two groups of older adults (cognitively intact and mild cognitive impairment) demonstrated significant reduction in brain activation intensity after completing a 12-week supervised treadmill walking with moderate intensity relative to baseline. These findings suggest exercise may improve neural efficiency during semantic memory retrieval in mild cognitive impairment (MCI) and cognitively intact older adults and may lead to improvements in cognitive function (J. C. Smith et al., 2013).

In spite of the aforementioned evidence, our understating remains, at present, limited regarding the effects of exercise with short duration on semantic memory activation in older adults. To our best knowledge, no literature has measured semantic memory fMRI BOLD activation immediately following a single bout of exercise in older adults. Considering that the regular bout of exercise is building-block of chronic exercise (Basso & Suzuki, 2016), understanding the changes induced by a singular bout of exercise may provide novel insight into the association between exercise and memory.

Therefore, this study will investigate the effect of acute exercise on BOLD semantic memory activation patterns using task-activated fMRI in 30 healthy older adults. Participants will go through two experimental visits (acute exercise and seated rest) with counterbalanced order on separate days. 30 minutes of each condition is immediately followed by fMRI scan with semantic memory task. The fMRI task will involve a low effort, high-accuracy semantic

memory task in which participants discriminate famous from not famous names (Douville et al., 2005).

Research Questions and Hypotheses

1) Is a single session of aerobic exercise associated with improvements in neural efficiency during semantic memory retrieval?

Smith et al. (2013) have reported that two groups of older adults (cognitively intact and mild cognitive impairment) demonstrated significant reduction in brain activation intensity after completing a 12-week supervised treadmill walking with moderate intensity relative to baseline. These findings suggest exercise may improve neural efficiency during semantic memory retrieval in mild cognitive impairment (MCI) and cognitively intact older adults and may lead to improvements in cognitive function. Additionally, our pilot study data regarding the differential impacts of acute exercise intensity on semantic memory activation investigated BOLD activation before and after moderate-intensity exercise (~60 % of HR_{max}) and high-intensity exercise (~75% of HR_{max}). 13 healthy young adults (18-29 years) showed significant reduction in BOLD activation following acute moderate-intensity exercise compared to baseline. High intensity exercise also resulted in reduced BOLD semantic memory activation, but the reduction elicited by a moderate bout of exercise was greater than from a vigorous bout of exercise. Based on these results, it is assumed that the decrease in activation induced by exercise may indicate reduction in neural workload for completing the semantic memory task and therefore enhanced neural efficiency. Therefore, it is hypothesized that acute exercise may significantly reduce brain activation during semantic memory retrieval compared to a rest condition and this reduction

may indicate improved neural efficiency elicited by performing acute bout of exercise in older adults.

2) Does acute exercise enhance semantic memory performance?

To measure semantic memory performance, we propose to use FNT, which takes low effort and have demonstrated high accuracy. Various participants have performed the test in previous studies including older and younger adults (Douville et al., 2005; Nielson et al., 2006), high risk for AD and low risk for AD, physically active and sedentary (Seidenberg, Guidotti, Nielson, Woodard, Durgerian, Antuono, et al., 2009; J. C. Smith, Nielson, Woodard, Seidenberg, Durgerian, et al., 2011) and MCI patients (J. C. Smith et al., 2013; Woodard et al., 2009). Participants showed high accuracy rate with mean performance levels exceeding 80% correct in MCI patients for and older adults with high risk for cognitive decline also demonstrated over 80% accuracy. Especially, 12-week treadmill training did not significantly enhance behavioral indices of FNT for both healthy controls and MCI patients (J. C. Smith et al., 2013). The low task difficulty of FNT allows to detect differences in brain activation during successful memory retrieval only, resulting in activation maps not confounded by incorrect name recognition trials (Douville et al., 2005) and whether this differs between experimental and control conditions. Thus, it is predicted that participants will perform equally well following rest compared to after acute exercise.

3) Do famous names with different time epochs generate differences in brain activation after exercise?

Functional MRI studies have indicated that recent memories activate the hippocampal complex more than remote memories. Haist, Gore, and Mao (2001) presented famous faces from six decades (1940s to 1990s) to older participants during fMRI scanning. The result indicated significantly increased activation in the right anterior hippocampus for recently famous faces (1990s and 1980s). Famous faces in the 1990s and 1980s also produced increased activity in the right entorhinal cortex relative to famous faces from the previous for decades (1940s to 1970s). Also, increased signal activation for recent famous faces compared to remote famous faces were examined in healthy controls. Another study compared the brain activation during retrieval of newly-learned faces to famous faces. The finding suggested that recognition of famous faces was associated with a widespread and greater network of brain activation relative to recognition of recently encoded faces (Leveroni et al., 2000). It was also found that hippocampus, temporopolar cortex, and amygdala exhibited gradually decreasing activity when participants recalled memories from 1-12 years ago (C. N. Smith & Squire, 2009). The greatest MRI signal intensity was found during retrieval of the recently famous names (Douville et al., 2005). Another study demonstrated that when 15 healthy older and 15 healthy younger adults performed FNT, older adults exhibited greater activation on various brain regions compared to younger adults. The result suggested that activation associated with the recent names was similar to the enduring ones (became famous in the 1950s and are still well known today). Older adults showed wider network of brain activation on recent names relative to younger adults. Also, analysis in older group resulted in significantly greater activation in the recent condition compared to enduring condition, while no significant difference were observed in younger group (Nielson et al., 2006). In agreement with these findings, it is assumed that

the recent famous names would show the greatest activation compared to enduring conditions followed by remote names after both acute bout of exercise and rest.

Specific Aims and Hypotheses

Specific Aim #1: To determine the effects of acute exercise on brain activation during semantic memory retrieval.

Hypothesis #1: We hypothesize that brain activation during semantic memory retrieval after acute exercise will be significantly lower compared to after seated rest.

Specific Aim #2: To determine whether the effect of acute exercise on performance of semantic memory retrieval task is different compared to rest.

Hypothesis #2: We hypothesize that participants will perform equally well on the FNT after rest compared to after exercise.

Specific Aim #3: To compare brain activation of different time epochs after exercise and rest.

Hypothesis #3a: We predict that recent famous names may demonstrate the greatest brain activation relative to remote famous names following both acute exercise and seated-rest.

Hypothesis #3b: This exploratory analysis has no previous evidence, so that no prediction has been made.

CHAPTER III: METHODS

Participants

26 physically fit, right-handed older adults (age: 55-85 years) were recruited to participate in the study. Participants were pre-screened with a structured screening interview using MRI screening form regarding the presence of metal implants, pacemakers, aneurysm clips and other potential safety hazards to ensure their safety. Participants were excluded if they reported a history of stroke, diabetes, high blood pressure, neurological disease, major psychiatric disturbance, or substance abuse, or were taking psychoactive prescriptive medications. Prior to the baseline MRI scan, all participants were administered the Mini Mental State Exam (MMSE) (Folstein, Folstein, & McHugh, 1975), which is a 30-point questionnaire used to screen for global cognitive impairment and dementia. Eligible individuals then provided written informed consent that was approved by the Institutional Review Board at the University of Maryland. Prior to fMRI scan, participants underwent a mock MRI scan session and practiced the famous name recognition task. Participants were also instructed to eat usual meals and to finish meals 4 hours before the experiment, avoid alcohol 12 hours before the experiment and not to consume caffeine during the 4 hours prior to participation each day (Ferré & O'Brien, 2011). Participants who complete the fMRI scanning and exercise testing sessions were paid for their participation. This study was conducted according to the Helsinki Declaration of 1975 (World Medical Association, 2008). This study protocol was approved aby the institutional Review Board at the University of Maryland.

Exercise task

Participants then completed a 30-minutes continuous cycling on a Monark cycle ergometer (Varberg, Sweden) located directly outside of the fMRI scanner. In order to measure the intensity of the exercise conditions, three assessments including RPE, HR, and work rate were recorded every five-minutes. Prior to each session, participants were fitted with a HR monitor (Polar Electro, Kempele, Finland) and standardized instructions were provided regarding the use of the Borg 6-20 RPE scale (Borg, 1970) before adjusting the seat-height. 5-minutes of warm-up session then was administered prior to 20-min exercise session. During the exercise session, participants were asked to pedal at an intensity corresponding with an RPE of 15 (associated with the verbal anchor 'Hard'). Pedal cadence was maintained between 60 to 80 rpm. Following the cessation of exercise, 5-minutes of cool-down was completed before participants was immediately escorted back to the scanner. Using a within-subject design, the order of the experimental conditions (seated-rest and exercise) was counterbalanced across participants to minimize the possibility of learning or habituation effects.

Functional MRI the Famous Name Recognition Task (FNT)

Semantic memory activation was assessed using the FNT immediately following seated-rest and exercise sessions in fMRI scanner. Participants were instructed to respond as quickly and accurately as possible to identify a set of famous name stimuli. The fMRI task stimuli consisted of 30 names of easily recognized prominent entertainers, politicians, or sport figures obtained through magazines, trivia books, and the Internet (e.g., Ringo Starr) and 30 names of non-famous individuals chosen from a local phone book (Nielson et al., 2006). Only names with a high rate of identification (> 90% correct for targets and foils) were

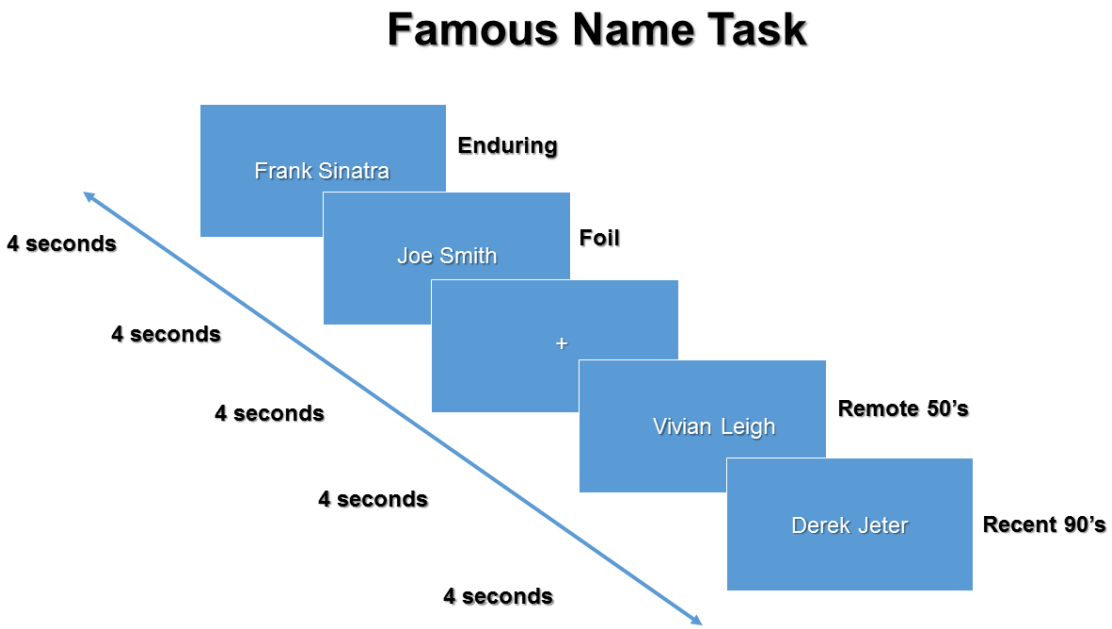


Figure 2. Above is the description of famous name task that participants will see in the scanner. As an event-related design, the names from different time epochs (recent, remote, and enduring) will be appeared in randomized order. Participants will be asked to press button 1 for famous names and 2 for not famous names as quickly as possible. Previous studies showed that performance accuracy for this task is over 80% (Nielson et al., 2006). Only correct trials will be used for analysis.

selected from an original pool of 784 names (Douville et al., 2005). Stimuli were presented for 4 seconds each with randomly interspersed 4 seconds intervals with a single centrally placed fixation crosshair at an overall 2:1 (names:fixation) ratio. Participants were instructed to make a right index finger key press if the name is famous and a right middle finger key press if the name is not famous. Both accuracy (% correct) and response time (millisecond) were recorded. The imaging run began and ended with 12-second of fixation. Run order was counterbalanced across subjects and the participant saw different names each session. Only correct trials were used for analysis.

fMRI Acquisition

Whole-brain, event–related fMRI was conducted on a Siemens 3.0 Tesla MR scanner (Magnetom Trio Tim Syngo, Munich, Germany). A 32-channel head coil was used for radio frequency transmission and reception. Foam padding was positioned within the head coil to minimize head movement within the coil. A high-resolution T1-weighted anatomical image was required for co-registration with the following sequence parameters: Magnetization Prepared Rapid Acquisition of Gradient Echo (MPRAGE), matrix = 256, field of view (FOV) = 230mm, voxel size = 0.9 × 0.9 × 0.9 mm, slices = 192 (sagittal plane, acquired right to left), slice thickness = 0.9mm, repetition time (TR) = 1900 ms, echo time (TE) = 2.32 ms, inversion time (TI) = 900 ms, flip angle = 9°, and sequence duration = 4:26 min. The FNT even-related data was acquired using the following sequence parameters: single-shot gradient echo planar images, matrix = 64, FOV = 192mm, voxel size = 3.0 × 3.0 × 3.0 mm, slices = 36, slice thickness = 3.0 mm, TR/TE = 2000/24 ms, volumes = 175, flip angle = 70°, bandwidth = 2232 Hz/Px, multi-slice mode = Interleaved, and sequence duration = 5:56 min.

Image Analysis

Functional images were processed using the Analysis of Functional NeuroImages (AFNI) software package (Cox, 1996). For each image time series, the first 3 TRs were excluded, and each subsequent point was time-shifted to the beginning of the TR. The time series were spatially registered to correct head motions and the estimated head motion parameters were used as additional repressors in the design matrix to further reduce effects of head motion. It was followed by the spatial normalization where the mean fMRI volume was first aligned to the participant's high-resolution anatomical image for co-registration. We then used the standardized processing script for transforming the images into standard stereotaxic

space and spatial smoothing with a 4mm Gaussian full-width half-maximum filter (Eklund, Nichols, & Knutsson, 2015). Group analyses were performed using the hemodynamic response functions (HRFs) for Famous and Non-Famous names.

Functional Region of Interest (fROI) and Statistical Analysis

In spite of the high task accuracy rate, estimation of HRFs for identification of famous names and rejection of non-famous names was restricted to correct trials. 3dttest++ paired comparison was then used to see the activation difference between the two conditions (Exercise vs Rest). Clustsim function in the 3dttest++ was used to set the clustsize (pthreshold 0.01, alpha level 0.05, NN=1, bi-sided). A voxel-wise analysis was used to determine differences in spatial extent of activation between the conditions. Semantic memory activation was defined as regions where the AUG for Famous names was significantly different from that of Non-Famous names (J. C. Smith, Nielson, Woodard, Seidenberg, Durgerian, et al., 2011; Woodard et al., 2009). For each condition, ROI maps showing Famous versus Non-Famous activation in comparison to 0 were created for each condition. The maps for each condition were combined to create a disjunction mask by conjoining activated regions identified in the spatial extent analysis across post-exercise and post-rest conditions. Any regions that demonstrated significant difference were identified as major ROIs. Any voxel deemed activated by the subtraction of activations of Non-famous names from those of Famous names (Famous versus Non-famous) across conditions contributed to the ROI map. The mean intensity of each ROI and compare the conditions (exercise versus rest) using repeated measures analysis of variance (ANOVA) within SPSS. As a post-hoc analysis, the large ROIs were further divided into isolated brain regions, based on a standardized anatomical mask where the mean intensity between the two conditions was

compared. Regions that were not included to the large ROIs, but showed significantly greater activation in the Exercise condition were added to this analysis. The mean intensities were extracted from each region for the exercise and rest condition respectively, before analyzing the statistical difference using repeated measure ANOVA in SPSS.

The only available study from which to estimate the effect size for acute exercise comes from the previous study by Smith and colleagues (J. C. Smith et al., 2013). Based on average effects size from that 12-week exercise intervention, a priori power analysis indicated that a sample size of 8 would be sufficient to detect a significant effect with a power of 0.8 and the standardized effect size of Cohen's d = -1.1023. However, because this proposed study will add participants to an already ongoing investigation, we conducted a sensitivity analysis (α value: 0.05, Power: 0.80, and total sample size: 26) which resulted in effect size of 0.529. Based on this analysis, we assume that we would detect the result with effect size of 0.529.

CHAPTER IV: RESULTS

Participant Characteristics

Figure 3 describes the flow chart of participant recruitment. Of the 32 participants who completed entire study protocol, six participants were excluded from the analysis because of failure to complete the task on one of the visits. Five additional participants' data were excluded from all analyses due to button errors during recording their response during the FNT task. Table 1 reports characteristics results for participants who completed the entire experiments. Only physically and cognitively healthy participants were included in the study.

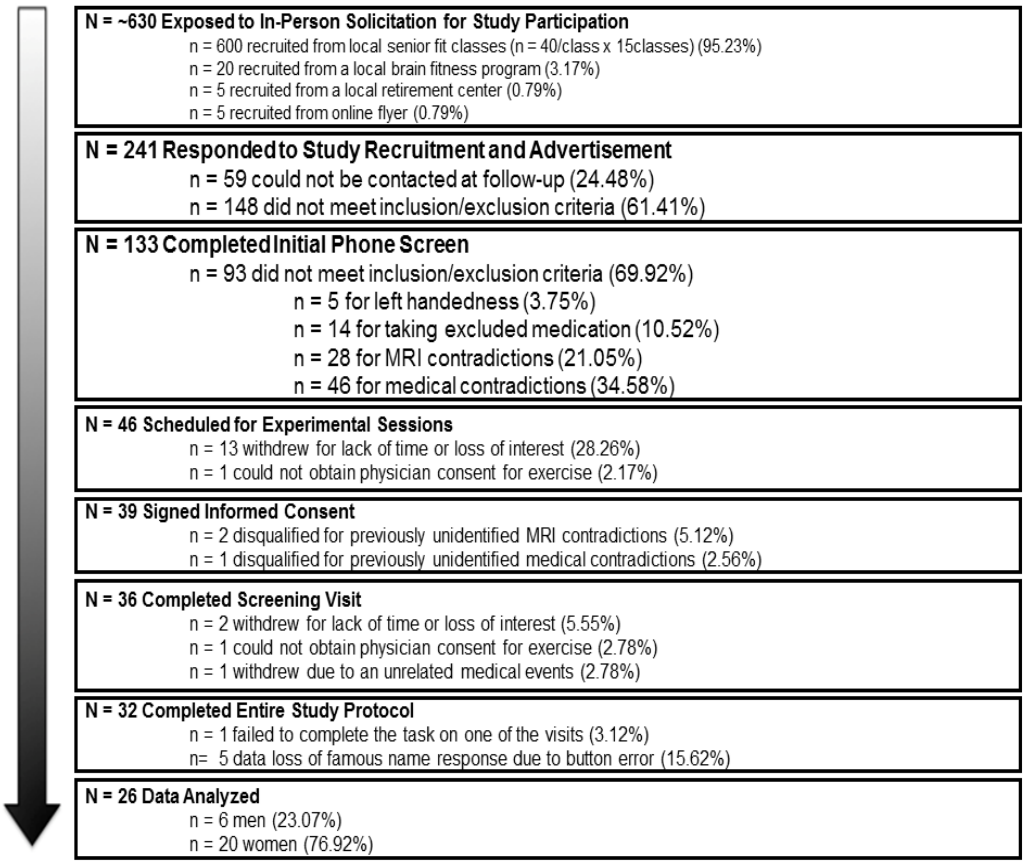


Figure 3. Flow chart of participant recruitment, eligibility screening, enrollment, withdrawals, and the final sample included in the fMRI analysis (n = 26).

Table 1. Demographic information, physical characteristics, and cognitive function of study participants.

		Total Sample (n = 26)	
		Mean	SD
Demographics			
	Age (years)	65.9	7.2
	Sex (n,%)		
	Male	6.0	23.1
	Female	20.0	76.9
	Race (n,%)		
	White	20 (77.0%)	
	Black	2 (7.7%)	
	Hispanic	2 (7.7%)	
	Asian	2 (7.7%)	
	Education (n,%)		
	≤ College	9 (34.6%)	
	≥ Graduate	17 (65.4%)	
Physical characteristics			
	Height (cm)	166.5	8.5
	Weight (kg)	73.6	14.1
	BMI (kg/m^2)	26.1	4.3
	HR (BPM)		
	Age-Predicted HR_{Max}	154.0	7.2
	$HR_{Resting}$	64.8	6.4
Cognitive function			
	MMSE	29.3	1.0

SD, standard deviation; BMI, body mass index; MMSE, Mini-Mental Status Exam; HR, heart rate; BPM, beats per minute; Age-predicted HR_{Max}, Age predicted maximal heart rate; $HR_{Resting}$, resting heart rate.

Exercise Manipulation Check – HR, RPE and fMRI task performance

Data from the exercise and rest conditions are reported in Table 2. HR (±SD) was significantly greater in the exercise condition (136.1±18.4 bpm) compared to the rest condition (66.3±9.2 bpm) [Condition main effect, $F(1,25) = 331.44$, $p < 0.001$, $\eta^2 = 0.930$]. Similarly, the exercise condition showed significantly greater RPE (14.5±1.4) relative to the rest condition (6.1±0.4) [Condition main effect, $F(1,25) = 945.562$, $p < 0.001$, $\eta^2 = 0.974$]. The mean RPE value during the exercise was most closely associated with the verbal anchor "Hard", indicating that participants performed exercise at subjective exertion level of moderate intensity.

During the performance of the FNT, the mean RT (±SD) for famous names was 1141.1±282.7 ms during the exercise and 1148.2±267.6 ms during the rest. The mean RT (±SD) for famous names did not show significant difference between the two conditions [Condition main effect, $F(1,25) = 0.083$, $p = 0.775$, $\eta^2 = 0.0037$]. The mean RT (±SD) for non-famous names was 1413.6±363.4 ms during the exercise and 1449.2±267.6 ms during the rest. The mean RT (±SD) for non-famous names also were not significantly different in the two conditions [Condition main effect, $F(1,25) = 0.656$, $p = 0.426$, $\eta^2 = 0.026$]. The mean task performance for famous names was similar between exercise (88.3±17.9 %) and rest (89.4±15.5 %) [Condition main effect, $F(1,25) = 0.332$, $p = 0.570$, $\eta^2 = 0.013$] and the performances were not significantly different as a function of condition. The participants correctly identified greater than 92% of the non-famous names and there was no significant condition main effect [Condition main effect, $F(1,25) = 0.001$, $p = 0.971$, $\eta^2 = 0.000$].

Table 2. Exercise and fMRI task outcome data for study participants.

		Total Sample (n = 26)				Condition Main Effect
		Exercise		Rest		
		Mean	SD	Mean	SD	p-value (η^2_p)
HR (BPM)		136.1	18.4	66.3	9.2	**< 0.001 (0.930)**
RPE		14.5	1.4	6.1	0.4	**< 0.001 (0.974)**
Famous RT (ms)		1141.4	282.7	1148.2	267.6	0.775 (0.004)
	Remotely Famous RT (ms)	1197.8	334.2	1214.5	318.5	0.680 (0.007)
	Recently Famous RT (ms)	1267.9	353.0	1260.3	328.4	0.851 (0.001)
	Enduringly Famous RT (ms)	981.7	228.7	998.2	254.17	0.449 (0.023)
Non-Famous RT (ms)		1413.6	363.4	1449.2	349.9	0.426 (0.026)
Correct Famous Acc (%)		88.3	17.9	89.4	15.5	0.570 (0.013)
	Remotely Famous Acc (%)	83.5	24.2	81.9	25.1	0.694 (0.006)
	Recently Famous Acc (%)	87.7	17.3	88.8	17.3	0.523 (0.016)
	Enduringly Famous Acc (%)	93.8	17.0	96.9	12.3	0.174 (0.082)
Correct Non-Famous (%)		92.1	16.0	92.1	16.8	0.971 (0.000)

P-values and effect sizes reflect between and within group differences. SD, standard deviation; RPE, rate of perceived exertion; HR, heart rate; BPM, beats per minute; Acc, Accuracy; RT, response time; ms, millisecond; percentage of heart rate reserve; η^2_p, partial eta squared. Bold indicates p < 0.05.

Semantic Memory fMRI Activation – Spatial Extent Analysis (Famous versus Non-Famous)

Results of voxel-wise analysis maps showing regions that were activated in the comparison of Famous versus Non-famous names at the post-exercise and post-rest intervention are presented in Figure 4 (see Table 3 for activation loci and volumes). The Famous > Non-famous subtraction resulted three large brain regions showing a greater intensity of semantic processing-related activation after Exercise compared to Rest. These three large ROIs were further divided into nine isolated brain regions, based on a standardized anatomical mask, for post-hoc analysis where mean intensity between the two conditions was compared.

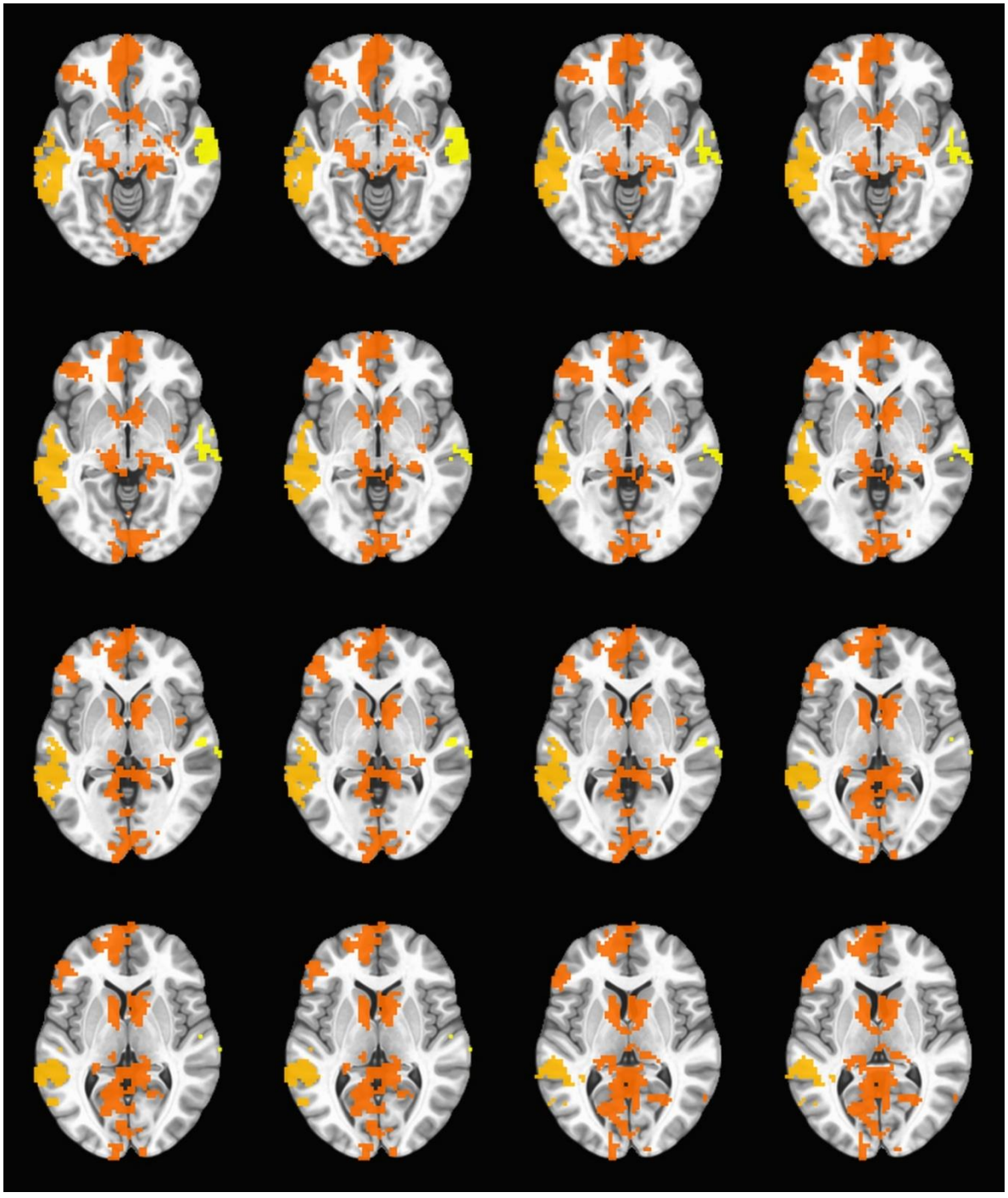


Figure 4. A montage of axial slices showing the disjunction (OR) mask that demonstrates the fROIs demonstrating significant differences between Famous and Non-famous name conditions activated by either the exercise or rest conditions. Yellow indicates the strongest activation followed by light orange and by dark orange.

Table 3. Location and spatial extent of three major ROIs from a voxel-wise analysis comparing Famous versus Non-famous names identification for post-exercise and post-rest conditions. Regions are shown in Figure 4.

Side	Region	BA	Exercise > Rest			
			x	**y**	**z**	**vol**
	Famous > Non-Famous					
ROI 1						
L	Parahippocampal Gyrus	35, 36	17	2	-22	0.27
L	Hippocampus	28, 34, 35	30	24	-9	0.63
L	Fusiform Gyrus	20	43	8	-26	1.39
L	Superior Temporal Gyrus	38	43	-5	-17	1.76
L	Middle Temporal Gyrus	13, 21	51	-5	-17	1.7
ROI 2						
R	Parahippocampal Gyrus	28, 36	-23	-3	-17	0.26
R	Hippocampus	34	-15	17	22	0.63
ROI 3						
R	Fusiform Gyrus	19	-49	68	-20	1.22
R	Middle Occipital Gyrus	37	-35	70	-22	1.5

Semantic Memory fMRI Activation – fROI Analysis

The analysis of mean activation intensity (%AUG) in three large major fROIs (Famous vs Non-famous) revealed significant main effects of Condition (Exercise vs Rest) in two regions (see Table 4) [ROI1: Condition main effect, $F(1,25) = 6.120$, $p = 0.021$, $\eta^2 = 0.203$; ROI2: Condition main effect, $F(1,25) = 3.949$, $p = 0.058$, $\eta^2 = 0.141$; ROI3: Condition main effect, $F(1,25) = 4.591$, $p = 0.042$, $\eta^2 = 0.160$]. Using the disjunction mask (Figure 4), the ROIs were further explored in a way that the large regions were divided into anatomically isolated brain regions. Regions that were not included to the large regions identified in the initial spatial extent analysis, but showed high activation in the Exercise condition (see Appendix E) were added to this analysis. The mean activation intensities were extracted for each condition (exercise vs rest) in the individual brain regions and were compared using SPSS. Table 5 reports semantic memory-related activation (Famous > Non-famous) analysis of nine small ROIs. Results showed significantly greater in post-exercise relative to post-rest in hippocampus, bilateral fusiform gyrus, right lingual gyrus, bilateral occipital gyrus, and right thalamus. Although *p*-value was greater than alpha level, bilateral hippocampal gyrus demonstrated a trend of increasing semantic memory activation following exercise. Figure 5 describes the comparison between the conditions in the five fROIs that survived the FDR threshold for the main effect of condition.

Table 4. Three major ROIs derived from disjunction maps of the participants at the post-exercise and post-rest scans compared the mean percent area under the curve of each region.

						Total Sample (n = 26)				**Condition Main Effect**
						Post-Exercise		**Post-Rest**		
ROI	BA	*x*	*y*	*z*	vol	Mean	SD	Mean	SD	p-value (η^2_p)
1	29,34,35,46	17	1.5	-25.5	4.10	0.10	0.07	0.06	0.08	**0.021 (0.203)**
2	18,19	35	65	-20	0.82	0.08	0.06	0.03	0.08	**0.042 (0.161)**
3	19,21,22	0	25	7	0.78	0.10	0.08	0.07	0.10	0.058 (0.141)

Table 5. Nine fROIs derived from by disjunction of the voxel-wise maps of the participants at the post-exercise and post-rest scans, compared the mean percent area under the curve of each region.

								Total Sample (n = 26)				**Condition Main Effect**
								Post-Exercise		**Post-Rest**		
#	Side	Region	BA	*x*	*y*	*z*	vol	Mean	SD	Mean	SD	p-value (η^2_p)
A	B	Parahippocampal Gyrus	34.35,36	17	2	-22	0.53	0.07	0.11	0.02	0.10	0.094 (0.108)
B	B	Hippocampus	28,34,35	30	24	-9	1.26	0.07	0.09	0.03	0.06	**0.029 (0.177)**
C	B	Fusiform Gyrus	19	37	67	-18	2.57	0.04	0.08	0.00	0.10	**0.046 (0.150)**
D	L	Superior Temporal Gyrus	13,21,38	43	-6	0	1.76	0.05	0.08	0.01	0.10	0.108 (0.100)
E	L	Middle Temporal Gyrus	21,22	43	77	-10	1.91	0.09	0.11	0.07	0.12	0.363 (0.033)
F	L	Middle Occipital Gyrus	19	43	79	-10	1.51	0.06	0.14	-0.02	0.14	**0.027 (0.181)**
G	R	Lingual Gyrus	19, 37	22	84	-15	0.89	0.07	0.08	0.02	0.11	**0.031 (0.173)**
H	R	Thalamus	17	-1	25	10	1.26	0.06	0.06	0.01	0.09	**0.029 (0.176)**
I	B	Posterior Cingulate	29,30,31	-1	56	10	0.90	0.07	0.08	0.02	0.11	0.616 (0.010)

P-values and effect sizes reflect between condition differences. SD, standard deviation; η^2_p, partial eta squared. Bold indicates $p < 0.05$.

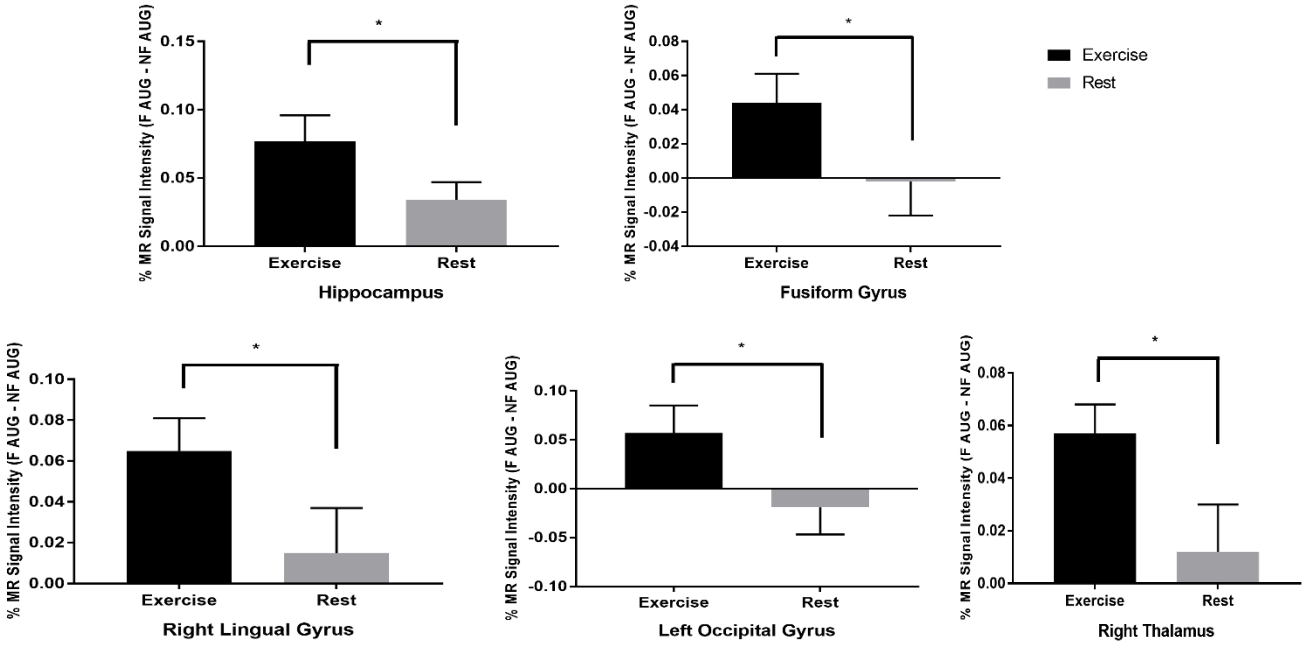


Figure 5. Bar graphs represent mean MR intensity difference in Famous and Non-Famous name change for the condition effect (Exercise versus Rest) in the 5 fROIs with significant difference (significant difference at $p < 0.05$; F: Famous; NF: Non-Famous name).*

Semantic Memory fMRI Activation – Spatial Extent Analysis (Exploratory Analysis)

Results of the voxel-wise analysis comparing the Enduringly Famous and Non-Famous names are presented in Figure 6. Three extensively connected regions ROIs were found for Enduringly Famous versus Non-Famous names (Table 6) and these were broken into smaller fROIs that showed significant activation in at least one of the conditions. Figure 7 shows the comparison of Recently Famous versus Non-Famous names. Greater semantic memory processing for Non-famous name compared to Recently Famous names was found (Non-Famous > Recently Famous) in two major fROIs. The two fROIs were divided into three small isolated regions (shown in Table 7). Regions that were activated in the comparison of Remotely Famous and Non-Famous names at the post-exercise and post-rest intervention are presented in Figure 8. Paired t-test (3dttest++ in AFNI) between conditions (Exercise versus Rest) for the subtraction of activation during Non-Famous from Remotely Famous names reported no statistical difference.

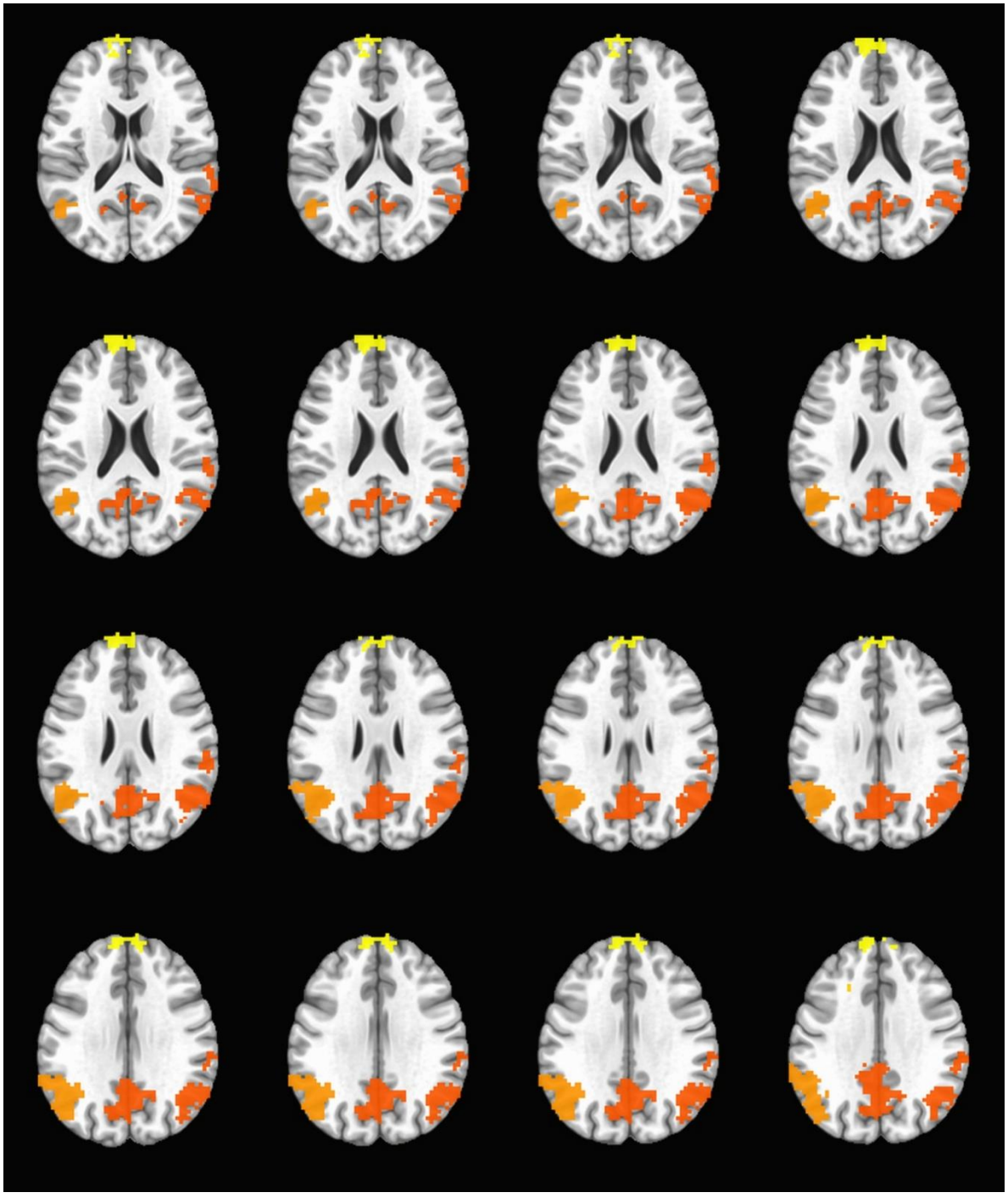


Figure 6. A montage of axial slices showing disjunction (OR) mask that demonstrates the fROIs demonstrating significant differences between Enduringly Famous and Non-famous name conditions activated by either the exercise or rest conditions. Yellow indicates the strongest activation followed by light orange and by dark orange.

Table 6. Location and spatial extent of three major ROIs from a voxel-wise analysis comparing Enduringly Famous versus Non-famous name identification for post-exercise and post-rest conditions. Regions are shown in Figure 6.

Side	Region	BA	Exercise > Rest			
			x	y	z	vol
	Enduringly Famous > Non-Famous					
ROI 1						
L	Fusiform Gyrus	19,37	35	62	-20	1.34
L	Cerebellum	3,4	10	41	76	1.31
B	Parahippocampal Gyrus	20	32	40	-20	0.53
L	Lingual Gyrus	18	4	86	-4	0.95
L	Middle Occipital Gyrus	37	37	67	-20	1.51
ROI 2						
L	Inferior Parietal Lobule	40	59	50	40	1.56
L	Supramarginal Gyrus	40	48	45	33	1.66
L	Superior Parietal Lobule	5, 7	-18	77	57	1.01
L	Postcentral Gyrus	5	39	48	66	1.31
L	Precuneus	7	30	53	54	1.47
ROI 3						
R	Superior Temporal Gyrus	22, 42	-67	35	10	1.87
R	Middle Temporal Gyrus	19, 42	-65	55	-2	1.85
R	Inferior Temporal Gyrus	37	-55	67	-1	1.61
R	Middle Frontal Gyrus	6	-34	15	51	0.94

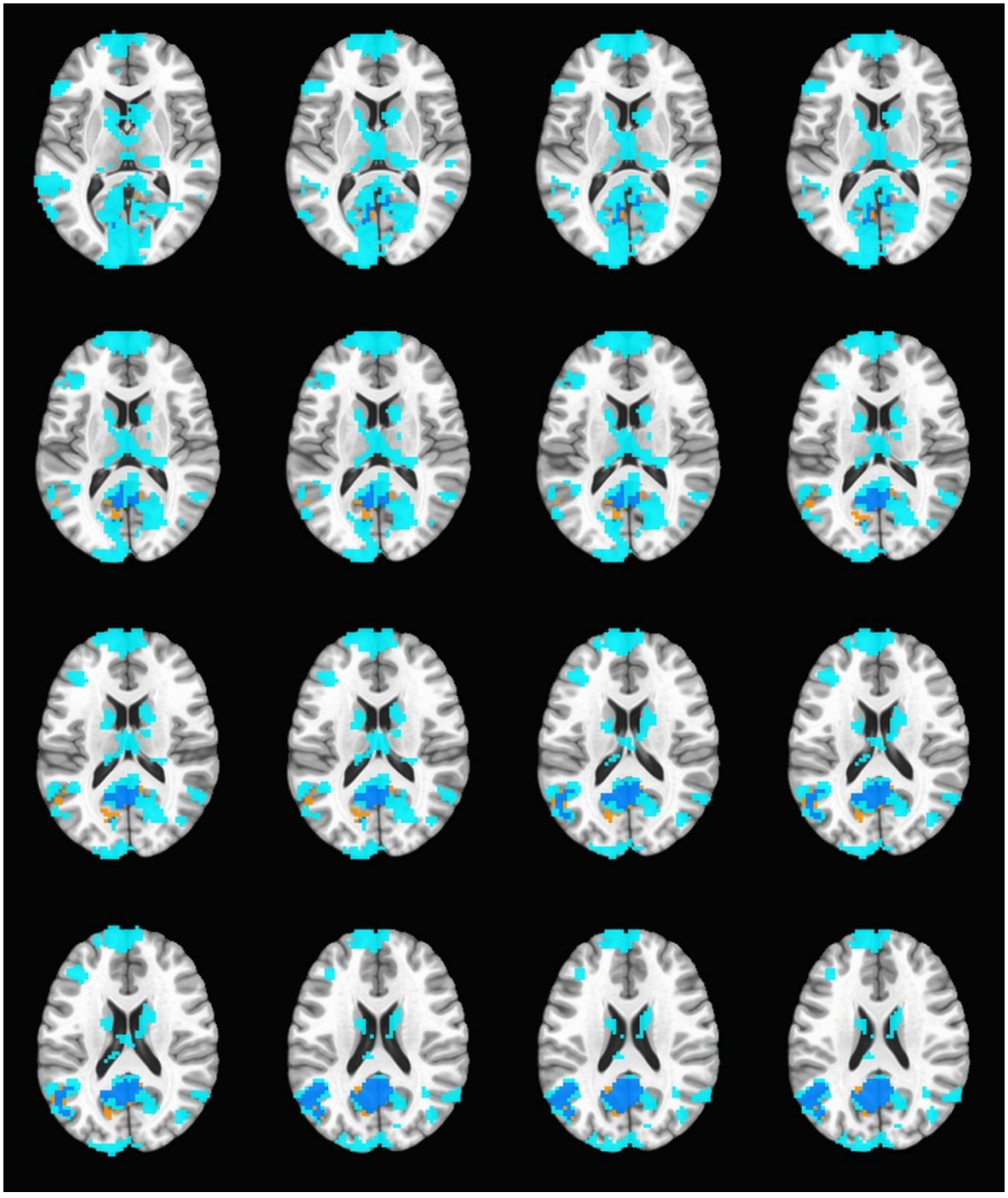


Figure 7. A montage of axial slices showing disjunction (OR) mask that demonstrates the fROIs demonstrating significant differences between Recently Famous and Non-famous name conditions activated by either the exercise or rest conditions. Light blue indicates areas activated during the exercise, orange activated during the rest, and blue activated during the both conditions.

Table 7. Location and spatial extent of two major ROIs from a voxel-wise analysis comparing Recently Famous versus Non-famous name identification for post-exercise and post-rest conditions. Regions are shown in Figure 7.

Side	Region	BA	Exercise > Rest			
			x	y	z	vol
	Recently Famous < Non-Famous					
ROI 1						
L	Superior Temporal Gyrus	38	35	-10	-29	1.94
ROI 2						
L	Lingual Gyrus	18	26	83	-11	0.95
L	Fusiform Gyrus	19	12	82	-19	1.34

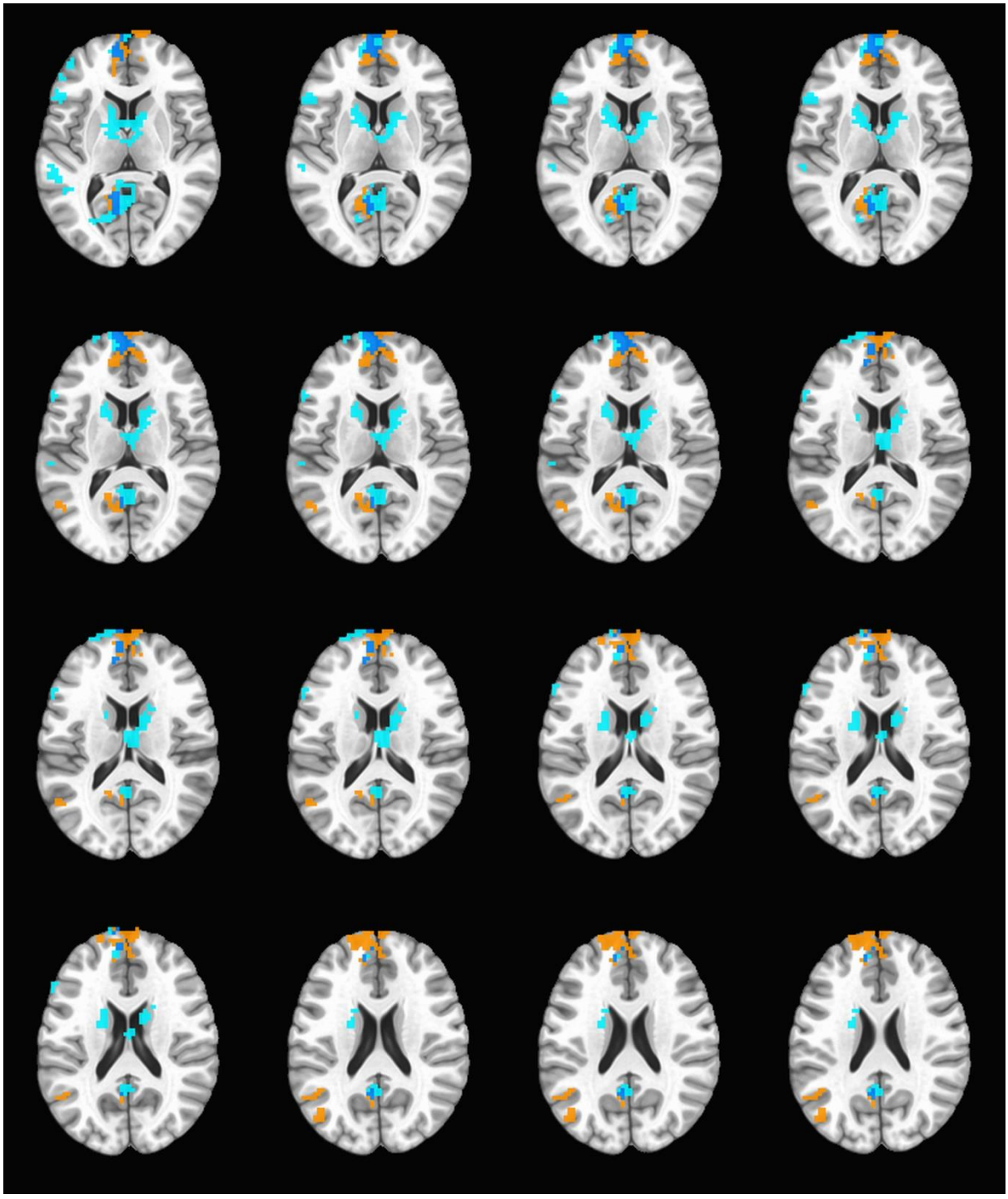


Figure 8. A montage of axial slices showing disjunction (OR) mask that demonstrates the fROIs demonstrating significant differences between Remotely Famous and Non-famous name conditions activated by either the exercise or rest conditions. Light blue indicates areas activated during the exercise, orange activated during the rest, and blue activated during the both condition

Semantic Memory fMRI Activation – fROI Analysis (Exploratory Analysis)

Table 8 reports significant main effects of condition in 14 regions for Enduringly Famous versus Non-Famous names comparison [ROI1: Condition main effect, $F(1,25) = 6.304$, $p = 0.019$, $\eta^2 = 0.201$, ROI2: Condition main effect, $F(1,25) = 3.930$, $p = 0.059$, $\eta^2 = 0.136$, ROI3: Condition main effect, $F(1,25) = 4.463$, $p = 0.045$, $\eta^2 = 0.151$]. Post-hoc analysis comparing mean activation intensity in anatomically isolated regions between conditions was administered to examine the main effect of condition. Regions that were not included to the large ROIs, but showed significantly greater activation in the Exercise condition (see Appendix E) were added to this analysis. The mean intensities were extracted from each region for the exercise and rest condition respectively, before analyzing the statistical difference (shown in Table 9). Results showed that Left fusiform gyrus, bilateral lingual gyrus, left middle occipital gyrus, bilateral inferior parietal lobule, and right superior temporal gyrus demonstrate that post-exercise was associated with significantly greater semantic memory activation (Enduringly Famous > Non-Famous) relative post-rest. Figure 8 describes the comparison between the conditions in the five fROIs that survived the FDR threshold for the main effect of condition. Bilateral superior lobule, left postcentral gyrus, right middle temporal gyrus, bilateral parahippocampal gyrus, left cerebellum, and left precuneus demonstrated a trend of increasing semantic memory activation following exercise, even though the *p*-values were greater than alpha level.

Significant main effects of condition in two fROIs in the comparison of Recently famous and Non-famous name is presented in Table 10 [ROI1: Condition main effect, $F(1,25) = 3.964$, $p = 0.058$, $\eta^2 = 0.137$, ROI2: Condition main effect, $F(1,25) = 1.617$, $p = 0.215$, $\eta^2 = 0.06$]. To observe the activation difference in smaller regions, further analysis was

administered and revealed none of the regions showing statistically significant difference between two conditions (Exercise versus Rest).

Table 8. Three major ROIs derived from by disjunction of the voxel-wise maps of Enduringly Famous versus Non-famous names at the post-exercise and post-rest scans, compared the mean percent area under the curve of each region.

						Total Sample (n = 26)				**Condition Main Effect**
						Post-Exercise		**Post-Rest**		
ROI	BA	*x*	*y*	*z*	vol	Mean	SD	Mean	SD	p-value (η^2_p)
1	19, 37	35	62	-20	7.64	0.12	0.10	0.04	0.12	**0.019 (0.201)**
2	40	59	50	40	1	0.13	0.12	0.08	0.10	0.059 (0.136)
3	22,42	-35	50	62	1.57	0.09	0.07	0.05	0.10	**0.045 (0.151)**

Table 9. Fourteen fROIs derived from by disjunction of the voxel-wise maps for Enduringly Famous name versus Non-famous names of the participants at the post-exercise and post-rest scans, compared the mean percent area under the curve of each region.

								Total Sample (n = 26)			**Condition Main Effect**
								Post-Exercise		**Post-Rest**	
#	Side	Region	BA	*x*	*y*	*z*	vol	Mean	SD	Mean	SD	p-value (η^2_p)
A	L	Fusiform Gyrus	19, 37	35	62	-20	1.34	0.03	0.12	-0.04	0.11	**0.007 (0.259)**
B	L	Cerebellum	19	34	75	-20	6.83	0.03	0.10	-0.02	0.10	0.109 (0.099)
C	B	Parahippocampal Gyrus	20	32	40	-20	0.53	0.00	0.11	0.06	0.18	0.114 (0.097)
D	L	Lingual Gyrus	18	4	86	-4	0.95	0.06	0.14	-0.03	0.14	**0.015 (0.215)**
E	L	Middle Occipital Gyrus	37	37	67	-20	1.51	0.06	0.23	-0.07	0.15	**0.015 (0.214)**
F	L	Inferior Parietal Lobule	40	59	50	40	1.56	0.08	0.12	0.03	0.09	**0.041 (0.156)**
G	L	Supramarginal Gyrus	40	48	45	33	1.66	0.06	0.11	0.03	0.10	0.222 (0.059)
H	L	Superior Parietal Lobule	5,7	-18	77	57	1.01	0.06	0.10	0.00	0.13	0.069 (0.126)
I	L	Postcentral Gyrus	5	39	48	66	1.31	0.03	0.10	0.00	0.09	0.094 (0.108)
J	L	Precuneus	7	30	53	54	1.47	0.09	0.12	0.04	0.13	0.117 (0.095)
K	R	Superior Temporal Gyrus	22,42	-67	35	10	1.87	0.06	0.11	-0.02	0.10	**0.019 (0.202)**
L	R	Middle Temporal Gyrus	19,42	-65	55	-2	1.85	0.08	0.11	0.02	0.12	0.078 (0.119)
N	R	Inferior Temporal Gyrus	37	-55	67	-1	1.61	0.05	0.17	0.00	0.10	0.135 (0.087)
M	R	Middle Frontal Gyrus	6	-34	15	51	0.94	0.02	0.63	-0.01	0.10	0.236 (0.056)

P-values and effect sizes reflect between condition differences. SD, standard deviation; η^2_p, partial eta squared. Bold indicates p < 0.05.

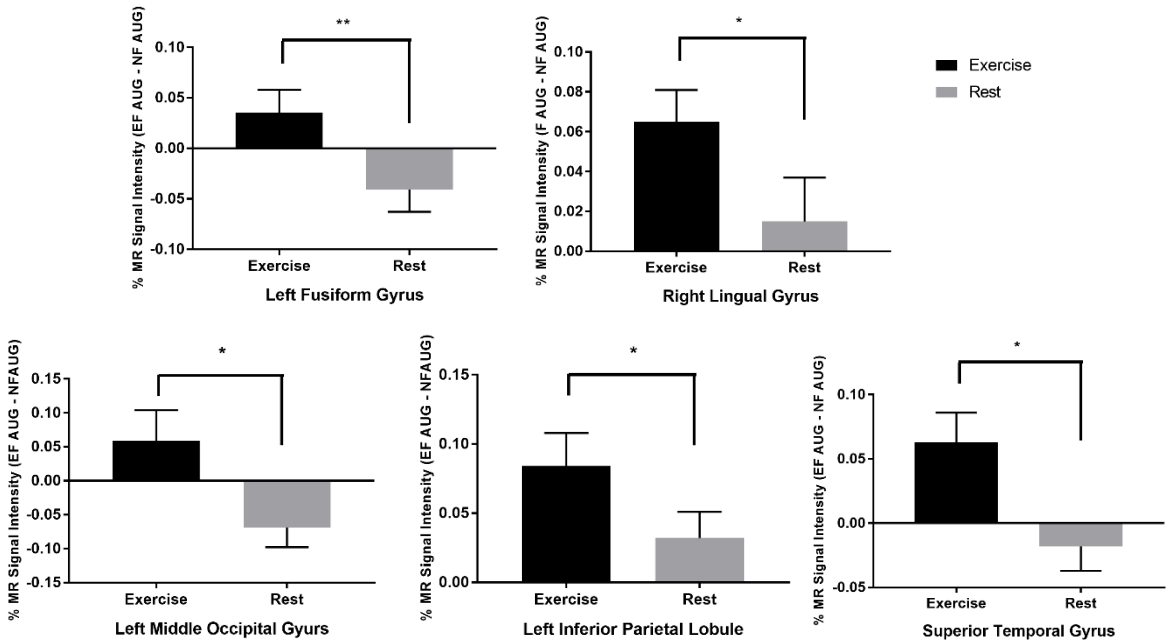


Figure 8. Bar graphs represent mean percent MR intensity difference in Enduringly Famous and Non-Famous name change for the condition effect (Exercise versus Rest) in the 5 fROIs with significant difference (significant difference at $p < 0.05$; ** $p < 0.01$; EF: Enduringly Famous; NF: Non-Famous name).*

Table 10. Two major ROIs derived from by disjunction of the voxel-wise maps of Recently Famous versus Non-famous names at the post-exercise and post-rest scans, compared the mean percent area under the curve of each region.

						Total Sample (n = 26)				**Condition Main Effect**
						Post-Exercise		**Post-Rest**		
ROI	BA	*x*	*y*	*z*	vol	Mean	SD	Mean	SD	p-value (η^2_p)
1	18, 19	25	82	-10	2.00	-0.13	0.87	-0.08	0.14	0.058 (0.137)
2	21, 28, 38	34	-10	28	1.37	-0.14	0.11	-0.10	0.17	0.215 (0.061)

Table 11. Three fROIs derived from by disjunction of the voxel-wise maps for Recently Famous name versus Non-famous names of the participants at the post-exercise and post-rest scans, compared the mean percent area under the curve of each region.

								Total Sample (n = 26)				**Condition Main Effect**
								Post-Exercise		**Post-Rest**		
#	Side	Region	BA	*x*	*y*	*z*	vol	Mean	SD	Mean	SD	p-value (η^2_p)
A	L	Superior Temporal Gyrus	38	35	-10	-29	1.94	-0.07	0.12	-0.03	0.20	0.219 (0.060)
B	L	Lingual Gyrus	18	26	83	-11	0.95	-0.10	0.11	-0.05	0.12	0.156 (0.079)
C	L	Fusiform Gyrus	19	12	81	-19	1.34	-0.11	0.12	-0.05	0.18	0.139 (0.085)

P-values and effect sizes reflect between condition differences. SD, standard deviation; η^2_p, partial eta squared. Bold indicates p < 0.05.

CHAPTER V: Discussion

Famous versus Non-Famous Names

HR and RPE were significantly higher during the exercise session compared to the rest, indicating that we used a sound experimental manipulation to determine if neural function during memory retrieval could be affected among older adults. In addition, our fMRI results provide the first evidence that acute bout of aerobic exercise can influence brain activation patterns within memory-related brain circuits in healthy older adults. Specifically, we have shown that greater semantic memory activation is observed after performing a single session of exercise.

Our research begs the question as to why semantic memory activation is greater after performing a 30-min aerobic exercise compared to seated-rest. Results we found exhibited completely opposite pattern from our hypothesis where we predicted reduced sematic memory activation following acute exercise. To answer this question, it is important to examine possible neurophysiological evidence that may underlie the effects of acute exercise on cognition and brain function. Acute bout of exercise has been shown to increase perfusion (Ogoh et al., 2014; J. C. Smith et al., 2010) and the increased perfusion is associated with extensive neural recruitment during cognitive tasks (J. C. Smith, Nielson, Woodard, Seidenberg, Durgerian, et al., 2011). The cholinergic effects of a single session of exercise may influence neural circuits associated with semantic memory and stimulated neural network may allow semantic processing networks to engage in a greater extent than engaging in rest, possibly attenuating the accumulation of beta-amyloid (Adlard, Perreau, Pop, & Cotman, 2005). The scaffolding theory of aging and cognition (STAC) theory suggests that the greater neural activation during memory retrieval in cognitively intact older adults may

reflect neural reserve or successful compensation (Park & Reuter-Lorenz, 2009). Previous cross-sectional (J. C. Smith, Nielson, Woodard, Seidenberg, Durgerian, et al., 2011) and longitudinal evidence (L Woodard et al., 2012) support the idea that greater extent and intensity of fMRI activation during the FNT is associated with cognitive stability over time. Beside the extended neural recruitment, well-documented neurophysiological evidence regrading the effects of acute exercise includes stimulated transcription, expression of neural growth factors (e.g. brain derived neurotropic factor, insulin like growth fator-1) and neurogenesis particularly in the dentate gyrus of the hippocampal regions (Intlekofer & Cotman, 2013; Trejo, Carro, & Torres-Aleman, 2001; Van Praag, Shubert, Zhao, & Gage, 2005). Taken together, the current findings suggest that acute exercise promotes engagement of the extended semantic memory networks and the greater engagement may reflect enhanced cognitive function in healthy older adults.

Another question our study needs to address is why acute exercise and long-term exercise intervention result in conflicting semantic memory activation pattern. We speculated that performing a 30-min aerobic exercise would engender reduction in semantic memory activation. Our prediction was based on a 12-week walking exercise intervention study demonstrating that increased maximal aerobic capacity following the intervention led to an associated decrease in semantic memory fMRI activation in MCI participants and cognitively intact older adults (J. C. Smith et al., 2013). The previous finding suggested that the reduced neural activation during the FNT may indicate enhanced efficiency through a decreased neural workload during successful engagement of semantic memory networks. As the effect of chronic exercise is accumulated effects of a series of acute exercises, we hypothesized that performing an acute exercise would also reduce sematic memory activation. However, the current and previous results may lead to a conclusion that short-term and long-term exercises

may affect semantic memory activation differently. Acute exercise comes with immediate physiological change such as increase in HR, perfusion, and cerebral blood flow. On the other hand, long-term exercise intervention leads to gradual improvement in fitness, including increased $VO2_{max}$ and enhanced ability to perform exercise at higher percentage of $VO2_{max}$. The difference in physiological response may have to do with differences in ways that acute and chronic exercises influence semantic memory function. Acute exercise may enhance cognition by recruiting extensive neural circuits represented as greater brain activation and accumulation of these effects may lead to increased efficiency in neural workload which is shown as reduced fMRI activation. Therefore, our fMRI results complement the previously published study (J. C. Smith et al., 2013) by showing that both acute and chronic exercise may differently benefit the neural networks related to memory retrieval.

This study has employed a low effort and high accuracy semantic memory task which instructs participants to discriminate between Famous and Non-Famous names (Douville et al., 2005). Hantke et al. (2013) has suggested that semantic memory fMRI activation may be better predictors of longitudinal cognitive change than episodic memory fMRI tasks, while another groups have shown that future cognitive decline can be predicted by fMRI activation during episodic memory tasks (Bookheimer et al., 2000; O'brien et al., 2010). The FNT we used has two major advantages over episodic memory tasks. First, the FNT is inherently easy to perform, so that both memory impaired and cognitively intact persons can perform the task with a high degree of accuracy. As shown in several previous studies from our research group, the FNT can be successfully performed and produces reliable fMRI activation in a wide range of participants including older and younger adults (Douville et al., 2005; Nielson et al., 2006), individuals with high risk for AD (Seidenberg,

Guidotti, Nielson, Woodard, Durgerian, Antuono, et al., 2009; J. C. Smith, Nielson, Woodard, Seidenberg, Durgerian, et al., 2011) and those diagnosed with MCI (J. C. Smith et al., 2013; Woodard et al., 2009). Second, the even-related fMRI design allows the exclusion of incorrect trials and thus only successful memory trials are used for the analysis (Seidenberg et al., 2013). The use of an even-related procedure may have reduced error-based contributions to the functional maps (Woodard et al., 2009). Our results concur with the previous FNT studies (J. C. Smith et al., 2013; J. C. Smith, Nielson, Woodard, Seidenberg, Durgerian, et al., 2011) in terms of the FNT task performance, with no significant difference in RT and accuracy between two conditions. The consistent memory retrieval performance between conditions (Exercise versus Rest), paired with the inclusion of only correct trials, eliminates any confounding influence of task difficulty or performance and associated task-unrelated activation. That is, we examined the effects of acute exercise on successful semantic memory retrieval by observing a greater neural activation, without the confounding effects of improved task performance.

Since it was designed, many findings using the FNT have demonstrated that it is effective in detecting semantic activation in hippocampal regions (Douville et al., 2005; Hantke et al., 2013; Nielson et al., 2006; Seidenberg et al., 2009; Sugarman et al., 2012; Woodard et al., 2009; Woodard et al., 2010). In the current study, we also identified that greater activation induced by acute bout of exercise was particularly evident in the hippocampus. Beneficial effects of exercise on hippocampus are well established by previous evidence. Regular participation in PA and associated enhancement in cardiorespiratory fitness are associated with attenuation of age-related brain tissue atrophy, especially within the hippocampus (S. J. Colcombe et al., 2006; Erickson et al., 2010; Gordon et al., 2008). Also, regular exercise decreases amyloid burden in the frontal and temporal cortices in the

hippocampus (Adlard et al., 2005). Considering the positive effects of exercise on hippocampus, the greater hippocampal activation during semantic memory retrieval in our study may indicate protective effects from acute bout of exercise. Thus, accumulated effects of performing acute exercise may lead to healthy cognitive aging for older adults (Bannerman et al., 2004). We also demonstrated that cortical regions closely located to hippocampus including bilateral parahippocamapal gyrus and left superior temporal gyrus showed trends of greater semantic memory activation. Although these regions did not demonstrate statistically significantly greater activation following acute exercise, it may be that acute bout of exercise stimulates activation not only within hippocampus activation, but also within cortical regions involved in sematic memory retrieval. This suggests that regions nearby hippocampus may also be benefited from the protective effects from acute exercise.

While the hippocampus is an important region activated by the task, greater exercise-induced activation is consistently observed in subcortical regions such as fusiform gyrus and lingual gyrus during successful semantic memory retrieval. Previous functional imaging experiments have shown that fusiform and lingual gyrus are preferentially responsive to famous faces (Kapur, Friston, Young, Frith, & Frackowiak, 1995; Maguire, Frith, & Cipolotti, 2001). Greater activation in these regions may indicate acute exercise enhances neural response to Famous names which can be translated as enhanced accessibility in semantic memory.

The FNT activates semantic memory networks as well as a broader neural network that supports semantic memory retrieval (Seidenberg, Guidotti, Nielson, Woodard, Durgerian, Antuono, et al., 2009; J. C. Smith, Nielson, Woodard, Seidenberg, Durgerian, et al., 2011). The semantic memory network includes cortical regions that overlap with the so called ‘default mode network (DMN)’ that includes the posterior cingulate (PCC) and

precuneus, temporal lobe, and regions of the frontal cortex (Broyd et al., 2009; Buckner, Andrews-Hanna, & Schacter, 2008; Gusnard & Raichle, 2001; Horn, Ostwald, Reisert, & Blankenburg, 2014; Qi et al., 2010). The importance of examining these regions lies in the fact that DMN has been associated with Alzheimer's pathology and a progressive loss of communication within the network as cognitive decline develops (Greicius, Srivastava, Reiss, & Menon, 2004; Lustig et al., 2003; Supekar, Menon, Rubin, Musen, & Greicius, 2008; Zhang & Raichle, 2010; Zhou et al., 2008). Specifically, the PCC and precuneus are associated with the accumulation of amyloid-β plaque (Buckner et al., 2009) and accelerated atrophy, underscoring its potential role as a biomarker of preclinical pathology, particularly AD (Albert, 2011; Buckner et al., 2005; Huang, Wahlund, Svensson, Winblad, & Julin, 2002; Zhou et al., 2008). In this study, main effect of exercise was not found in the DMM regions. This may due to the fact that the effect elicited by exercise for the DMN may not be as strong as that for hippocampus. Task-free resting state scan is explicitly designed to measure spatially distinct but temporally coherent brain regions that are connected either directly or indirectly (Andrews-Hanna et al., 2007; Wang et al., 2010). The DMN is known to be effectively examined during the resting state fMRI scan where participants undergo a period of wakeful rest, without external stimuli or performing a goal-directed task (Ferreira & Busatto, 2013; Raichlen et al., 2016). A recent study identified found greater connectivity between DMN and medial prefrontal cortex following a single session of exercise in older adults (Weng et al., 2017). Taken our research and Weng et al. (2017) together, resting state scan may be an effective measurement to examine compared to the FNT, when it comes to observe the effect of exercise on the DMN.

Exploratory Analysis for Different Time Epochs

As an exploratory analysis, the Famous names were split into three epochs (Enduring, Remote, and Recent) and each of those were compared to Non-Famous names to observe the effect of exercise on semantic memories of different time epochs. Our results provide the first evidence that an acute bout exercise induces greater sematic memory activation in the comparison of Enduringly Famous versus Non-Famous names. Interestingly, in the comparison of Recently Famous versus Non-Famous names, activation for Non-Famous names was greater followed by 30-min exercise. The comparison of Remotely Famous versus Non-Famous names did not show statistical difference in activation intensity between conditions (Exercise versus Rest).

Nielson et al. (2006) and Woodard et al. (2007) demonstrated the fastest RT and highest accuracy rate for Enduringly Famous names compared to Remote and Recent names. RT, which is often considered as a measure of task difficulty, was also the fastest during retrieval of Enduring names. Participants also made the least errors in the Enduring condition. These suggest that Enduring names are associated with the lowest levels of task difficulty. Previous fMRI studies reported that greater activation in older adults reflects greater difficulty or effort for retrieval process (Salthouse, 1996). Slowed RT is particularly common when task demands are high which is associated with increased prefrontal activation (Klingberg, O'Sullivan, & Roland, 1997; Stuss et al., 1999). Completely opposite from these previous evidence, our results demonstrated that greater activation is associated with better task performance (faster RT and high accuracy rate). Considering that acute exercise is related to enhanced memory function, it is assumed that greater activation during the retrieval of enduring memory indicates greater neural recruitment and associated cognitive improvement, not greater difficulty or effort for retrieval process.

Enduringly Famous names versus Non-famous names resulted in significantly greater activation in inferior parietal lobule, a regions that constitutes the DMN. Although the *p*-value was greater than alpha level, left precuneus also demonstrated a trend of greater activation after exercise. This may suggest that comparing Enduringly Famous to Non-Famous names is effective indicator in examining the effect of acute exercise on the DMN. Greater activation in these regions during the retrieval of Enduring names may suggest enhanced connectivity within the region. One of the most common neurodegenerative signs associated with the progression of age is poorer network connectivity in the DMN (Agosta et al., 2012; Andrews-Hanna et al., 2007; Damoiseaux et al., 2007; Meier et al., 2012). Previous reports have shown that pathological and structural changes in the DMN connectivity could serve as valid and reliable hallmarks for the aging and neuronal and psychological diseases such as autism, schizophrenia, depression, post-traumatic stress disorder as well as AD (Greicius et al., 2004; Lustig et al., 2003; Supekar et al., 2008; Zhang & Raichle, 2010; Zhou et al., 2008). Greater activation in the DMN following acute bout of exercise may suggest that observing the activation in the DMN in response to exercise could provide an opportunity to test the effect of exercise on aging brain.

While Enduringly Famous names showed greater activation as a function of exercise, the absence of within group activation difference between Remotely Famous and Non-Famous names was found. Since the names were carefully selected based on recognition accuracy scores derived from a normative sample of older adults (Douville et al., 2005), we could be confident that remote names were likely to be recognized by people over the age of 65 and accordingly, the current finding suggests that Remote names demonstrated over 80% in accuracy. This allows us to speculate that the activation difference is not due to unfamiliarity of Remote names compared to Enduring ones. One possibility that induced the

difference is that Remotely Famous names were potentially less personally meaningful than Enduring names. Enduringly Famous people who have remained in the public domain for several decades and their information continues to easily accessible (Seidenberg, Guidotti, Nielson, Woodard, Durgerian, Zhang, et al., 2009). In contrast, the Remotely conditions include people whose popularity was restricted to the past and much likely to have discontinued exposure into the more recent time intervals (Seidenberg, Guidotti, Nielson, Woodard, Durgerian, Zhang, et al., 2009). Remote memories, therefore, is prone to substantial individual variability in the time frame and context of the initial encoding of a person's name or historical event as well as the differences in frequency or recency of subsequent exposure (Douville et al., 2005). Enduringly Famous names, on the other hand, has been continually exposed than Remotely Famous names and the continuous exposure may have allowed Enduring names to be well-consolidated semantic information. We also cannot dismiss the possibility that Enduring names may carry greater autobiographical (episodic) significance which would make it personally meaningful to participants (Seidenberg, Guidotti, Nielson, Woodard, Durgerian, Zhang, et al., 2009). Well-consolidated memory with autobiographical component may well-interact with the effect elicited by acute exercise, so that greater activation was observed only for Enduring names. Thus, the frequency of exposure and associated emotionality or vividness (Westmacott & Moscovitch, 2003) may account for the greater semantic memory activation pattern during retrieval of Enduring names after acute exercise, suggesting enhanced accessibility in semantic memory compared to Remotely Famous names.

Nielson et al. (2006) has been previously reported that older adults had significantly greater magnitude of semantic memory activation in 15 of 20 clusters including four left prefrontal clusters, bilateral temporal, right hippocampal, right insula, bilateral posterior

cingulate, right thalamus, and right fusiform regions during retrieval of Recently Famous names. Douville et al. (2005) also found that hippocampus and parahippocampal gyrus demonstrated significant activity in response to Recently Famous names. In this study, we found that the activation for Non-Famous names was greater relative to Recently Famous names. In order to examine what has caused the discrepant results, we need to examine the characteristic of Recently Famous Names. Older adults may have had more recent exposure to Recent names, but these likely have had far fewer total exposures. Recently encoded semantic information, therefore, are information that has less of an opportunity to be consolidated and are highly likely unstable and decays rapidly (Nielson et al., 2006). Viewed from this perspective, Recent names could represent a low semantic memory compared to Enduring names which is high semantic memory. It is also possible that the greater activation for Non-Famous compared to Recently Famous names were specific to our participants.

Limitations and Future Directions

Although the current study provides evidence for the link between acute exercise on semantic memory activation, it could not assess the effect of systemic and regular participation in long-term exercise on semantic memory activation. Considering the dearth of understanding on the effect of long-term exercise, future studies are in need of measuring the impact of chronic exercise on semantic memory activation compared to no-treatment. Also, it is beyond the scope of the present study to determine if acute exercise influences other cognitive domains. An important direction for future research is to investigate the effect of acute exercise on other cognitive domains including executive function using the fMRI BOLD signal. Additionally, this study is not able to answer to a question regarding the effect of acute exercise on older adults diagnosed with neurodegenerative symptoms such as MCI

and AD, since only physically healthy, cognitively asymptomatic older adults participated in this study. Also, given that many genetic factors play a mediating role in the effects of exercise on cognitive function, it is also important to study joint impacts of exercise and gene status including apolipoprotein (APOE-e4 allele) and BDNF val66met on cognition. It is also important to look at the changes in pBDNF level, a mediating factor between exercise and cognitive function. Future studies should investigate the effect of resistance training on semantic memory activation. Understanding the effects of various exercises may allow for the optimization of generating effective exercise intervention programs to improve cognitive function. In regards to possible discrepancy associated with the epoch categories, factors including recency and frequency of exposure, valence, arousal, and extent of knowledge about names from these three categories should be considered in the future. Lastly, additional levels of semantic knowledge for person-identity (e.g. reason for fame, associative relationships, specific events or attributes) that reflect the richness of the memory representation should also be taken into account for future semantic memory studies.

Conclusions

In summary, a 30-min aerobic exercise intervention in healthy older adults resulted in greater semantic memory activation relative to rest. Greater fMRI semantic memory-related activation following the acute bout of exercise suggests that acute exercise may improve neural engagement during successful memory retrieval. This further suggests that a single session of exercise may promote cognitive improvement and enhanced brain function in older adults. Whether or not these effects apply to cognitively impaired older adults and how long the effects last remain to be determined.

APENDICES

Appendix A. Consent Form for Participation

University of Maryland College Park

Initials _____ *Date* _____

Project Title	**Effects of Exercise on Brain Function**
Purpose of the Study	*This research project is being conducted by **J. Carson Smith, Ph.D.**, at the University of Maryland, College Park, and we are inviting you to participate because you are in good health. The primary objective of this study is to examine the effects of exercise on brain function, as measured by fMRI. In addition, we aim to determine whether sleep history and/or genetic profile might influence these effects.*
Procedures	*The procedures in this study involve fMRI, stationary bike exercise, DNA collection by mouthwash/cheek swab, and wrist-worn actigraphy.* *This study involves the use of MRI, which will involve the following procedures:* *1. The MRI scans usually last approximately 60 minutes and will never last longer than 2 hours. You may be asked to participate in two sessions (taking place on different days).* *2. Before entering the MRI scanning room, you will be required to complete an MRI screening checklist, which ensures that it is safe for you to enter the scanner.* *3. After completing the checklist, you will be asked to remove all metal objects from your person. MRIs are known to blank out magnetic strips on credit cards, so you must leave your wallet as well as your watch and any other metallic object outside the scanner room (you can place it in a locked cabinet, which we will provide to you).* *4. For the MRI scan, you will lie on the patient bed, and be given instructions either to relax throughout the scanning procedures or, for example, to view or listen to stimuli, and in some cases, respond (e.g., using a response keypad or other equipment). For head/brain MRI, an MRI head coil will surround your head (a head coil is an apparatus that is used to measure signals emitted from your brain). Your head will be supported with foam pads to make you more comfortable and to help you to keep your head still. Pillows and other cushions may be used (e.g., under your knees) to make you more comfortable.* *5. You can end your participation at any time. You can be heard in the control room on a speaker system. Also, you will be provided with a squeeze bulb, which you can squeeze to let the MRI operator know that you need attention. If you signal that you wish to stop the*

	scanning, the operator will immediately enter the scanning room and assist you in exiting the scanner and patient bed. *6. When the MRI takes images, it makes loud buzzing and clicking noises. You will be given ear-protection to make the noise tolerable.* *7. For the study, you will be asked to complete three visits on different days, lasting a total of about 6 hours. Visit 1 will last approximately one hour and visits 2 and 3 each will last approximately two and a half hours. On visit 1, you will complete several questionnaires about your general health and physical activity, as well as brief tests of your cognitive abilities. You will also be provided with an orientation, including a mock MRI scanner, to all of the study procedures for visits 2 and 3. Physician consent we be required to participate in the study if you are male ≥ age 45 or female ≥ age 55.* *8. Visits 2 and 3 will involve the MRI scan, the exercise or rest session, and a short battery of cognitive tests. You will wear a heart rate monitor strap around your chest and under your clothing.* *9. During visits 2 and 3 before engaging in rest or exercise we will measure your heart rate during 10-minutes of seated rest. During this time we will ask that you sit quietly and relax (you will not be allowed any external stimuli, e.g. phone, ipod, reading material, etc.)* *10. Prior to each scanning session you will experience either the rest or exercise condition. The exercise will be performed at a moderate intensity on a stationary bike and will last 30 minutes. You will be provided with brief warm-up and cool-down periods as well as water. During and after the exercise sessions you will be asked to rate how you feel. The rest condition will proceed in the same fashion, the only difference being that you will not exercise, but rather sit quietly in a chair for an equal period of time. After the experimental condition (rest/exercise), you will be given 10 minutes to recover before undergoing the scan.* *11. An actigraphy device, which looks similar to a wristwatch, will be worn to continuously measure your sleep patterns for at least three consecutive days preceding the initial MRI visit. The watch will be worn at all times (except during bathing, swimming, or other potential water exposures).* *12. At the end of the screening day you will be asked to provide a DNA sample. You will be given a sterile collection tube containing approximately 10 ml (less than a mouthful) of Scope mouthwash, as is available for over the counter use, and asked to swish that amount of mouthwash vigorously in your mouth for approximately 45 seconds and then spit the mouthwash back into the collection container. A second method of DNA collection will also be available*

	upon request that includes collection of buccal cells using foam cheek swabs. You will not receive the results of the genetic tests because we are not an approved clinical testing facility.
Potential Risks and Discomforts	*There may be some risks from participating in this research study. Potential risks and discomforts related to MRI are as follows:* *MRI screening interview: You may be uncomfortable completing the interview. For instance, there are questions about whether you may be pregnant, and about the existence of tattoos and piercings on your body. You may choose to not answer questions that make you uncomfortable, but in that case you will not be able to participate in the experiment.* ***The Maryland Neuroimaging Center (MNC) is not a medical facility, does not do clinical work, and an MRI scan at the MNC is not a medical test. It is designed to address research questions and it is not the kind of scan that can be used for any clinical purpose. In fact, if there is an unusual finding in the scan, the MRI technician, or the researcher may not even detect it. However, if the technician or researcher sees something in the scan that appears unusual, the scan will be sent without any personal identifiers to a certified neuroradiologist at the Radiology Department at the National Children's Hospital for further review. If the neuroradiologist concurs that this unusual finding should be investigated further by a physician, you will be notified by the principle investigator leading the study.*** *MRI has not been shown to produce health problems in normal, healthy individuals. The scanner does not produce ionizing radiation. No medication, needle stick, or injections of drug or contrast agents are involved. There are hundreds of scanners of this type used in the U.S. and abroad, both to assist doctors in clinical diagnoses and for research.* *Because of the strong magnetic fields used for MRI scanners, persons who have magnetic life-support devices (e.g., pacemakers and aneurysm clips), metal prostheses or other metallic objects (e.g. cochlear implants, steel pins implanted to help repair and strengthen broken bones, metal fragments from previous injuries) cannot participate in this research.* ***MRI may be harmful to an unborn child. If you are of childbearing potential (that is, if you are a woman with sexual partner(s) and do not use an adequate birth control method), you must be excluded. Reliable birth control (i.e. oral, implanted, or barrier methods) should be used by all participants and/or their sexual partner to prevent pregnancy while participating in MRI scanning. If you find that you were pregnant while undergoing MRI, you should notify your physician immediately. If you use an IUD for birth control you***

	will be excluded unless you can document the model of the IUD and we can verify its safety for the MRI environment. *The radio frequency energy used in the MRI scan has produced burns (most of them minor) in about one in a million cases. If you feel any burning sensation you should immediately inform the staff, so that the scan can be terminated. In rare instances, warming of the skin has also occurred. If you feel any warming sensation, please inform the staff immediately, so that the scan can be interrupted.* *During the MRI scan you will be asked to view a series of pictures, lasting about 10 minutes. These pictures have been judged previously as subjectively pleasant, neutral, or unpleasant. Some of the pictures contain content that may be considered objectionable, such as disfigured bodies and threatening people. You will be shown examples of the types of pictures you may see. If for any reason you feel uncomfortable viewing any of the pictures, you may discontinue your participation without penalty.* *While there is no evidence of increased risk with multiple scans, the risks associated with multiple scans are not known.* *Potential risks and discomforts related to exercise are as follows:* *There is an extremely small risk for a fatal event during moderate intensity exercise and a very small risk of a non-fatal event. Your risk will be minimized by having the exercise administered by trained personnel and/or an exercise physiologist and having your physician review your medical record and determining if you are safe to exercise.* *Potential risks related to DNA collection are minimal. There are no known risks or hazards associated with the mouthwash rinse or the buccal swab technique, though the sensation of the mouthwash can be uncomfortable for some people.* *There are no known risks or hazards associated with wearing the actigraphy device.* *After the MRI scan you will engage in a series of brief cognitive tasks. During one of the tasks you will be asked to name as many words as possible within 60 seconds. The task administrator will be recording your words by hand and using an audio recording device. If for any reason you feel uncomfortable being audio recorded, you can opt for hand recording only, without penalty.*
Potential Benefits	*This research is not designed to help you personally, but the results may help the investigator learn more about how exercise affects brain function.*

Confidentiality	*Any potential loss of confidentiality will be minimized by using a unique alphanumeric code, not your name, to identify your data. Only the PI will hold the key to that code.* *Concerning the MRI portion of this study, potential loss of confidentiality will be minimized by storing the screening form in a locked cabinet at the MNC, and by storing MRI data in password protected and firewalled computers.* *Genetic data will be kept confidential. After collection of the DNA sample, all unique personal identifiers will be removed. All other data will be stored in a locked cabinet in the principal investigator's laboratory or office.* *If we write a report or article about this research project, your identity will be protected to the maximum extent possible. Your information may be shared with representatives of the University of Maryland, College Park or governmental authorities if you or someone else is in danger or if we are required to do so by law.*
Medical Treatment	*The University of Maryland does not provide any medical, hospitalization or other insurance for participants in this research study, nor will the University of Maryland provide any medical treatment or compensation for any injury sustained as a result of participation in this research study, except as required by law.*
Compensation	*You will receive $50 for your participation. You will be responsible for any taxes assessed on the compensation.* *If you will earn $100 or more as a research participant in this study, you must provide your name, address and SSN to receive compensation.* *If you do not earn over $100 only your name and address will be collected to receive compensation. If you do not participate in all sessions, your payment will be prorated based on the number of visits you completed. In addition to the $50, you will also receive an image of your brain, your sleep analysis, and a small snack (provided after each experimental day). If requested, you may also receive your results from the cognitive tasks. However, you must understand that all results from this study are strictly for research purposes only and not for diagnosis or clinical use.*
Right to Withdraw and Questions	*Your participation in this research is completely voluntary. You may choose not to take part at all. If you decide to participate in this research, you may stop participating at any time. If you decide not to participate in this study or if you stop participating at any time, you will not be penalized or lose any benefits to which you otherwise qualify.* *If you decide to stop taking part in the study, if you have questions,*

	concerns, or complaints, or if you need to report an injury related to the research, please contact the investigator, J. Carson Smith, Ph.D., at: Department of Kinesiology, School of Public Health Building, Room 2351, College Park, MD, 20742-2611; phone: 301-405-0344; email: carson@umd.edu	
Participant Rights	*If you have questions about your rights as a research participant or wish to report a research-related injury, please contact:* **University of Maryland College Park** **Institutional Review Board Office** **1204 Marie Mount Hall** **College Park, Maryland, 20742** **E-mail: irb@umd.edu** **Telephone: 301-405-0678** *This research has been reviewed according to the University of Maryland, College Park IRB procedures for research involving human subjects.*	
Statement of Consent	*Your signature indicates that you are at least 18 years of age; you have read this consent form or have had it read to you; your questions have been answered to your satisfaction and you voluntarily agree to participate in this research study. You will receive a copy of this signed consent form.* *If you agree to participate, please sign your name below.*	
Signature and Date	**NAME OF PARTICIPANT [Please Print]**	
	SIGNATURE OF PARTICIPANT	
	DATE	

Appendix B. Mini-Mental State Examination (MMSE)

Mini-Mental State Examination (MMSE)

Patient's Name: _____ Date: _____

***Instructions:* Ask the questions in the order listed. Score one point for each correct response within each question or activity.**

Maximum Score	Patient's Score	Questions
5		"What is the year? Season? Date? Day of the week? Month?"
5		"Where are we now: State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible. Number of trials: _____
5		"I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, …) Stop after five answers. Alternative: "Spell WORLD backwards." (D-L-R-O-W)
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.
1		"Repeat the phrase: 'No ifs, ands, or buts.'"
3		"Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of blank paper.)
1		"Please read this and do what it says." (Written instruction is "Close your eyes.")
1		"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)
1		"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.) 
30		TOTAL

(Adapted from Rovner & Folstein, 1987)

1

Source: www.medicine.uiowa.edu/igec/tools/cognitive/MMSE.pdf

Provided by NHCQF, 0106-410

Instructions for administration and scoring of the MMSE

Orientation (10 points):

- Ask for the date. Then specifically ask for parts omitted (e.g., "Can you also tell me what season it is?"). One point for each correct answer.
- Ask in turn, "Can you tell me the name of this hospital (town, county, etc.)?" One point for each correct answer.

Registration (3 points):

- Say the names of three unrelated objects clearly and slowly, allowing approximately one second for each. After you have said all three, ask the patient to repeat them. The number of objects the patient names correctly upon the first repetition determines the score (0-3). If the patient does not repeat all three objects the first time, continue saying the names until the patient is able to repeat all three items, up to six trials. Record the number of trials it takes for the patient to learn the words. If the patient does not eventually learn all three, recall cannot be meaningfully tested.
- After completing this task, tell the patient, "Try to remember the words, as I will ask for them in a little while."

Attention and Calculation (5 points):

- Ask the patient to begin with 100 and count backward by sevens. Stop after five subtractions (93, 86, 79, 72, 65). Score the total number of correct answers.
- If the patient cannot or will not perform the subtraction task, ask the patient to spell the word "world" backwards. The score is the number of letters in correct order (e.g., dlrow=5, dlorw=3).

Recall (3 points):

- Ask the patient if he or she can recall the three words you previously asked him or her to remember. Score the total number of correct answers (0-3).

Language and Praxis (9 points):

- Naming: Show the patient a wrist watch and ask the patient what it is. Repeat with a pencil. Score one point for each correct naming (0-2).
- Repetition: Ask the patient to repeat the sentence after you ("No ifs, ands, or buts."). Allow only one trial. Score 0 or 1.
- 3-Stage Command: Give the patient a piece of blank paper and say, "Take this paper in your right hand, fold it in half, and put it on the floor." Score one point for each part of the command correctly executed.
- Reading: On a blank piece of paper print the sentence, "Close your eyes," in letters large enough for the patient to see clearly. Ask the patient to read the sentence and do what it says. Score one point only if the patient actually closes his or her eyes. This is not a test of memory, so you may prompt the patient to "do what it says" after the patient reads the sentence.
- Writing: Give the patient a blank piece of paper and ask him or her to write a sentence for you. Do not dictate a sentence; it should be written spontaneously. The sentence must contain a subject and a verb and make sense. Correct grammar and punctuation are not necessary.
- Copying: Show the patient the picture of two intersecting pentagons and ask the patient to copy the figure exactly as it is. All ten angles must be present and two must intersect to score one point. Ignore tremor and rotation.

(Folstein, Folstein & McHugh, 1975)

Interpretation of the MMSE

Method	Score	Interpretation
Single Cutoff	<24	Abnormal
Range	<21	Increased odds of dementia
	>25	Decreased odds of dementia
Education	21	Abnormal for 8th grade education
	<23	Abnormal for high school education
	<24	Abnormal for college education
Severity	24-30	No cognitive impairment
	18-23	Mild cognitive impairment
	0-17	Severe cognitive impairment

Sources:

- Crum RM, Anthony JC, Bassett SS, Folstein MF. Population-based norms for the mini-mental state examination by age and educational level. *JAMA*. 1993;269(18):2386-2391.
- Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12:189-198.
- Rovner BW, Folstein MF. Mini-mental state exam in clinical practice. *Hosp Pract*. 1987;22(1A):99, 103, 106, 110.
- Tombaugh TN, McIntyre NJ. The mini-mental state examination: a comprehensive review. *J Am Geriatr Soc*. 1992;40(9):922-935.

Appendix C. Data Collection Sheet

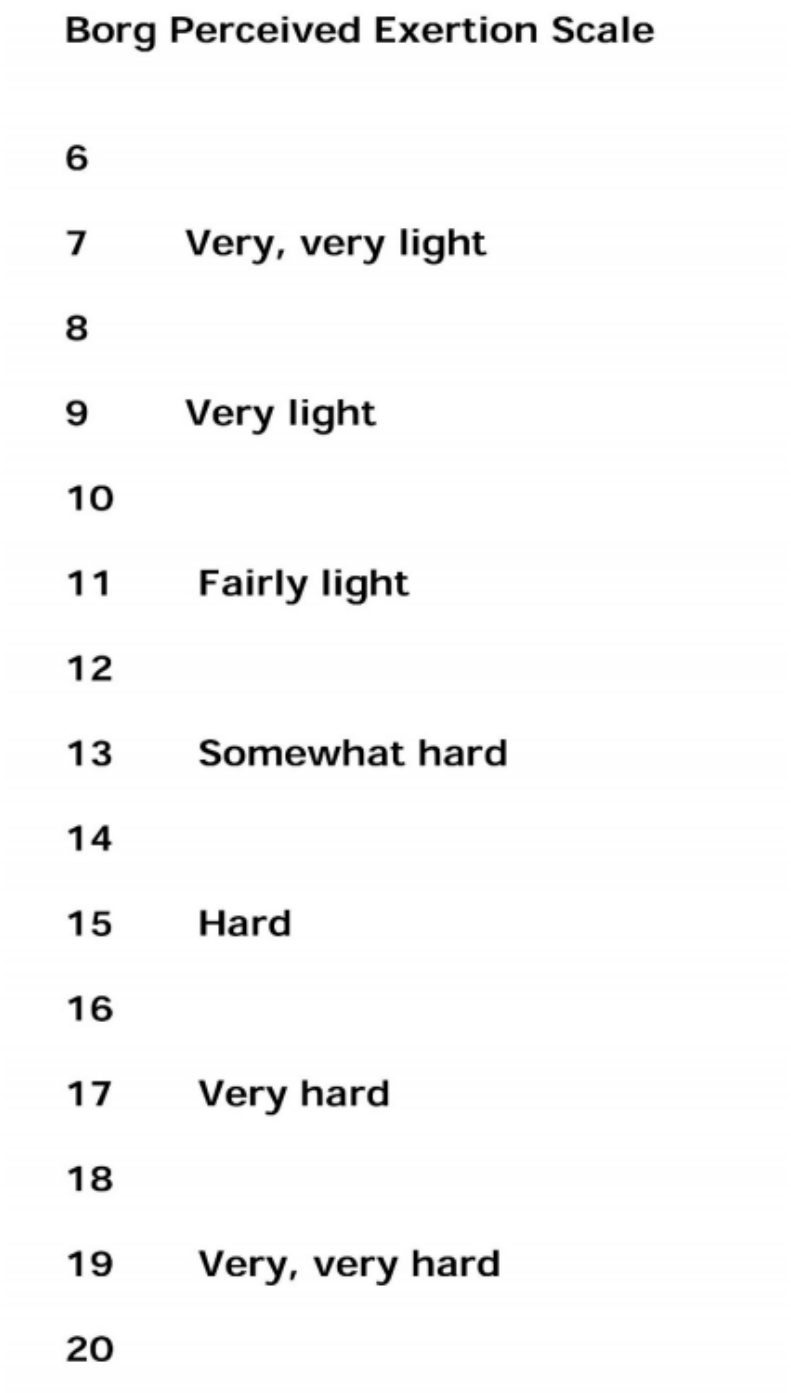
Exercise/Rest Data Sheet

Sub ID: _____ Date: _____ Condition: _____

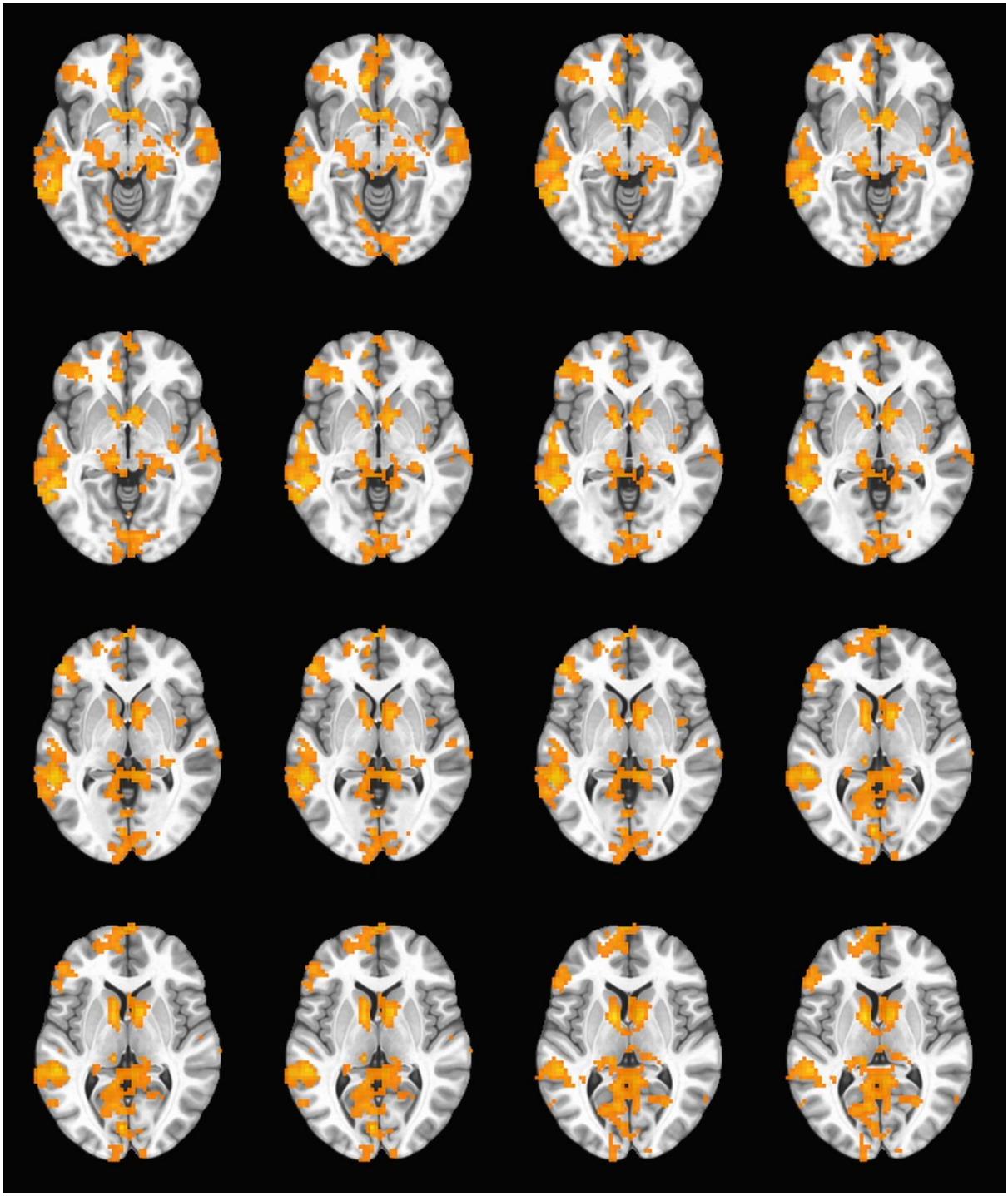
Start Time: _____ End Time: _____ RA: _____

Time	Watts	HR	RPE	PAIN	SAM-V	SAM-A
Rest						
Warm Up (0-5 min)						
Stage 1 (5-10 min)						
Stage 2 (10-15 min)						
Stage 3 (15-20 min)						
Stage 4 (20-25 min)						
Cool Down (25-30 min)						
Post-Exercise (5 min post)						

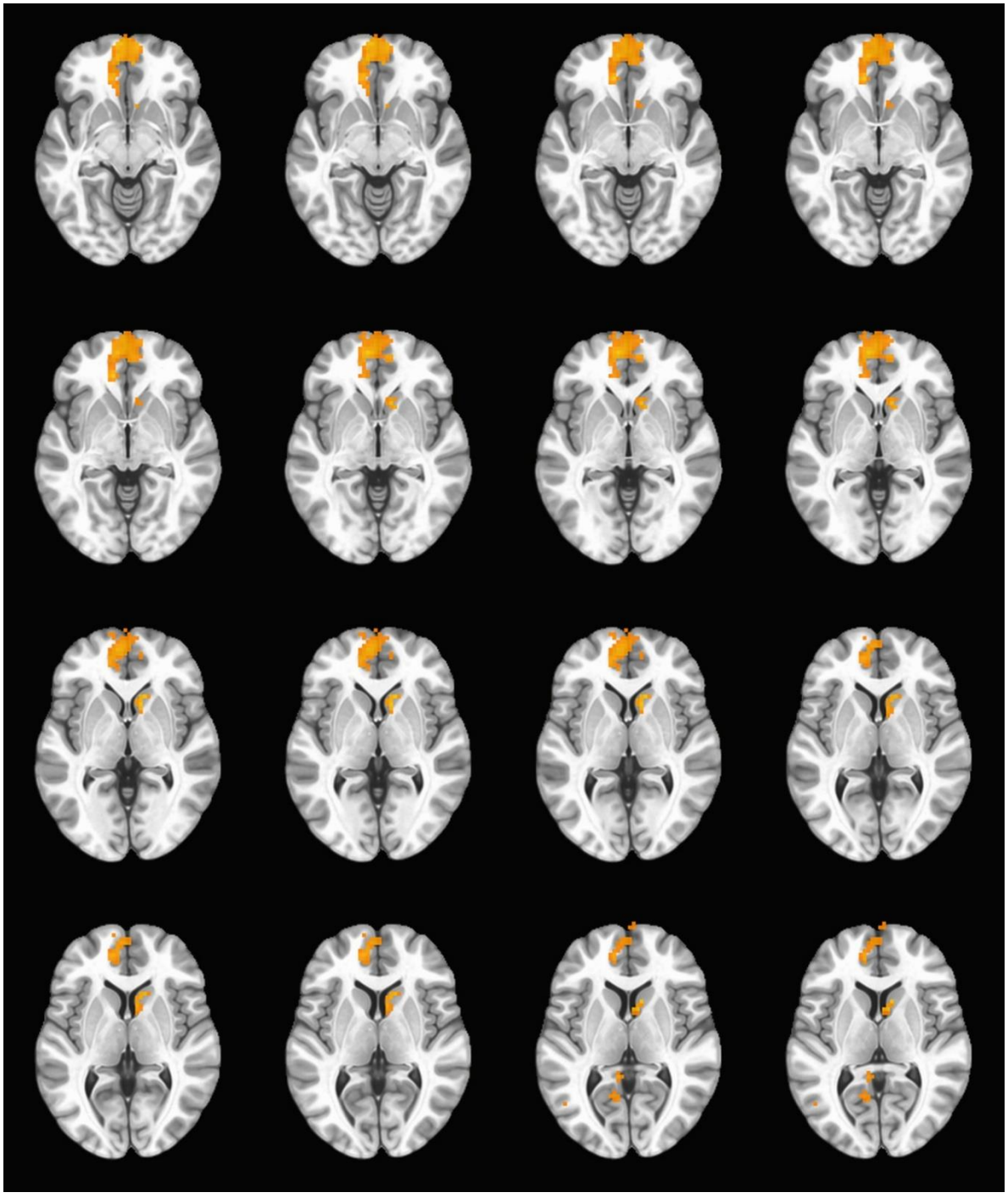
Appendix D. Borg's Ratings of Perceived Exertion Scale



Appendix E. Supplementary Tables and Figures



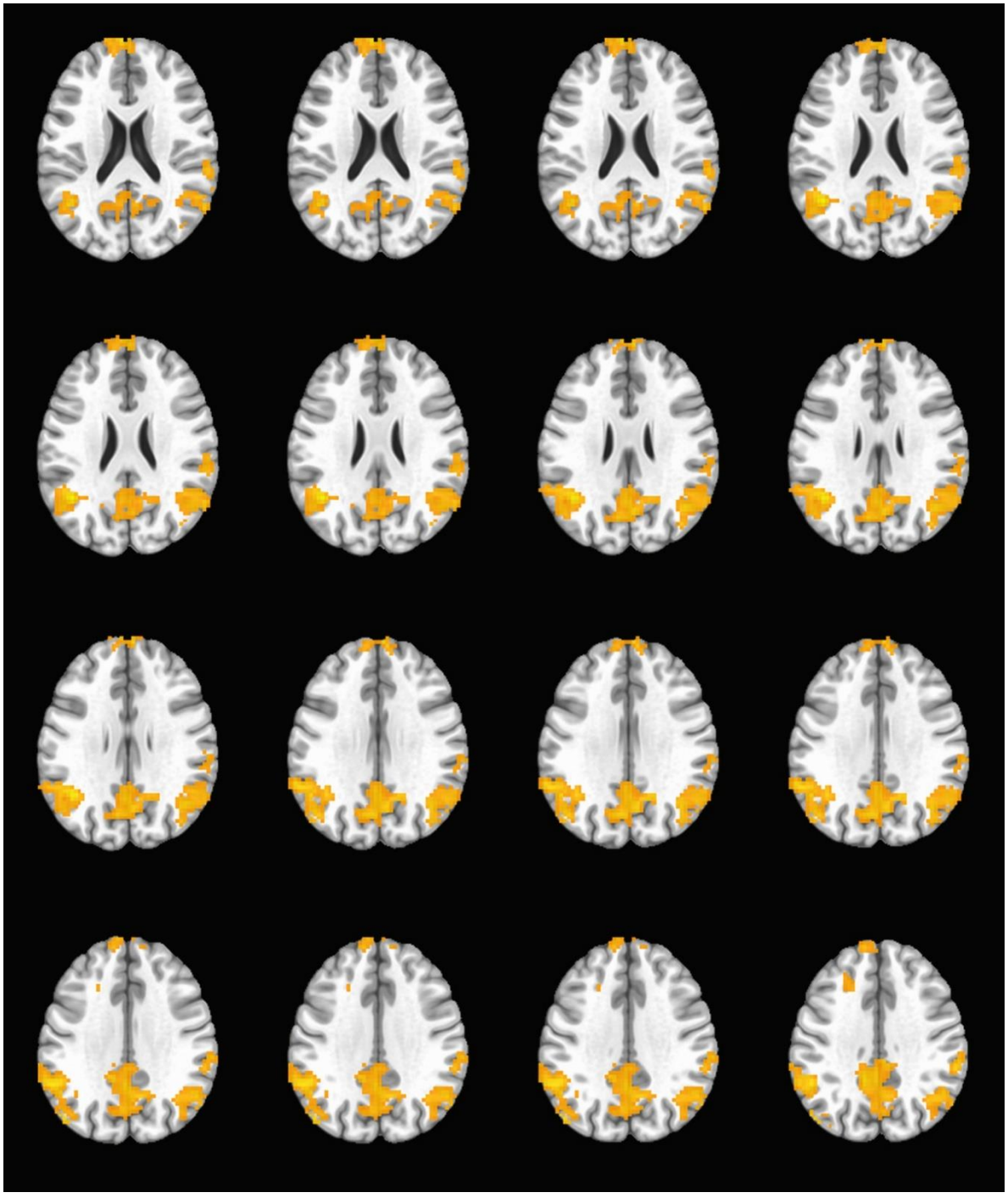
Suppl. Figure 1. *A montage of axial slices showing the fROIs demonstrating significant differences between Famous and Non-famous name conditions activated after the exercise condition.*



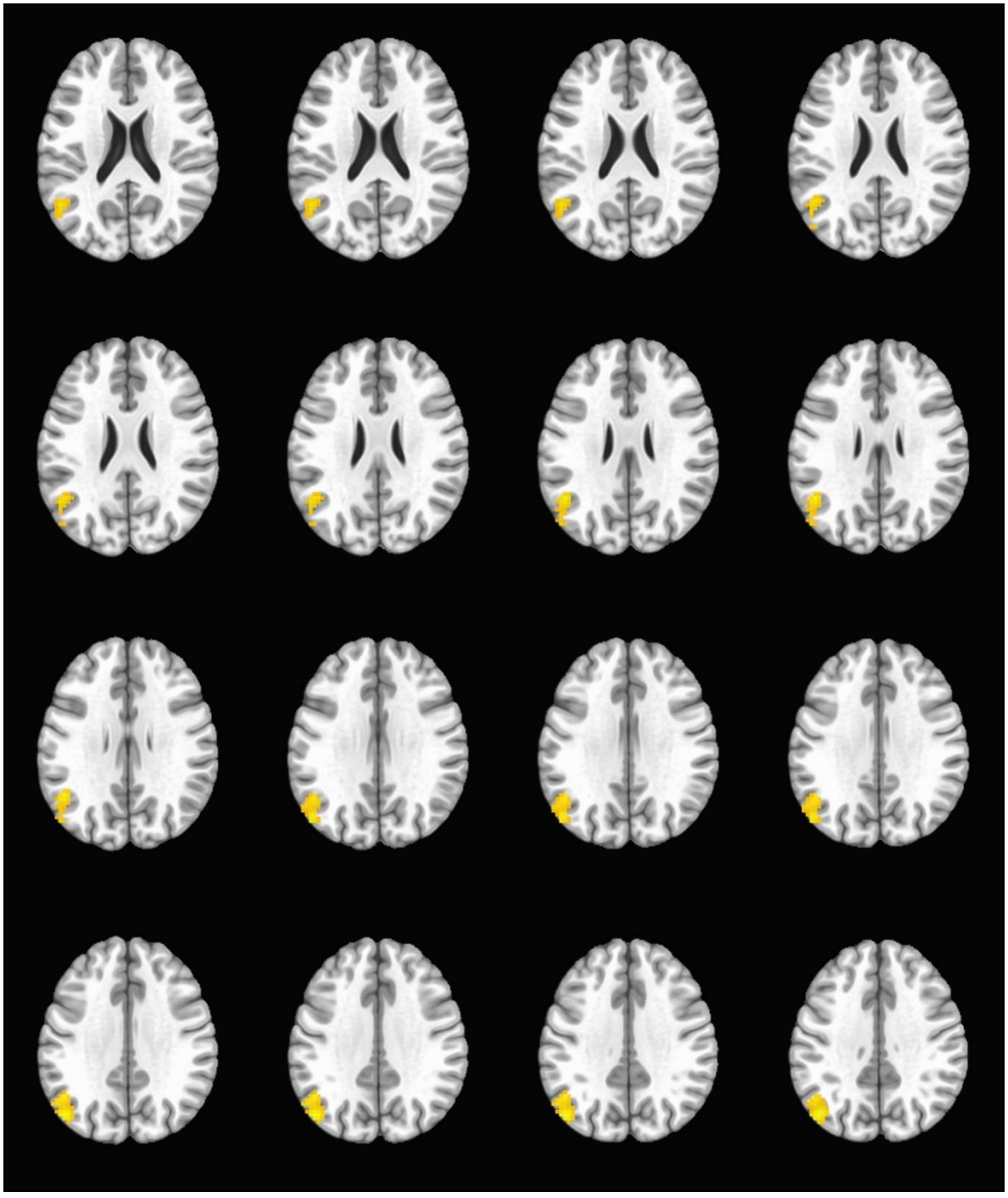
Suppl. Figure 2. *A montage of axial slices showing the fROIs demonstrating significant differences between Famous and Non-famous name conditions activated after the rest condition.*

Suppl. Table 1. *Location and spatial extent of activated regions from a voxel-wise analysis comparing Famous versus Non-famous names identification for post-exercise and post-rest conditions. Regions are shown in supplementary Figure 1 (exercise) and 2 (rest), respectively.*

			Participants (n = 26)							
Side	**Region**	**BA**	**Post-Exercise**				**Post-Rest**			
	Famous > Non-Famous		**x**	**y**	**z**	**vol**	**x**	**y**	**z**	**vol**
R	Lingual Gyrus	17,18	13	-96	-7	17.30				
L	Medial Frontal Gyrus	10	-2	68	6	6.90	-2	68	-5	3.62
L	Middle Temporal Gyrus	21,22,37	-67	-51	1	5.26				
R	Middle Temporal Gyrus	21	63	-5	-9	1.07				
L	Posterior Cingulate	30					-2	-50	20	1.90
L	Angular Gyrus	39					-47	-73	40	1.40
R	Fusiform Gyrus	19	-49	68	-20	1.22				
R	Middle Occipital Gyrus	37	-35	70	-22	1.5				



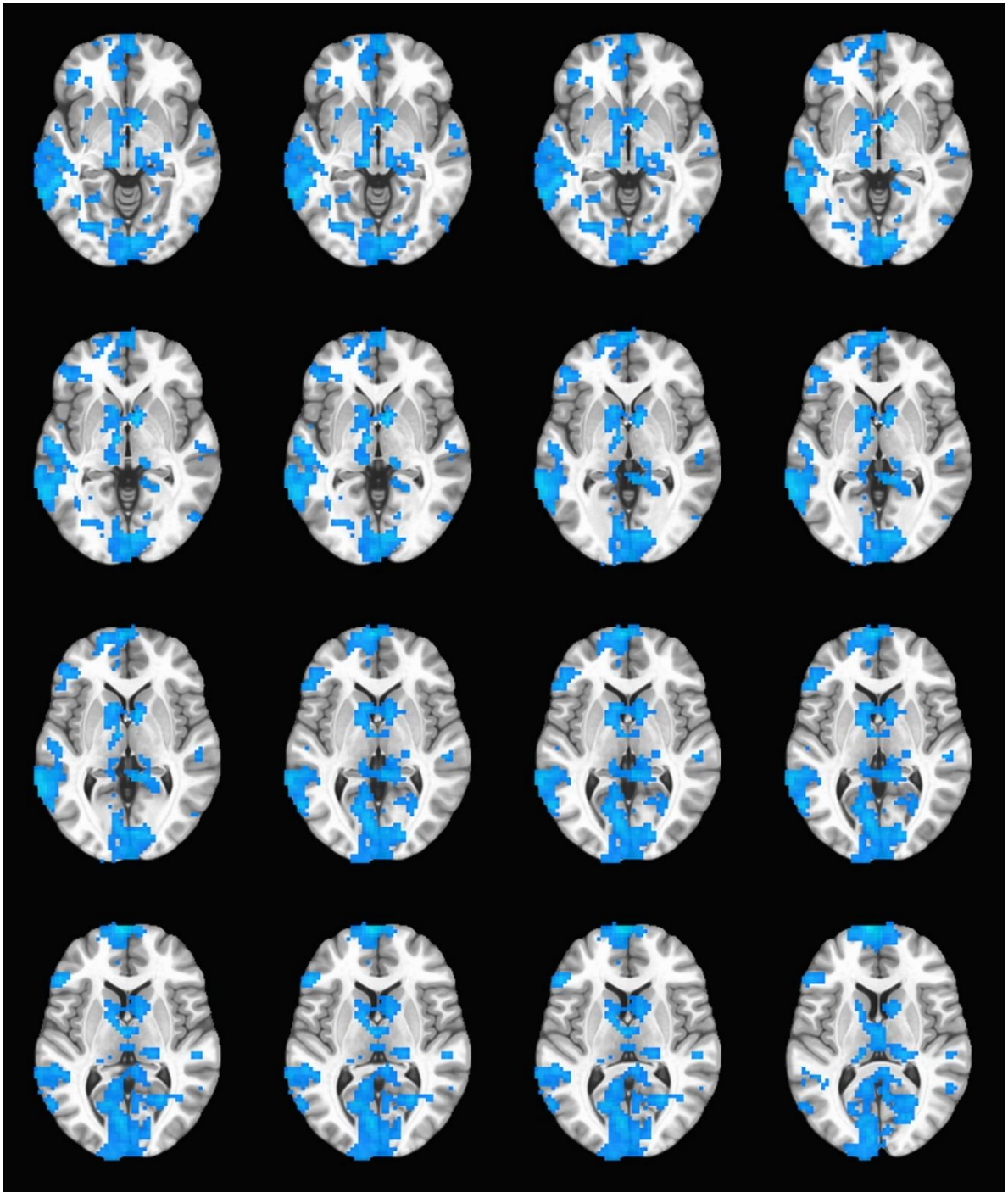
Suppl. Figure 3. *A montage of axial slices showing the fROIs demonstrating significant differences between Enduringly Famous and Non-famous name conditions activated after the exercise condition.*



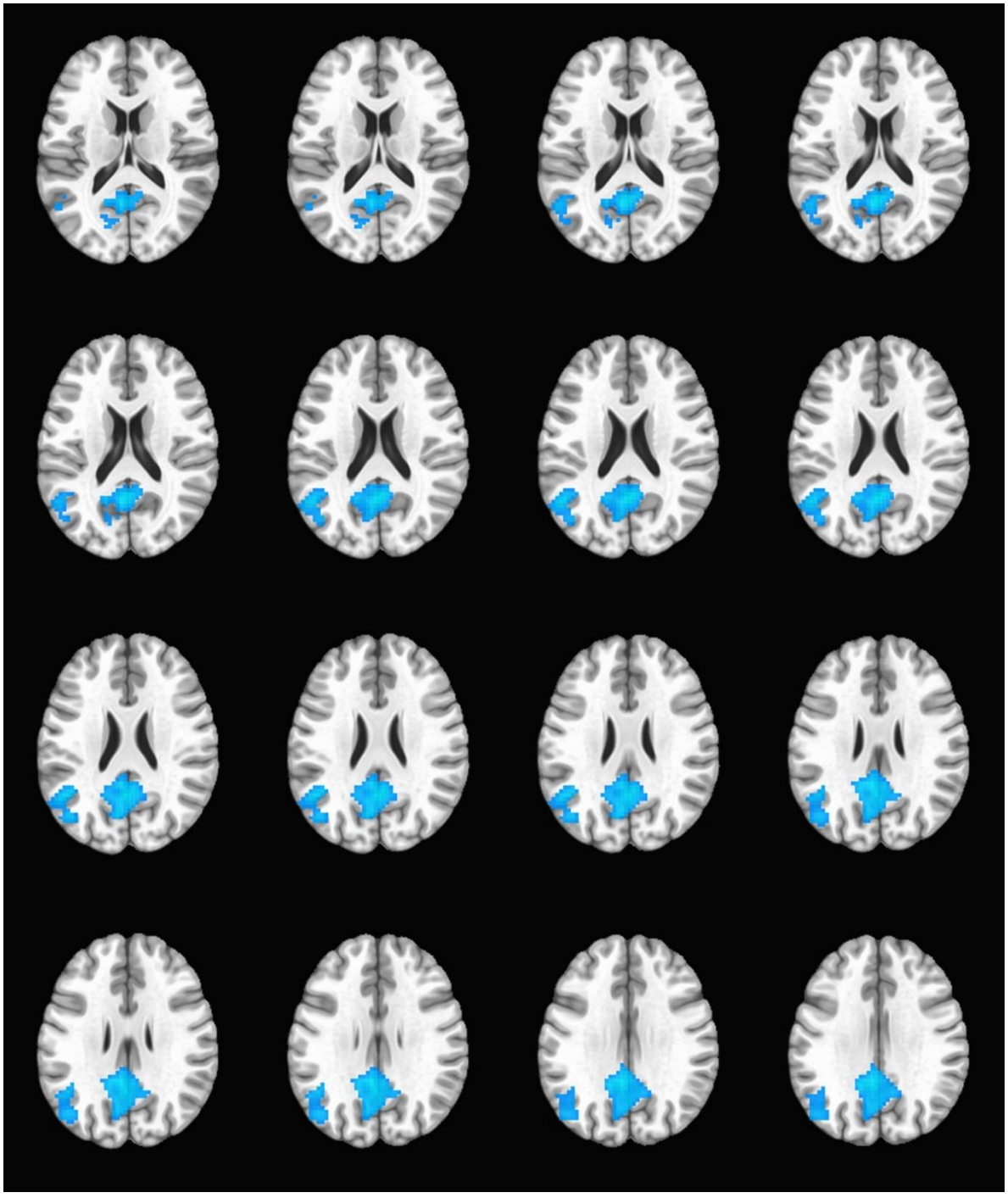
Suppl. Figure 4. *A montage of axial slices showing the fROIs demonstrating significant differences between Enduringly Famous and Non-famous name conditions activated after the rest condition.*

Suppl. Table 2. *An exploratory analysis of location and spatial extent of activated regions from a voxel-wise analysis comparing Enduringly Famous versus Non-famous name identification for post-exercise and post-rest conditions. Regions are shown in supplementary Figure 3 (exercise) and 4 (rest), respectively.*

			Participants (n = 26)							
Side	**Region**	**BA**	**Post-Exercise**				**Post-Rest**			
			x	**y**	**z**	**vol**	**x**	**y**	**z**	**vol**
	<u>Enduringly Famous > Non-Famous</u>									
L	Posterior Cingulate	23,31	2	50	25	4.86				
L	Inferior Parietal Lobule	7,40	-44	-66	51	1.60				
L	Superior Frontal Gyrus	8,9	-20	47	43	0.95				
L	Medial Frontal Gyrus	10	-2	68	6	0.94				
L	Angular Gyrus	39					-52	-70	38	0.61



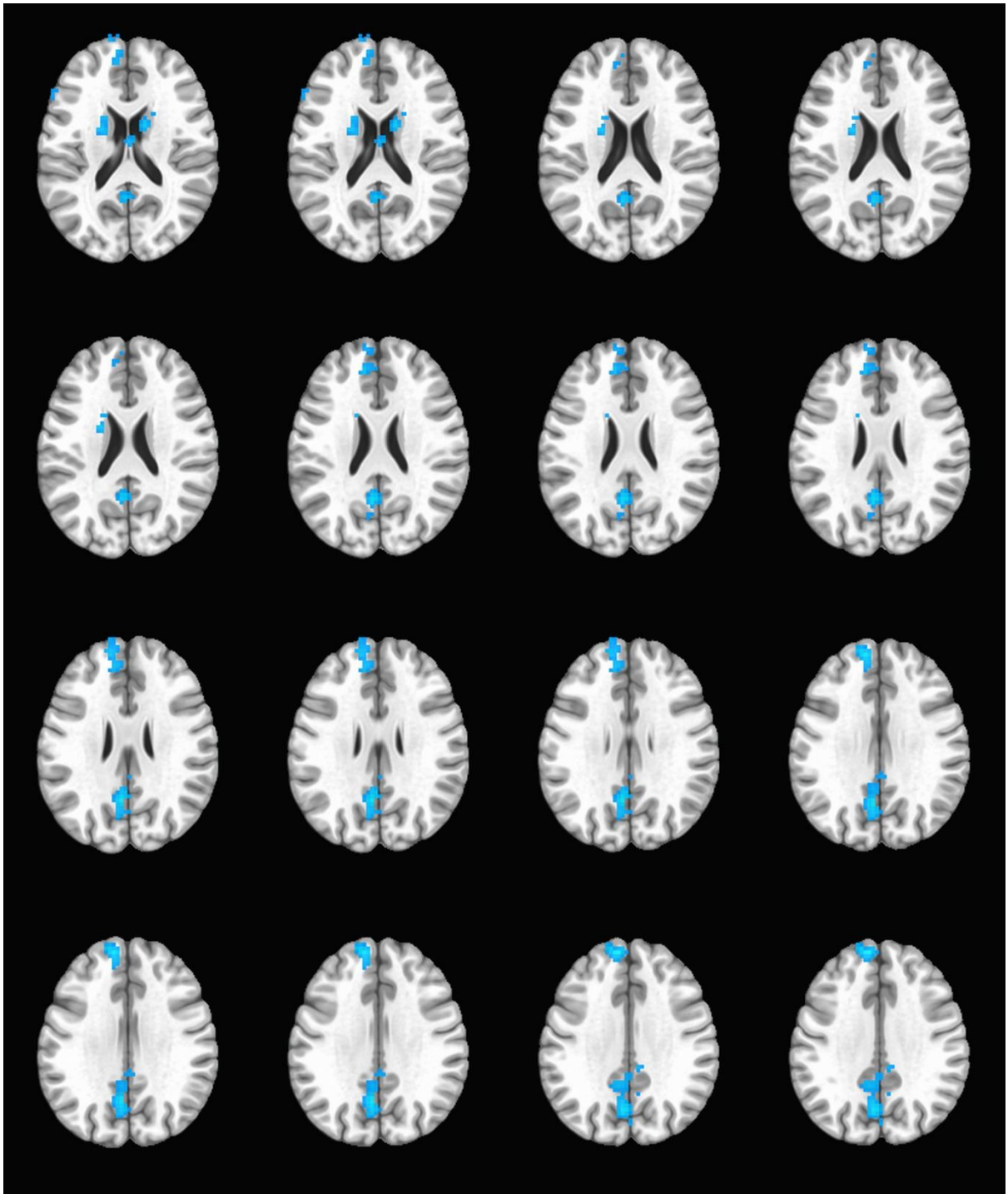
Suppl. Figure 5. *A montage of axial slices showing the fROIs demonstrating significant differences between Recently Famous and Non-famous name conditions activated after the exercise condition.*



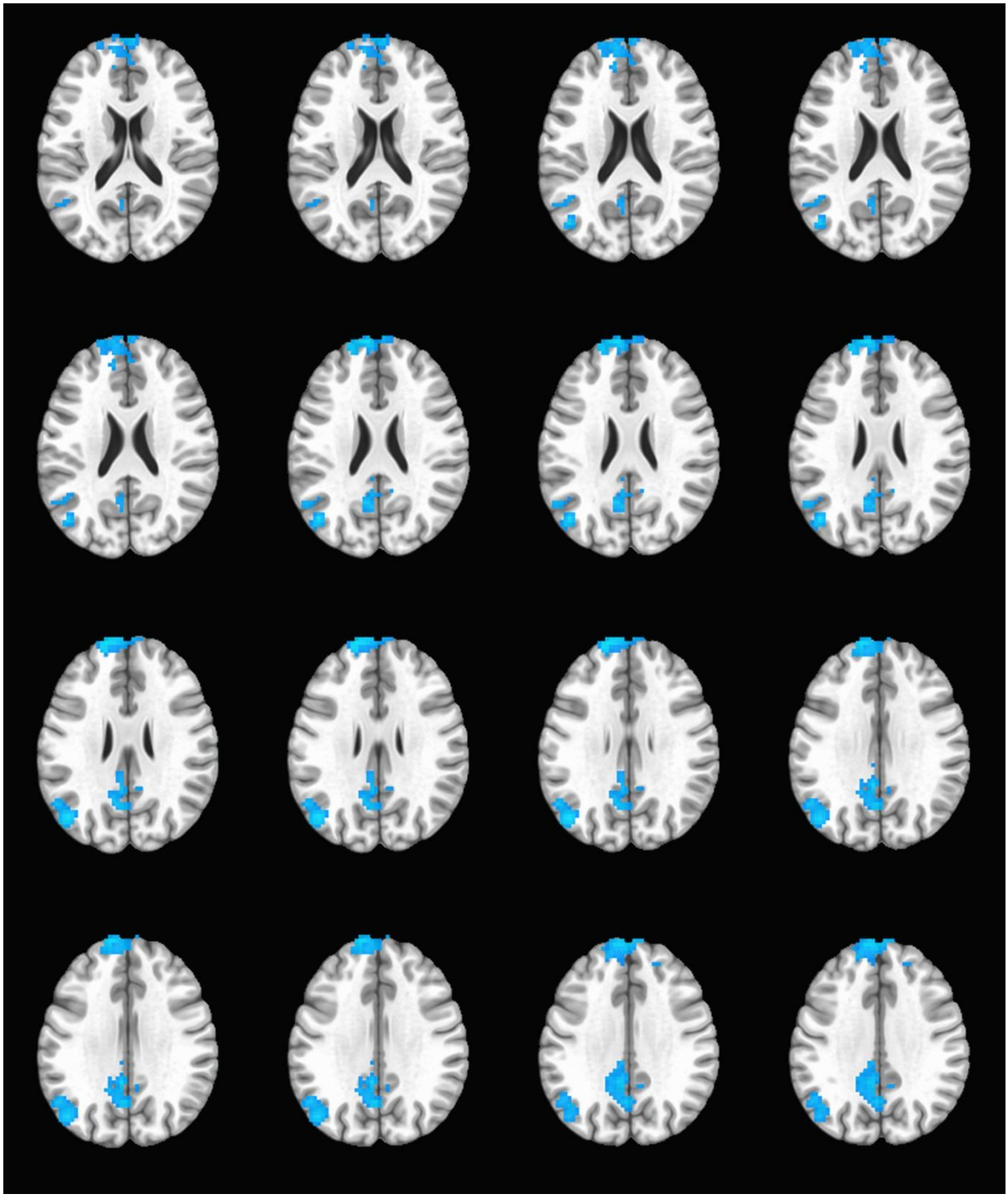
Suppl. Figure 6. *A montage of axial slices showing the fROIs demonstrating significant differences between Recently Famous and Non-famous name conditions activated after the rest condition.*

Suppl. Table 3. *An exploratory analysis of location and spatial extent of activated r egions from a voxel-wise analysis comparing Recently Famous versus Non-famous name identification for post-exercise and post-rest conditions. Regions are shown in supplementary Figure 5 (exercise) and 6 (rest), respectively.*

			Participants (n = 26)							
Side	**Region**	**BA**	**Post-Exercise**				**Post-Rest**			
	Recently Famous < Non-Famous		**x**	**y**	**z**	**vol**	**x**	**y**	**z**	**vol**
R	Cingulate Gyrus	23,31	4	-47	28	27.87				
L	Medial Frontal Gyrus	10,25	-11	35	-14	5.43				
L	Inferior Frontal Gyrus	46	-35	34	13	0.96				
L	Precuneus	7					-2	-61	34	2.52
R	Superior Frontal Gyrus	11					4	59	-10	1.49
L	Middle Temporal Gyrus	39					-47	-70	29	1.00



Suppl. Figure 7. *A montage of axial slices showing the fROIs demonstrating significant differences between Remotely Famous and Non-famous name conditions activated after the exercise condition.*



Suppl. Figure 8. *A montage of axial slices showing the fROIs demonstrating significant differences between Remotely Famous and Non-famous name conditions activated after the rest condition.*

Reference

Adlard, P. A., Perreau, V. M., Pop, V., & Cotman, C. W. (2005). Voluntary exercise decreases amyloid load in a transgenic model of Alzheimer's disease. *Journal of Neuroscience*, *25*(17), 4217–4221.

Agosta, F., Pievani, M., Geroldi, C., Copetti, M., Frisoni, G. B., & Filippi, M. (2012). Resting state fMRI in Alzheimer's disease: beyond the default mode network. *Neurobiology of Aging*, *33*(8), 1564–1578.

Ahlskog, J. E., Geda, Y. E., Graff-Radford, N. R., & Petersen, R. C. (2011). Physical exercise as a preventive or disease-modifying treatment of dementia and brain aging. In *Mayo Clinic Proceedings* (Vol. 86, pp. 876–884). Elsevier. Retrieved from http://www.sciencedirect.com/science/article/pii/S0025619611652191

Ainslie, P. N., Cotter, J. D., George, K. P., Lucas, S., Murrell, C., Shave, R., … Atkinson, G. (2008). Elevation in cerebral blood flow velocity with aerobic fitness throughout healthy human ageing. *The Journal of Physiology*, *586*(16), 4005–4010.

Albert, M. S. (2011). Changes in cognition. *Neurobiology of Aging*, *32*, S58–S63.

Andrews-Hanna, J. R., Snyder, A. Z., Vincent, J. L., Lustig, C., Head, D., Raichle, M. E., & Buckner, R. L. (2007). Disruption of large-scale brain systems in advanced aging. *Neuron*, *56*(5), 924–935.

Arthurs, O. J., & Boniface, S. (2002). How well do we understand the neural origins of the fMRI BOLD signal? *Trends in Neurosciences*, *25*(1), 27–31.

Association, W. M., & others. (2008). Declaration of Helsinki. Ethical principles for medical research involving human subjects. *Http://Www. Wma. Net/e/Policy/B3. Htm*. Retrieved from http://ci.nii.ac.jp/naid/10021949345/

Ball, K., Owsley, C., Sloane, M. E., Roenker, D. L., & Bruni, J. R. (1993). Visual attention problems as a predictor of vehicle crashes in older drivers. *Investigative Ophthalmology & Visual Science*, *34*(11), 3110–3123.

Bannerman, D. M., Rawlins, J. N. P., McHugh, S. B., Deacon, R. M. J., Yee, B. K., Bast, T., … Feldon, J. (2004). Regional dissociations within the hippocampus—memory and anxiety. *Neuroscience & Biobehavioral Reviews*, *28*(3), 273–283.

Basso, J. C., Shang, A., Elman, M., Karmouta, R., & Suzuki, W. A. (2015). Acute exercise improves prefrontal cortex but not hippocampal function in healthy adults. *Journal of the International Neuropsychological Society*, *21*(10), 791–801.

Basso, J. C., & Suzuki, W. A. (n.d.). The Effects of Acute Exercise on Mood, Cognition, Neurophysiology and Neurochemical Pathways: A Review. *Brain Plasticity*, (Preprint), 1–26.

Binder, J. R., & Desai, R. H. (2011). The neurobiology of semantic memory. *Trends in Cognitive Sciences*, *15*(11), 527–536.

Bishop, N. A., Lu, T., & Yankner, B. A. (2010). Neural mechanisms of ageing and cognitive decline. *Nature*, *464*(7288), 529.

Blumenthal, J. A., Babyak, M. A., Moore, K. A., Craighead, W. E., Herman, S., Khatri, P., … others. (1999). Effects of exercise training on depression in older men and women. *Archives of Internal Medicine*, *159*, 2349–2356.

Bookheimer, S. Y., Strojwas, M. H., Cohen, M. S., Saunders, A. M., Pericak-Vance, M. A., Mazziotta, J. C., & Small, G. W. (2000). Patterns of brain activation in people at risk for Alzheimer's disease. *New England Journal of Medicine*, *343*(7), 450–456.

Borg, G. (1970). Perceived exertion as an indicator of somatic stress. *Scandinavian Journal of Rehabilitation Medicine*, *2*(2), 92.

Broyd, S. J., Demanuele, C., Debener, S., Helps, S. K., James, C. J., & Sonuga-Barke, E. J. (2009). Default-mode brain dysfunction in mental disorders: a systematic review. *Neuroscience & Biobehavioral Reviews*, *33*(3), 279–296.

Buckner, R. L., Andrews-Hanna, J. R., & Schacter, D. L. (2008). The brain's default network. *Annals of the New York Academy of Sciences*, *1124*(1), 1–38.

Buckner, R. L., Sepulcre, J., Talukdar, T., Krienen, F. M., Liu, H., Hedden, T., … Johnson, K. A. (2009). Cortical hubs revealed by intrinsic functional connectivity: mapping, assessment of stability, and relation to Alzheimer's disease. *Journal of Neuroscience*, *29*(6), 1860–1873.

Buckner, R. L., Snyder, A. Z., Shannon, B. J., LaRossa, G., Sachs, R., Fotenos, A. F., … Morris, J. C. (2005). Molecular, structural, and functional characterization of Alzheimer's disease: evidence for a relationship between default activity, amyloid, and memory. *Journal of Neuroscience*, *25*(34), 7709–7717.

Budde, H., Voelcker-Rehage, C., Pietra\s syk-Kendziorra, S., Ribeiro, P., & Tidow, G. (2008). Acute coordinative exercise improves attentional performance in adolescents. *Neuroscience Letters*, *441*(2), 219–223.

Carter, S. F., Caine, D., Burns, A., Herholz, K., Ralph, L., & Matthew, A. (2012). Staging of the cognitive decline in Alzheimer's disease: insights from a detailed neuropsychological investigation of mild cognitive impairment and mild Alzheimer's disease. *International Journal of Geriatric Psychiatry*, *27*(4), 423–432.

Chertkow, H., Whatmough, C., Saumier, D., & Duong, A. (2008). Cognitive neuroscience studies of semantic memory in Alzheimer's disease. *Progress in Brain Research*, *169*, 393–407.

Coelho, F. G. de M., Vital, T. M., Stein, A. M., Arantes, F. J., Rueda, A. V., Camarini, R., … Santos-Galduroz, R. F. (2014). Acute aerobic exercise increases brain-derived neurotrophic factor levels in elderly with Alzheimer's disease. *Journal of Alzheimer's Disease*, *39*(2), 401–408.

Colcombe, S. J., Erickson, K. I., Scalf, P. E., Kim, J. S., Prakash, R., McAuley, E., … Kramer, A. F. (2006). Aerobic exercise training increases brain volume in aging humans. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *61*(11), 1166–1170.

Colcombe, S., & Kramer, A. F. (2003). Fitness effects on the cognitive function of older adults: a meta-analytic study. *Psychological Science*, *14*(2), 125–130.

Cotman, C. W., & Engesser-Cesar, C. (2002). Exercise enhances and protects brain function. *Exercise and Sport Sciences Reviews*, *30*(2), 75–79.

Cox, R. W. (1996). AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Computers and Biomedical Research*, *29*(3), 162–173.

Damoiseaux, J. S., Beckmann, C. F., Arigita, E. S., Barkhof, F., Scheltens, P., Stam, C. J., … Rombouts, S. (2007). Reduced resting-state brain activity in the "default network" in normal aging. *Cerebral Cortex*, *18*(8), 1856–1864.

DiPietro, L. (2001). Physical activity in aging: changes in patterns and their relationship to health and function. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *56*(suppl_2), 13–22.

Douville, K., Woodard, J. L., Seidenberg, M., Miller, S. K., Leveroni, C. L., Nielson, K. A., … Rao, S. M. (2005). Medial temporal lobe activity for recognition of recent and remote famous names: an event-related fMRI study. *Neuropsychologia*, *43*(5), 693–703.

Eklund, A., Nichols, T. E., & Knutsson, H. (2016). Cluster failure: why fMRI inferences for spatial extent have inflated false-positive rates. *Proceedings of the National Academy of Sciences*, 201602413.

Eklund, A., Nichols, T., & Knutsson, H. (2015). Can parametric statistical methods be trusted for fMRI based group studies? *ArXiv Preprint ArXiv:1511.01863*. Retrieved from https://arxiv.org/abs/1511.01863

Erickson, K. I., Prakash, R. S., Voss, M. W., Chaddock, L., Heo, S., McLaren, M., … others. (2010). Brain-derived neurotrophic factor is associated with age-related decline in hippocampal volume. *Journal of Neuroscience*, *30*(15), 5368–5375.

Erickson, K. I., Voss, M. W., Prakash, R. S., Basak, C., Szabo, A., Chaddock, L., … others. (2011). Exercise training increases size of hippocampus and improves memory. *Proceedings of the National Academy of Sciences*, *108*(7), 3017–3022.

Esiri, M. M., Nagy, Z., Smith, M. Z., Barnetson, L., & Smith, A. D. (1999). Cerebrovascular disease and threshold for dementia in the early stages of Alzheimer's disease. *The Lancet*, *354*(9182), 919–920.

Etnier, J. L., Wideman, L., Labban, J. D., Piepmeier, A. T., Pendleton, D. M., Dvorak, K. K., & Becofsky, K. (2016). The effects of acute exercise on memory and brain-derived neurotrophic factor (BDNF). *Journal of Sport and Exercise Psychology*, *38*(4), 331–340.

Ferré, S., & O'Brien, M. C. (2011). Alcohol and caffeine: the perfect storm. *Journal of Caffeine Research*, *1*(3), 153–162.

Ferreira, L. K., & Busatto, G. F. (2013). Resting-state functional connectivity in normal brain aging. *Neuroscience & Biobehavioral Reviews*, *37*(3), 384–400.

Ferris, L. T., Williams, J. S., & Shen, C.-L. (2007). The effect of acute exercise on serum brain-derived neurotrophic factor levels and cognitive function. *Medicine & Science in Sports & Exercise*, *39*(4), 728–734.

Florindo, A. A., Latorre, M. do R. D., Jaime, P. C., Tanaka, T., Pippa, M. G., & Zerbini, C. A. (2002). Past and present habitual physical activity and its relationship with bone

mineral density in men aged 50 years and older in Brazil. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *57*(10), M654–M657.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, *12*(3), 189–198.

Gómez-Pinilla, F., Ying, Z., Roy, R. R., Molteni, R., & Edgerton, V. R. (2002). Voluntary exercise induces a BDNF-mediated mechanism that promotes neuroplasticity. *Journal of Neurophysiology*, *88*(5), 2187–2195.

Gordon, B. A., Rykhlevskaia, E. I., Brumback, C. R., Lee, Y., Elavsky, S., Konopack, J. F., … Gratton, G. (2008). Neuroanatomical correlates of aging, cardiopulmonary fitness level, and education. *Psychophysiology*, *45*(5), 825–838.

Gorelick, P. B., Scuteri, A., Black, S. E., DeCarli, C., Greenberg, S. M., Iadecola, C., … others. (2011). Vascular contributions to cognitive impairment and dementia. *Stroke*, *42*(9), 2672–2713.

Greicius, M. D., Srivastava, G., Reiss, A. L., & Menon, V. (2004). Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. *Proceedings of the National Academy of Sciences of the United States of America*, *101*(13), 4637–4642.

Gusnard, D. A., & Raichle, M. E. (2001). Searching for a baseline: functional imaging and the resting human brain. *Nature Reviews Neuroscience*, *2*(10), 685–694.

Haist, F., Gore, J. B., & Mao, H. (2001). Consolidation of human memory over decades revealed by functional magnetic resonance imaging. *Nature Neuroscience*, *4*(11), 1139.

Hantke, N., Nielson, K. A., Woodard, J. L., Breting, L. M. G., Butts, A., Seidenberg, M., … others. (2013). Comparison of semantic and episodic memory BOLD fMRI activation in predicting cognitive decline in older adults. *Journal of the International Neuropsychological Society*, *19*(1), 11–21.

Henry, J. D., Crawford, J. R., & Phillips, L. H. (2004). Verbal fluency performance in dementia of the Alzheimer's type: a meta-analysis. *Neuropsychologia*, *42*(9), 1212–1222.

Hohn, A., Leibrock, J., Bailey, K., & Barde, Y.-A. (1990). Identification and characterization of a novel member of the nerve growth factor/brain-derived neurotrophic factor family. *Nature*, *344*(6264), 339.

Horn, A., Ostwald, D., Reisert, M., & Blankenburg, F. (2014). The structural–functional connectome and the default mode network of the human brain. *Neuroimage*, *102*, 142–151.

Hötting, K., Schickert, N., Kaiser, J., Röder, B., & Schmidt-Kassow, M. (2016). The effects of acute physical exercise on memory, peripheral BDNF, and cortisol in young adults. *Neural Plasticity*, *2016*. Retrieved from https://www.hindawi.com/journals/np/2016/6860573/abs/

Hsieh, S.-S., Chang, Y.-K., Fang, C.-L., & Hung, T.-M. (2016). Acute Resistance Exercise Facilitates Attention Control in Adult Males without an Age-Moderating Effect. *Journal of Sport and Exercise Psychology*, *38*(3), 247–254.

Huang, C., Wahlund, L.-O., Svensson, L., Winblad, B., & Julin, P. (2002). Cingulate cortex hypoperfusion predicts Alzheimer's disease in mild cognitive impairment. *BMC Neurology*, *2*(1), 9.

Huettel, S. A., Song, A. W., & McCarthy, G. (2004). *Functional magnetic resonance imaging* (Vol. 1). Sinauer Associates Sunderland. Retrieved from https://pdfs.semanticscholar.org/b917/f1d5f55a44446d45a14f2f0192375108aa0e.pdf

Ide, K., & Secher, N. H. (2000). Cerebral blood flow and metabolism during exercise. *Progress in Neurobiology*, *61*(4), 397–414.

Intlekofer, K. A., & Cotman, C. W. (2013). Exercise counteracts declining hippocampal function in aging and Alzheimer's disease. *Neurobiology of Disease*, *57*, 47–55.

Jonker, C., Geerlings, M. I., & Schmand, B. (2000). Are memory complaints predictive for dementia? A review of clinical and population-based studies. *International Journal of Geriatric Psychiatry*, *15*(11), 983–991.

Kapur, N., Friston, K. J., Young, A., Frith, C. D., & Frackowiak, R. S. J. (1995). Activation of human hippocampal formation during memory for faces: a PET study. *Cortex*, *31*(1), 99–108.

Klingberg, T., O'Sullivan, B. T., & Roland, P. E. (1997). Bilateral activation of fronto-parietal networks by incrementing demand in a working memory task. *Cerebral Cortex (New York, NY: 1991)*, *7*(5), 465–471.

Kyeremanteng, C., James, J., Mackay, J., & Merali, Z. (2012). A study of brain and serum brain-derived neurotrophic factor protein in Wistar and Wistar-Kyoto rat strains after electroconvulsive stimulus. *Pharmacopsychiatry*, *45*(06), 244–249.

L Woodard, J., A Sugarman, M., A Nielson, K., Carson Smith, J., Seidenberg, M., Durgerian, S., … A Matthews, M. (2012). Lifestyle and genetic contributions to cognitive decline and hippocampal structure and function in healthy aging. *Current Alzheimer Research*, *9*(4), 436–446.

Labban, J. D., & Etnier, J. L. (2011). Effects of acute exercise on long-term memory. *Research Quarterly for Exercise and Sport*, *82*(4), 712–721.

Leirer, O., Morrow, D. G., Pariante, G. M., & Sheikh, J. I. (1988). Elders' nonadherence, its assessment, and computer assisted instruction for medication recall training. *Journal of the American Geriatrics Society*, *36*(10), 877–884.

Leveroni, C. L., Seidenberg, M., Mayer, A. R., Mead, L. A., Binder, J. R., & Rao, S. M. (2000). Neural systems underlying the recognition of familiar and newly learned faces. *Journal of Neuroscience*, *20*(2), 878–886.

Logothetis, N. K. (2008). What we can do and what we cannot do with fMRI. *Nature*, *453*(7197), 869–878.

Logsdon, R. G., Gibbons, L. E., McCurry, S. M., & Teri, L. (2002). Assessing quality of life in older adults with cognitive impairment. *Psychosomatic Medicine*, *64*(3), 510–519.

Lonie, J. A., Herrmann, L. L., Tierney, K. M., Donaghey, C., O'carroll, R., Lee, A., & Ebmeier, K. P. (2009). Lexical and semantic fluency discrepancy scores in aMCI and early Alzheimer's disease. *Journal of Neuropsychology*, *3*(1), 79–92.

Lustig, C., Snyder, A. Z., Bhakta, M., O'Brien, K. C., McAvoy, M., Raichle, M. E., … Buckner, R. L. (2003). Functional deactivations: change with age and dementia of the Alzheimer type. *Proceedings of the National Academy of Sciences*, *100*(24), 14504–14509.

Maguire, E. A., Frith, C. D., & Cipolotti, L. (2001). Distinct neural systems for the encoding and recognition of topography and faces. *Neuroimage*, *13*(4), 743–750.

Martin, A., & Chao, L. L. (2001). Semantic memory and the brain: structure and processes. *Current Opinion in Neurobiology*, *11*(2), 194–201.

Meier, T. B., Desphande, A. S., Vergun, S., Nair, V. A., Song, J., Biswal, B. B., … Prabhakaran, V. (2012). Support vector machine classification and characterization of age-related reorganization of functional brain networks. *Neuroimage*, *60*(1), 601–613.

Mu, J.-S., Li, W.-P., Yao, Z.-B., & Zhou, X.-F. (1999). Deprivation of endogenous brain-derived neurotrophic factor results in impairment of spatial learning and memory in adult rats. *Brain Research*, *835*(2), 259–265.

Neeper, S. A., Gomez-Pinilla, F., Choi, J., Cotman, C., & others. (1995). *Exercise and brain neurotrophins*. University of California, Irvine. Retrieved from http://search.proquest.com/openview/c31beb2320322a65eb3303102e98d10f/1.pdf?pq-origsite=gscholar&cbl=40569

Neeper, S. A., Gómez-Pinilla, F., Choi, J., & Cotman, C. W. (1996). Physical activity increases mRNA for brain-derived neurotrophic factor and nerve growth factor in rat brain. *Brain Research*, *726*(1), 49–56.

Nielson, K. A., Douville, K. L., Seidenberg, M., Woodard, J. L., Miller, S. K., Franczak, M., … Rao, S. M. (2006). Age-related functional recruitment for famous name recognition: an event-related fMRI study. *Neurobiology of Aging*, *27*(10), 1494–1504.

Nouchi, R., Taki, Y., Takeuchi, H., Sekiguchi, A., Hashizume, H., Nozawa, T., … Kawashima, R. (2014). Four weeks of combination exercise training improved executive functions, episodic memory, and processing speed in healthy elderly people: evidence from a randomized controlled trial. *Age*, *36*(2), 787–799.

O'brien, J. L., O'keefe, K. M., LaViolette, P. S., DeLuca, A. N., Blacker, D., Dickerson, B. C., & Sperling, R. A. (2010). Longitudinal fMRI in elderly reveals loss of hippocampal activation with clinical decline. *Neurology*, *74*(24), 1969–1976.

Ogawa, S., Lee, T.-M., Kay, A. R., & Tank, D. W. (1990). Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proceedings of the National Academy of Sciences*, *87*(24), 9868–9872.

Ogawa, S., Tank, D. W., Menon, R., Ellermann, J. M., Kim, S. G., Merkle, H., & Ugurbil, K. (1992). Intrinsic signal changes accompanying sensory stimulation: functional brain mapping with magnetic resonance imaging. *Proceedings of the National Academy of Sciences*, *89*(13), 5951–5955.

Ogoh, S., Tsukamoto, H., Hirasawa, A., Hasegawa, H., Hirose, N., & Hashimoto, T. (2014). The effect of changes in cerebral blood flow on cognitive function during exercise. *Physiological Reports*, *2*(9), e12163.

Palmer, K. K., Miller, M. W., & Robinson, L. E. (2013). Acute exercise enhances preschoolers' ability to sustain attention. *Journal of Sport and Exercise Psychology*, *35*(4), 433–437.

Pan, W., Banks, W. A., Fasold, M. B., Bluth, J., & Kastin, A. J. (1998). Transport of brain-derived neurotrophic factor across the blood–brain barrier. *Neuropharmacology*, *37*(12), 1553–1561.

Pardridge, W. M. (2007). Blood–brain barrier delivery. *Drug Discovery Today*, *12*(1), 54–61.

Pardridge, W. M., Wu, D., & Sakane, T. (1998). Combined use of carboxyl-directed protein pegylation and vector-mediated blood-brain barrier drug delivery system optimizes brain uptake of brain-derived neurotrophic factor following intravenous administration. *Pharmaceutical Research*, *15*(4), 576–582.

Park, D. C., & Reuter-Lorenz, P. (2009). The adaptive brain: aging and neurocognitive scaffolding. *Annual Review of Psychology*, *60*, 173–196.

Pauling, L., & Coryell, C. D. (1936). The magnetic properties and structure of hemoglobin, oxyhemoglobin and carbonmonoxyhemoglobin. *Proceedings of the National Academy of Sciences*, *22*(4), 210–216.

Pereira, A. C., Huddleston, D. E., Brickman, A. M., Sosunov, A. A., Hen, R., McKhann, G. M., … Small, S. A. (2007). An in vivo correlate of exercise-induced neurogenesis in the adult dentate gyrus. *Proceedings of the National Academy of Sciences*, *104*(13), 5638–5643.

Poduslo, J. F., & Curran, G. L. (1996). Permeability at the blood-brain and blood-nerve barriers of the neurotrophic factors: NGF, CNTF, NT-3, BDNF. *Molecular Brain Research*, *36*(2), 280–286.

Qi, Z., Wu, X., Wang, Z., Zhang, N., Dong, H., Yao, L., & Li, K. (2010). Impairment and compensation coexist in amnestic MCI default mode network. *Neuroimage*, *50*(1), 48–55.

Raichlen, D. A., Bharadwaj, P. K., Fitzhugh, M. C., Haws, K. A., Torre, G.-A., Trouard, T. P., & Alexander, G. E. (2016). Differences in resting state functional connectivity between young adult endurance athletes and healthy controls. *Frontiers in Human Neuroscience*, *10*.

Rasmussen, P., Brassard, P., Adser, H., Pedersen, M. V., Leick, L., Hart, E., … Pilegaard, H. (2009). Evidence for a release of brain-derived neurotrophic factor from the brain during exercise. *Experimental Physiology*, *94*(10), 1062–1069.

Raz, N., Lindenberger, U., Rodrigue, K. M., Kennedy, K. M., Head, D., Williamson, A., … Acker, J. D. (2005). Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. *Cerebral Cortex*, *15*(11), 1676–1689.

Rejeski, W. J., & Mihalko, S. L. (2001). Physical activity and quality of life in older adults. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *56*(suppl_2), 23–35.

Rowe, J. W., & Kahn, R. L. (2000). Successful aging and disease prevention. *Advances in Renal Replacement Therapy*, *7*(1), 70–77.

Ruscheweyh, R., Willemer, C., Krüger, K., Duning, T., Warnecke, T., Sommer, J., … others. (2011). Physical activity and memory functions: an interventional study. *Neurobiology of Aging*, *32*(7), 1304–1319.

Russo-Neustadt, A. A., Alejandre, H., Garcia, C., Ivy, A. S., & Chen, M. J. (2004). Hippocampal brain-derived neurotrophic factor expression following treatment with reboxetine, citalopram, and physical exercise. *Neuropsychopharmacology*, *29*(12), 2189.

Salmon, D. P., Butters, N., & Chan, A. S. (1999). The deterioration of semantic memory in Alzheimer's disease. *Canadian Journal of Experimental Psychology/Revue Canadienne de Psychologie Expérimentale*, *53*(1), 108.

Salthouse, T. A. (1996). The processing-speed theory of adult age differences in cognition. *Psychological Review*, *103*(3), 403.

Seals, D. R., Hagberg, J. M., Hurley, B. F., Ehsani, A. A., & Holloszy, J. O. (1984). Endurance training in older men and women. I. Cardiovascular responses to exercise. *Journal of Applied Physiology*, *57*(4), 1024–1029.

Seidenberg, M., Guidotti, L., Nielson, K. A., Woodard, J. L., Durgerian, S., Antuono, P., … Rao, S. M. (2009). Semantic memory activation in individuals at risk for developing Alzheimer disease. *Neurology*, *73*(8), 612–620.

Seidenberg, M., Guidotti, L., Nielson, K. A., Woodard, J. L., Durgerian, S., Zhang, Q., … Rao, S. M. (2009). Semantic knowledge for famous names in mild cognitive impairment. *Journal of the International Neuropsychological Society*, *15*(1), 9–18.

Seidenberg, M., Kay, C. D., Woodard, J. L., Nielson, K. A., Smith, J. C., Kandah, C., … others. (2013). Recognition of famous names predicts cognitive decline in healthy elders. *Neuropsychology*, *27*(3), 333.

Seifert, T., Brassard, P., Wissenberg, M., Rasmussen, P., Nordby, P., Stallknecht, B., … others. (2010). Endurance training enhances BDNF release from the human brain. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, *298*(2), R372–R377.

Smith, C. N., & Squire, L. R. (2009). Medial temporal lobe activity during retrieval of semantic memory is related to the age of the memory. *Journal of Neuroscience*, *29*(4), 930–938.

Smith, J. C., Nielson, K. A., Antuono, P., Lyons, J.-A., Hanson, R. J., Butts, A. M., … Verber, M. D. (2013). Semantic memory functional MRI and cognitive function after exercise intervention in mild cognitive impairment. *Journal of Alzheimer's Disease*, *37*(1), 197–215.

Smith, J. C., Nielson, K. A., Woodard, J. L., Seidenberg, M., Durgerian, S., Antuono, P., … Rao, S. M. (2011). Interactive effects of physical activity and APOE-ε4 on BOLD semantic memory activation in healthy elders. *Neuroimage*, *54*(1), 635–644.

Smith, J. C., Nielson, K. A., Woodard, J. L., Seidenberg, M., Verber, M. D., Durgerian, S., … Lancaster, M. A. (2011). Does physical activity influence semantic memory activation

in amnestic mild cognitive impairment? *Psychiatry Research: Neuroimaging*, *193*(1), 60–62.

Smith, J. C., Paulson, E. S., Cook, D. B., Verber, M. D., & Tian, Q. (2010). Detecting changes in human cerebral blood flow after acute exercise using arterial spin labeling: implications for fMRI. *Journal of Neuroscience Methods*, *191*(2), 258–262.

Smith, P. J., Blumenthal, J. A., Hoffman, B. M., Cooper, H., Strauman, T. A., Welsh-Bohmer, K., … Sherwood, A. (2010). Aerobic exercise and neurocognitive performance: a meta-analytic review of randomized controlled trials. *Psychosomatic Medicine*, *72*(3), 239.

Snider, W. D. (1994). Functions of the neurotrophins during nervous system development: what the knockouts are teaching us. *Cell*, *77*(5), 627–638.

Soler, R. M., Dolcet, X., Encinas, M., Egea, J., Bayascas, J. R., & Comella, J. X. (1999). Receptors of the glial cell line-derived neurotrophic factor family of neurotrophic factors signal cell survival through the phosphatidylinositol 3-kinase pathway in spinal cord motoneurons. *Journal of Neuroscience*, *19*(21), 9160–9169.

Spaan, P. E., Raaijmakers, J. G., & Jonker, C. (2005). Early assessment of dementia: the contribution of different memory components. *Neuropsychology*, *19*(5), 629.

Spirduso, W. W., & Cronin, D. L. (2001). Exercise dose–response effects on quality of life and independent living in older adults. *Medicine & Science in Sports & Exercise*. Retrieved from http://psycnet.apa.org/psycinfo/2001-01104-003

Story, M., Nanney, M. S., & Schwartz, M. B. (2009). Schools and obesity prevention: creating school environments and policies to promote healthy eating and physical activity. *The Milbank Quarterly*, *87*(1), 71–100.

Stummer, W., Weber, K., Tranmer, B., Baethmann, A., & Kempski, O. (1994). Reduced mortality and brain damage after locomotor activity in gerbil forebrain ischemia. *Stroke*, *25*(9), 1862–1869.

Stuss, D. T., Toth, J. P., Franchi, D., Alexander, M. P., Tipper, S., & Craik, F. I. (1999). Dissociation of attentional processes in patients with focal frontal and posterior lesions. *Neuropsychologia*, *37*(9), 1005–1027.

Sugarman, M. A., Woodard, J. L., Nielson, K. A., Seidenberg, M., Smith, J. C., Durgerian, S., & Rao, S. M. (2012). Functional magnetic resonance imaging of semantic memory as a presymptomatic biomarker of Alzheimer's disease risk. *Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease*, *1822*(3), 442–456.

Supekar, K., Menon, V., Rubin, D., Musen, M., & Greicius, M. D. (2008). Network analysis of intrinsic functional brain connectivity in Alzheimer's disease. *PLoS Computational Biology*, *4*(6), e1000100.

T O'Brien, J., Erkinjuntti, T., Reisberg, B., Roman, G., Sawada, T., Pantoni, L., … others. (2003). Vascular cognitive impairment. *The Lancet Neurology*, *2*(2), 89–98.

Thomas, S. N., Schroeder, T., Secher, N. H., & Mitchell, J. H. (1989). Cerebral blood flow during submaximal and maximal dynamic exercise in humans. *Journal of Applied Physiology*, *67*(2), 744–748.

Thulborn, K. R., Waterton, J. C., Matthews, P. M., & Radda, G. K. (1982). Oxygenation dependence of the transverse relaxation time of water protons in whole blood at high field. *Biochimica et Biophysica Acta (BBA)-General Subjects*, *714*(2), 265–270.

Trejo, J. L., Carro, E., & Torres-Aleman, I. (2001). Circulating insulin-like growth factor I mediates exercise-induced increases in the number of new neurons in the adult hippocampus. *Journal of Neuroscience*, *21*(5), 1628–1634.

Tulving, E., & others. (1972). Episodic and semantic memory. *Organization of Memory*, *1*, 381–403.

Van Praag, H., Shubert, T., Zhao, C., & Gage, F. H. (2005). Exercise enhances learning and hippocampal neurogenesis in aged mice. *Journal of Neuroscience*, *25*(38), 8680–8685.

Vance, D. E., Wadley, V. G., Ball, K. K., Roenker, D. L., & Rizzo, M. (2005). The effects of physical activity and sedentary behavior on cognitive health in older adults. *Journal of Aging and Physical Activity*, *13*(3), 294–313.

Vaynman, S., & Gomez-Pinilla, F. (2006). Revenge of the "sit": how lifestyle impacts neuronal and cognitive health through molecular systems that interface energy metabolism with neuronal plasticity. *Journal of Neuroscience Research*, *84*(4), 699–715.

Vaynman, S., Ying, Z., & Gomez-Pinilla, F. (2004). Hippocampal BDNF mediates the efficacy of exercise on synaptic plasticity and cognition. *European Journal of Neuroscience*, *20*(10), 2580–2590.

Vega, S. R., Strüder, H. K., Wahrmann, B. V., Schmidt, A., Bloch, W., & Hollmann, W. (2006). Acute BDNF and cortisol response to low intensity exercise and following ramp incremental exercise to exhaustion in humans. *Brain Research*, *1121*(1), 59–65.

Wang, L., Negreira, A., LaViolette, P., Bakkour, A., Sperling, R. A., & Dickerson, B. C. (2010). Intrinsic interhemispheric hippocampal functional connectivity predicts individual differences in memory performance ability. *Hippocampus*, *20*(3), 345–351.

Warburton, D. E., Nicol, C. W., & Bredin, S. S. (2006). Health benefits of physical activity: the evidence. *Canadian Medical Association Journal*, *174*(6), 801–809.

Weinberg, L., Hasni, A., Shinohara, M., & Duarte, A. (2014). A single bout of resistance exercise can enhance episodic memory performance. *Acta Psychologica*, *153*, 13–19.

Weng, T. B., Pierce, G. L., Darling, W. G., Falk, D., Magnotta, V. A., & Voss, M. W. (2017). The Acute Effects of Aerobic Exercise on the Functional Connectivity of Human Brain Networks. *Brain Plasticity*, *2*(2), 171–190.

Westmacott, R., & Moscovitch, M. (2003). The contribution of autobiographical significance to semantic memory. *Memory & Cognition*, *31*(5), 761–774.

Winter, B., Breitenstein, C., Mooren, F. C., Voelker, K., Fobker, M., Lechtermann, A., … others. (2007). High impact running improves learning. *Neurobiology of Learning and Memory*, *87*(4), 597–609.

Woo, J. (2000). Relationships among diet, physical activity and other lifestyle factors and debilitating diseases in the elderly. *European Journal of Clinical Nutrition*, *54*(S3), S143.

Woodard, J. L., Seidenberg, M., Nielson, K. A., Antuono, P., Guidotti, L., Durgerian, S., … others. (2009). Semantic memory activation in amnestic mild cognitive impairment. *Brain*, *132*(8), 2068–2078.

Woodard, J. L., Seidenberg, M., Nielson, K. A., Miller, S. K., Franczak, M., Antuono, P., … Rao, S. M. (2007). Temporally graded activation of neocortical regions in response to memories of different ages. *Journal of Cognitive Neuroscience*, *19*(7), 1113–1124.

Zhang, D., & Raichle, M. E. (2010). Disease and the brain's dark energy. *Nature Reviews Neurology*, *6*(1), 15–28.

Zhou, Y., Dougherty, J. H., Hubner, K. F., Bai, B., Cannon, R. L., & Hutson, R. K. (2008). Abnormal connectivity in the posterior cingulate and hippocampus in early Alzheimer's disease and mild cognitive impairment. *Alzheimer's & Dementia*, *4*(4), 265–270.