THE ASSOCIATION OF PHYSICAL ACTIVITY AND PHYSICAL FITNESS WITH FUNCTIONAL CONNECTIVITY, EFFICIENCY, AND COGNITIVE FUNCTION IN OLDER ADULTS

By Marissa A. Gogniat, M.S.

University of Georgia

(Under the Direction of L. Stephen Miller)

ABSTRACT

The number of older adults in the United States is growing at an unprecedented rate which places a significant burden on the healthcare system. Therefore, it is important to study health and wellness factors that may provide neuroprotection for the brain in the aging process. Exercise interventions and physical activity have been shown to positively impact cognition in older adults but the mechanisms underlying this neuroprotection are still not fully understood. The present study examined the impacts of physical activity and fitness on the association between functional connectivity and cognitive functioning in older adults using seed-to-voxel, ROI-to-ROI anti-correlated networks, and graph theory analyses. It was hypothesized that physical activity and fitness would moderate the associations between cognitive functioning and key brain network functional connectivity and network anti-correlations. Results suggest that greater physical activity in later life is associated with greater functional connectivity and physical activity and fitness may serve as protective factors for the aging brain. Implications and future directions are discussed.

INDEX WORDS: aging, physical activity, fitness, functional connectivity

THE ASSOCIATION OF PHYSICAL ACTIVITY AND PHYSICAL FITNESS WITH FUNCTIONAL CONNECTIVITY, EFFICIENCY, AND COGNITIVE FUNCTION IN OLDER ADULTS

By Marissa A. Gogniat

BS, Emory University, 2015

BA, Emory University, 2015

MS, University of Georgia, 2019

A Dissertation Submitted to the Graduate Faculty of The University of Georgia in Partial Fulfillment of the Requirements for the Degree

DOCTOR OF PHILOSOPHY

ATHENS, GEORGIA

2021

THE ASSOCIATION OF PHYSICAL ACTIVITY AND PHYSICAL FITNESS WITH FUNCTIONAL CONNECTIVITY, EFFICIENCY, AND COGNITIVE FUNCTION IN OLDER ADULTS

by

MARISSA A. GOGNIAT

Major Professor: L. Stephen Miller
Committee: Lawrence Sweet
Ellen Evans

Electronic Version Approved:

Ron Walcott
Vice Provost for Graduate Education and Dean of the Graduate School
The University of Georgia
August 2021

ACKNOWLEDGEMENTS

It truly "takes a village" to complete a PhD in Clinical Psychology, and I have so much gratitude for the innumerable people who are part of my village.

Many thanks to my UGA masters, research comprehensive exam, and dissertation committee (Steve, Larry Sweet, Ellen Evans), who have taken time to mentor and shape me as a researcher. I am very grateful to my mentor, Dr. Steve Miller, who took a chance on a 22-year-old undergrad from an animal vision lab and gave me the skills and confidence to be successful. There isn't enough room in the acknowledgments to note all of the ways that he advocated for my success as a researcher, clinician, and person. Many thanks to Kim Mason, who was my mom away from home and lent so much time, energy, and laughs to make me a competent neuroimager. Many thanks to my labmates Cutter and Catherine, who I consider my first unofficial mentors and now friends. Many thanks to my labmate Kharine Jean, who taught me the true meaning of giving back. I'll never be able to articulate my thanks to my labmate Talia Robinson, whose true and unwavering friendship sustained me through the highs and lows of the past 6 years. To our great UGA Clinical Psych program cohort (Tony, Grace, Chelsea, Brandon, Joanie), each one of you at some point helped me out (and some of you a lot!) and I feel lucky to call you friends.

To my parents, who instilled in me that nothing worth having ever comes easy and taught me the value of education. To my sisters, aunts, uncles, cousins, grandpa, and in-laws, who have always been there to cheer me on. To my Uncle Paul, who always asks about what I have been working on and provides invaluable advice and encouragement. To both of my late grandmothers, who inspired and encouraged me by their example and supported me through the beginning of this journey. You are so greatly missed. To my friends from many different phases of life who have provided encouragement, an ear to listen, or understanding. Last and certainly not least, the most gratitude to my husband, who cried happy tears when I got the offer to join the program at UGA 7 years ago. I have endless gratitude for all of the sacrifices you have made and all of the love and encouragement you have provided to ensure my success.

TABLE OF CONTENTS

LIST OF TABLES

Page

LIST OF FIGURES

Page

CHAPTER 1

INTRODUCTION

The number of older adults in the United States is growing at an unprecedented rate. Current statistics predict that the population of older adults will nearly double in size in the next 40 years (Mather, Jacobsen, & Pollard, 2015; US Census Bureau, 2018). This places a significant burden on the healthcare system, as older adults are at greater risk for cognitive decline (Salthouse, 2003; Salthouse, 2010), physical disability (Heikkinen, 2006; Manini, 2011), and social isolation (Shankar, McMunn, Banks, & Steptoe, 2011). Therefore, it is important to study lifestyle factors that may provide neuroprotection for the brain in the aging process. Exercise interventions and physical activity have been shown to positively impact cognition in older adults (Colcombe & Kramer, 2003; Kelly, Loughrey, Lawlor, Robertson, Walsh & Brennan, 2014; Northey et al., 2018), but the mechanisms underlying this neuroprotection still are not fully understood. There is a need to fill the gap in this literature on our understanding of the connection between physical activity and positive impacts on cognition in aging. Understanding these mechanisms can inform future intervention work in this area by providing a reliable indicator of change. The present study aims to add to this literature by examining the impacts of physical activity and fitness on the association between functional connectivity in the brain of healthy older adults and cognitive performance. In addition, the present study seeks to examine the associations between physical activity and fitness and the efficiency of these functional connections in the brains in healthy older adults.

Cognition and Aging

Theories. The normal aging process is characterized by a documented decline in some cognitive domains including processing speed, reasoning, and the ability to acquire and retrieve memories, while other cognitive domains such as crystallized intelligence remain stable over time (Salthouse, 2010; Harada, Natelson Love, & Triebel, 2014; Murman, 2015). This pattern of decline mirrors the retrogenesis hypothesis of aging, which posits that the areas of the brain that were last to fully develop are the first to experience decline because the myelination in those areas has been less reinforced (Huttenlocher, & Dabholkar, 1997; Stricker et al., 2009; Brickman et al., 2012). This theory links changes in cognition seen in aging (e.g., declines in working memory, reasoning) with structural changes in the brain. However, there is great individual variability in cognitive decline, and common sources of pathology (e.g., amyloid, neurofibrillary tangles, macroscopic infarcts, and neocortical Lewy bodies) have been shown to explain approximately 41% of the variance in cognitive decline in aging, leaving a large percentage of factors unaccounted for (Boyle et al., 2013). The theory of cognitive reserve attempts to explain this phenomenon by positing that the brain can tolerate age-related changes in individuals by using pre-existing cognitive processing approaches or by employing compensatory approaches (Stern, 2003; Stern, 2012). Several factors have been shown to positively impact an individual's cognitive reserve including education, occupational complexity, activity level (i.e., activities that challenge physical, social, and cognitive abilities), and socioeconomic status (Stern, 2012). In a similar vein, the Scaffolding Theory of Aging and Cognition (STAC) is another theory that has attempted to explain the variability in cognitive function in older adulthood (Park

& Reuter-Lorenz, 2009). This theory posits that the aging brain is negatively impacted by both changes in brain structure and function, and the brain must employ compensatory scaffolding to combat this degradation and preserve cognitive function. Studies have shown that older adults employ this compensatory scaffolding by recruiting additional brain regions to solve cognitive tasks as compared to younger adults (Langenecker, Nielson, & Rao, 2004; Madden et al., 2007; Dumas, 2015). In the revised version of the STAC model (STAC-r; Reuter-Lorenz & Park, 2014) compensatory scaffolding is thought to be enhanced by lifestyle factors such as physical activity and new learning. All of these models attempt to explain how lifestyle factors impact cognitive outcomes in the aging process.

Executive Function and Working Memory. Executive functions describe a family of top-down processes that include planning, inhibition, and cognitive flexibility (Diamond, 2013). Working memory describes the process of actively maintaining and manipulating information over short periods of time, thus employing attentional control (Miyake & Shah, 1999; McCabe et al., 2010). While distinctions are often made between executive functions and working memory in both clinical and research settings, executive functions and working memory share some similar neuroanatomical overlap, with executive functions typically being thought to be associated with frontal areas (e.g., the prefrontal cortex) which corresponds with some areas implicated in working memory performance in older adults (Otero & Barker, 2014; Eriksson et al., 2015). These cognitive domains have been shown to be negatively impacted by aging (Raz & Rodrigue, 2006; Kirova, Bays, & Lagalwar, 2015; Murman, 2015), as these areas are some of the last to be fully formed and connected in development and are thus often the first to be impacted in the aging process (Arain et al., 2013). This can be problematic for older adults, as executive abilities and working memory have been shown to be related to functional ability and independence in older adulthood (Jefferson, Paul, Ozonoff, & Cohen, 2006; Razani et al., 2007; Vaughan & Giovanello, 2010). Therefore, there is a need to examine lifestyle factors that may prevent or buffer the decline of executive function and working memory abilities in older adulthood in order to preserve functional ability and independence.

Brain Mechanisms in Cognitive Decline. There are many changes in the structure and function of the aging brain that are linked to cognitive decline specifically in executive functioning and working memory. It has long been posited that large, macroscopic losses in brain volume in the aging process are likely to be representative of neurodegenerative processes (e.g., Alzheimer's Disease, Frontotemporal Dementia) due to changes in and loss of dendritic arbors, spines, and synapses (Harada, Natelson Love, & Triebel, 2013; Kolb & Whishaw, 1998; Peters, 2006), and thus have a largely negative impact on cognition (Buckner, 2004; Peters, 2006; Raji et al., 2009). However, there are mixed findings on whether smaller decreases in brain volume in healthy older adults are linked to changes in cognitive functioning at a level we can currently detect or is meaningful to functional ability and independence (Kaup, Mirzakhanian, Jeste, & Eyler, 2011; Gogniat et al., 2018). In addition to large, volumetric changes resulting in cognitive decline in aging, the preservation of the microstructure properties (e.g., fractional anisotropy, radial diffusivity) of the white matter tracts in the frontal lobes as measured by diffusion tensor imaging (DTI) has been shown to be related to better executive function and processing speed (Grieve et al., 2007; Jacobs et al., 2013; Daselaar et al., 2015). Additional changes in white matter that occur with aging are white matter lesions (DeCarli et al., 2005; Raz & Rodrigue, 2006), which have also been linked to worse executive function (Bombois et al., 2007; Debette et al., 2007) and working memory performance (Vannorsdall, T.D., Waldstein, S.R., Kraut, M., Pearlson, G.D., & Schretlen, 2009) in older adults.

Additional mechanisms that are thought to impact executive function and working memory in aging are functional brain changes. In general, there is increased activation in the aging brain (i.e., typically in the prefrontal cortex) during working memory and executive function tasks (Spreng, Wojtowicz, & Grady, 2010; Suzuki et al., 2018). As mentioned previously when discussing STAC, the aging brain often employs compensatory strategies such as the recruitment of additional brain regions (e.g., parietal and prefrontal) to perform cognitive tasks (Langenecker, Nielson, & Rao, 2004; Madden et al., 2007; Dumas, 2015). In addition, the aging brain is more likely to recruit bilaterally when completing working memory tasks as compared to younger adults who only need to recruit laterally (Cappell, Gmeindl, & Reuter-Lorenz, 2010). These studies demonstrate that there are functional changes in the aging brain that require more brain resources (i.e., increased activation) to complete working memory and executive functioning tasks. In addition to changes in activation, changes in the functional connectivity of the aging brain have been shown to impact executive function and working memory. The aging brain has been shown to be less functionally connected in several brain networks including the default mode network (DMN) an area thought to be housed in the ventromedial prefrontal cortex and posterior cingulate cortex. The DMN is traditionally viewed as a network that is active at rest and inactive during external cognitive tasks

(Raichle et al., 2001; Uddin, Clare Kelly, Biswal, Xavier Castellanos, & Milham, 2009; Ferreira et al., 2016). The dorsal attention network (DAN), a network based in the intraparietal sulcus and the frontal eye fields, is active during tasks that require voluntary and sustained attention is also thought to be negatively impacted by aging (Fox, Corbetta, Snyder, Vincent, & Raichle, 2006; Tomasi & Volkow, 2012). Greater functional connectivity in the DMN and in the DAN are related to greater working memory and executive function in older adults (Andrews-Hanna et al., 2007; Damoiseaux et al. 2008; Majerus, Péters, Bouffier, Cowan, & Phillips, 2018). In addition, aging impacts the strength of brain network anticorrelations, which are essentially networks that are strongly negatively correlated, indicating that they have theoretically opposed functional roles (Fox et al., 2005; Fox, Zhang, Snyder, & Raichle, 2009). An example of anticorrelated networks are the DMN and DAN, whose negative correlations have been shown to weaken with age (Wu et al., 2011; Ferreira et al., 2016). The strength of anticorrelations between the DMN and DAN are related to executive function and working memory performance across the lifespan (Hampson, Driesen, Roth, Gore, & Constable, 2010; Anticevic et al., 2012; Franzmeier et al., 2017). Finally, there are alterations in global efficiency (i.e., the communication between regions that are not neighboring) and local efficiency (i.e., the communication between regions that are neighboring) of the brain that occur with aging. Compared to younger adults, older adults are more likely to have greater global efficiency and lower local efficiency because they need to recruit additional networks to compensate for alterations in connectivity (Cao et al., 2014; Song et al., 2014; Iordan et al., 2018). These alterations in the structure and function of the aging brain have an impact on working memory and executive function. Therefore, there is a need to examine lifestyle factors that may buffer the impacts of structural and functional change in the aging brain on working memory and executive function.

Physical Activity and Aging

Effect on Cognition. The effect of exercise interventions on cognitive function in older adults has been a burgeoning area of research. Meta-analyses have examined the impact of exercise interventions on cognition for healthy older adults (Colcombe & Kramer, 2003; Kelly et al., 2014; Northey et al., 2018; Sanders, Hortobagyi, la Bastide-van Gemert, van der Zee, & van Heuvelen, 2019) and older adults with mild cognitive impairment (MCI; Gates, Singh, Sachdev, & Valenzuela, 2013; Song, Yu, Li, & Lei, 2018; Wang, Yu, Wang, Tan, Meng, & Tan, 2014) and found that these interventions result in significant improvements in cognitive function. In particular, the improvements in cognitive function are often seen in executive function and working memory abilities (Colcombe & Kramer, 2003; Kelly et al., 2014; Northey et al., 2018; Sanders et al., 2019). However, exercise intervention programs require a large commitment on behalf of the older adult, and there are many barriers to participation (Bethancourt, Rosenberg, Beatty, & Arterburn, 2014). Consequently, there is interest in how current physical activity level and physical fitness are related to cognitive function in older adults.

Cross-Sectional Studies. Several studies have examined the impact of self-reported or currently measured physical activity on cognition in older adults. These studies have found positive associations between self-reported level of physical activity on questionnaires (Weuve et al., 2004; Frith, & Loprinzi, 2017; Jeong & Jang, 2017) and cognitive performance. However, self-report measures of physical activity have the potential to introduce bias in recall and reporting of physical activity (Rzewnicki, Auweele, & De Bourdeaudhuij, 2003). In addition, collateral report and performance-based measures of functional ability in older adulthood have been shown to more strongly relate to cognitive performance than self-report, indicating the importance of objective measures of ability in older adulthood (Mitchell & Miller, 2008). Recent studies have employed accelerometry and actigraphy to get an objective measure of older adults' physical activity and have found associations between physical activity level and cognitive function (Barnes et al., 2008; Kerr et al., 2013; Iso-Markku et al., 2018). Using objective devices to record the activity level of older adults has allowed for aspects of physical activity to be examined (e.g., intensity of activity, number of steps, distance traveled, etc.). Some studies have found that the intensity of physical activity has the greatest association to current cognitive ability for older adults (Angevaren et al., 2007; Brown et al., 2012; Kerr et al., 2013; Zhu et al., 2015) while others have posited that simply moving around throughout the day (i.e., number of steps) is significantly related to cognition and specifically executive function ability (Barnes et al., 2008; Buchman, Wilson, & Bennett, 2008). Additionally, physical fitness level measured via performance-based measures has been shown to be related to executive function performance in older adults (Churchill et al., 2002; McGough et al., 2011; Ferreira et al., 2015), often showing greater associations than physical activity level because it is a more specific measure of cardiorespiratory fitness (Sherwood et al., 2019). The use of performance-based measures to examine physical activity and physical fitness level in older adults allows for more accurate and specific information to be examined in its association with cognitive function ability.

Mechanisms of Action. There are several proposed mechanisms by which physical activity and exercise interventions may positively impact cognitive function in the aging brain. These include physical activity and exercise interventions increasing the production of brain derived neurotrophic factor (BDNF), which is neuroprotective for neuronal tissues (Erickson et al., 2011; Otsuka et al., 2016). In addition, increases in physical activity result in increased cerebral perfusion and blood flow (Wolters et al., 2017; Alfini, Weiss, Nielson, Verber, & Smith, 2019), which provides oxygen and metabolites to neural tissue. Other peripheral regulatory mechanisms that support neuronal brain function (e.g., acetylcholine, estrogen, corticosteroids, IGF-1) have also been shown to be related to increases in physical activity (Gligoroska, & Manchevska, 2012; Gelfo, Mandolesi, Serra, Sorrentino, & Caltagirone, 2018). In conjunction with these molecular mechanisms of change following physical activity and exercise interventions, changes in the structure (e.g., white matter microstructure, volume, white matter lesions) and function of the brain (e.g., functional connectivity, efficiency) following physical activity and exercise interventions have also been proposed as the mechanisms by which physical activity results in improved cognitive function in aging (Colcombe et al., 2006; Voss et al., 2010; Nishiguchi et al., 2015; Oberlin et al., 2015; Torres, Strack, Fernandez, Tumey, & Hitchcock, 2015; Voss et al., 2016).

Physical Activity, Functional Connectivity, and Efficiency. A relatively new and understudied area is how physical activity and exercise interventions may impact the functional connectivity of the aging brain. A recent review (Stillman, Donofry, & Erickson, 2019) examined the current state of the literature concerning the associations between physical activity and functional connectivity for older adults and found relatively few studies on this topic. There are several cross-sectional studies which have examined aspects of these associations with a particular focus on the brain networks that are most susceptible to aging. Boraxbekk and colleagues (2016) found that self-reported physical activity of the previous decade was related to DMN functional connectivity in older adults. Using objectively measured physical activity, Veldsman and colleagues (2017) showed that physical activity level was related to DAN functional connectivity in older adults with a stroke history. Others have examined physical fitness and its association with functional connectivity in older adults. Voss and colleagues (2010) showed that functional connectivity in the DMN (i.e., both specific and global) mediated the association between aerobic fitness and executive function in older adults, indicating that greater fitness may preserve the functional connections in the DMN. However, when comparing physical activity and physical fitness, Voss and colleagues (2016) showed that there was an association between physical fitness, not current physical activity level, and executive function for older adults that was mediated by DMN and DAN functional connectivity. Finally, the literature examining the associations between physical activity and global and local efficiency is extremely sparse. Kawagoe, Onoda, and Yamaguchi (2017) examined the associations between executive function, global efficiency, local efficiency, and physical fitness in older adults. They found that global efficiency was positively associated with executive function and physical fitness, while local efficiency was negatively associated with executive function and physical fitness. The authors posited that while the findings for global efficiency were intuitive, their hypothesis for why local efficiency was negatively related to executive function and physical fitness was because of the tendency of high functioning older adults to have connections across a broader range of brain areas at the expense of local efficiency (i.e., a compensatory mechanism). In addition, a recent study by Yue and colleagues (2020) examined the impact of Tai Chi practice on network efficiency in Chinese female older adults and found no difference in global and local efficiency between those that engaged in Tai Chi and those that walked, although local efficiency attributes expressed positive trends in favor of Tai Chi practice. While these studies give us some insight into the associations between physical activity, physical fitness, executive function, and measures of functional connectivity and efficiency, this area is ripe for exploration using multiple methods of assessment, the examination of anti-correlations, and a greater exploration of global and local efficiency of networks susceptible to the effects of aging.

Functional Connectivity and Graph Theory

Definitions. Resting state functional connectivity measures the temporal dependency of neural activity of regions and networks in the brain that occurs while someone is at rest. Like fMRI, resting state functional connectivity captures changes in BOLD activation over time. Our brains are composed of networks that may be functionally and anatomically separate but are constantly sharing information with each other, which can provide us with detailed information on the functional consequences of alteration in this communication (Aertsen, Gerstein, Habib& Palm, 1989; Van Den Heuvel & Pol, 2010). In addition, functional connectivity gives us information that is captured in a relatively short amount of time on the temporal activity of the brain that is independent of any task.

Graph theory posits that the brain is made up of a complex series of nodes (e.g., anatomical elements) and edges (e.g., relationships between nodes). This methodology models the overall connectivity of the brain while characterizing the topological organization (Bullmore & Sporns, 2009; Wang, Zu, & He, 2010). Graph theory methodology can be utilized to determine global and local efficiency of the brain. Local efficiency describes "small-world" organization, meaning a node is highly interconnected (i.e., has many edges) with neighboring nodes, and therefore there is a very short average travel distance between the nodes of the network (Van Den Heuvel & Pol, 2010). The local efficiency of a network is calculated as the average global efficiency across all nodes in the local subgraph of node *n* (the subgraph consisting only of nodes neighboring node *n*) and the equation for local efficiency of the network is as follows, where |G| represents the number of nodes in graph G (Whitfield-Gabrieli, & Nieto-Castanon, 2012): $E^{Local}(\mathrm{G}) = \frac{1}{|G|} * \sum_{n}^{E_{local}}(G).$ On the other hand, the global efficiency of a network is described as a node that is highly interconnected to nodes that are not neighboring but are further away in distance and thus more globally connected (Latora & Marchiori, 2001; Wang, Zu, & He, 2010). The global efficiency of a network is calculated as the average inverse shortest path distance from node *n* to all other nodes in the graph. This is calculated as follows (Whitfield-Gabrieli, & Nieto-Castanon, 2012): $E^{Global}(\mathrm{G}) = \frac{1}{|G|} * \sum_{n}^{E_{global}}(G).$ These measures help us to operationalize the connectivity patterns among brain regions and quantitatively analyze this organization (Wang et al., 2010). The organization of the human brain is such that both high local efficiency and high global efficiency are optimized, and alterations in this optimization can tell us important information about how lifestyle may influence the efficiency of the brain.

Current Study

The proposed study expanded upon the limited current state of the literature in this area to explore the impact of physical activity and physical fitness on functional connectivity and cognition in older adults and has several aims. The first aim was to examine whether executive function/working memory performance was related to DMN and DAN functional connectivity in healthy older adults, and whether physical activity and physical fitness moderated this association. We hypothesized that better executive function and working memory performance would be related to greater DMN and DAN connectivity. We also hypothesized that physical activity level and physical fitness would moderate the association between both executive function/working memory and DMN/DAN functional connectivity such that higher levels of physical activity/fitness would buffer the association between lower executive function/working memory and DAN/DMN connectivity. The second aim was to evaluate whether executive function/working memory performance was related to DMN and DAN anti-correlations in healthy older adults, and whether physical activity/fitness moderate this association. We hypothesized that physical activity and physical fitness would moderate the association between executive function/working memory and DMN and DAN anticorrelations such that higher levels of physical activity and physical fitness would buffer the association between lower DMN and DAN anti-correlations and executive function/working memory. The final aim was to evaluate whether physical activity and physical fitness level in healthy older results was related to whole brain local and global efficiency. We hypothesized that greater physical activity and physical fitness would be significantly associated with both greater global efficiency and greater local efficiency, as evidence indicates that there is greater whole brain connectivity and lower local connectivity in aging (Cao et al., 2014; Song et al., 2014; Iordan et al., 2018).

CHAPTER 2

METHODS

Participants

Participants were a total of 51 community-dwelling older adults, aged 65-85 years, from the surrounding community of a southeastern college town. These participants were recruited over a four-year period. Some participants' data were already acquired as part of a previously completed pilot intervention study, but for the purpose of the present study, only data from their baseline assessments (pre-intervention) was used. All participants completed sessions that included neuropsychological testing, physical activity and fitness measurements, and magnetic resonance imaging (MRI). Participants were eligible if they had no self-reported major neurological (e.g., Alzheimer's, Parkinson's) or psychiatric disorders, were right-handed, Native English speakers, and were compatible with the MRI environment (i.e., no metal implants, no recent surgeries, etc). Participants were excluded if their cognitive functioning was below mild cognitive impairment (MCI) as indicated by their performance on the MMSE (totals score < 24). Informed consent was obtained from all participants and the Declaration of Helsinki was followed.

Physical Activity and Fitness

Physical Activity. Physical activity was measured using NL-1000 Accelerometers (New Lifestyles, Inc.; Lee's Summit, Missouri, USA). This measures physical activity intensity, number of steps, and distance covered using a piezoelectric strain gauge. Participants in this study wore the NL-1000 on their waist for 7 days. For adults, activity intensity levels of 1 to 3 capture light activity (e.g., analogous to typical easy walking), levels 4 to 6 indicate moderate activity (e.g., analogous to typical jogging levels of activity), and levels 7 to 9 are categorized as vigorous activity (e.g., analogous to sprinting activity) as captured by changes to the piezoelectric strain gauge. Moderate/Vigorous Physical Activity (MVPA) is a measurement of the time spent in moderate to vigorous activity and is captured when the device is set to record activity between levels 4 to 9 (NL-1000 Activity Monitor: user's guide & record book, 2005). Time spent in MVPA was broken down into 24-hour increments and the amount of time spent in MVPA was displayed in days up to day 7 on the device. MVPA has been shown to be both valid and reliable in measuring physical activity level in children and adults (Ayabe et al., 2006; McClain & Tudor-Locke, 2009). These settings were used in the current study. In the current study, MVPA was calculated as the average time in seconds per day spent in moderate to vigorous physical activity over the span of seven days using the following equation: Average MVPA = [(Total Time MVPA Day 1 + Total Time MVPA Day 2 + Total Time MVPA Day 3 + Total Time MVPA Day 4 + Total Time MVPA Day 5 + Total Time MVPA Day 6 + Total Time MVPA Day 7)/7]. In addition, the average number of steps taken per day over the span of seven days was calculated as follows: Average Steps = [(Total Steps Day 1 + Total Steps Day 2 + Total Steps Day 3 + Total Steps Day 4 + Total Steps Day 5 + Total Steps Day 6 + Total Steps Day 7)/7]. Accelerometry data was obtained from 47 participants.

Physical Fitness. Physical fitness will be assessed by a 6-minute walk test (6MWT) using the protocol described by Peeters and Mets (1996). The walking course took place in building hallways with predetermined and measured distances prior to each session.

Distance travelled along the course was recorded. Participants were instructed to walk as quickly as they could and cover the most distance over a 6-minute time period. Distance covered over the time period was measured in meters. Participants were instructed to wear comfortable clothing and shoes and to take breaks as necessary. The 6MWT has been shown to be reliable and valid in discriminating physical capacity and fitness in older adults (Bautmans, Lambert, & Mets, 2004; Mangan & Judge, 1994; Sperandio et al., 2015), as performance has been shown to have convergent validity with treadmill testing (Rikli & Jones, 1998) which is a common way to determine cardiorespiratory fitness level (Huggett, Connelly, & Overend, 2005). 6MWT data was obtained from 51 participants.

Cognitive Measures

Executive Function. Each participant received neuropsychological testing by a trained graduate student. All participants were administered the Delis-Kaplan Executive Function System (DKEFS) Color-Word Interference Test, the DKEFS Verbal Fluency Test, and the DKEFS Trail Making Test, which are subtests of the full DKEFS battery. The DKEFS Trail-making Test, Verbal Fluency, and Color Word Interference were chosen because they have good psychometric properties, measure non-verbal and verbal executive function, and have relatively brief administration times (Delis et al., 2004). For the Trail Making Test, a scaled score will be calculated for Condition 4: Number-Letter Switching, which measures the ability to set-shift. For Verbal Fluency, a scaled score for Category Switching will be calculated, which measures the ability to generate words that fall under categories while being able to set-shift. For the Color-Word Inference Test, a scaled score will be calculated for Condition 4: Inhibition/Switching, which measures verbal inhibition and set-shifting (D-KEFS; Delis, Kaplan, & Kramer, 2001). All scaled scores were then averaged together for each participant to create an executive function composite specific to set-shifting. In order to determine whether these three subtests were correlated with each other and were thus measuring similar constructs, a Cronbach's alpha based on standardized items (Bland & Altman, 1997) was calculated (α=.607) indicating an acceptable fit for a small number of items (Hinton, Brownlow, McMurray, & Cozens, 2004).

Working memory. Working memory was measured by the scaled scores from the Letter-Number Sequencing subtest of the Wechsler Adult Intelligence Scales, 4th Edition (WAIS-IV) and Symbol Span subtest scaled scores from the Wechsler Memory Scales, 4th Edition (WMS-IV) for each participant (Wechsler, 2008; Wechsler, 2009). The Letter-Number Sequencing subtest assesses working memory by requiring the participant to reorder verbally presented strings of numbers and letters in consecutive order that increase in span with successful completions. The Symbol Span subtest assesses working memory by requiring participants to remember visually presented symbols in order that increase in number with successful completions. These complex span tasks that require storage and processing are commonly used to assess working memory (Conway et al., 2005). Scaled scores for each participant were then averaged together to create a working memory composite score. Cronbach's alpha (α=.607) based on standardized items indicated an acceptable fit.

Imaging Acquisition

Brain images were acquired using a General Electric (GE; Waukesha, WI) 3 T Signa HDx MRI system. A high-resolution 3D T1-weighted fast spoiled gradient recall echo sequence was used to collect structural scans (TR = 7.5 ms; TE = < 5ms;

FOV = 256 × 256 mm matrix; flip angle = 20°; slice thickness = 1.2 mm; 154 axial slices) with an acquisition time of 6 minutes and 20 seconds. This protocol collected 176 images.

Resting state functional scans were aligned to each participant's anterior commissure-posterior commissure (AC-PC) line, collected axially, and used a T2*-weighted single shot EPI sequence (TR = 5000 ms; TE = 25 ms; 90° RF pulse; acquisition matrix = 128 × 128; FOV = 220 × 220 mm; in-plane resolution = 220/128 mm; slice thickness = 2 mm; 60 interleaved axial slices). Total acquisition time was 9 minutes and 25 seconds. 108 volumes were acquired.

Magnitude and phase images were also acquired, lasting 1 minute and 40 seconds each, for fieldmap-based unwarping (TR = 700 ms; TE = 5.0/7.2 ms; FOV = 220 × 220 mm matrix; flip angle = 30°; slice thickness = 2 mm; 60 interleaved slices).

Imaging Processing

The resting state functional scans were pre-processed using the default pre-processing pipeline in the CONN toolbox from the Neuroimaging Tools & Resources Collaboratory (v.18.b; www.nitrc.org/projects/conn; Whitfield-Gabrieli & Nieto-Castanon, 2012). This toolbox is an open source software that allows for the analysis of functional connectivity using resting state data. CONN's default pre-processing pipeline includes realigning and unwarping the data, centering the coordinates, applying a slice-time correction, outlier detection (using ART-based identification of outlier scans for scrubbing; www.nitric.org/projects/artifact_detect), direct functional and structural segmentation and normalization (using simultaneous Grey Matter/White Matter/CSF segmentation and MNI normalization), and functional smoothing. In addition, functional scans were denoised in CONN to remove physiological effect, subject movement, and other confounding effects from the BOLD signal. Within the CONN Toolbox, cortical and subcortical ROIs were defined by the Harvard-Oxford atlas (Frazier et al., 2005; Desikan et al., 2006; Makris et al., 2006; Goldstein et al., 2007) and cerebellar parcellations were based on the Automated Anatomical Labelling (AAL) Atlas (Tzourio-Mazoyer et al., 2002). Labelled networks within the CONN Toolbox including the DMN and DAN were derived from an independent component analysis using 497 participants from the Human Connectome Project (Van Essen et al., 2013).

Seed-to-voxel analyses were conducted *a priori* to examine the level of functional connectivity between the DAN/DMN and every voxel in the brain, which produces seed-based correlation (SBC) maps for each participant. ROIs/seeds were defined by coordinates provided by the CONN toolbox. SBC maps contain Fisher r to z transformed bivariate correlation coefficients between each seed/ROI BOLD timeseries (averaged across all voxels within an ROI) and an individual voxel BOLD timeseries. Group summary maps of SBC maps for each participant were used in statistical analyses (voxel-wise FDR-corrected $p<.05$). The DMN consists of four ROIs (lateral parietal R & L, medial prefrontal cortex, posterior cingulate cortex) as does the DAN (frontal eye field R & L, intraparietal sulcus R & L). The connectivity in all ROIs in the network was averaged.

ROI-to-ROI analyses were conducted *a priori* to examine the level of functional connectivity bilaterally between regions that compose the DMN and regions that compose the DAN with greater sensitivity, as these networks are expected to be anti-correlated with each other (Fox et al., 2005). ROI-to-ROI analyses produced ROI-to-ROI based correlation (RRC) maps for each participant in the same way as seed-to-voxel analyses but by substituting the target voxel BOLD time series with a target ROI time series. Group summary maps of RRC maps for each participant were used in statistical analyses (voxel-wise FDR-corrected $p<.05$).

To examine the global and local properties of the whole brain in healthy older adults, graph theory analyses were applied in CONN. Whole brain global efficiency was computed as the average inverse distance for all possible pairs of nodes and represents the efficiency of information transfer among all ROIs. The local efficiency was computed as the average of the inverse shortest path lengths among the ROIs in the immediately connected neighborhood of an ROI. At the whole brain network level, local efficiency represents the average sub-network efficiency across all ROIs and reflects the ability to effectively compensate for the localized failure of a single node (Smith et al., 2018). Calculation of global efficiency and local efficiency cost was set at .15 and corrected for multiple comparisons (FDR-corrected $p<.05$). Adjacency matrix thresholding is typically implemented using a fixed network cost level (e.g. keeping the strongest 15% of connections) in order to allow sensitive between-network comparisons of other graph measures of interest (Whitfield-Gabrieli, & Nieto-Castanon, 2012; Goparaju, Rana, Calabro, & Vaina, 2014).

Statistical Analyses

To test the moderating effect of physical activity and fitness on the association between executive function/working memory and functional connectivity of DMN/DAN networks using seed-to-voxel analyses, contrasts were run in CONN to determine whether significant executive functioning/working memory x physical activity and fitness interactions existed. When significant interactions existed, executive function/working memory and physical activity and fitness were discretized into “high” and “low” groups and between-subjects contrasts were conducted within CONN to properly interpret the directionality of the results.

To test the moderating effect of physical activity and fitness on the association between executive function and DMN/DAN anti-correlations, we used a moderated regression analysis, as it is the recommended method for testing for the effects of interactions (Cohen, Cohen, West & Aiken, 1983). Data was analyzed using the Statistical Package for Social Sciences (IBM SPSS Version 26.0). The independent variable in our analyses was the DMN/DAN anti-correlation coefficient extracted for each participant and the dependent variable was executive function/working memory. The moderator variables used in the analyses were physical activity and physical fitness measures (i.e., MVPA, steps, 6MWT). All variables in the model were measured continuously. To determine the main effects of the predictor variables on executive function/working memory, multiple linear regression analyses of DMN/DAN anti-correlations, and physical activity/fitness and DMN/DAN anti-correlations were conducted (i.e., DMN/DAN anti-correlation entered into step 1 of the regression model, physical activity/fitness entered in step 2, with executive function/working memory as the dependent variable). To determine the interaction effect of the moderator, product terms for the standardized independent variables were created. The DMN/DAN anticorrelation x physical activity/fitness interaction term was included in the model in step 3.

To analyze the association between global and local efficiency of the whole brain and physical activity/fitness, a series of linear regressions were run in CONN to determine the strength of the associations between global and local efficiency and three physical activity/fitness related constructs (i.e., MVPA, steps, 6MWT).

Power Analysis

To ensure that the sample size is sufficient to detect the hypothesized effects (i.e., that the sample is large enough to detect at least a small effect) power analyses were conducted using GPower (Erdfelder, Faul, & Buchner, 1996). Given the limitations in previous literature on this topic, *a priori* power analyses were run to determine the sample size needed to detect a small effect based on three predictors in the moderation models (i.e., executive function/working memory, physical activity/fitness, executive function/working memory x physical activity/fitness). GPower was utilized with power (1 - β) set at 0.80 and α = .05 using the a priori setting Linear Multiple Regression: Fixed model, R2 deviation from zero. This analysis revealed that a sample size of 75 would yield an f^2 value of .015, which is the minimum sample size needed to detect a small to medium effect (Cohen, 1988). In the linear regression models with only 1 predictor (i.e., physical activity/fitness predicting efficiency), only 54 participants were needed to detect a small to medium effect ($f^2 \leq .15$). Given the halt in data collection due to the ongoing COVID-19 pandemic, only data from 51 participants were able to be analyzed. Therefore, post hoc power analyses indicate that the current sample size would provide enough power to detect a medium to large effect with three predicters (f^2 =.23) and a medium effect with one predictor (f^2 =.16).

CHAPTER 3

PHYSICAL ACTIVITY MODERATES THE ASSOCIATION BETWEEN EXECUTIVE FUNCTION AND FUNCTIONAL CONNECTIVITY IN OLDER ADULTS[1]

[1] To be submitted to *Behavioural Brain Research* by Marissa Ann Gogniat

Abstract

Recent evidence suggests that physical activity may influence the functional connectivity of the aging brain. The purpose of this study was to examine the influence of physical activity on the association between executive function and functional connectivity of key brain networks and graph theory metrics in community-dwelling older adults. Participants were 47 older adults (M = 73 years; SD = 5.92) who participated in neuropsychological testing, physical activity measurements, and magnetic resonance imaging (MRI). Seed-to-voxel moderation analyses and graph theory analyses were conducted. Physical activity was significantly positively associated with default mode network functional connectivity (DMN FC; Posterior Cingulate Gyrus, *p*-FDR = .005; Frontal Pole (L), *p*-FDR = .005; Posterior Cingulate Gyrus, *p*-FDR = .006; Superior Frontal Gyrus (L), *p*-FDR = .016) and dorsal attention network functional connectivity (DAN FC; Inferior Frontal Gyrus Pars Opercularis (R), *p*-FDR = .044). The interaction between physical activity and executive function on the DMN FC and DAN FC was analyzed. The interaction between executive function and physical activity was significantly associated with DMN FC. When this significant interaction was probed, the association between physical activity and DMN FC differed between levels of high and low executive function such that the association was only significant at levels of high executive function. These results suggest that greater physical activity in later life is associated with greater DMN and DAN FC and provides evidence for the importance of physical activity in cognitively healthy older adults.

Introduction

As the number of older adults continues to grow at an unprecedented rate, there is a need to examine the neuroprotective effects of health and wellness factors that promote healthy aging. While long touted as good for physical health, several meta-analyses have found that exercise interventions positively impact cognitive function in older adulthood (Colcombe & Kramer, 2003; Kelly, Loughrey, Lawlor, Robertson, Walsh & Brennan, 2014; Northey et al., 2018; Sanders et al., 2019). Self-reported and objectively measured physical activity have also been shown to be positively associated with cognitive functioning in aging (Weuve et al., 2004; Frith, & Loprinzi, 2017; Jeong & Jang, 2017; Barnes et al., 2008; Kerr et al., 2013; Iso-Markku et al., 2018). Using objective devices to record the activity level of older adults has allowed for aspects of physical activity to be examined (e.g., intensity of activity, number of steps, distance traveled). Some studies have found that the intensity of physical activity has the greatest association to current cognitive ability for older adults (Angevaren et al., 2007; Brown et al., 2012; Kerr et al., 2013; Zhu et al., 2015) while others have posited that simply moving around throughout the day (i.e., number of steps) is significantly related to cognition and specifically to executive function ability (Barnes et al., 2008; Buchman, Wilson, & Bennett, 2008). The use of performance-based measures to examine physical activity in older adults allows for more accurate and specific information to be examined in its association with cognitive functional ability.

Exercise interventions have been shown to impact cognitive function in aging, particularly executive function (Angevaren et al., 2007; Colcombe & Kramer, 2003; Smith et al., 2010). Executive functions involve the integration of several cognitive processes including inhibitory control, working memory, set-shifting, and cognitive flexibility to support higher order cognitive functions such as problem solving, decision-making, and planning and are one of the earliest domains effected by aging related cognitive decline (Diamond, 2013; Clark et al., 2012; Johnson, Lui, & Yaffe, 2007; Thibeau et al., 2016). Executive functioning ability is crucial to maintaining functional independence in aging and the preservation of this ability has been of great interest to researchers and clinicians (Vaughan & Giovanello, 2010). A component of executive functions, set-shifting ability, is related to several outcomes in older adulthood such as risk of fall, subjective cognitive complaints, and everyday functioning (Geiger, Reed, Combs, Boggero, & Segerstrom, 2019; Higby et al., 2016; McAlister & Schmitter-Edgecomb, 2016; McKay, Lang, Ting, & Hackney, 2017; Mitchell & Miller, 2008). Better executive functioning performance in older adulthood has also been shown to be have specific underpinnings such as greater functional connectivity in both the default mode network (DMN) and in the dorsal attention network (DAN; Andrews-Hanna et al., 2007; Damoiseaux et al. 2008; Majerus, Péters, Bouffier, Cowan, & Phillips, 2018). Therefore, there is a need to examine how physical activity might interact with executive function to impact the functioning of the aging brain.

A relatively new and emerging area examines how physical activity may impact the functional connectivity (FC) of the aging brain. A recent review (Stillman, Donofry, & Erickson, 2019) examined the current state of the literature concerning the associations between physical activity and FC for older adults and found relatively few studies on this topic. There are several cross-sectional studies which have examined aspects of these associations with a particular focus on the brain networks that are most susceptible to aging including the DMN and DAN. Boraxbekk and colleagues (2016) showed that self-reported physical activity of the previous decade was related to DMN FC in older adults. Using objectively measured physical activity, Veldsman and colleagues (2017) found that physical activity level was related to DAN FC in older adult stroke survivors. Other have examined the associations between physical activity and fitness, FC, and cognition. Voss and colleagues (2010) showed that FC in the DMN mediated the association between aerobic fitness and executive function in older adults. In addition, Voss and colleagues (2016) also showed an association between physical fitness and executive function for older adults that was mediated by DMN and DAN FC. The current literature indicates an association between physical activity and DMN and DAN FC in aging, but less is known about how executive function might play into this association.

Finally, the literature examining the associations between physical activity and graph theory metrics such as global and local efficiency is extremely sparse. Graph theory posits that the brain is made up of a complex series of nodes (e.g., anatomical elements) and edges (e.g., relationships between nodes) and this methodology can model the overall connectivity of the brain and thus characterizes this organization (Bullmore & Sporns, 2009; Wang, Zu, & He, 2010). This methodology can be used to determine global and local efficiency of the brain. Kawagoe, Onoda, and Yamaguchi (2017) examined the associations between executive function, global efficiency, local efficiency, and physical fitness in older adults. They found that global efficiency was positively associated with executive function and physical fitness, while local efficiency was negatively associated with executive function and physical fitness. The authors posited that while the findings for global efficiency were intuitive, their hypothesis for why local efficiency was negatively related to executive function and physical fitness was because of the tendency of high functioning older adults to have connections across a broader range of brain areas at the expense of local efficiency (i.e., a compensatory mechanism). In addition, a recent study by Yue and colleagues (2020) examined the impact of Tai Chi practice on network efficiency in Chinese female older adults and found no difference in global and local efficiency between those that engaged in Tai Chi and those that walked, although local efficiency attributes expressed positive trends in favor of Tai Chi practice. While these studies give us some insight into the associations between physical activity, physical fitness, executive function, and measures of functional connectivity and efficiency, this area is ripe for a greater exploration of global and local efficiency of networks susceptible to the effects of aging.

The purpose of the current study was to expand upon the limited current state of the literature in this area by exploring the impact of physical activity on FC and executive function in older adults. This study had several aims. The first aim was to examine whether executive function performance was related to DMN and DAN FC in community-dwelling older adults and to examine whether physical activity moderated this association. We hypothesized that better executive function performance would be related to greater DMN and DAN connectivity. We also hypothesized that physical activity would moderate the association between both executive function and DMN/DAN FC such that higher levels of physical activity would buffer the association between lower executive function and DAN/DMN FC. The second aim was to evaluate whether physical activity was related to whole brain local and global efficiency for community-dwelling older adults. We hypothesized that greater physical activity would be significantly associated with both greater global efficiency and greater local efficiency, as evidence indicates that there is greater whole brain connectivity and lower local connectivity in aging (Cao et al., 2014; Song et al., 2014; Iordan et al., 2018).

Methods

Participants

Participants were a total of 47 community-dwelling older adults (aged 65+ years) from the surrounding community of a southeastern college town recruited over a four-year period. Some participants' data were acquired as part of a separate intervention study, but for the purpose of the present study, only data from their baseline assessments (pre-intervention) was used. All participants completed sessions that included neuropsychological testing, physical activity and fitness measurements, and magnetic resonance imaging (MRI). Participants were eligible if they had no self-reported major neurological (e.g., Alzheimer's, Parkinson's) or psychiatric disorders, were right-handed, Native English speakers, and were compatible with the MRI environment (i.e., no metal implants, no recent surgeries, etc). Participants were excluded if their cognitive functioning was below mild cognitive impairment (MCI) as indicated by their performance on the MMSE (totals score < 24). Informed consent was obtained from all participants and the Declaration of Helsinki was followed.

Physical Activity

Physical activity (PA) was measured using NL-1000 Accelerometers (New Lifestyles, Inc.; Lee's Summit, Missouri, USA). This measures PA intensity, number of steps, and distance covered using a piezoelectric strain gauge. Participants in this study wore the NL-1000 on their waist for 7 days and completed a log to ensure adequate wear time (e.g., at least 8 hours per day; Prescott et al., 2020). The average number of steps taken per day over the span of seven days was calculated as follows: Average Steps = [(Total Steps Day 1 + Total Steps Day 2 + Total Steps Day 3 + Total Steps Day 4 + Total Steps Day 5 + Total Steps Day 6 + Total Steps Day 7)/7].

Neuropsychological Measures

Each participant received neuropsychological assessment by a trained graduate student. All participants were administered the Delis-Kaplan Executive Function System (DKEFS) Color-Word Interference Test, the DKEFS Verbal Fluency Test, and the DKEFS Trail Making Test, which are subtests of the full DKEFS battery. The DKEFS Trail-making Test, Verbal Fluency, and Color Word Interference have good psychometric properties, measure non-verbal and verbal executive function, and have relatively brief administration times (Delis et al., 2004). For the Trail Making Test, a scaled score was calculated for Condition 4: Number-Letter Switching, which measures the ability to set-shift. For Verbal Fluency, a scaled score for Category Switching was calculated, which measures the ability to generate words that fall under categories while being able to set-shift. For the Color-Word Inference Test, a scaled score was calculated for Condition 4: Inhibition/Switching, which measures verbal inhibition and set-shifting (D-KEFS; Delis, Kaplan, & Kramer, 2001). All scaled scores were then averaged together for each participant to create an executive function composite specific to set-shifting. In order to determine whether these three subtests were correlated with each other and were thus measuring similar constructs, a Cronbach's alpha based on standardized items (Bland & Altman, 1997) was calculated (α=.607) indicating an acceptable fit for a small number of items (Hinton, Brownlow, McMurray, & Cozens, 2004).

Neuroimaging

MRI Acquisition. Brain images were acquired using a General Electric (GE; Waukesha, WI) 3T Signa HDx MRI system. A high-resolution 3D T1-weighted fast spoiled gradient recall echo sequence was used to collect structural scans (TR = 7.5 ms; TE = < 5ms; FOV = 256 × 256 mm matrix; flip angle = 20°; slice thickness = 1.2 mm; 154 axial slices) with an acquisition time of 6 minutes and 20 seconds. This protocol collected 176 images. Resting state functional scans were aligned to each participant's anterior commissure-posterior commissure (AC-PC) line, collected axially, and used a T2*-weighted single shot EPI sequence (TR = 5000 ms; TE = 25 ms; 90° RF pulse; acquisition matrix = 128 × 128; FOV = 220 × 220 mm; in-plane resolution = 220/128 mm; slice thickness = 2 mm; 60 interleaved axial slices). Total acquisition time was 9 minutes and 25 seconds. 108 volumes were acquired.

Resting State Pre-processing. The resting state functional scans were pre-processed using the default pre-processing pipeline in the CONN toolbox from the Neuroimaging Tools & Resources Collaboratory (v.18.b; www.nitrc.org/projects/conn; Whitfield-Gabrieli & Nieto-Castanon, 2012). The CONN Toolbox default pre-processing pipeline includes realigning and unwarping the data, centering the coordinates, applying a slice-time correction, outlier detection (using ART-based identification of outlier scans for scrubbing; www.nitric.org/projects/artifact_detect), direct functional and structural segmentation and normalization (using simultaneous Grey Matter/White Matter/CSF segmentation and MNI normalization), and functional smoothing. In addition, functional scans were denoised in CONN to remove physiological effect, subject movement, and other confounding effects from the BOLD signal. Within the CONN Toolbox, cortical and subcortical ROIs were defined by the Harvard-Oxford atlas (Frazier et al., 2005; Desikan et al., 2006; Makris et al., 2006; Goldstein et al., 2007), Automated Anatomical Labelling (AAL) Atlas (Tzourio-Mazoyer et al., 2002), and CONN default networks.

Seed-to-Voxel Analyses. Seed-to-voxel analyses were conducted *a priori* to examine the level of functional connectivity between the DMN and every voxel in the brain and the DAN and every voxel in the brain, which produces seed-based correlation (SBC) maps for each participant. ROIs/seeds were defined by coordinates provided by the CONN toolbox regarding the DMN and DAN. SBC maps contain Fisher r to z transformed bivariate correlation coefficients between each seed/ROI BOLD timeseries (averaged across all voxels within an ROI) and an individual voxel BOLD timeseries. Group summary maps of SBC maps for each participant were used in statistical analyses (voxel-wise FDR-corrected $p<.05$). The DMN consists of four ROIs (lateral parietal R & L, medial prefrontal cortex, posterior cingulate cortex) as does the DAN (frontal eye field R & L, intraparietal sulcus R & L). The connectivity in all ROIs in the network was averaged.

The associations between executive function and DMN/DAN connectivity and the associations between physical activity and DMN/DAN connectivity were examined. To test the moderating effect of physical activity and fitness on the association between executive function and functional connectivity of DMN/DAN using seed-to-voxel analyses, contrasts were run in CONN to determine whether significant executive function x physical activity interactions existed. When significant interactions existed, executive function and physical activity were discretized into “high” and “low” groups and between-subjects contrasts were conducted within CONN to interpret the directionality of the results.

Graph Theory Analyses. To examine the global and local properties of the whole brain and the impact of physical activity on these properties, graph theory analyses were applied in CONN. Network ROIs in CONN were defined by independent cluster analyses (ICA) by CONN software creators. Whole brain global efficiency was computed as the average inverse distance for all possible pairs of nodes and represents the efficiency of information transfer among all ROIs. The local efficiency was computed as the average of the inverse shortest path lengths among the ROIs in the immediately connected neighborhood of an ROI. At the whole brain network level, local efficiency represents the average sub-network efficiency across all ROIs and reflects the ability to effectively compensate for the localized failure of a single node (Smith et al., 2018). Calculation of global efficiency and local efficiency cost was set at .15 and corrected for multiple comparisons (FDR-corrected $p<.05$). Adjacency matrix thresholding is typically implemented using a fixed network cost level (e.g. keeping the strongest 15% of connections) in order to allow sensitive between-network comparisons of other graph measures of interest (Whitfield-Gabrieli, & Nieto-Castanon, 2012; Goparaju, Rana, Calabro, & Vaina, 2014).

Results

Descriptive Characteristics

Table 3.1 provides means and standard deviations for sociodemographic characteristics. The average age was 72.96 years (SD = 5.92). Slightly over half (61.7%) of the participants were female and a majority of the participants were White (91.5%). On average, participants had completed 16.96 years (SD = 2.45) of education. The average steps per day (M = 5360.91; SD = 3223.83) was below most recommended average steps per day for older adults (Garber et al., 2011; Tudor-Locke et al., 2011; Kraus et al., 2019). Our sample fell in the average range on the composite measure of executive functioning (M = 11.65; SD = 2.44).

Seed-to-Voxel Analyses

Executive function was not significantly associated with DMN FC, but it was significantly related to DAN FC in our sample (Inferior Frontal Gyrus, Pars Triangularis (L), *p*-FDR = .045). Physical activity was significantly positively associated with DMN FC (Posterior Cingulate Gyrus, *p*-FDR = .005; Frontal Pole (L), *p*-FDR = .005; Posterior Cingulate Gyrus, *p*-FDR = .006; Superior Frontal Gyrus (L), *p*-FDR = .016; Figure 3.1) and DAN FC (Inferior Frontal Gyrus Pars Opercularis (R), *p*-FDR = .044; Figure 3.2). The interaction between executive function and PA was significantly associated with DMN FC (see Table 3.2). When this significant interaction between executive function and physical activity was probed, the association between physical activity and DMN FC differed between levels of high and low executive function such that the association was only significant at levels of high executive function. The interaction between executive function and physical activity was not significantly associated with DAN FC.

Whole Brain Graph Theory Analyses

Contrary to our hypothesis, physical activity was not significantly associated with whole brain global efficiency (t (45) = -0.77, p = 0.45) or whole brain local efficiency (t (45) = 0.29, p = 0.77).

Discussion

The protective effects of physical activity on the brain have been well-documented in aging, but the mechanisms by which physical activity is neuroprotective is less understood. The current study sought to examine how physical activity impacts the association between executive function and resting state brain connectivity. Importantly, we utilized an objective measure of physical activity as well as seed-to-voxel and graph theory analyses. Consistent with the existing literature, we hypothesized that better executive function performance would be related to greater DMN and DAN connectivity. We also hypothesized that physical activity would moderate the association between both executive function and DMN/DAN FC such that higher levels of physical activity would buffer the association between lower executive function and DAN/DMN FC.

Our first hypothesis was partially supported. Executive function was not significantly associated with DMN FC, but it was significantly related to DAN FC with frontal areas. This significant finding is in line with research that has demonstrated stronger positive connectivity between dorsal attention and frontoparietal networks on an executive functioning task (Tian et al., 2013). However, this is not universally seen in the literature, as some studies have failed to find any association between common resting state networks (i.e., including the DMN) and cognitive performance in older adulthood (Onoda, Ishihara, & Yamaguchi, 2012; Ferreira & Busatto, 2013; Geerligs et al., 2015). This indicates the need for future replication and additional exploration. Interestingly, physical activity was significantly positively associated with DMN FC in frontal and parietal areas associated with reasoning and emotional regulation. Physical activity was only significantly positively related to DAN FC with the inferior frontal gyrus pars opercularis, an area in the frontal lobe involved in language production and semantic processing. This finding adds to the growing literature demonstrating an association between physical activity and increased functional connectivity in aging (Boraxbekk et al., 2016; Veldsman et al., 2017).

Notably, there was a significant interaction between executive function and physical activity on DMN FC. When this interaction was probed, the association between physical activity and DMN FC differed between levels of high and low executive function such that the association was only significant at high levels of executive functioning. This suggests that that older adults may see the greatest benefit of physical activity on DMN FC if they are already performing at high levels of executive function and provides evidence for the importance of physical activity in cognitively healthy older adults. Increasing physical activity in high executive functioning older adults may act as buffer against age-related DMN FC decline and supports lifestyle factors such as physical activity as enhancing compensatory scaffolding in the aging brain (Reuter-Lorenz & Park, 2014). In addition, this finding suggests that interventions may consider boosting both physical activity and executive functioning in tandem to achieve preserve or improve the functional connectivity of the aging brain.

Our second hypothesis was not supported. Physical activity was not significantly associated with whole brain global or local efficiency in our sample. It is possible that physical activity does have an impact on efficiency in more localized and specific ways that was missed by examining efficiency using whole brain metrics. In addition, there may have been a small effect and we did not have enough power based on our sample size to detect it. Future studies should consider examining efficiency in regions of interest. Given that this sample was engaging in far less PA than is recommended by CDC guidelines (CDC, 2021), it would be important to examine this relationship in a group of older adults with a wider range of physical activity levels.

There are several limitations that should be considered. First, this study was correlational and thus limits causal conclusions that can be drawn. While it was hypothesized that physical activity impacted the association between cognition and brain function, it is possible that these relationships are also bidirectional (Daly, McMinn, & Allan, 2015) and should be explored in future studies. Additionally, our measurement of physical activity was a time-limited (i.e., one week) sample of current activity and may not represent historical physical activity. Future studies might consider tracking physical activity over time. Our sample was highly educated, racially homogenous, cognitively intact, and relatively sedentary, which may have implications for the generalizability of the results. While a limit to generalizability, the ability to find effects in a highly educated sample indicates that effects may be greater for those with lower levels of education and thus lower cognitive reserve. In addition, this sample was modestly sized, and thus power was limited to conduct additional analyses. Despite these limitations, the current study contributes to our understanding of how physical activity may impact cognition and the functional connectivity of the aging brain. These analyses provide insight into the neuroprotective effects of physical activity and may inform future research in this important area.

References

Andrews-Hanna JR, Snyder A, Vincent J, Lustig C, Head D, Raichle M, Buckner R. (2007). Disruption of large-scale brain systems in advanced aging. *Neuron, 56,* 924–935. doi: 10.1016/j.neuron.2007.10.038

Angevaren, M., Vanhees, L., Wendel-Vos, W., Verhaar, H. J., Aufdemkampe, G., Aleman, A., & Verschuren, W. M. (2007). Intensity, but not duration, of physical activities is related to cognitive function. *European Journal of Cardiovascular Prevention & Rehabilitation, 14*(6), 825-830. doi: 10.1097/HJR.0b013e3282ef995b

Barnes, D.E., Blackwell, T., Stone, K.L., Goldman, S.E., Hillier, T., & Yaffe, K. (2008). Cognition in older women: The importance of daytime movement. Journal of the *American Geriatrics Society, 56*, 1658–1664. doi: 10.1111/j.15325415.2008.01841.x

Bland J., & Altman D. (1997). Statistics notes: Cronbach's alpha. *BMJ,* 314, 572. doi: 10.1136/bmj.314.7080.572

Boraxbekk, C.-J., Salami, A., Wåhlin, A., & Nyberg, L. (2016). Physical activity over a decade modifies age-related decline in perfusion, gray matter volume, and functional connectivity of the posterior default-mode network—A multimodal approach. *NeuroImage, 131*, 133–141. doi: 10.1016/j.neuroimage.201 5.12.010

Brown, B.M., Peiffer, J.J., Sohrabi, H.R., Mondal, A., Gupta, V.B., & Rainey-Smith, S.R. (2012). Intense physical activity is associated with cognitive performance in the elderly. *Translational Psychiatry, 2*, e191. doi: 10.1038/tp.2012.118

Buchman, A. S., Wilson, R. S., & Bennett, D. A. (2008). Total daily activity is associated with cognition in older persons. *The American Journal of Geriatric Psychiatry, 16*(8), 697-701. doi: 10.1097/JGP.0b013e31817945f6

Bullmore, E., & Sporns, O. (2009). Complex brain networks: graph theoretical analysis of structural and functional systems. *Nature reviews neuroscience, 10*(3), 186. doi: 10.1038/nrn2575

Cao, M., Wang, J.H., Dai, Z.J., Cao, X.Y., Jiang, L.L., Fan, F.M., ..., Yong, He. (2014). Topological organization of the human brain functional connectome across the lifespan. *Dev. Cogn. Neurosci. 7*, 76–93. doi: 10.1016/j.dcn.2013.11.004

Centers for Disease Control. (2021). How much physical activity do older adults need? Retrieved from https://www.cdc.gov/physicalactivity/basics/older_adults/index.htm

Clark, L. R., Schiehser, D. M., Weissberger, G. H., Salmon, D. P., Delis, D. C., & Bondi, M. W. (2012). Specific measures of executive function predict cognitive decline in older adults. *Journal of the International Neuropsychological Society*, *18*(1), 118-127. doi: 10.1017/S1355617711001524

Colcombe, S., & Kramer, A.F. (2003). Fitness effects on the cognitive function of older adults: A meta-analytic study. *Psychological science, 14*, 125-130. doi: 10.1111/1467-9280.t01-101430

Daly, M., McMinn, D., & Allan, J. L. (2015). A bidirectional relationship between physical activity and executive function in older adults. *Frontiers in human neuroscience, 8,* 1044. doi: 10.3389/fnhum.2014.01044

Damoiseaux JS, Beckmann CF, Arigita EJ, Barkhof F, Scheltens P, Stam CJ, Smith SM, & Rombouts SA. (2008). Reduced resting-state brain activity in the "default network" in normal aging. *Cerebral Cortex, 18*, 1856–1864. doi: 10.1093/cercor/bhm207

Delis, D.C., Kaplan, E., & Kramer, J. H. (2001a). *Delis-Kaplan Executive Function System (D-KEFS)*. San Antonio, TX: The Psychological Corporation

Delis, D.C., Kramer, J.H., Kaplan, E., & Holdnack, J. (2004). Reliability and validity of the Delis-Kaplan Executive Function System: An update. *Journal of the International Neuropsychological Society*, *10*, 301-303. doi: 10.1017/S1355617704102191

Desikan, R. S., Ségonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., Buckner, R. L., Dale, A. M., Maguire, R. P., Hyman, B. T., Albert, M. S., & Killiany, R. J. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *NeuroImage*, *31*(3), 968–980. doi: 10.1016/j.neuroimage.2006.01.021

Diamond, A. (2013). Executive functions. *Annual review of psychology*, *64*, 135-168. doi: 10.1146/annurev-psych-113011-143750

Ferreira, L. K., & Busatto, G. F. (2013). Resting-state functional connectivity in normal brain aging. *Neuroscience & Biobehavioral Reviews, 37*(3), 384-400. doi: 10.1016/j.neubiorev.2013.01.017.

Frazier, J. A., Chiu, S., Breeze, J. L., Makris, N., Lange, N., Kennedy, D. N., Herbert, M. R., Bent, E. K., Koneru, V. K., Dieterich, M. E., Hodge, S. M., Rauch, S. L., Grant, P. E., Cohen, B. M., Seidman, L. J., Caviness, V. S., & Biederman, J.

(2005). Structural brain magnetic resonance imaging of limbic and thalamic volumes in pediatric bipolar disorder. T*he American journal of psychiatry, 162*(7), 1256–1265. doi: 10.1176/appi.ajp.162.7.1256

Frith, E., & Loprinzi, P. D. (2017). The association between physical activity and cognitive function with considerations by social risk status. *Europe's journal of psychology, 13,* 767–775. doi:10.5964/ejop.v13i4.1471

Garber, C. E., Blissmer, B., Deschenes, M. R., Franklin, B. A., Lamonte, M. J., Lee, I. M., Nieman, D. C., Swain, D. P., & American College of Sports Medicine (2011). American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Medicine and science in sports and exercise, 43*(7), 1334–1359. doi: 10.1249/MSS.0b013e318213fefb

Geerligs L., Renken R. J., Saliasi E., Maurits N. M., & Lorist M. M. (2015). A brain-wide study of age-related changes in functional connectivity. *Cereb. Cortex 25*, 1987–1999. doi: 10.1093/cercor/bhu012

Geiger, P. J., Reed, R. G., Combs, H. L., Boggero, I. A., & Segerstrom, S. C. (2019). Longitudinal associations among older adults' neurocognitive performance, psychological distress, and self-reported cognitive function. *Psychology & neuroscience*, *12*(2), 224. doi: 10.1037/pne0000155

Goldstein, J. M., Seidman, L. J., Makris, N., Ahern, T., O'Brien, L. M., Caviness, V. S., Jr, Kennedy, D. N., Faraone, S. V., & Tsuang, M. T. (2007). Hypothalamic abnormalities in schizophrenia: sex effects and genetic vulnerability. *Biological psychiatry*, *61*(8), 935–945. doi: 10.1016/j.biopsych.2006.06.027

Goparaju, B., Rana, K. D., Calabro, F. J., & Vaina, L. M. (2014). A computational study of whole-brain connectivity in resting state and task fMRI. *Medical science monitor: international medical journal of experimental and clinical research, 20*, 1024–1042. doi:10.12659/MSM.891142

Higby, E., Cahana-Amitay, D., Vogel-Eyny, A., Spiro III, A., Albert, M. L., & Obler, L. K. (2019). The role of executive functions in object-and action-naming among older adults. *Experimental Aging Research*, *45*(4), 306-330. doi: 10.1080/0361073X.2019.1627492

Hinton, P. R., Brownlow, C., McMurray, I., & Cozens, B. (2004). SPSS explained. East Sussex, UK: Routledge.

Iordan, A. D., Cooke, K. A., Moored, K. D., Katz, B., Buschkuehl, M., Jaeggi, S. M., . . . Reuter-Lorenz, P. A. (2018). Aging and network properties: Stability over time and links with learning during working memory training. *Frontiers in Aging Neuroscience, 9*(419). doi: 10.3389/fnagi.2017.00419

Iso-Markku, P., Waller, K., Vuoksimaa, E., Vähä-Ypyä, H., Lindgren, N., Heikkilä, K., … Kujala, U. M. (2018). Objectively measured physical activity profile and cognition in Finnish elderly twins. *Alzheimer's & dementia 4*, 263–271. doi: 10.1016/j.trci.2018.06.007

Jeong, S., & Jang, J. Y. (2017). Association between physical activity and cognitive dysfunction in the Korean: a cross-sectional study. *Exercise Medicine, 1.* doi: 10.26644/em.2017.003

Johnson, J. K., Lui, L. Y., & Yaffe, K. (2007). Executive function, more than global cognition, predicts functional decline and mortality in elderly women. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *62*(10), 1134-1141. doi: 10.1093/gerona/62.10.1134.

Kawagoe, T., Onoda, K., & Yamaguchi, S. (2017). Associations among executive function, cardiorespiratory fitness, and brain network properties in older adults. *Scientific reports, 7,* 40107. doi:10.1038/srep40107

Kelly, M. E., Loughrey, D., Lawlor, B. A., Robertson, I. H., Walsh, C., & Brennan, S. (2014). The impact of exercise on the cognitive functioning of healthy older adults: a Systematic review and meta-analysis. *Ageing research reviews, 16*, 12-31. doi: 10.1016/j.arr.2014.05.002

Kerr, J., Marshall, S. J., Patterson, R. E., Marinac, C. R., Natarajan, L., Rosenberg, D., ... & Crist, K. (2013). Objectively measured physical activity is related to cognitive function in older adults. *Journal of the American Geriatrics Society, 61*(11), 1927-1931. doi: 10.1249/MSS.0000000000001079

Kraus, W. E., Janz, K. F., Powell, K. E., Campbell, W. W., Jakicic, J. M., Troiano, R. P., ... & 2018 Physical Activity Guidelines Advisory Committee. (2019). Daily step counts for measuring physical activity exposure and its relation to health. *Medicine and science in sports and exercise, 51*(6), 1206. doi: 10.1249/MSS.0000000000001932

Majerus, S., Péters, F., Bouffier, M., Cowan, N., & Phillips, C. (2018). The dorsal attention network reflects both encoding load and top–down control during working memory. *Journal of cognitive neuroscience, 30*(2), 144-159. doi: 10.1162/jocn_a_01195.

Makris, N., Goldstein, J. M., Kennedy, D., Hodge, S. M., Caviness, V. S., Faraone, S. V., Tsuang, M. T., & Seidman, L. J. (2006). Decreased volume of left and total anterior insular lobule in schizophrenia. *Schizophrenia research, 83*(2-3), 155–171. doi: 10.1016/j.schres.2005.11.020

McAlister, C., & Schmitter-Edgecombe, M. (2016). Everyday functioning and cognitive correlates in healthy older adults with subjective cognitive concerns. *The Clinical neuropsychologist*, *30*(7), 1087–1103. doi: 10.1080/13854046.2016.1190404

McKay, J., Lang, K. C., Ting, L., & Hackney, M. (2017). A cross-sectional study of set shifting impairments and falling in individuals with and without Parkinson's disease. *BioRxiv*, 146332. doi: 10.1101/146332

Mitchell, M., & Miller, L. S. (2008). Prediction of functional status in older adults: the ecological validity of four Delis-Kaplan Executive Function System tests. *Journal of clinical and experimental neuropsychology, 30*(6), 683–690. doi: 10.1080/13803390701679893

Northey, J. M., Cherbuin, N., Pumpa, K. L., Smee, D. J., & Rattray, B. (2018). Exercise interventions for cognitive function in adults older than 50: a systematic review with meta-analysis. *Br J Sports Med, 52*(3), 154-160. doi: 10.1136/bjsports-2016-096587

Onoda K., Ishihara M., Yamaguchi S. (2012). Decreased functional connectivity by aging is associated with cognitive decline. *J. Cogn. Neurosci. 24*, 2186–2198. doi: 10.1162/jocn_a_00269

Prescott, S., Traynor, J. P., Shilliday, I., Zanotto, T., Rush, R., & Mercer, T. H. (2020). Minimum accelerometer wear-time for reliable estimates of physical activity and sedentary behaviour of people receiving haemodialysis. *BMC nephrology, 21*, 230. doi: 10.1186/s12882-020-01877-8

Reuter-Lorenz, P. A., & Park, D. C. (2014). How does it STAC up? Revisiting the scaffolding theory of aging and cognition. *Neuropsychology review, 24*(3), 355–370. doi: 10.1007/s11065-014-9270-9

Sanders, L., Hortobágyi, T., la Bastide-van Gemert, S., van der Zee, E. A., & van Heuvelen, M. (2019). Dose-response relationship between exercise and cognitive function in older adults with and without cognitive impairment: A systematic review and meta-analysis. *PloS one*, *14*(1), e0210036. doi: 10.1371/journal.pone.0210036

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. *Psychosom Med, 72*, 239–252. doi: 10.1097/PSY.0b013e3181d14633

Smith, R., Sanova, A., Alkozei, A., Lane, R. D., & Killgore, W. (2018). Higher levels of trait emotional awareness are associated with more efficient global information integration throughout the brain: a graph-theoretic analysis of resting state functional connectivity. *Social cognitive and affective neuroscience, 13*(7), 665–675. doi: 10.1093/scan/nsy047

Song, J., Birn, R. M., Boly, M., Meier, T. B., Nair, V. A., Meyerand, M. E., et al. (2014). Age-related reorganizational changes in modularity and functional connectivity of human brain networks. *Brain Connect. 4,* 662–676. doi: 10.1089/brain.2014.0286

Stillman, C. M., Donofry, S. D., & Erickson, K. I. (2019). Exercise, fitness and the aging brain: A Review of functional connectivity in aging. *Archives of Psychology, 3*(4). doi: 0.31296/aop.v3i4.98

Thibeau, S., McFall, G. P., Wiebe, S. A., Anstey, K. J., & Dixon, R. A. (2016). Genetic factors moderate everyday physical activity effects on executive functions in aging: Evidence from the Victoria Longitudinal Study. *Neuropsychology*, 30(1), 6. doi: 10.1037/neu0000217

Tian, L., Kong, Y., Ren, J., Varoquaux, G., Zang, Y., & Smith, S. M. (2013). Spatial vs. temporal features in ICA of resting-state fMRI–A quantitative and qualitative investigation in the context of response inhibition. *PLoS One, 8*(6), e66572. doi: 10.1371/journal.pone.0066572

Tudor-Locke, C., Craig, C. L., Aoyagi, Y., Bell, R. C., Croteau, K. A., De Bourdeaudhuij, I., ... & Blair, S. N. (2011). How many steps/day are enough? For older adults and special populations. *International journal of behavioral nutrition and physical activity, 8*(1), 1-19. doi: 10.1186/1479-5868-8-80

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B., & Joliet, M., (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain., *NeuroImage, 15*, 273–289. doi: 10.1006/nimg.2001.0978

Vaughan, L., & Giovanello, K. (2010). Executive function in daily life: age-related influences of executive processes on instrumental activities of daily living. *Psychology and aging*, *25*(2), 343. doi: 10.1037/a0017729

Veldsman, M., Churilov, L., Werden, E., Li, Q., Cumming, T., & Brodtmann, A. (2017). Physical activity after stroke is associated with increased interhemispheric connectivity of the dorsal attention network. *Neurorehabilitation and Neural Repair, 31*(2), 157–167. doi: 10.1177/1545968316666958

Voss, M. W., Erickson, K. I., Prakash, R. S., Chaddock, L., Malkowski, E., Alves, H., ... Kramer, A. F. (2010). Functional connectivity: A source of variance in the association between cardiorespiratory fitness and cognition? *Neuropsychologia, 48*(5), 1394–1406. doi: 10.1016/j.neuropsycholog ia.2010.01.005

Voss, M. W., Weng, T. B., Burzynska, A. Z., Wong, C. N., Cooke, G. E., Clark, R., ... Kramer, A. F. (2016). Fitness, but not physical activity, is related to functional integrity of brain networks associated with aging. *NeuroImage, 131*, 113–125. doi: 10.1016/j.neuroimage.201 5.10.044

Wang, J., Zuo, X., & He, Y. (2010). Graph-based network analysis of resting-state functional MRI. *Frontiers in systems neuroscience, 4,* 16. doi:10.3389/fnsys.2010.00016

Weuve, J., Kang, J.H., Manson, J.E., Breteler, M.M.B., Ware, J.H., Grodstein, F. (2004). Physical activity, including walking, and cognitive function in older women. *JAMA, 292*, 1454–1461. doi:10.1001/jama.292.12.1454

Whitfield-Gabrieli, S., & Nieto-Castanon, A. (2012). Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. *Brain connectivity, 2*(3), 125-141. Doi: 10.1089/brain.2012.0073

Yue, C., Zou, L., Mei, J., Moore, D., Herold, F., Müller, P., Yu, Q., Liu, Y., Lin, J., Tao, Y., Loprinzi, P., & Zhang, Z. (2020). Tai Chi training evokes significant changes in brain white matter network in older women. *Healthcare (Basel, Switzerland*), 8, 57. doi: 10.3390/healthcare8010057

Zhu, W., Howard, V. J., Wadley, V. G., Hutto, B., Blair, S. N., Vena, J. E., ... & Hooker, S. P. (2015). Association between objectively measured physical activity and cognitive function in older adults—The Reasons for geographic and racial differences in stroke study. *Journal of the American Geriatrics Society, 63*(12), 2447-2454. doi: 10.1111/jgs.13829.

Table 3.1

Sample Demographics and Key Study Variables

Variable	% or M (SD)
Demographics	
Age	72.96 (5.92)
Sex (% female)	61.7%
Race (% White)	91.5%
Years of Education	16.96 (2.45)
Average Steps (day)	5360.91 (3223.83)
DKEFS Composite	11.65 (2.44)

DKEFS = Delis Kaplan Executive Function System

Table 3.2

Moderation Analyses

	Clusters (x,y,z)	Size (Voxels)	p-FDR	Area
DMN FC				
PA	-12, -44, +04	56	.005	Posterior Cingulate Gyrus
	-04, +54, -04	55	.005	Frontal Pole (L)
	+10, -44, +08	51	.006	Posterior Cingulate Gyrus
	-20, +18, +52	40	.016	Superior Frontal Gyrus (L)
PA x EF	+64, -44, -10	42	.007	Middle Temporal Gyrus (R)
DAN FC				
EF	-46, +36, +10	47	.024	Inferior Frontal Gyrus, Pars Triangularis (L)
PA	+52, +14, +22	45	.044	Inferior Frontal Gyrus, Pars Opercularis (R)

EF = Executive Function; PA = Physical Activity; DMN = Default Mode Network; DAN = Dorsal Attention Network; FC = Functional Connectivity

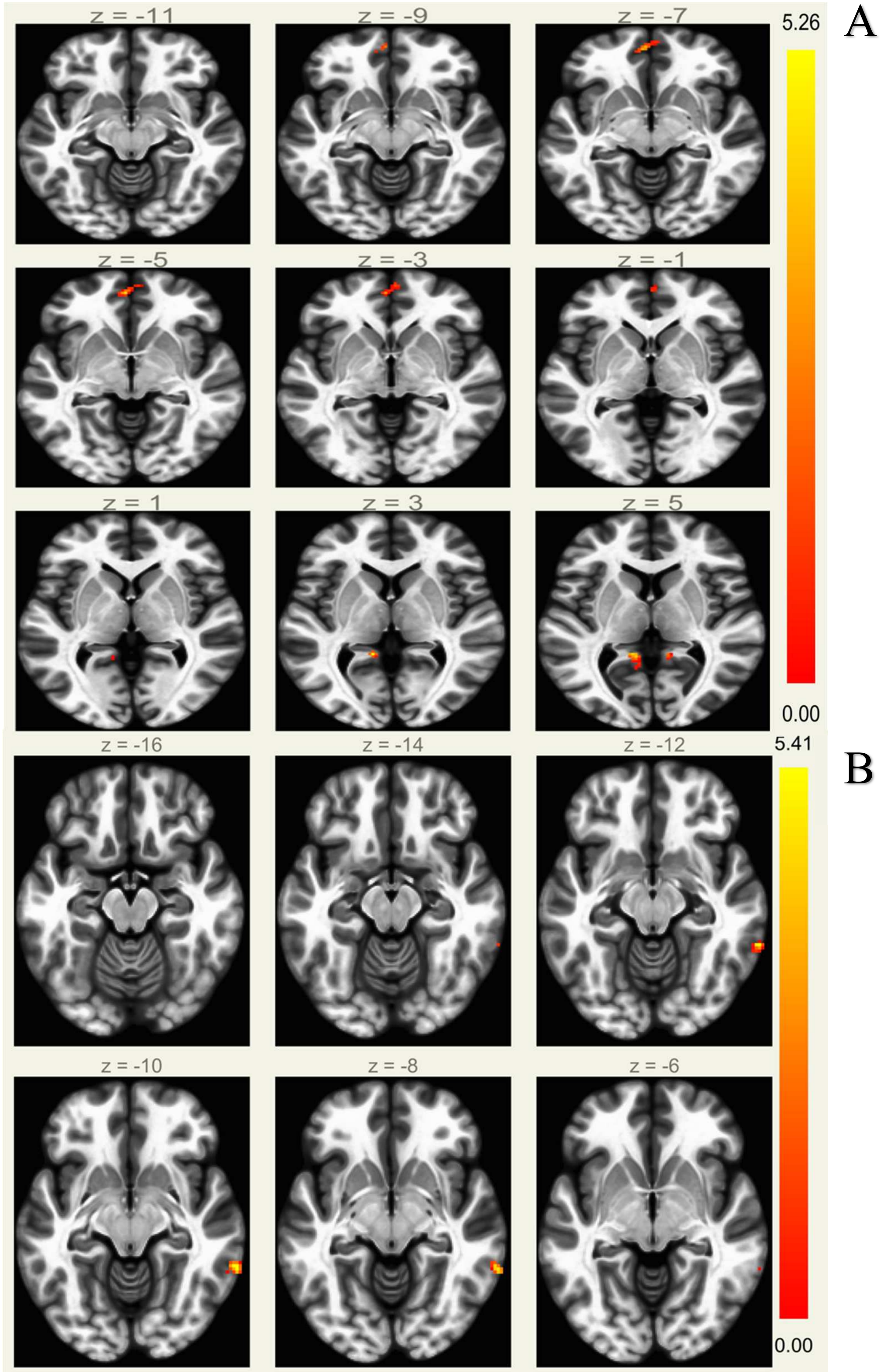

Figure 3.1. Default Mode Network Functional Connectivity Results. Physical activity was significantly positively associated with Default Mode Network functional connectivity (A). The interaction between executive function and physical activity was significantly associated with Default Mode Network Functional Connectivity (B).

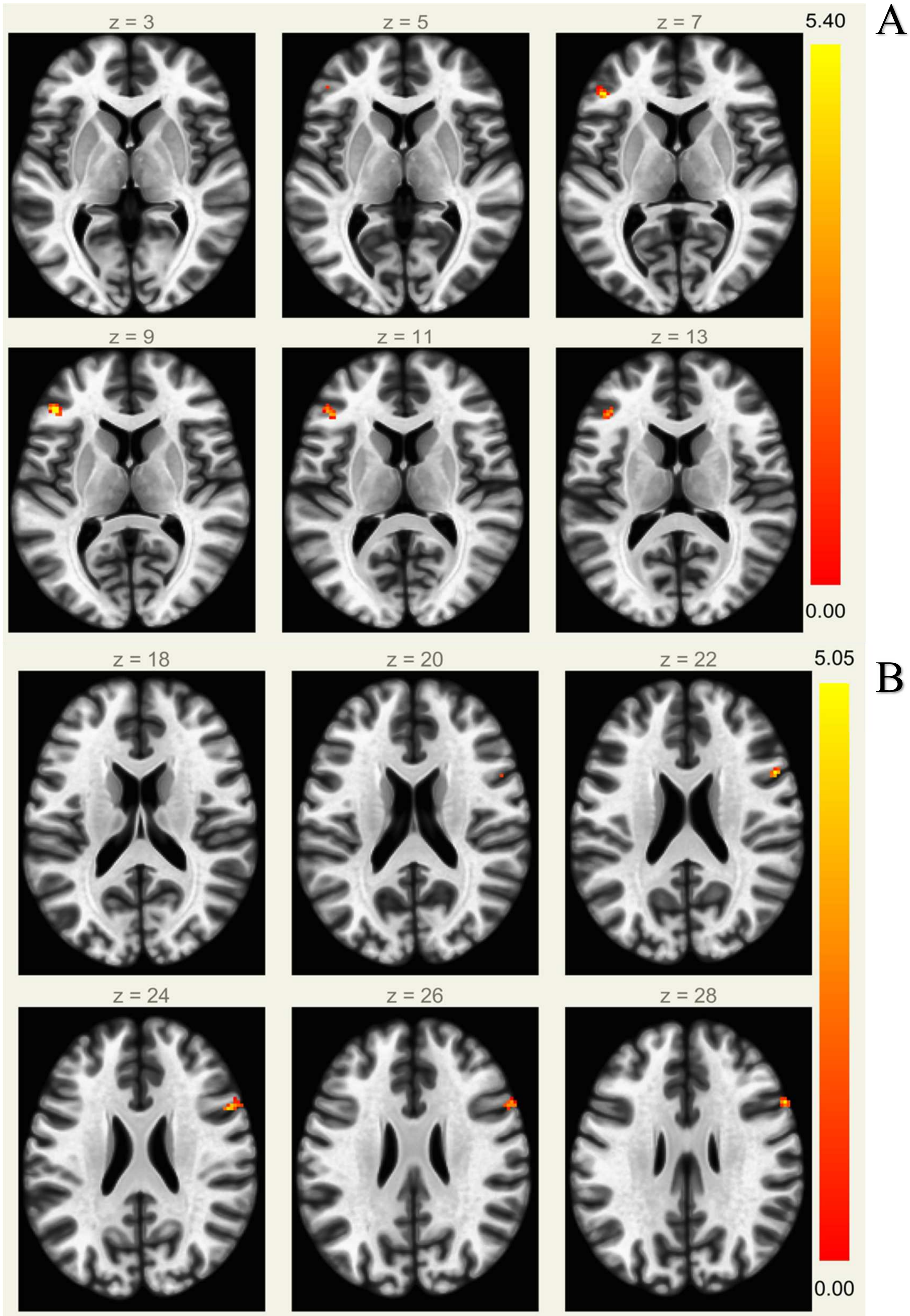

Figure 3.2. Dorsal Attention Network Functional Connectivity Results. Executive function was significantly positively associated with Dorsal Attention Network Functional Connectivity (A). Physical activity was significantly positively associated with Dorsal Attention Network Functional Connectivity (B).

CHAPTER 4

PHYSICAL ACTIVITY AND FITNESS MODERATE THE ASSOCIATION BETWEEN EXECUTIVE FUNCTION AND ANTI-CORRELATED NETWORKS IN THE AGING BRAIN[2]

[2] To be submitted to *Frontiers in Aging Neuroscience* by Marissa Ann Gogniat

Abstract

Physical activity and fitness have been shown to be neuroprotective in the aging process, but the exact mechanisms underlying this neuroprotection need to be further evaluated. The current study sought to examine the influence of physical activity and fitness on the association between executive function and the strength of anti-correlated brain networks in community-dwelling older adults. Participants were 51 older adults (M = 72.94 years, SD = 6.12) who participated in neuropsychological testing, physical activity and fitness measurements, and magnetic resonance imaging (MRI). Moderated regression analysis was used to analyze the influence of physical activity and fitness on the association between cognitive performance and the anti-correlation between the Default Mode Network (DMN) and Dorsal Attention Network (DAN). There was a significant main effect of physical activity and fitness on executive function, and no main effect of DMN/DAN anti-correlations on executive function. There was a significant moderating effect of average steps and the six-minute walk test (6MWT) on the relationship between DMN/DAN anti-correlations and executive function, suggesting that for individuals with the lowest levels of DMN/DAN anti-correlation, higher physical activity and fitness is associated with greater executive function. Results indicate physical activity and fitness may serve as protective factors for the aging brain.

Introduction

It is important to examine lifestyle factors that may provide neuroprotection for the brain in the aging process. Exercise interventions and physical activity have been shown to positively impact cognition in older adults (Colcombe & Kramer, 2003; Kelly, Loughrey, Lawlor, Robertson, Walsh & Brennan, 2014; Northey et al., 2018), but the mechanisms underlying this neuroprotection are still not fully understood. There is a need to understand these mechanisms in order to inform future prevention and intervention work targeting cognitive decline associated with normal and pathological aging through exercise. The present study aims to add to this literature by examining the impacts of physical activity and fitness on the association between functional connectivity in the aging brain and executive function.

Numerous studies have examined the impact of physical activity on cognition in older adults. As self-report of physical activity may be subject to bias, many recent studies have utilized accelerometry and actigraphy to obtain an objective measure of older adults' physical activity. These studies found associations between physical activity level and cognitive function (Barnes et al., 2008; Kerr et al., 2013; Iso-Markku et al., 2018). The ability to objectively record physical activity has allowed for components such as intensity, number of steps, and distance traveled to be examined in tandem. While many studies propose that the intensity of the physical activity has the greatest association with cognitive ability in older adulthood, (Angevaren et al., 2007; Brown et al., 2012; Kerr et al., 2013; Zhu et al., 2015) others suggest that just the amount of movement is significantly related to cognition and specifically executive function ability (Barnes et al., 2008; Buchman, Wilson, & Bennett, 2008). Additionally, physical fitness level measured via performance-based measures has been shown to be related to executive function performance in older adults (Churchill et al., 2002; McGough et al., 2011; Ferreira et al., 2015), often showing greater associations than physical activity level because it is a more specific measure of cardiorespiratory fitness (Sherwood et al., 2019). Using objective measures of physical activity and fitness can allow for more ecologically valid information to be gathered on the association between these measures and cognition in older adulthood.

While exercise interventions have been shown to positively impact cognitive function in aging, evidence from meta-analyses indicates that the largest impact may be on executive function (Angevaren et al., 2007; Colcombe & Kramer, 2003; Smith et al., 2010; Sanders et al., 2019). Executive function encompasses many different higher order cognitive processes including inhibition, cognitive flexibility, working memory, planning, and fluency, and is essential for maintaining independence and quality of life in older adulthood (Diamond, 2013; Clark et al., 2012; Johnson, Lui, & Yaffe, 2007; Thibeau et al., 2016). Executive function ability has been shown to be negatively impacted by aging (Raz & Rodrigue, 2006; Kirova, Bays, & Lagalwar, 2015; Murman, 2015), as the brain areas that house these abilities are some of the last to be fully formed and connected in development and are thus often the first to be impacted in the aging process (Arain et al., 2013). Therefore, the preservation of executive function abilities in the aging process using physical activity and exercise training has been of great interest to researchers and clinicians.

Several recent studies have examined the associations between physical activity and fitness and the functional connectivity of the aging brain. Self-reported physical activity has been shown to be related to functional connectivity in older adults (Dorsman et al., 2020), including key networks effected by aging such as the default mode network (DMN; Boraxbekk et al., 2016). The DMN is traditionally viewed as a network that is active at rest and inactive during external cognitive tasks (Raichle et al., 2001; Uddin, Clare Kelly, Biswal, Xavier Castellanos, & Milham, 2009; Ferreira et al., 2016). In addition, objectively measured physical activity level has been associated with functional connectivity in the dorsal attention network (DAN), a network that is involved in sustained attention and is negatively impacted by aging (Fox, Corbetta, Snyder, Vincent, & Raichle, 2006; Veldsman et al., 2017). Others have examined physical fitness and its association with functional connectivity in older adults. Voss and colleagues (2010) showed that functional connectivity in the DMN (i.e., both specific and global) mediated the association between aerobic fitness and executive function in older adults, indicating that greater fitness may preserve the functional connections in the DMN. However, when comparing physical activity and physical fitness, Voss and colleagues (2016) showed that there was an association between physical fitness, not current physical activity level, and executive function for older adults that was mediated by DMN and DAN functional connectivity.

While several studies have examined the associations between physical activity and functional connectivity, the impact of physical activity and fitness on the functional connectivity of anti-correlated brain networks in aging is unknown. The aging process negatively impacts the strength of brain network anti-correlations, which are networks that are strongly negatively correlated and have theoretically opposed functional roles during rest (Fox et al., 2005; Fox, Zhang, Snyder, & Raichle, 2009). A prime example of anti-correlated networks is the DMN and DAN, whose negative correlations have been shown to weaken with age (Wu et al., 2011; Ferreira et al., 2016). The strength of anti-correlations between the DMN and DAN are related to executive function and working memory performance across the lifespan (Hampson, Driesen, Roth, Gore, & Constable, 2010; Anticevic et al., 2012; Franzmeier et al., 2017). Therefore, there is a need to examine whether physical activity and fitness might impact the association between DMN/DAN anti-correlations and executive function in older adults.

The purpose of the current study was to evaluate whether DMN/DAN anti-correlations were related to executive function performance in healthy older adults, and whether physical activity and fitness measures (i.e., steps, MVPA, 6MWT) moderate this association. Based on prior literature, we hypothesized that DMN/DAN anti-correlations and physical activity and fitness measures would be significantly associated to executive function performance. We also hypothesized that physical activity and physical fitness measures would moderate the association between DMN/DAN anti-correlations and executive function performance such that higher levels of physical activity and physical fitness would buffer the association between lower DMN/DAN anti-correlations and executive function.

Methods

Participants

Participants were 51 community-dwelling older adults (aged 65+ years) from the surrounding community of a southeastern college town recruited over a four-year period. Some participants' data were acquired as part of a separate intervention study, but for the purpose of the present study, only data from their baseline assessments (pre-intervention) was used. All participants engaged in sessions that included neuropsychological testing, physical activity and fitness measurements, and magnetic resonance imaging (MRI). Participants were eligible if they had no self-reported major neurological (e.g., Alzheimer's, Parkinson's) or psychiatric disorders, were right-handed, Native English speakers, and were compatible with the MRI environment (i.e., no metal implants, no recent surgeries, etc). Participants were excluded if their cognitive functioning was below mild cognitive impairment (MCI) as indicated by their performance on the MMSE (totals score < 24). Informed consent was obtained from all participants and the Declaration of Helsinki was followed.

Physical Activity and Fitness

Physical Activity. Physical activity was measured using NL-1000 Accelerometers (New Lifestyles, Inc.; Lee's Summit, Missouri, USA). These accelerometers measure physical activity intensity, number of steps, and distance covered using a piezoelectric strain gauge. Participants in this study wore the accelerometer on their waist for 7 days. For adults, activity intensity levels of 1 to 3 capture light activity (e.g., analogous to typical easy walking), levels 4 to 6 indicate moderate activity (e.g., analogous to typical jogging levels of activity), and levels 7 to 9 are categorized as vigorous activity (e.g., analogous to sprinting activity) as captured by changes to the piezoelectric strain gauge. Moderate/Vigorous Physical Activity (MVPA) is a measurement of the time spent in moderate to vigorous activity and is captured when the device is set to record activity between levels 4 to 9 (NL-1000 Activity Monitor: user's guide & record book, 2005). Time spent in MVPA was broken down into 24-hour increments and the amount of time spent in MVPA was displayed in days up to day 7 on the device. MVPA has been shown to be both valid and reliable in measuring physical activity level in children and adults (Ayabe et al., 2006; McClain & Tudor-Locke, 2009). These settings were used in the current study. In the current study, MVPA was calculated as the average time in seconds per day spent in moderate to vigorous physical activity over the span of seven days using the following equation: Average MVPA = [(Total Time MVPA Day 1 + Total Time MVPA Day 2 + Total Time MVPA Day 3 + Total Time MVPA Day 4 + Total Time MVPA Day 5 + Total Time MVPA Day 6 + Total Time MVPA Day 7)/7]. In addition, the average number of steps taken per day over the span of seven days was calculated as follows: Average Steps = [(Total Steps Day 1 + Total Steps Day 2 + Total Steps Day 3 + Total Steps Day 4 + Total Steps Day 5 + Total Steps Day 6 + Total Steps Day 7)/7]. Usable accelerometry data was obtained from 47 participants.

Physical Fitness. Physical fitness was assessed by the 6-minute walk test (6MWT) using the protocol described by Peeters and Mets (1996). The walking course took place in indoor building hallways with predetermined and measured distances prior to each session. Distance travelled along the course was recorded. Participants were instructed to walk as quickly as they could and cover the most distance over a 6-minute time period. Distance covered over the time period was measured in meters. Participants were instructed to wear comfortable clothing and shoes and to take breaks as necessary. The 6MWT has been shown to be reliable and valid in discriminating physical capacity and fitness in older adults (Bautmans, Lambert, & Mets, 2004; Mangan & Judge, 1994; Sperandio et al., 2015), and performance has been shown to have convergent validity with treadmill testing (Rikli & Jones, 1998) which is a common way to determine cardiorespiratory fitness level (Huggett, Connelly, & Overend, 2005). 6MWT data was obtained from all 51 participants.

Neuropsychological Measures

Each participant received neuropsychological testing by a trained graduate student. All participants were administered the Delis-Kaplan Executive Function System (DKEFS) Color-Word Interference Test, the DKEFS Verbal Fluency Test, and the DKEFS Trail Making Test, which are subtests of the full DKEFS battery. The DKEFS Trail-making Test, Verbal Fluency, and Color Word Interference have good psychometric properties, measure non-verbal and verbal executive function, and have relatively brief administration times (Delis et al., 2004). For the Trail Making Test, a scaled score was calculated for Condition 4: Number-Letter Switching, which measures the ability to set-shift. For Verbal Fluency, a scaled score for Category Switching was calculated, which measures the ability to generate words that fall under categories while being able to set-shift. For the Color-Word Inference Test, a scaled score was calculated for Condition 4: Inhibition/Switching, which measures verbal inhibition and set-shifting (D-KEFS; Delis, Kaplan, & Kramer, 2001). All scaled scores were then averaged together for each participant to create an executive function composite specific to set-shifting. In order to determine whether these three subtests were correlated with each other and were thus measuring similar constructs, a Cronbach's alpha based on standardized items (Bland & Altman, 1997) was calculated (α=.607) indicating an acceptable fit for a small number of items (Hinton, Brownlow, McMurray, & Cozens, 2004).

Neuroimaging

MRI Acquisition. Brain images were acquired using a General Electric (GE; Waukesha, WI) 3 T Signa HDx MRI system. A high-resolution 3D T1-weighted fast spoiled gradient recall echo sequence was used to collect structural scans (TR = 7.5 ms; TE = < 5ms; FOV = 256 × 256 mm matrix; flip angle = 20°; slice thickness = 1.2 mm; 154 axial slices) with an acquisition time of 6 minutes and 20 seconds. This protocol collected 176 images. Resting state functional scans were aligned to each participant's anterior commissure-posterior commissure (AC-PC) line, collected axially, and used a T2*-weighted single shot EPI sequence (TR = 5000 ms; TE = 25 ms; 90° RF pulse; acquisition matrix = 128 × 128; FOV = 220 × 220 mm; in-plane resolution = 220/128 mm; slice thickness = 2 mm; 60 interleaved axial slices). Total acquisition time was 9 minutes and 25 seconds. 108 volumes were acquired.

Resting State Pre-processing. The resting state functional scans were pre-processed using the default pre-processing pipeline in the CONN toolbox from the Neuroimaging Tools & Resources Collaboratory (v.18.b; www.nitrc.org/projects/conn; Whitfield-Gabrieli & Nieto-Castanon, 2012). The CONN Toolbox default pre-processing pipeline includes realigning and unwarping the data, centering the coordinates, applying a slice-time correction, outlier detection (using ART-based identification of outlier scans for scrubbing; www.nitric.org/projects/artifact_detect), direct functional and structural segmentation and normalization (using simultaneous Grey Matter/White Matter/CSF segmentation and MNI normalization), and functional smoothing. In addition, functional scans were denoised in CONN to remove physiological effect, subject movement, and other confounding effects from the BOLD signal. Within the CONN Toolbox, cortical and subcortical ROIs were defined by the Harvard-Oxford atlas (Frazier et al., 2005; Desikan et al., 2006; Makris et al., 2006; Goldstein et al., 2007), Automated Anatomical Labelling (AAL) Atlas (Tzourio-Mazoyer et al., 2002), and CONN default networks.

ROI-to-ROl Analyses. ROI-to-ROI analyses were conducted to examine the level of functional connectivity bilaterally between regions that compose the DMN and regions that compose the DAN with greater sensitivity, as these networks are expected to be anti-correlated with each other (Fox et al., 2005). In particular, the anti-correlation between the medial prefrontal cortex (DMN ROI) and left intraparietal sulcus (DAN ROI) was chosen because it was the strongest ROI-to-ROI anti-correlation value from all possible DMN and DAN ROI-to-ROI combinations in this sample. ROI-to-ROI analyses produced ROI-to-ROI based correlation (RRC) maps for each participant in the same way as seed-to-voxel analyses but by substituting the target voxel BOLD time series with a target ROI time series. Group summary maps of RRC maps for each participant were used in statistical analyses (voxel-wise FDR-corrected $p<.05$).

To test the moderating effect of physical activity and fitness on the association between DMN/DAN anti-correlations and executive function, we used a moderated regression analysis, as it is the recommended method for testing for the effects of interactions (Cohen, Cohen, West & Aiken, 1983). Data was analyzed using the Statistical Package for Social Sciences (IBM SPSS Version 26.0). The independent variable in our analyses was the DMN/DAN anti-correlation coefficient extracted for each participant and the dependent variable was executive function. The moderator variables used in the analyses were physical activity and physical fitness measures (i.e., MVPA, steps, 6MWT). All variables in the model were measured continuously. To determine the main effects of the predictor variables on executive function, multiple linear regression analyses of DMN/DAN anticorrelations, and physical activity/fitness and DMN/DAN anti-correlations were conducted (i.e., DMN/DAN anti-correlation entered into step 1 of the regression model, physical activity/fitness entered in step 2, with executive function as the dependent variable). To determine the interaction effect of the moderator, product terms for the standardized independent variables were created. The DMN/DAN anti-correlation x physical activity/fitness interaction term was included in the model in step 3. The significance of R^2 in both the main effects and interaction model was evaluated. The Hayes Process Macro (Hayes, 2017) was used to probe and visualize the moderation.

Results

Descriptive Characteristics

Table 4.1 provides means and standard deviations for sociodemographic characteristics. The average age was 72.94 years (SD = 6.12). Slightly over half (56.9%) of the participants were female and a majority of the participants were White (92.2%). On average, participants had completed 17.06 years (SD = 2.43) of education. The average steps per day (M = 5360.91; SD = 3223.83) was below most recommended averages for older adults, as was the average daily time spent in MVPA (M = 772.15 sec; SD = 966.15; Garber et al., 2011; Tudor-Locke et al., 2011; Kraus et al., 2019; CDC, 2021). The average 6MWT performance was in line with similar community-dwelling older adult samples (Steffen, Hacker & Mollinger, 2002). Our sample fell in the average range on the composite measure of executive functioning (M = 11.54 SD = 2.45).

Steps

Results of the regression analysis using steps as the physical activity variable of interest indicated no significant effect of DMN/DAN anti-correlations on executive function ($F(1, 45) = .574$, $R^2 = .013$, $p = .453$). There was a significant main effect of steps on executive function, with steps explaining 26% more of the variance in executive functioning above and beyond DMN/DAN anti-correlations ($F(2, 44) = 8.027$, $\Delta R^2 = .255$, $p < .001$). The interaction term accounted for a small but significant amount of variance above and beyond DMN/DAN anti-correlation and steps, indicating that a moderation was occurring ($F(3, 43) = 7.230$, $\Delta R2 = .068$, $p = .042$). The results of the moderator analysis, including visualization of coefficients for the main effects and interaction term are presented in Table 4.2 and Figure 4.1.

This statistical model was replicated using Hayes Process Macro to probe for conditional e□ects, as it allows for the visualization by plotting the relationship between DMN/DAN anti-correlations and executive function performance at di□erent levels of the moderator. Results of these analyses are displayed in Figure 4.2. This graph depicts the relationship between DMN/DAN anti-correlations and executive function performance at mean-centered low (-1 SD), moderate (mean), and high steps (+1 SD). There is a trend detected such that the magnitude and direction of this relationship di□ers based on level of steps. Specifically, we see that the slope and magnitude of the relationship is greatest at lower levels of steps, and as steps increases, the magnitude of this relationship weakens. While the conditional e□ect nears significance at low levels of the moderator, the magnitude of this e□ect decreases with increasing steps and moderate and high levels of the moderator are not significant conditional effects. The conditional effects are displayed in Table 4.3.

MVPA

Results of the regression analysis using MVPA as the physical activity variable of interest indicated no significant effect DMN/DAN anti-correlations on executive function ($F(1, 45) = .574$, $R^2 = .013$, $p = .453$). There was a significant main effect of MVPA on executive function, with steps explaining 12% more of the variance in executive functioning above and beyond DMN/DAN anti-correlations ($F(2, 44) = 3.318$, $\Delta R^2 = .118$, $p = .046$). The interaction term did not account for a significant amount of variance above and beyond DMN/DAN anti-correlations and MVPA, indicating that no moderation was occurring ($F(3, 43) = 3.356$, $\Delta R2 = .059$, $p = .085$). The results of this analysis, including visualization of coefficients for the main effects are presented in Table 4.2 and Figure 4.1.

6MWT

Results of the regression analysis using the 6MWT as the variable of interest indicated no significant effect DMN/DAN anti-correlations on executive function ($F(1, 49) = .487$, $R^2 = .010$, $p = .489$). There was a significant main effect of the 6MWT on executive function, with the 6MWT explaining 14% more of the variance in executive function above and beyond DMN/DAN anti-correlations ($F(2, 48) = 4.241$, $\Delta R^2 = .140$, $p = .007$). The interaction term accounted for a significant amount of variance above and beyond DMN/DAN anti-correlation and the 6MWT, indicating that a moderation was occurring ($F(3, 47) = 8.113$, $\Delta R2 = .191$, $p = .001$). The results of the moderator analysis, including visualization of coefficients for the main effects and interaction term are presented in Table 4.2 and Figure 4.1.

This statistical model was replicated using Hayes Process Macro to probe for visualization of conditional effects (Figure 4.2.) This graph depicts the relationship between DMN/DAN anti-correlations and executive function performance at mean-centered low (-1 SD), moderate (mean), and high (+1 SD) 6MWT performance. There is a trend detected such that the magnitude and direction of this relationship differs based on 6MWT performance. Specifically, we see that the slope is negative, and magnitude of the relationship is strongest at low levels of 6MWT performance. At high levels of 6MWT performance, the magnitude of the relationship is less strong, but the slope is positive. The conditional effect is significant at both low and high levels of the moderator. The conditional effects are displayed in Table 4.3.

Discussion

Previous evidence suggests that physical activity and fitness are neuroprotective in the aging process. The current study sought to examine the associations between anti-correlated brain networks and executive function performance in healthy older adults, and whether physical activity and fitness measures moderated this association. Consistent with previous literature, all measures of physical activity (MVPA and steps) and fitness (6MWT) were significantly positively associated with executive function, indicating that increased physical activity and fitness were related to better executive functioning performance. However, contrary to our hypotheses, the anti-correlation between DMN and DAN networks was not significantly associated with executive function. While unexpected, there is evidence that similar resting state anti-correlated networks are greatly reduced in the aging process and therefore may not be associated significantly associated with cognitive functioning (Keller et al., 2015). Additional studies and further replication examining the associations between anti-correlated networks and cognitive function in aging is needed.

The results from the moderated regression analyses indicated that both steps and the 6MWT moderated the association between DMN/DAN anti-correlations and executive function, while MVPA did not. In the moderation model examining steps, the conditional effect was such that the magnitude of the relationship between DMN/DAN anti-correlations and executive function was strongest at lower levels of steps, and as steps increased, the magnitude of the relationship was weaker. This suggests that for those whose brains are less optimally anti-correlated, greater steps is associated with greater executive function performance. This finding supports the STAC-r model (Reuter-Lorenz & Park, 2014), which posits that lifestyle factors such as physical activity might act as compensatory scaffolding to support brain health and thus the maintenance of cognitive function in aging. It is also particularly important because it suggests that physical activity might impact both the functioning of the brain and cognitive outcomes, further supporting the use of physical activity as an intervention.

In the moderation model examining the 6MWT, the conditional effect was such that it was strongest at low levels of fitness but was also significant at high levels of fitness. The conditional effect at low levels of fitness is a similar effect found in the steps model, suggesting that for those with the lowest levels of network anti-correlation, higher fitness is associated with greater executive function. The significant conditional effect at high levels of fitness was somewhat unexpected, as the slope suggests that as brain networks become more anti-correlated, executive function is reduced in individuals with high levels of fitness. It is possible that this effect represents the idea that chronic, high intensity exercise frequently engaged in by high-fit older adults may actually have some detrimental effects on the brain and cognition, with possible mechanisms including increased inflammation and cortisol production (Traustadóttir, Bosch, Cantu, & Matt, 2004; Corrazza et al., 2014), a reduction in mitochondria, and blood glucose dysfunction (Flockhart et al., 2021). This may also account for why we do not see any association with the intensity of physical activity (measured via MVPA) and executive function as well as no moderating effect of MVPA on the association between DMN/DAN anti-correlations and executive function. In addition, it is worth noting that DMN/DAN anti-correlations were not significantly associated with executive function in this model and this effect should be interpreted with that in mind. Further exploration is needed to examine at what level the stress of chronic exercise may actually have negative impacts on the brain and cognition.

To the authors' knowledge, this study is first to examine the impact of physical activity and fitness on the associations between DMN/DAN anti-correlations and executive function in older adults and suggests that higher levels of fitness might be neuroprotective for both brain function and cognitive function. However, this study has some limitations that should be considered in light of generalizability and future study replication. This study was cross-sectional, which limits the causality of the results. While there is evidence to suggest that physical activity modifies brain structure, which in turn modifies brain function, it is also possible that these processes have bidirectional components (e.g., brain function might also impact how much an individual engages in exercise). This sample of community-dwelling older adults was mostly White, relatively sedentary, and highly educated, which limits the generalizability of these findings but also indicates that effects might be even greater for those with lower levels of education (i.e., lower cognitive reserve). Future studies should consider replication with a larger, more representative sample that includes greater variability in physical activity, education levels, and race. In addition, future studies might consider how additional anti-correlated brain networks are impacted by physical activity and fitness in older adulthood.

References

Anticevic, A., Cole, M.W., Murray, J.D., Corlett, P.R., Wang, X.J., & Krystal, J.H., (2012). The role of default network deactivation in cognition and disease. *Trends Cognitive Sciences 16,* 584e592. doi: 10.1016/j.tics.2012.10.008

Ayabe, M., Katamoto, S., Kumahara, H., Naito, H., Tanaka, H., & Brubaker, P.H. (2006). Validity and reliability of the simple assessment of the time spent in moderate to vigorous intensity physical activity under the controlled conditions. *Med Sci Sports Exerc*, *38*, S555. doi:10.1249/00005768-200605001-02310

Barnes, D.E., Blackwell, T., Stone, K.L., Goldman, S.E., Hillier, T., & Yaffe, K. (2008). Cognition in older women: The importance of daytime movement. Journal of the *American Geriatrics Society, 56*, 1658–1664. doi: 10.1111/j.15325415.2008.01841.x

Bautmans, I., Lambert, M., & Mets, T. (2004). The six-minute walk test in community dwelling elderly: influence of health status. *BMC geriatrics*, *4*, 6. doi: 10.1186/1471-2318-4-6

Bland J., & Altman D. (1997). Statistics notes: Cronbach's alpha. *BMJ,* 314, 572. doi: 10.1136/bmj.314.7080.572

Boraxbekk, C.-J., Salami, A., Wåhlin, A., & Nyberg, L. (2016). Physical activity over a decade modifies age-related decline in perfusion, gray matter volume, and functional connectivity of the posterior default-mode network—A multimodal approach. *NeuroImage, 131*, 133–141. doi: 10.1016/j.neuroimage.201 5.12.010

Brown, B.M., Peiffer, J.J., Sohrabi, H.R., Mondal, A., Gupta, V.B., & Rainey-Smith, S.R. (2012). Intense physical activity is associated with cognitive performance in the elderly. *Translational Psychiatry, 2*, e191. doi: 10.1038/tp.2012.118

Buchman, A. S., Wilson, R. S., & Bennett, D. A. (2008). Total daily activity is associated with cognition in older persons. *The American Journal of Geriatric Psychiatry, 16*(8), 697-701. doi: 10.1097/JGP.0b013e31817945f6

Centers for Disease Control. (2021). How much physical activity do older adults need? Retrieved from https://www.cdc.gov/physicalactivity/basics/older_adults/index.htm

Churchill, J. D., Galvez, R., Colcombe, S., Swain, R. A., Kramer, A. F., & Greenough, W. T. (2002). Exercise, experience and the aging brain. *Neurobiology of aging, 23*(5), 941-955. doi: 10.1016/s0197-4580(02)00028-3.

Clark, L. R., Schiehser, D. M., Weissberger, G. H., Salmon, D. P., Delis, D. C., & Bondi, M. W. (2012). Specific measures of executive function predict cognitive decline in older adults. *Journal of the International Neuropsychological Society*, *18*(1), 118-127. doi: 10.1017/S1355617711001524

Cohen, J., Cohen, P., West, S. G., & Aiken, L. S. (1983). Applied multivariate regression/correlation analysis for the behavioral sciences.

Colcombe, S., & Kramer, A.F. (2003). Fitness effects on the cognitive function of older adults: A meta-analytic study. *Psychological science, 14*, 125-130. doi: 10.1111/1467-9280.t01-101430

Corazza, D. I., Sebastião, É., Pedroso, R. V., Andreatto, C. A. A., de Melo Coelho, F. G., Gobbi, S., ... & Santos-Galduróz, R. F. (2014). Influence of chronic exercise on serum cortisol levels in older adults. *European Review of Aging and Physical Activity, 11*(1), 25-34. doi: /10.1007/s11556-013-0126-8

Delis, D.C., Kaplan, E., & Kramer, J. H. (2001). *Delis-Kaplan Executive Function System (D-KEFS)*. San Antonio, TX: The Psychological Corporation.

Delis, D.C., Kramer, J.H., Kaplan, E., & Holdnack, J. (2004). Reliability and validity of the Delis-Kaplan Executive Function System: An update. *Journal of the International Neuropsychological Society*, *10*, 301-303. doi: 10.1017/S1355617704102191

Desikan, R. S., Ségonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., Buckner, R. L., Dale, A. M., Maguire, R. P., Hyman, B. T., Albert, M. S., & Killiany, R. J. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *NeuroImage*, *31*(3), 968–980. doi: 10.1016/j.neuroimage.2006.01.021

Diamond A. (2013). Executive functions. *Annual review of psychology, 64*, 135–168. doi:10.1146/annurev-psych-113011-143750

Dorsman, K. A., Weiner-Light, S., Staffaroni, A. M., Brown, J. A., Wolf, A., Cobigo, Y., ... & Casaletto, K. B. (2020). Get moving! Increases in physical activity are associated with increasing functional connectivity trajectories in typically aging adults. *Frontiers in aging neuroscience, 12*. doi: 10.3389/fnagi.2020.00104

Ferreira, N. V., Cunha, P. J., da Costa, D. I., dos Santos, F., Costa, F. O., Consolim-Colombo, F., & Irigoyen, M. C. (2015). Association between functional performance and executive cognitive functions in an elderly population including patients with low ankle–brachial index. *Clinical interventions in aging, 10*, 839. doi: 10.2147/CIA.S69270

Ferreira, L. K., Regina, A. C. B., Kovacevic, N., Martin, M. D. G. M., Santos, P. P., Carneiro, C. D. G., ... & Busatto, G. F. (2016). Aging effects on whole-brain functional connectivity in adults free of cognitive and psychiatric disorders. *Cerebral cortex, 26*(9), 3851-3865. doi: 10.1093/cercor/bhv190

Flockhart, M., Nilsson, L. C., Tais, S., Ekblom, B., Apró, W., & Larsen, F. J. (2021). Excessive exercise training causes mitochondrial functional impairment and decreases glucose tolerance in healthy volunteers. *Cell Metabolism.* doi: 10.1016/j.cmet.2021.02.017

Fox, M. D., Snyder, A. Z., Vincent, J. L., Corbetta, M., Van Essen, D. C., & Raichle, M. E. (2005). The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proceedings of the National Academy of Sciences of the United States of America, 102*(27), 9673–9678. doi: 10.1073/pnas.0504136102

Fox, M. D., Corbetta, M., Snyder, A. Z., Vincent, J. L., & Raichle, M. E. (2006). Spontaneous neuronal activity distinguishes human dorsal and ventral attention systems. *Proceedings of the National Academy of Sciences, 103*(26), 10046-10051. doi: 10.173/pnas.0604187103

Franzmeier, N., Buerger, K., Teipel, S., Stern, Y., Dichgans, M., Ewers, M., & Alzheimer's Disease Neuroimaging Initiative (ADNI). (2017). Cognitive reserve moderates the association between functional network anti-correlations and memory in MCI. *Neurobiology of aging, 50,* 152-162. doi: 10.1016/j.neurobiolaging.2016.11.013

Frazier, J. A., Chiu, S., Breeze, J. L., Makris, N., Lange, N., Kennedy, D. N., Herbert, M. R., Bent, E. K., Koneru, V. K., Dieterich, M. E., Hodge, S. M., Rauch, S. L., Grant, P. E., Cohen, B. M., Seidman, L. J., Caviness, V. S., & Biederman, J. (2005). Structural brain magnetic resonance imaging of limbic and thalamic volumes in pediatric bipolar disorder. T*he American journal of psychiatry, 162*(7), 1256–1265. doi: 10.1176/appi.ajp.162.7.1256

Garber, C. E., Blissmer, B., Deschenes, M. R., Franklin, B. A., Lamonte, M. J., Lee, I. M., Nieman, D. C., Swain, D. P., & American College of Sports Medicine (2011). American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Medicine and science in sports and exercise, 43*(7), 1334–1359. doi: 10.1249/MSS.0b013e318213fefb

Goldstein, J. M., Seidman, L. J., Makris, N., Ahern, T., O'Brien, L. M., Caviness, V. S., Jr, Kennedy, D. N., Faraone, S. V., & Tsuang, M. T. (2007). Hypothalamic abnormalities in schizophrenia: sex effects and genetic vulnerability. *Biological psychiatry*, *61*(8), 935–945. doi: 10.1016/j.biopsych.2006.06.027

Hampson, M., Driesen, N., Roth, J. K., Gore, J. C., & Constable, R. T. (2010). Functional connectivity between task-positive and task-negative brain areas and its relation to working memory performance. *Magnetic resonance imaging, 28*(8), 1051-1057. doi: 10.1016/j.mri.2010.03.021

Hayes, A. F. (2017). Introduction to mediation, moderation, and conditional process analysis: A regression-based approach. Guilford Publications.

Hinton, P. R., Brownlow, C., McMurray, I., & Cozens, B. (2004). SPSS explained. East Sussex, UK: Routledge.

Huggett, D.L., Connelly, D.M., & Overend, T.J. (2005). Maximal aerobic capacity testing of older adults: A Critical review. *The Journals of Gerontology: Series A*, *1,* 57–66. doi: 10.1093/gerona/60.1.57

Iso-Markku, P., Waller, K., Vuoksimaa, E., Vähä-Ypyä, H., Lindgren, N., Heikkilä, K., … Kujala, U. M. (2018). Objectively measured physical activity profile and cognition in Finnish elderly twins. *Alzheimer's & dementia 4*, 263–271. doi:10.1016/j.trci.2018.06.007

Johnson, J. K., Lui, L. Y., & Yaffe, K. (2007). Executive function, more than global cognition, predicts functional decline and mortality in elderly women. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *62*(10), 1134-1141. doi: 10.1093/gerona/62.10.1134.

Keller, J. B., Hedden, T., Thompson, T. W., Anteraper, S. A., Gabrieli, J. D., & Whitfield-Gabrieli, S. (2015). Resting-state anticorrelations between medial and lateral prefrontal cortex: association with working memory, aging, and individual differences. *Cortex; a journal devoted to the study of the nervous system and behavior*, *64*, 271–280. doi: 10.1016/j.cortex.2014.12.001

Kelly, M. E., Loughrey, D., Lawlor, B. A., Robertson, I. H., Walsh, C., & Brennan, S. (2014). The impact of exercise on the cognitive functioning of healthy older adults: A Systematic review and meta-analysis. *Ageing research reviews, 16*, 12-31. doi: 10.1016/j.arr.2014.05.002

Kerr, J., Marshall, S. J., Patterson, R. E., Marinac, C. R., Natarajan, L., Rosenberg, D., ... & Crist, K. (2013). Objectively measured physical activity is related to cognitive function in older adults. *Journal of the American Geriatrics Society, 61*(11), 1927-1931. doi: 10.1249/MSS.0000000000001079

Kirova, A. M., Bays, R. B., & Lagalwar, S. (2015). Working memory and executive function decline across normal aging, mild cognitive impairment, and Alzheimer's disease. *BioMed research international*, 2015. doi: 10.1155/2015/748212

Kraus, W. E., Janz, K. F., Powell, K. E., Campbell, W. W., Jakicic, J. M., Troiano, R. P., ... & 2018 Physical Activity Guidelines Advisory Committee. (2019). Daily step counts for measuring physical activity exposure and its relation to health. *Medicine and science in sports and exercise, 51*(6), 1206. doi: 10.1249/MSS.0000000000001932

Makris, N., Goldstein, J. M., Kennedy, D., Hodge, S. M., Caviness, V. S., Faraone, S. V., Tsuang, M. T., & Seidman, L. J. (2006). Decreased volume of left and total anterior insular lobule in schizophrenia. *Schizophrenia research, 83*(2-3), 155–171. doi: 10.1016/j.schres.2005.11.020

Mangan D, & Judge J. (1994). Reliability and validation of the six minute walk. *J Am Geriatr Soc*., *42*, SA73.

McClain, J. & Tudor-Locke, C. (2009). Objective monitoring of physical activity in children: Considerations for instrument selection. *J Sci Med Sport, 12*, 526–533. doi: 10.1016/j.jsams.2008.09.012

McGough, E. L., Kelly, V. E., Logsdon, R. G., McCurry, S. M., Cochrane, B. B., Engel, J. M., & Teri, L. (2011). Associations between physical performance and executive function in older adults with mild cognitive impairment: gait speed and the timed "up & go" test. *Physical therapy, 91*(8), 1198-1207. doi: 10.2522/ptj.20100372

Murman, D. L. (2015). The Impact of age on cognition. *Seminars in Hearing*, *36*, 111–121. doi: 10.1055/s-0035-1555115

New Lifestyles. (2005). NL-1000 Activity Monitor: User's guide & record book. Lees Summit, MO: New-Lifestyles Inc.

Northey, J. M., Cherbuin, N., Pumpa, K. L., Smee, D. J., & Rattray, B. (2018). Exercise interventions for cognitive function in adults older than 50: a systematic review with meta-analysis. *Br J Sports Med, 52*, 154-160. doi: 10.1136/bjsports-2016-096587

Peeters, P. & Mets, T. (1996). The 6-minute walk as an appropriate exercise test in elderly patients with chronic heart failure. *J Gerontol A Biol Sci Med Sci, 51*, M147–51. doi: 10.1093/gerona/51a.4.m147

Raichle, M.E., MacLeod, A.M., Snyder, A.Z., Powers, W.J., Gusnard, D.A., & Shulman, G.L. (2001). A default mode of brain function. *Proc Natl Acad Sci U S A*., *98*(2):676–82. doi: 10.1073/pnas.98.2.676

Raz, N., & Rodrigue, K. M. (2006). Differential aging of the brain: patterns, cognitive correlates and modifiers. *Neuroscience & Biobehavioral Reviews, 30*(6), 730-748. doi: 10.1016/j.neubiorev.2006.07.001

Reuter-Lorenz, P. A., & Park, D. C. (2014). How does it STAC up? Revisiting the scaffolding theory of aging and cognition. *Neuropsychology review, 24*(3), 355–370. doi: 10.1007/s11065-014-9270-9

Rikli, R. E., & Jones, C. J. (1998). The reliability and validity of a 6-minute walk test as a measure of physical endurance in older adults. *Journal of aging and physical activity, 6*(4), 363-375. doi: 10.1123/japa.6.4.363

Sanders, L., Hortobágyi, T., la Bastide-van Gemert, S., van der Zee, E. A., & van Heuvelen, M. (2019). Dose-response relationship between exercise and cognitive function in older adults with and without cognitive impairment: A Systematic review and meta-analysis. *PloS one*, *14*, e0210036. doi: 10.1371/journal.pone.0210036

Sherwood, J. J., Inouye, C., Webb, S. L., Zhou, A., Anderson, E. A., & Spink, N. S. (2019). Relationship between physical and cognitive performance in community dwelling, ethnically diverse older adults: a cross-sectional study. *PeerJ, 7*, e6159. doi: 10.7717/peerj.6159

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. *Psychosom Med, 72*, 239–252. doi: 10.1097/PSY.0b013e3181d14633

Sperandio, E. F., Arantes, R. L., Matheus, A. C., Silva, R. P., Lauria, V. T., Romiti, M., … Dourado, V. Z. (2015). Intensity and physiological responses to the 6-minute walk test in middle-aged and older adults: a comparison with cardiopulmonary exercise testing. *Brazilian journal of medical and biological research, 48*, 349–353. doi:10.1590/1414-431X20144235.

Steffen, T. M., Hacker, T. A., & Mollinger, L. (2002). Age- and gender-related test performance in community-dwelling elderly people: Six-Minute Walk Test, Berg Balance Scale, Timed Up & Go Test, and gait speeds. *Physical therapy, 82*(2), 128–137. doi: 10.1093/ptj/82.2.128

Thibeau, S., McFall, G. P., Wiebe, S. A., Anstey, K. J., & Dixon, R. A. (2016). Genetic factors moderate everyday physical activity effects on executive functions in aging: Evidence from the Victoria Longitudinal Study. *Neuropsychology*, *30*(1), 6. doi: 10.1037/neu0000217

Traustadóttir, T., Bosch, P. R., Cantu, T., & Matt, K. S. (2004). Hypothalamic-pituitary-adrenal axis response and recovery from high-intensity exercise in women: effects of aging and fitness. *The Journal of Clinical Endocrinology & Metabolism, 89*(7), 3248-3254. doi: 10.1210/jc.2003-031713

Tudor-Locke, C., Craig, C. L., Aoyagi, Y., Bell, R. C., Croteau, K. A., De Bourdeaudhuij, I., ... & Blair, S. N. (2011). How many steps/day are enough? For older adults and special populations. *International journal of behavioral nutrition and physical activity, 8*(1), 1-19. doi: 10.1186/1479-5868-8-80

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B., & Joliet, M., (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain., *NeuroImage, 15*, 273–289. doi: 10.1006/nimg.2001.0978

Uddin, L. Q., Clare Kelly, A. M., Biswal, B. B., Xavier Castellanos, F., & Milham, M. P. (2009). Functional connectivity of default mode network components: correlation, anticorrelation, and causality. *Human brain mapping, 30*(2), 625-637. doi: 10.1002/hbm.20531

Veldsman, M., Churilov, L., Werden, E., Li, Q., Cumming, T., & Brodtmann, A. (2017). Physical Activity After Stroke Is Associated With Increased Interhemispheric Connectivity of the Dorsal Attention Network. *Neurorehabilitation and Neural Repair, 31*(2), 157–167. doi: 10.1177/1545968316666958

Voss, M. W., Erickson, K. I., Prakash, R. S., Chaddock, L., Malkowski, E., Alves, H., ... Kramer, A. F. (2010). Functional connectivity: A source of variance in the association between cardiorespiratory fitness and cognition? *Neuropsychologia, 48*(5), 1394–1406. doi: 10.1016/j.neuropsycholog ia.2010.01.005

Voss, M. W., Weng, T. B., Burzynska, A. Z., Wong, C. N., Cooke, G. E., Clark, R., ... Kramer, A. F. (2016). Fitness, but not physical activity, is related to functional integrity of brain networks associated with aging. *NeuroImage, 131*, 113–125. doi: 10.1016/j.neuroimage.201 5.10.044

Whitfield-Gabrieli, S., & Nieto-Castanon, A. (2012). Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. *Brain connectivity, 2*(3), 125-141. doi: 10.1089/brain.2012.0073

Wu J.T., Wu, H.Z., Yan, C.G., Chen, W.X., Zhang, H.Y., He, Y., & Yang H.S. (2011). Aging-related changes in the default mode network and its anti-correlated networks: a resting-state fMRI study. *Neurosci Lett. 504*, 62–67. doi: 10.1016/j.neulet.2011.08.059

Zhu, W., Howard, V. J., Wadley, V. G., Hutto, B., Blair, S. N., Vena, J. E., ... & Hooker, S. P. (2015). Association between objectively measured physical activity and cognitive function in older adults—The Reasons for Geographic and Racial Differences in Stroke Study. *Journal of the American Geriatrics Society, 63*(12), 2447-2454. doi: 10.1111/jgs.13829.

Table 4.1

Sample Demographics and Key Study Variables

Variable	% or M (SD)
Demographics	
Age	72.94 (6.12)
Sex (% female)	56.9%
Race (% White)	92.2%
Years of Education	17.06 (2.43)
Steps (day)	5360.91 (3223.83)
MVPA (sec/day)	772.15 (966.15)
6MWT (m)	469.12 (102.93)
DKEFS Composite	11.54 (2.45)

MVPA = moderate to vigorous physical activity; 6MWT = 6-minute walk test; DKEFS = Delis Kaplan Executive Function System

Table 4.2

Model Summary for Primary Moderator Analyses

Model	R	R^2	Adjusted R^2	Standard Error of the Estimate	R^2 Change	F Change	Significant F Change
1	.112	.013	-.009	2.456	.013	.574	.453
2	.517	.267	.234	2.139	.255	15.298	.000
3	.579	.335	.289	2.061	.068	4.396	.042
4	.112	.013	-.009	2.456	.013	.574	.453
5	.362	.131	.092	2.330	.118	5.997	.018
6	.436	.190	.133	2.276	.059	3.114	.085
7	.099	.010	-.010	2.464	.010	.487	.489
8	.388	.150	.115	2.306	.140	7.927	.007
9	.584	.341	.299	2.052	.191	13.625	.001

1. Predictors: (Constant) DMN-DAN Anti-correlation
2. Predictors: (Constant) DMN-DAN Anti-correlation, Steps
3. Predictors: (Constant) DMN-DAN Anti-correlation, Steps, Anti-correlation x Steps

4. Predictors: (Constant) DMN-DAN Anti-correlation
5. Predictors: (Constant) DMN-DAN Anti-correlation, MVPA
6. Predictors: (Constant) DMN-DAN Anti-correlation, MVPA, Anti-correlation x MVPA

7. Predictors: (Constant) DMN-DAN Anti-correlation
8. Predictors: (Constant) DMN-DAN Anti-correlation, 6MW
9. Predictors: (Constant) DMN-DAN Anti-correlation, 6MW, Anti-correlation x 6MWT

Table 4.3

Conditional Effects at Values of Moderator

Moderator	Effect	SE	t	*p*	LLCI	ULCI
Steps						
-3223.827	-6.267	3.334	-1.880	.067	-12.990	.456
.000	-2.459	2.122	-1.159	.253	-6.738	1.820
3223.827	1.348	2.458	.549	.586	-3.608	6.305
6MW						
-102.931	-7.391	1.900	-3.890	<.001	-11.214	-3.569
.000	-1.058	1.687	-.627	.534	-4.451	2.336
102.931	5.276	2.521	2.093	.042	.204	10.348

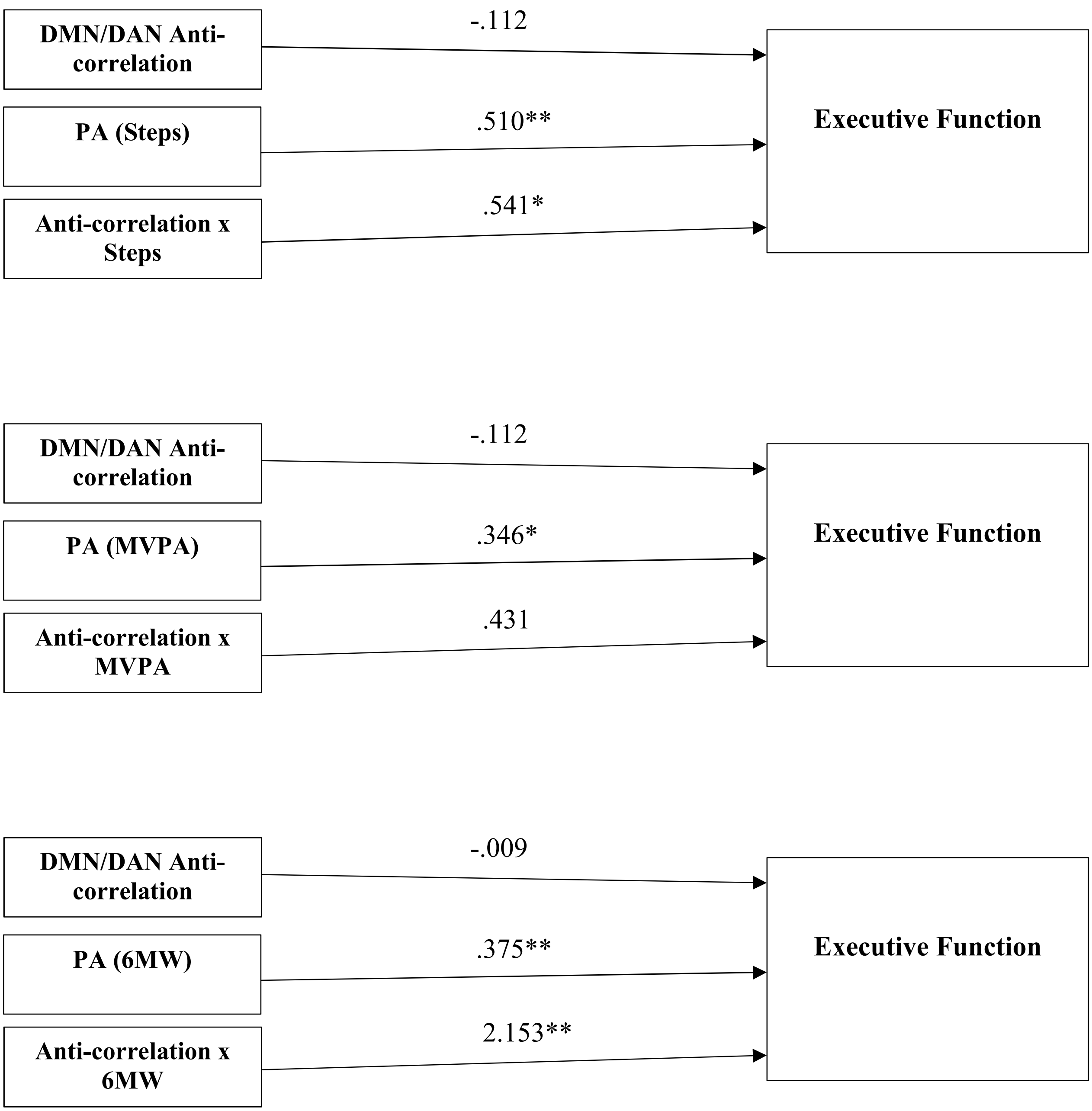

Figure 4.1 Moderation statistical model with standardized β coefficients
**p*<.05, ***p*<.*01*

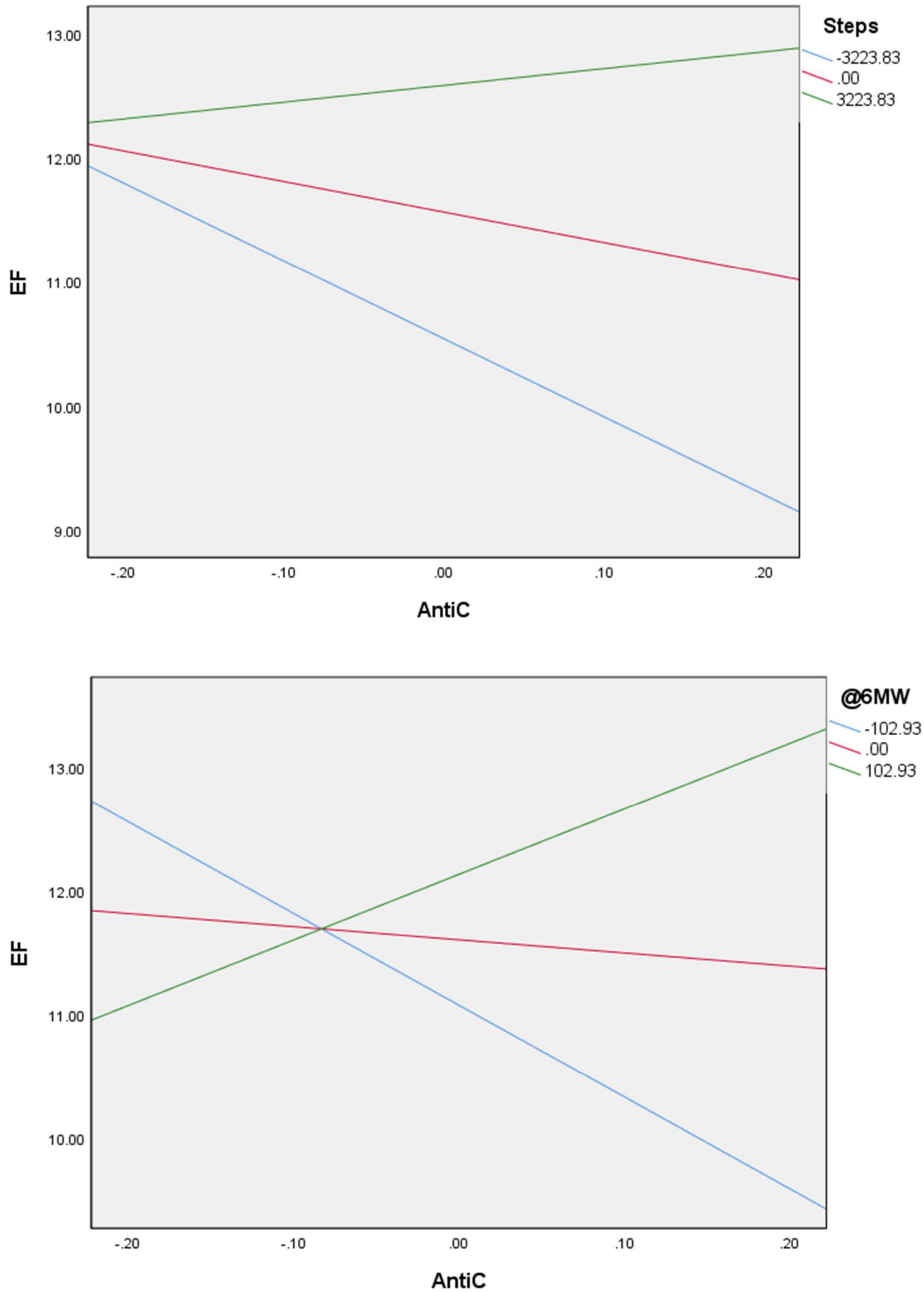

Figure 4.2 Visualization of Interaction Effects
AntiC = Anti-correlation between DMN and DAN; EF = executive function; 6MW = six-minute walk test

CHAPTER 5

GENERAL DISCUSSION

As people continue to live longer (Canudas-Romo, DuGoff, Wu, Ahmed, & Anderson, 2016), there is a need to mitigate the negative impacts of aging on the brain and cognitive function. Recent evidence suggests that exercise interventions and physical activity are neuroprotective to the aging brain (Iso-Markku et al., 2018; Northey et al., 2018; Sanders, Hortobagyi, la Bastide-van Gemert, van der Zee, & van Heuvelen, 2019), but the mechanisms underlying this neuroprotection have not been fully elucidated. While there is some evidence to suggest that exercise interventions and physical activity may impact the structure of the aging brain (Colcombe et al., 2006; Voss et al., 2010; Nishiguchi et al., 2015; Oberlin et al., 2015), emerging literature suggests that there are also changes in the brain's functional connectivity (Voss et al., 2016; Boraxbekk et al., 2016; Veldsman et al., 2017; Yue et al., 2020). Importantly, functional connectivity has been associated with cognitive functioning outcomes in aging (Andrews-Hanna et al., 2007; Damoiseaux et al. 2008; Majerus, Péters, Bouffier, Cowan, & Phillips, 2018). The overall goal of the current research project was to expand upon the current literature by examining the impacts of physical activity and fitness on the association between functional connectivity and cognitive function through several methodologies. The aims presented in Chapter 3 were to (1): examine whether executive function performance was related to DMN and DAN FC in community-dwelling older adults and to examine whether physical activity moderated this association, and (2): evaluate whether physical activity was related to whole brain local and global efficiency for community-dwelling older adults. The aims presented in Chapter 4 were to (1): evaluate whether DMN/DAN anti-correlations were related to executive function performance in healthy older adults, and (2), evaluate whether physical activity and fitness measures moderated that association. The results from these studies are presented in detail in Chapters 3 and 4. The integration of several themes and trends including resting state methodology and physical activity and fitness are examined.

Resting State Methodology

To assess these aims and hypotheses, we used several different resting state functional MRI methodologies. The first methodology utilized was seed-to-voxel analyses, which is a commonly used resting state methodology (see Chapter 3 and Appendices Table 1.1-1.5). Utilizing the DMN and DAN separately as seeds, the associations between cognitive constructs (i.e., executive function and working memory) and DMN/DAN functional connectivity as moderated by physical activity and fitness measures were examined. Overall, seed-to-voxel analyses yielded important information not only on areas of significant functional connectivity between the DMN/DAN and various areas of the brain, but also elucidated an interactive effect of physical activity on the association between cognition and DMN/DAN functional connectivity.

The most specific measure used to quantify the impact of physical activity and fitness on the association between functional connectivity and cognitive function was ROI-to-ROI analyses (see Chapter 4 and Appendices Table 1.6), which allows for the functional connectivity between two areas of interest to be examined. ROIs were chosen from the DMN and DAN and the anti-correlation of their functional connectivity was extracted. Similar to seed-to-voxel analyses, there was an interactive effect of physical activity and fitness on the association between DMN/DAN anti-correlations and cognitive function. This is important to note, as both seed-to-voxel analyses and ROI-to-ROI analyses found significant interactive effects of physical activity and fitness on brain-behavior relationships. Future studies should continue to consider the interactive effects of physical activity and fitness with a continued focus on tailoring interventions to provide the most benefit.

The most global measure used to quantify the impact of physical activity and fitness on resting state methodology was analyses using grapy theory metrics (see Chapter 3). Contrary to our hypotheses, we did not find any impact of amount and intensity of physical activity or physical fitness on whole brain global and local efficiency. Given the limited prior literature using these metrics, whole brain analyses seemed warranted; however, this lack of specificity may have contributed to the null results found. Future studies might consider examining the local and global efficiency of specifics ROIs including networks.

Physical Activity and Fitness

To address our aims, we utilized different measures of physical activity and fitness. Average steps was included to signify the overall amount of activity someone engaged in. MVPA was included as a measure of intensity of exercise and thought to be a proxy measure of amount of aerobic exercise engaged in. The 6MWT was included as a measure of current cardiorespiratory fitness. Current literature exists to support the predictive ability of overall physical activity (Barnes et al., 2008; Buchman, Wilson, & Bennett, 2008), intensity of physical activity (Angevaren et al., 2007; Brown et al., 2012;

Kerr et al., 2013; Zhu et al., 2015), and fitness level (Churchill et al., 2002; McGough et al., 2011; Ferreira et al., 2015; Sherwood et al., 2019) as they relate to cognitive function and functional connectivity in aging. Traditionally, aerobic exercise has been touted for brain health based on its downstream biological effects including impact on vasculature (Bherer, Erickson, & Liu-Ambrose, 2013). In addition, recent evidence suggests that more movement, regardless of intensity, might be protective. This is likely because for some older adults, more movement represents interaction with others and with their environment. This type of movement may be more feasible for those with physical limitations and increases in frailty that often accompany aging. Cardiorespiratory fitness level, while measured at one point in time, is thought to reflect more longstanding physical activity amount and intensity (Hayes, Hayes, Cadden & Verfaellie, 2013).

Several important patterns emerged based on physical activity and fitness measure used. As shown in Chapter 3 and Appendices Tables 1.1-1.5, MVPA and steps were significantly associated with DAN and DMN functional connectivity while the 6MWT was not. In addition, significant MVPA x Executive Function/Working Memory and Steps x Executive Function/Working Memory interactions on DMN FC were present while these interactions were not found for the 6MWT. This indicates that for our sample, steps and MVPA might be more predictive measures than our measure of fitness. There are several reasons why this may be the case. While average steps and MVPA was captured over a week, the 6MWT was captured at a single moment in time and thus may be subject to more inaccuracy than measures that are averaged over time with multiple timepoints. In addition, fitness is impacted by many factors such as body composition, sex, age, and other biologically based factors (Schnurr et al., 2016; Ghosh et al., 2019;

Kind et al., 2019), and this may have contributed to the lack of associations with functional connectivity and interactions with cognitive function compared to steps and MVPA.

As shown in Chapter 4 and Appendices Table 1.6, we see that steps, MVPA, and the 6MWT are all significantly associated with executive function and working memory. However, only significant Steps x DMN/DAN anti-correlation interaction and 6MWT x DMN/DAN anti-correlation interaction on executive function and working memory were present while these interactions were not found for MVPA. Taken with the information presented above, average steps was the only physical activity and fitness measure that was consistently related to brain function and cognition in aging across these studies. This provides more evidence that higher intensity physical activity may not be better than just engaging in any physical activity, which previous research supports (Gothe, 2020). Future studies might utilize this information to target an increase in movement in sedentary older adult populations instead of trying to institute an aerobically challenging intervention that may require high motivation and limited follow-through and maintenance.

Conclusion

Taken together, the present research study suggests that physical activity and fitness may serve as protective factors for the aging brain and cognitive function. Several innovative resting state functional MRI methodologies were utilized, and future studies should seek to replicate and expand upon these methods. Three measures of physical activity and fitness were examined. Overall, average steps seemed to be the most predictive measure of brain and cognitive outcomes in our sample. Future studies might consider including this measure when examining physical activity in similar populations. The present research study expands upon the current literature examining functional connectivity, physical activity and fitness, and cognition in older adults and can serve as a springboard for future research in this area.

REFERENCES

Aertsen, A. M., Gerstein, G. L., Habib, M. K., & Palm, G. (1989). Dynamics of neuronal firing correlation: modulation of "effective connectivity." *Journal of neurophysiology, 61*(5), 900-917.

Alfini, A.J., Weiss, L.R., Nielson, K.A., Verber, M.D., & Smith, J.C. (2019). Resting cerebral blood flow after exercise training in mild cognitive impairment. *Journal of Alzheimer's Disease, 67* (2), 671. doi: 10.3233/JAD-180728

Andrews-Hanna JR, Snyder A, Vincent J, Lustig C, Head D, Raichle M, Buckner R. (2007). Disruption of large-scale brain systems in advanced aging. *Neuron, 56,* 924–935. doi: 10.1016/j.neuron.2007.10.038

Angevaren, M., Vanhees, L., Wendel-Vos, W., Verhaar, H. J., Aufdemkampe, G., Aleman, A., & Verschuren, W. M. (2007). Intensity, but not duration, of physical activities is related to cognitive function. *European Journal of Cardiovascular Prevention & Rehabilitation, 14*(6), 825-830. doi: 10.1097/HJR.0b013e3282ef995b

Anticevic, A., Cole, M.W., Murray, J.D., Corlett, P.R., Wang, X.J., & Krystal, J.H., (2012). The role of default network deactivation in cognition and disease. *Trends Cognitive Sciences 16,* 584e592. doi: 10.1016/j.tics.2012.10.008

Arain, M., Haque, M., Johal, L., Mathur, P., Nel, W., Rais, A., … Sharma, S. (2013). Maturation of the adolescent brain. *Neuropsychiatric Disease and Treatment, 9*, 449–461. doi: 10.2147/NDT.S39776

Ayabe, M., Katamoto, S., Kumahara, H., Naito, H., Tanaka, H., & Brubaker, P.H. (2006). Validity and reliability of the simple assessment of the time spent in moderate to vigorous intensity physical activity under the controlled conditions. *Med Sci Sports Exerc*, *38*, S555. doi:10.1249/00005768-200605001-02310

Barnes, D.E., Blackwell, T., Stone, K.L., Goldman, S.E., Hillier, T., & Yaffe, K. (2008). Cognition in older women: The importance of daytime movement. Journal of the *American Geriatrics Society, 56*, 1658–1664. doi: 10.1111/j.15325415.2008.01841.x

Bautmans, I., Lambert, M., & Mets, T. (2004). The six-minute walk test in community dwelling elderly: influence of health status. *BMC geriatrics*, *4*, 6. doi: 10.1186/1471-2318-4-6

Bethancourt, H. J., Rosenberg, D. E., Beatty, T., & Arterburn, D. E. (2014). Barriers to and facilitators of physical activity program use among older adults. *Clinical medicine & research, 12*(1-2), 10–20. doi: 10.3121/cmr.2013.1171

Bherer, L., Erickson, K. I., & Liu-Ambrose, T. (2013). A review of the effects of physical activity and exercise on cognitive and brain functions in older adults. *Journal of aging research*, 2013. doi: 10.1155/2013/657508

Bland J., & Altman D. (1997). Statistics notes: Cronbach's alpha. *BMJ,* 314, 572. doi: 10.1136/bmj.314.7080.572

Brickman, A.M., Meier, I.B., Korgaonkar, M.S., Provenzano, F.A., Grieve, S.M., Siedlecki, K.L., … Zimmerman, M.E. (2012). Testing the white matter retrogenesis hypothesis of cognitive aging. *Neurobiology of Aging, 33*, 1699–1715. doi: 10.1016/j.neurobiolaging.2011.06.001

Brown, B.M., Peiffer, J.J., Sohrabi, H.R., Mondal, A., Gupta, V.B., & Rainey-Smith, S.R. (2012). Intense physical activity is associated with cognitive performance in the elderly. *Translational Psychiatry, 2*, e191. doi: 10.1038/tp.2012.118

Bombois, S., Debette, D., Delbeuck, X., Brauandet, A., Lepoittevin, S., Delmaire, C., … & Pasquier, F. (2007). Prevalence of subcortical vascular lesions and association with executive function in mild cognitive impairment subtypes. *Stroke, 38*, 2595-2597. doi: 10.1161/STROKEAHA.107.486407.

Boyle, P. A., Wilson, R. S., Yu, L., Barr, A. M., Honer, W. G., Schneider, J. A., & Bennett, D.A. (2013). Much of late life cognitive decline is not due to common neurodegenerative pathologies. *Annals of Neurology*, *74*(3), 478–489. doi: 10.1002/ana.23964

Boraxbekk, C.-J., Salami, A., Wåhlin, A., & Nyberg, L. (2016). Physical activity over a decade modifies age-related decline in perfusion, gray matter volume, and functional connectivity of the posterior default-mode network—A multimodal approach. *NeuroImage, 131*, 133–141. doi: 10.1016/j.neuroimage.201 5.12.010

Buchman, A. S., Wilson, R. S., & Bennett, D. A. (2008). Total daily activity is associated with cognition in older persons. *The American Journal of Geriatric Psychiatry, 16*(8), 697-701. doi: 10.1097/JGP.0b013e31817945f6

Buckner, R. L. (2004). Memory and executive function in aging and AD: multiple factors that cause decline and reserve factors that compensate. *Neuron, 44*(1), 195-208. doi: 10.1016/j.neuron.2004.09.006

Bullmore, E., & Sporns, O. (2009). Complex brain networks: graph theoretical analysis of structural and functional systems. *Nature reviews neuroscience, 10*(3), 186. doi: 10.1038/nrn2575

Canudas-Romo, V., DuGoff, E., Wu, A. W., Ahmed, S., & Anderson, G. (2016). Life expectancy in 2040: What do clinical experts expect? *North American Actuarial Journal*, *20*(3), 276-285. doi: 10.1080/10920277.2016.1179123

Cao, M., Wang, J.H., Dai, Z.J., Cao, X.Y., Jiang, L.L., Fan, F.M., ..., Yong, He. (2014). Topological organization of the human brain functional connectome across the lifespan. *Dev. Cogn. Neurosci. 7*, 76–93. doi: 10.1016/j.dcn.2013.11.004

Cappell, K. A., Gmeindl, L., & Reuter-Lorenz, P. A. (2010). Age differences in prefontal recruitment during verbal working memory maintenance depend on memory load. *Cortex*, *46*(4), 462–473. doi: 10.1016/j.cortex.2009.11.009

U.S. Census Bureau (2018). The U.S. Joins Other Countries With Large Aging Populations. Retrieved from https://www.census.gov/library/stories/2018/03/graying-america.html

Churchill, J. D., Galvez, R., Colcombe, S., Swain, R. A., Kramer, A. F., & Greenough, W. T. (2002). Exercise, experience and the aging brain. *Neurobiology of aging, 23*(5), 941-955. doi: 10.1016/s0197-4580(02)00028-3

Cohen, J., Cohen, P., West, S. G., & Aiken, L. S. (1983). Applied multivariate regression/correlation analysis for the behavioral sciences.

Colcombe, S., & Kramer, A.F. (2003). Fitness effects on the cognitive function of older adults: A meta-analytic study. *Psychological science, 14*, 125-130. doi: 10.1111/1467-9280.t01-101430

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*, 1166–1170. doi: 10.1093/gerona/61.11.1166

Cohen, J. (1988). Statistical power analysis for the behavioral sciences. 2nd.

Conway, A. R., Kane, M. J., Bunting, M. F., Hambrick, D. Z., Wilhelm, O., & Engle, R. W. (2005). Working memory span tasks: A methodological review and user's guide. *Psychonomic Bulletin & Review, 12*, 769–786. doi: 10.3758/BF03196772

Damoiseaux JS, Beckmann CF, Arigita EJ, Barkhof F, Scheltens P, Stam CJ, Smith SM, Rombouts SA. (2008). Reduced resting-state brain activity in the "default network" in normal aging. *Cerebral Cortex, 18*, 1856–1864. doi: 10.1093/cercor/bhm207

Daselaar, S.M., Iyengar, V., Davis, S.W., Eklund, K., Hayes, S.M., & Cabeza, R.E. (2015). Less wiring, more firing: Low-performing older adults compensate for impaired white matter with greater neural activity. *Cerebral Cortex, 25,* 983–990. doi: 10.1093/cercor/bht289

DeCarli, C., Massaro, J., Harvey, D., Hald, J., Tullberg, M., Au, R., … & Wolf, P.A. (2005). Measures of brain morphology and infarction in the Framingham Heart Study: Establishing what is normal. *Neurobiology of Aging, 26*, 491-510. doi: 10.1016/j.neurobiolaging.2004.05.004

Debette, S., Bombois, S., Bruandet, A., Delbeuck, X., Lepoittevin, S., Delmaire, C., … & Pasquier, F. (2007). Subcortical hyperintensities are associated with cognitive decline in patients with mild cognitive impairment. *Stroke, 38*(11), 2924-2930. doi: 10.1161/STROKEAHA.107.488403.

Delis, D.C., Kaplan, E., & Kramer, J. H. (2001). *Delis-Kaplan Executive Function System (D-KEFS)*. San Antonio, TX: The Psychological Corporation.

Delis, D.C., Kramer, J.H., Kaplan, E., & Holdnack, J. (2004). Reliability and validity of the Delis-Kaplan Executive Function System: An update. *Journal of the International Neuropsychological Society*, *10*, 301-303. doi: 10.1017/S1355617704102191

Desikan, R. S., Ségonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., Buckner, R. L., Dale, A. M., Maguire, R. P., Hyman, B. T., Albert, M. S., & Killiany, R. J. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *NeuroImage*, *31*(3), 968–980. doi: 10.1016/j.neuroimage.2006.01.021

Diamond A. (2013). Executive functions. *Annual review of psychology, 64*, 135–168. doi:10.1146/annurev-psych-113011-143750

Dumas, J.A. (2015). What is Normal Cognitive Aging? Evidence from Task-Based Functional Neuroimaging. *Current behavioral neuroscience reports, 2*(4), 256–261. doi:10.1007/s40473-015-0058-x

Erdfelder, E., Faul, F., & Buchner, A. (1996). GPOWER: A general power analysis program. *Behavior Research Methods, Instruments, & Computers, 28*, 1-11. doi: 10.3758/BF03203630

Erickson, K.I., Voss, M.W., Prakash, R.S., Basake, C., Szabof, A., Chaddock, L., … Kramer, A.F. (2011). Exercise training increases size of hippocampus and improves memory. *Proc Natl Acad Sci USA, 108,* 3017–3022. doi: 10.1073/pnas.1015950108

Eriksson, J., Vogel, E. K., Lansner, A., Bergström, F., & Nyberg, L. (2015). Neurocognitive architecture of working memory. *Neuron, 88*(1), 33–46. doi: 10.1016/j.neuron.2015.09.020

Ferreira, N. V., Cunha, P. J., da Costa, D. I., dos Santos, F., Costa, F. O., Consolim-Colombo, F., & Irigoyen, M. C. (2015). Association between functional performance and executive cognitive functions in an elderly population including patients with low ankle–brachial index. *Clinical interventions in aging, 10*, 839. doi: 10.2147/CIA.S69270

Ferreira, L. K., Regina, A. C. B., Kovacevic, N., Martin, M. D. G. M., Santos, P. P., Carneiro, C. D. G., ... & Busatto, G. F. (2016). Aging effects on whole-brain functional connectivity in adults free of cognitive and psychiatric disorders. *Cerebral cortex, 26*(9), 3851-3865. doi: 10.1093/cercor/bhv190

Fox, M. D., Snyder, A. Z., Vincent, J. L., Corbetta, M., Van Essen, D. C., & Raichle, M. E. (2005). The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proceedings of the National Academy of Sciences of the United States of America, 102*(27), 9673–9678. doi: 10.1073/pnas.0504136102

Fox, M. D., Corbetta, M., Snyder, A. Z., Vincent, J. L., & Raichle, M. E. (2006). Spontaneous neuronal activity distinguishes human dorsal and ventral attention systems. *Proceedings of the National Academy of Sciences, 103*(26), 10046-10051. doi: 10.173/pnas.0604187103

Fox, M. D., Zhang, D., Snyder, A. Z., & Raichle, M. E. (2009). The global signal and observed anticorrelated resting state brain networks. *Journal of neurophysiology, 101*(6), 3270–3283. doi:10.1152/jn.90777.2008

Franzmeier, N., Buerger, K., Teipel, S., Stern, Y., Dichgans, M., Ewers, M., & Alzheimer's Disease Neuroimaging Initiative (ADNI). (2017). Cognitive reserve moderates the association between functional network anti-correlations and memory in MCI. *Neurobiology of aging, 50,* 152-162. doi: 10.1016/j.neurobiolaging.2016.11.013

Frazier, J. A., Chiu, S., Breeze, J. L., Makris, N., Lange, N., Kennedy, D. N., Herbert, M. R., Bent, E. K., Koneru, V. K., Dieterich, M. E., Hodge, S. M., Rauch, S. L., Grant, P. E., Cohen, B. M., Seidman, L. J., Caviness, V. S., & Biederman, J. (2005). Structural brain magnetic resonance imaging of limbic and thalamic volumes in pediatric bipolar disorder. T*he American journal of psychiatry, 162*(7), 1256–1265. doi: 10.1176/appi.ajp.162.7.1256

Frith, E., & Loprinzi, P. D. (2017). The Association between physical activity and cognitive function with considerations by social risk status. *Europe's journal of psychology, 13,* 767–775. doi: 10.5964/ejop.v13i4.1471

Gates, N., Singh, M. A. F., Sachdev, P. S., & Valenzuela, M. (2013). The Effect of exercise training on cognitive function in older adults with mild cognitive impairment: a Meta-analysis of randomized controlled trials. *The American Journal of Geriatric Psychiatry, 21*(11), 1086-1097. doi: 10.1016/j.jagp.2013.02.018

Gelfo, F., Mandolesi, L., Serra, L., Sorrentino, G., & Caltagirone, C. (2018). The neuroprotective effects of experience on cognitive functions: evidence from animal studies on the neurobiological bases of brain reserve. *Neuroscience, 370*, 218-235. doi: 10.1016/j.neuroscience.2017.07.065

Ghosh, S., Hota, M., Chai, X., Kiranya, J., Ghosh, P., He, Z., ... & Bouchard, C. (2019). Exploring the underlying biology of intrinsic cardiorespiratory fitness through integrative analysis of genomic variants and muscle gene expression profiling. *Journal of Applied Physiology*, *126*(5), 1292-1314. doi: 10.1152/japplphysiol.00035.2018

Gligoroska, J. P., & Manchevska, S. (2012). The effect of physical activity on cognition - physiological mechanisms. *Materia socio-medica, 24*(3), 198–202. doi: 10.5455/msm.2012.24.198-202

Goldstein, J. M., Seidman, L. J., Makris, N., Ahern, T., O'Brien, L. M., Caviness, V. S., Jr, Kennedy, D. N., Faraone, S. V., & Tsuang, M. T. (2007). Hypothalamic abnormalities in schizophrenia: sex effects and genetic vulnerability. *Biological psychiatry*, *61*(8), 935–945. doi: 10.1016/j.biopsych.2006.06.027

Gogniat, M.A., Robinson, T.R., Mewborn, C.M., Jean, K.J., & Miller, L.S. (2018). Increased Body Mass Index is related to increased brain volume but not neuropsychological functioning in healthy older adults. *Behavioural Brain Research*, *343*, 235-240. doi: 10.1016/j.bbr.2018.04.029

Goparaju, B., Rana, K. D., Calabro, F. J., & Vaina, L. M. (2014). A computational study of whole-brain connectivity in resting state and task fMRI. *Medical science* *monitor: international medical journal of experimental and clinical research, 20*, 1024–1042. doi: 10.12659/MSM.891142

Gothe, N. P. (2020). Examining the effects of light versus moderate to vigorous physical activity on cognitive function in African American adults. *Aging & Mental Health,* 1-7. doi: 10.1080/13607863.2020.1768216

Grieve, S.M., Williams, L.M., Paul, R.H., Clark, C.R., & Gordon, E. (2007). Cognitive aging, executive function, and fractional anisotropy: A diffusion tensor MR imaging study. *American Journal of Neuroradiology, 28,* 226–235.

Hampson, M., Driesen, N., Roth, J. K., Gore, J. C., & Constable, R. T. (2010). Functional connectivity between task-positive and task-negative brain areas and its relation to working memory performance. *Magnetic resonance imaging, 28*(8), 1051-1057. doi: 10.1016/j.mri.2010.03.021

Harada, C.N., Natelson Love, M.C., & Triebel, K. (2013). Normal cognitive aging. *Clinics in Geriatric Medicine, 29*, 737–752. doi: 10.1016/j.cger.2013.07.002

Hayes, S. M., Hayes, J. P., Cadden, M., & Verfaellie, M. (2013). A review of cardiorespiratory fitness-related neuroplasticity in the aging brain. *Frontiers in aging neuroscience, 5,* 31. doi: 10.3389/fnagi.2013.00031

Heikkinen, E. (2006). Disability and physical activity in late life—research models and approaches. *European Review of Aging and Physical Activity*, *3*, 3.

Hinton, P. R., Brownlow, C., McMurray, I., & Cozens, B. (2004). SPSS explained. East Sussex, UK: Routledge.

Huggett, D.L., Connelly, D.M., Overend, T.J. (2005). Maximal aerobic capacity testing of older adults: A Critical review. *The Journals of Gerontology: Series A*, *1,* 57–66. doi: 10.1093/gerona/60.1.57

Huttenlocher, P. R., & Dabholkar, A. S. (1997). Regional differences in synaptogenesis in human cerebral cortex. Journal of comparative *Neurology, 387*(2), 167-178.

Iordan, A. D., Cooke, K. A., Moored, K. D., Katz, B., Buschkuehl, M., Jaeggi, S. M., . . . Reuter-Lorenz, P. A. (2018). Aging and network properties: Stability over time and links with learning during working memory training. *Frontiers in Aging Neuroscience, 9*(419). doi:10.3389/fnagi.2017.00419

Isingrini, M., Angel, L., Fay, S., Taconnat, L., Lemaire, P., & Bouazzaoui, B. (2015). Age-related differences in the reliance on executive control in working memory: role of task demand. *PloS one*, *10*(12), e0145361. doi: 10.1371/journal.pone.0145361

Iso-Markku, P., Waller, K., Vuoksimaa, E., Vähä-Ypyä, H., Lindgren, N., Heikkilä, K., … Kujala, U. M. (2018). Objectively measured physical activity profile and cognition in Finnish elderly twins. *Alzheimer's & dementia 4*, 263–271. doi: 10.1016/j.trci.2018.06.007

Jacobs, H.I.L., Leritz, E.C., Williams, V.J., Van Boxtel, M.P.J., van der Elst, W., Jolles, J., … Salat, D.H. (2013). Association between white matter microstructure, executive functions and processing speed in older adults: The impact of vascular health. *Human Brain Mapping, 34*, 77-95. doi: 10.1002/hbm.21412

Jefferson, A. L., Paul, R. H., Ozonoff, A., & Cohen, R. A. (2006). Evaluating elements of executive functioning as predictors of instrumental activities of daily living

(IADLs). *Archives of clinical neuropsychology, 21*(4), 311–320. doi: 10.1016/j.acn.2006.03.007

Jeong, S., & Jang, J. Y. (2017). Association between physical activity and cognitive dysfunction in the Korean: a cross-sectional study. *Exercise Medicine, 1.* doi: 10.26644/em.2017.003

Kaup, A. R., Mirzakhanian, H., Jeste, D. V., & Eyler, L. T. (2011). A review of the brain structure correlates of successful cognitive aging. *The Journal of neuropsychiatry and clinical neurosciences, 23(*1), 6–15. doi: 10.1176/appi.neuropsych.23.1.6

Kawagoe, T., Onoda, K., & Yamaguchi, S. (2017). Associations among executive function, cardiorespiratory fitness, and brain network properties in older adults. *Scientific reports, 7,* 40107. doi:10.1038/srep40107

Keller, J. B., Hedden, T., Thompson, T. W., Anteraper, S. A., Gabrieli, J. D., & Whitfield-Gabrieli, S. (2015). Resting-state anticorrelations between medial and lateral prefrontal cortex: association with working memory, aging, and individual differences. *Cortex, 64*, 271-280. doi: 10.1016/j.cortex.2014.

Kelly, M. E., Loughrey, D., Lawlor, B. A., Robertson, I. H., Walsh, C., & Brennan, S. (2014). The impact of exercise on the cognitive functioning of healthy older adults: a Systematic review and meta-analysis. *Ageing research reviews, 16*, 12-31. doi: 10.1016/j.arr.2014.05.002

Kerr, J., Marshall, S. J., Patterson, R. E., Marinac, C. R., Natarajan, L., Rosenberg, D., ... & Crist, K. (2013). Objectively measured physical activity is related to cognitive function in older adults. *Journal of the American Geriatrics Society, 61*(11), 1927-1931. doi: 10.1249/MSS.0000000000001079

Kind, S., Brighenti-Zogg, S., Mundwiler, J., Schüpbach, U., Leuppi, J. D., Miedinger, D., & Dieterle, T. (2019). Factors associated with cardiorespiratory fitness in a Swiss working population. *Journal of Sports Medicine, 2019.* doi: 10.1155/2019/5317961

Kirova, A. M., Bays, R. B., & Lagalwar, S. (2015). Working memory and executive function decline across normal aging, mild cognitive impairment, and Alzheimer's disease. *BioMed research international*, 2015. doi: 10.1155/2015/748212

Kolb, B., & Whishaw, I. Q. (1998). Brain plasticity and behavior. *Annual review of psychology, 49(*1), 43-64.

Langenecker, S. A., Nielson, K. A., & Rao, S. M. (2004). fMRI of healthy older adults during Stroop interference. *Neuroimage, 21*(1), 192-200. doi: 10.1016/j.neuroimage.2003.08.027

Latora V., & Marchiori M. (2001). Efficient behavior of small-world networks*. Physical Review Letters, 87*(19), 198701. doi: 10.1103/physrevlett.87.198701

Madden, D. J., Spaniol, J., Whiting, W. L., Bucur, B., Provenzale, J. M., Cabeza, R., ... & Huettel, S. A. (2007). Adult age differences in the functional neuroanatomy of visual attention: a combined fMRI and DTI study*. Neurobiology of aging, 28*(3), 459-476. doi: 10.1016/j.neurobiolaging.2006.01.005

Majerus, S., Péters, F., Bouffier, M., Cowan, N., & Phillips, C. (2018). The dorsal attention network reflects both encoding load and top–down control during working memory. *Journal of cognitive neuroscience, 30*(2), 144-159. doi: 10.1162/jocn_a_01195.

Makris, N., Goldstein, J. M., Kennedy, D., Hodge, S. M., Caviness, V. S., Faraone, S. V., Tsuang, M. T., & Seidman, L. J. (2006). Decreased volume of left and total anterior insular lobule in schizophrenia. *Schizophrenia research, 83*(2-3), 155–171. doi: 10.1016/j.schres.2005.11.020

Mangan D, & Judge J. (1994). Reliability and validation of the six minutes walk. *J Am Geriatr Soc*., *42*, SA73.

Manini T. (2011). Development of physical disability in older adults. *Current aging scienc*e, *4*, 184–191. doi: 10.2174/1874609811104030184

Mather, M. Jacobsen, L.A., & Pollard, K.M. (2015). Aging in the United States. *Population Bulletin, 70,* 2.

McCabe, D. P., Roediger, H. L., McDaniel, M. A., Balota, D. A., & Hambrick, D. Z. (2010). The relationship between working memory capacity and executive functioning: evidence for a common executive attention construct. *Neuropsychology*, *24*(2), 222–243. doi:10.1037/a0017619

McClain, J. & Tudor-Locke, C. (2009). Objective monitoring of physical activity in children: Considerations for instrument selection. *J Sci Med Sport, 12*, 526–533. doi: 10.1016/j.jsams.2008.09.012

McGough, E. L., Kelly, V. E., Logsdon, R. G., McCurry, S. M., Cochrane, B. B., Engel, J. M., & Teri, L. (2011). Associations between physical performance and executive function in older adults with mild cognitive impairment: gait speed and the timed “up & go” test. *Physical therapy, 91*(8), 1198-1207. doi: 10.2522/ptj.20100372

Mitchell, M., & Miller, L. S. (2008). Prediction of functional status in older adults: the ecological validity of four Delis-Kaplan Executive Function System tests. *Journal of clinical and experimental neuropsychology, 30*(6), 683–690. doi: 10.1080/13803390701679893

Miyake, A., & Shah, P. (1999). Models of working memory: Mechanisms of active maintenance and executive control. Cambridge University Press.

Murman, D. L. (2015). The Impact of age on cognition. *Seminars in Hearing*, *36*, 111–121. doi: 10.1055/s-0035-1555115

New Lifestyles. (2005). NL-1000 Activity Monitor: User's guide & record book. Lees Summit, MO: New-Lifestyles Inc.

Nishiguchi, S., Yamada, M., Tanigawa, T., Sekiyama, K., Kawagoe, T., Suzuki, M., …Tsuboyama, T. (2015). A 12-week physical and cognitive exercise program can improve cognitive function and neural efficiency in community-dwelling older adults: A Randomized controlled trial. *Journal of the American Geriatrics Society, 63*, 1355-1363. doi: 10.1111/jgs.13481

Oberlin, L.E., Verstynen, T.D., Burzynska, A.Z., Voss, M.W., Prakash, R.S., Chaddock-Heyman, L., … Erickson, K.I. (2016). White matter microstructure mediates the relationship between cardiorespiratory fitness and spatial working memory in older adults. *NeuroImage, 131*, 91–101. doi: 10.1016/j.neuroimage.2015.09.053

Otero T.M., & Barker L.A. (2014). The Frontal Lobes and Executive Functioning. In: Goldstein S., Naglieri J. (Eds.), Handbook of Executive Functioning, 29-44. New York: Springer.

Otsuka, S., Sakakima, H., Sumizono, M., Takada, S., Terashi, T., & Yoshida, Y. (2016). The neuroprotective effects of preconditioning exercise on brain damage and neurotrophic factors after focal brain ischemia in rats. *Behavioural Brain Research, 303*, 9-18. doi: 10.1016/j.bbr.2016.01.049

Northey, J. M., Cherbuin, N., Pumpa, K. L., Smee, D. J., & Rattray, B. (2018). Exercise interventions for cognitive function in adults older than 50: a systematic review with meta-analysis. *Br J Sports Med, 52*, 154-160. doi: 10.1136/bjsports-2016-096587

Park, D. C., & Reuter-Lorenz, P. (2009). The adaptive brain: Aging and neurocognitive scaffolding. *Annual Review of Psychology*, *60*, 173–196. doi: 10.1146/annurev.psych.59.103006.093656

Peeters, P. & Mets, T. (1996). The 6-minute walk as an appropriate exercise test in elderly patients with chronic heart failure. *J Gerontol A Biol Sci Med Sci, 51*, M147–51. doi: 10.1093/gerona/51a.4.m147

Peters, R. (2006). Ageing and the brain. *Postgraduate medical journal, 82*(964), 84–88. doi: 10.1136/pgmj.2005.036665

Raichle, M.E., MacLeod, A.M., Snyder, A.Z., Powers, W.J., Gusnard, D.A., & Shulman, G.L. (2001). A default mode of brain function. *Proc Natl Acad Sci U S A*., *98*(2):676–82. doi: 10.1073/pnas.98.2.676

Raji, C. A., Lopez, O. L., Kuller, L. H., Carmichael, O. T., & Becker, J. T. (2009). Age, Alzheimer disease, and brain structure. *Neurology, 73*(22), 1899–1905. doi: 10.1212/WNL.0b013e3181c3f293

Raz, N., & Rodrigue, K. M. (2006). Differential aging of the brain: patterns, cognitive correlates and modifiers. *Neuroscience & Biobehavioral Reviews, 30*(6), 730-748. doi: 10.1016/j.neubiorev.2006.07.001

Razani, J., Casas, R., Wong, J.T., Lu, P., Mendez, M., Alessi, C., & Josephson, K. (2007). The relationship between executive functioning and activities of daily living in patients with relatively mild dementia. *Applied Neuropsychology, 14*, 208–214. doi: 10.1080/09084280701509125

Reuter-Lorenz, P. A., & Park, D. C. (2014). How does it STAC up? Revisiting the scaffolding theory of aging and cognition. *Neuropsychology review, 24*(3), 355–370. doi: 10.1007/s11065-014-9270-9

Rikli, R. E., & Jones, C. J. (1998). The reliability and validity of a 6-minute walk test as a measure of physical endurance in older adults. *Journal of aging and physical activity, 6*(4), 363-375. doi: 10.1123/japa.6.4.363

Rzewnicki, R., Auweele, Y. V., & De Bourdeaudhuij, I. (2003). Addressing overreporting on the International Physical Activity Questionnaire (IPAQ) telephone survey with a population sample. *Public health nutrition, 6*(3), 299-305. doi: 10.1079/PHN2002427

Salthouse, T.A. (2003). Memory aging from 18 to 80. *Alzheimer Disease & Associated Disorders, 17*, 162–167. doi: 10.1097/00002093-200307000-00008

Salthouse, T.A. (2010). Selective review of cognitive aging. *Journal of the International Neuropsychological Society, 16,* 754–760. doi: 10.1017/S1355617710000706

Sanders, L. M., Hortobagyi, T., la Bastide-van Gemert, S., van der Zee, E. A., & van Heuvelen, M. J. (2019). Dose-response relationship between exercise and cognitive function in older adults with and without cognitive impairment: a systematic review and meta-analysis. *PloS one, 14*(1), e0210036. doi: 10.1371/journal.pone.0210036

Schnurr, T. M., Gjesing, A. P., Sandholt, C. H., Jonsson, A., Mahendran, Y., Have, C. T., Ekstrøm, C. T., Bjerregaard, A. L., Brage, S., Witte, D. R., Jørgensen, M. E., Aadahl, M., Thuesen, B. H., Linneberg, A., Eiberg, H., Pedersen, O., Grarup, N., Kilpeläinen, T. O., & Hansen, T. (2016). Genetic correlation between body fat percentage and cardiorespiratory fitness suggests common genetic etiology. *PloS one, 11*(11), e0166738. doi: 10.1371/journal.pone.0166738

Shankar, A., McMunn, A., Banks, J., & Steptoe, A. (2011). Loneliness, social isolation, and behavioral and biological health indicators in older adults. *Health Psychology, 30*, 377. doi: 10.1037/a0022826

Sherwood, J. J., Inouye, C., Webb, S. L., Zhou, A., Anderson, E. A., & Spink, N. S. (2019). Relationship between physical and cognitive performance in community dwelling, ethnically diverse older adults: a cross-sectional study. *PeerJ, 7*, e6159. doi: 10.7717/peerj.6159

Smith, R., Sanova, A., Alkozei, A., Lane, R. D., & Killgore, W. (2018). Higher levels of trait emotional awareness are associated with more efficient global information integration throughout the brain: a graph-theoretic analysis of resting state functional connectivity. *Social cognitive and affective neuroscience, 13*(7), 665–675. doi: 10.1093/scan/nsy047

Song, J., Birn, R. M., Boly, M., Meier, T. B., Nair, V. A., Meyerand, M. E., Prabhakaran, V. (2014). Age-related reorganizational changes in modularity and functional connectivity of human brain networks. *Brain Connect. 4,* 662–676. doi: 10.1089/brain.2014.0286

Song, D., Yu, D.S.F., Li, P.W.C., & Lei, Y. (2018). The effectiveness of physical exercise on cognitive and psychological outcomes in individuals with mild cognitive impairment: A systematic review and meta-analysis. *International Journal of Nursing Studies, 79,* 155-164. doi: 10.1016/j.ijnurstu.2018.01.002.

Sperandio, E. F., Arantes, R. L., Matheus, A. C., Silva, R. P., Lauria, V. T., Romiti, M., … Dourado, V. Z. (2015). Intensity and physiological responses to the 6-minute walk test in middle-aged and older adults: a comparison with cardiopulmonary exercise testing. *Brazilian journal of medical and biological research, 48*, 349–353. doi: 10.1590/1414-431X20144235.

Spreng, R. N., Wojtowicz, M., & Grady, C. L. (2010). Reliable differences in brain activity between young and old adults: a quantitative meta-analysis across multiple cognitive domains. *Neuroscience & Biobehavioral Reviews, 34*(8), 1178-1194. doi: 10.1016/j.neubiorev.2010.01.009

Stern, Y. (2002). What is cognitive reserve? Theory and research application of the reserve concept. *Journal of the International Neuropsychological Society, 8*, 448–460. doi: 10.1017/S1355617702813248

Stern, Y. (2012). Cognitive reserve in ageing and Alzheimer's disease. *Lancet Neurology, 11*, 1006–1012. doi: 10.1016/S1474-4422(12)70191-6

Stillman, C. M., Donofry, S. D., & Erickson, K. I. (2019). Exercise, fitness and the aging brain: A Review of functional connectivity in aging. *Archives of Psychology, 3*(4). doi: 0.31296/aop.v3i4.98

Stricker, N.H., Schweinsburg, B.C., Delano-Wood, L., Wierenga, C.E., Bangen, K.J., Haaland, K.Y., … Bondi, M.W. (2009). Decreased white matter integrity in late-myelinating fiber pathways in Alzheimer's disease supports retrogenesis. *NeuroImage, 45*, 10–16. doi: 10.1016/j.neuroimage.2008.11.027

Suzuki, M., Kawagoe, T., Nishiguchi, S., Abe, N., Otsuka, Y., Nakai, R., … Sekiyama, K. (2018). Neural correlates of working memory maintenance in advanced Aging: Evidence From fMRI. *Frontiers in aging neuroscience, 10*, 358. doi: 10.3389/fnagi.2018.00358

Takagi, D., Nishida, Y., & Fujita, D. (2015). Age-associated changes in the level of physical activity in elderly adults. *Journal of physical therapy science, 27(*12), 3685–3687. doi: 10.1589/jpts.27.3685

Torres, E. R., Strack, E. F., Fernandez, C. E., Tumey, T. A., & Hitchcock, M. E. (2015). Physical activity and white matter hyperintensities: A Systematic review of quantitative studies. *Preventive medicine reports, 2*, 319–325. doi: 10.1016/j.pmedr.2015.04.013

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B., & Joliet, M., (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain., *NeuroImage, 15*, 273–289. doi: 10.1006/nimg.2001.0978

Uddin, L. Q., Clare Kelly, A. M., Biswal, B. B., Xavier Castellanos, F., & Milham, M. P. (2009). Functional connectivity of default mode network components: correlation, anticorrelation, and causality. *Human brain mapping, 30*(2), 625-637. doi: 10.1002/hbm.20531

Van Den Heuvel, M. P., & Pol, H. E. H. (2010). Exploring the brain network: a review on resting-state fMRI functional connectivity. *European neuropsychopharmacology, 20*(8), 519-534. doi: 10.1016/j.euroneuro.2010.03.008

Van Essen, D.C., Smith, S.M., Barch, D.M., Behrens, T.E.J., Yacoub, E, Ugurbil, K., for the WU-Minn HCP Consortium. (2013). The WU-Minn Human Connectome Project: An overview. *NeuroImage 80*, 62-79. doi: 10.1016/j.neuroimage.2013.05.041

Vannorsdall, T.D., Waldstein, S.R., Kraut, M., Pearlson, G.D., & Schretlen, D.J. (2009). White matter abnormalities and cognition in a community sample. *Archives of Clinical Neuropsychology, 24*(3), 209-217. doi: 10.1093/arclin/acp037.

Vaughan, L., & Giovanello, K. (2010). Executive function in daily life: Age-related influences of executive processes on instrumental activities of daily living. *Psychology and Aging, 25*(2), 343-355. doi: 10.1037/a0017729

Veldsman, M., Churilov, L., Werden, E., Li, Q., Cumming, T., & Brodtmann, A. (2017). Physical activity after stroke is associated with increased interhemispheric connectivity of the dorsal attention network. *Neurorehabilitation and Neural Repair, 31*(2), 157–167. doi: 10.1177/15459683166669 58

Voss, M. W., Erickson, K. I., Prakash, R. S., Chaddock, L., Malkowski, E., Alves, H., ... Kramer, A. F. (2010). Functional connectivity: A source of variance in the association between cardiorespiratory fitness and cognition? *Neuropsychologia, 48*(5), 1394–1406. doi: 10.1016/j.neuropsycholog ia.2010.01.005

Voss, M. W., Weng, T. B., Burzynska, A. Z., Wong, C. N., Cooke, G. E., Clark, R., ... Kramer, A. F. (2016). Fitness, but not physical activity, is related to functional integrity of brain networks associated with aging. *NeuroImage, 131*, 113–125. doi: 10.1016/j.neuroimage.201 5.10.044

Wang, J., Zuo, X., & He, Y. (2010). Graph-based network analysis of resting-state functional MRI. *Frontiers in systems neuroscience, 4,* 16. doi: 10.3389/fnsys.2010.00016

Wechsler, D. (2008). Wechsler adult intelligence scale–Fourth Edition (WAIS–IV). San Antonio, TX: Pearson.

Wechsler, D. (2009). Wechsler memory scale–fourth edition (WMS-IV). San Antonio, TX: Pearson.

Weuve, J., Kang, J.H., Manson, J.E., Breteler, M.M.B., Ware, J.H., Grodstein, F. (2004). Physical activity, including walking, and cognitive function in older women. *JAMA, 292*, 1454–1461. doi: 10.1001/jama.292.12.1454

Whitfield-Gabrieli, S., & Nieto-Castanon, A. (2012). Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. *Brain connectivity, 2*(3), 125-141. doi: 10.1089/brain.2012.0073

Wolters, F. J., Zonneveld, H. I., Hofman, A., van der Lugt, A., Koudstaal, P. J., Vernooij, M. W., & Ikram, M. A. (2017). Cerebral perfusion and the risk of dementia: a population-based study. *Circulation, 136*(8), 719-728. doi: 10.1161/CIRCULATIONAHA

Wu J.T., Wu, H.Z., Yan, C.G., Chen, W.X., Zhang, H.Y., He, Y., & Yang H.S. (2011). Aging-related changes in the default mode network and its anti-correlated networks: a resting-state fMRI study. *Neurosci Lett. 504*, 62–67. doi: 10.1016/j.neulet.2011.08.059

Yue, C., Zou, L., Mei, J., Moore, D., Herold, F., Müller, P., Yu, Q., Liu, Y., Lin, J., Tao, Y., Loprinzi, P., & Zhang, Z. (2020). Tai Chi Training Evokes Significant Changes in Brain White Matter Network in Older Women. *Healthcare (Basel, Switzerland*), 8, 57. doi: 10.3390/healthcare8010057

Zhu, W., Howard, V. J., Wadley, V. G., Hutto, B., Blair, S. N., Vena, J. E., ... & Hooker, S. P. (2015). Association between objectively measured physical activity and cognitive function in older adults—The reasons for geographic and racial differences in stroke study. *Journal of the American Geriatrics Society, 63*(12), 2447-2454. doi: 10.1111/jgs.13829.

APPENDICES

Table 1.1

MVPA and Executive Function Seed-to-Voxel Moderation Analyses

	Clusters (x,y,z)	Size (Voxels)	p-FDR	Area
DMN FC				
MVPA	-32, +14, +64	201	.000	Superior Frontal Gyrus (L)
	+00, +68, -02	109	.000	Frontal Pole (R)
	+30, +28, +52	41	.019	Superior Frontal Gyrus (R)
	-12, +34, +16	36	.027	Anterior Cingulate Gyrus
	-12, -90, -30	32	.036	Cerebellum Crus 2 (L)
MVPA x EF	+66, -46, -12	40	.005	Middle Temporal Gyrus (R)
DAN FC				
EF	-46, +36, +10	47	.024	Inferior Frontal Gyrus, Pars Triangularis (L)
MVPA	+42, +52, +20	203	.000	Frontal Pole (R)
	-58, -60, +04	132	.000	Inferior Lateral Occipital Cortex (L)
	-48, +38, +18	83	.000	Frontal Pole (L)
	+56, +22, +14	67	.003	Inferior Frontal Gyrus, Pars Opercularis (R)
	-48, +50, -02	50	.006	Frontal Pole (L)
	-38, +22, -02	48	.006	Insular Cortex (L)
	+36, +04, +12	46	.007	Central Opercular Cortex (R)
	+46, -12, +10	34	.027	Heschl's Gyrus (R)
	+42, +26, +04	33	.027	Frontal Opercular Cortex (R)

+52, +12, +22	32	.028	Inferior Frontal Gyrus, Pars Opercularis (R)

EF = Executive Function; MVPA = Moderate to Vigorous Physical Activity; DMN = Default Mode Network; DAN = Dorsal Attention Network; FC = Functional Connectivity

Table 1.2

6MWT and Executive Function Seed-to-Voxel Moderation Analyses

	Clusters (x,y,z)	**Size (Voxels)**	**p-FDR**	**Area**
DAN FC				
EF	-46, +36, +10	47	.024	Inferior Frontal Gyrus, Pars Triangularis (L)
6MW x EF	-08, -86, +10	84	.001	Cuneal Cortex (R)
	-64, -20, -02	40	.050	Superior Temporal Gyrus, Posterior Division (L)

EF = Executive Function; 6MWT = 6-Minute Walk Test; DMN = Default Mode Network; DAN = Dorsal Attention Network; FC = Functional Connectivity

Table 1.3

Steps and Working Memory Seed-to-Voxel Moderation Analyses

	Clusters (x,y,z)	**Size (Voxels)**	**p-FDR**	**Area**
DMN FC				
WM	+02, +38, +30	65	.004	Paracingulate Gyrus (R)
Steps	-12, -44, +04	56	.005	Posterior Cingulate Gyrus
	-04, +54, -04	55	.005	Frontal Pole (L)
	+10, -44, +08	51	.006	Posterior Cingulate Gyrus
	-20, +18, +52	40	.016	Superior Frontal Gyrus (L)
Steps x WM	-36, +50, +22	189	.000	Frontal Pole (L)
	-34, -68, +56	39	.023	Superior Lateral Occipital Cortex (L)
DAN FC				
Steps	+52, +14, +22	45	.044	Inferior Frontal Gyrus, Pars Opercularis (R)
Steps x WM	+06, -66, +14	46	.025	Intracalcarine Cortex (R)

WM = Working Memory; DMN = Default Mode Network; DAN = Dorsal Attention Network; FC = Functional Connectivity

Table 1.4

MVPA and Working Memory Seed-to-Voxel Moderation Analyses

	Clusters (x,y,z)	**Size (Voxels)**	**p-FDR**	**Area**
DMN FC				
WM	+02, +38, +30	65	.004	Paracingulate Gyrus (R)
MVPA	-32, +14, +64	201	.000	Superior Frontal Gyrus (L)
	+00, +68, -02	109	.000	Frontal Pole (R)
	+30, +28, +52	41	.019	Superior Frontal Gyrus (R)
	-12, +34, +16	36	.027	Anterior Cingulate Gyrus
MVPA x WM	-36, -56, +38	164	.000	Superior Lateral Occipital Cortex (L)
	-42, +46, +06	74	.001	Frontal Pole (L)
	+36, -64, +46	58	.002	Superior Lateral Occipital Cortex (R)
	+22, +66, -02	33	.035	Frontal Pole (R)
DAN FC				
MVPA	+42, +52, +20	203	.000	Frontal Pole (R)
	-58, -60, +04	132	.000	Inferior Lateral Occipital Cortex (L)
	-48, +38, +18	83	.000	Frontal Pole (L)
	+56, +22, +14	67	.003	Inferior Frontal Gyrus, Pars Opercularis (R)
	-48, +50, -02	50	.006	Frontal Pole (L)
	-38, +22, -02	48	.006	Insular Cortex (L)
	+36, +04, +12	46	.007	Central Opercular Cortex (R)
	+46, -12, +10	34	.027	Heschl's Gyrus (R)
	+42, +26, +04	33	.027	Frontal Opercular Cortex (R)
	+52, +12, +22	32	.028	Inferior Frontal Gyrus, Pars Opercularis (R)

WM = Working Memory; MVPA = Moderate to Vigorous Physical Activity; DMN = Default Mode Network; DAN = Dorsal Attention Network; FC = Functional Connectivity

Table 1.5

6MWT and Working Memory Seed-to-Voxel Moderation Analyses

	Clusters (x,y,z)	**Size (Voxels)**	**p-FDR**	**Area**
DMN FC				
WM	+02, +38, +30	65	.004	Paracingulate Gyrus (R)
DAN FC				
6MW x WM	+02, -58, +10	55	.013	Precuneous Cortex

WM = Working Memory; 6MWT = 6-minute Walk Test; DMN = Default Mode Network; DAN = Dorsal Attention Network; FC = Functional Connectivity

Table 2.1

Model Summary for Primary Moderator Analyses Predicting Working Memory

Model	R	R^2	Adjusted R^2	Standard Error of the Estimate	R^2 Change	F Change	Significant F Change
1	.033	.001	-.022	1.234	.001	.047	.830
2	.501	.251	.216	1.081	.250	14.336	.000
3	.565	.320	.271	1.043	.069	4.246	.046
4	.033	.001	-.022	1.234	.001	.047	.830
5	.339	.114	.074	1.175	.114	5.545	.023
6	.416	.173	.114	1.150	.058	2.938	.094
7	.019	.000	-.020	1.239	.000	.018	.895
8	.382	.146	.110	1.157	.146	8.024	.007
9	.586	.343	.300	1.026	.197	13.769	.001

1. Predictors: (Constant) DMN-DAN Anti-correlation
2. Predictors: (Constant) DMN-DAN Anti-correlation, Steps
3. Predictors: (Constant) DMN-DAN Anti-correlation, Steps, Anti-correlation x Steps

4. Predictors: (Constant) DMN-DAN Anti-correlation
5. Predictors: (Constant) DMN-DAN Anti-correlation, MVPA
6. Predictors: (Constant) DMN-DAN Anti-correlation, MVPA, Anti-correlation x MVPA

7. Predictors: (Constant) DMN-DAN Anti-correlation
8. Predictors: (Constant) DMN-DAN Anti-correlation, 6MW
9. Predictors: (Constant) DMN-DAN Anti-correlation, 6MW, Anti-correlation x 6MWT