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2019

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Intrinsic and task based interactions between structural and functional connectivity in midlife: implications for age-related brain vulnerability.

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Dissertation

Presented to the Faculty of the Graduate School of

The University of Texas at Austin

in Partial Fulfillment

of the Requirements

for the Degree of

Doctor of Philosophy

The University of Texas at Austin

August 2019

Abstract

Intrinsic and task based interactions between structural and functional connectivity in midlife: implications for age-related brain vulnerability.

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The University of Texas at Austin, 2019

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The proportion of older adults is increasing as people live longer, projecting a financial burden on society because of retirement and care costs. Cognitive functioning is a critical factor in functional independence and quality of life in older age. Although several theories explaining the relationship between brain aging and cognitive decline have been proposed, a unified understanding is lacking. The overarching goal of the current dissertation was to better characterize age related brain and cognitive changes in midlife in order to identify targets for future interventions. Midlife likely offers an optimal time for interventions that prevent or delay cognitive decline before an overwhelming accumulation of pathology. The three Aims of the dissertation used a large sample of middle-aged adults with neuropsychological testing, a metabolic health assessment, and multimodal magnetic resonance imaging. Together, the Aims identified age related changes in the brain, the effects on cognitive functioning, and examined potential mechanisms. Aim #1 reported that white matter structure was associated with network efficiency among the default mode and frontoparietal networks. Aim #2 reported that age was associated with a failure to inhibit the default mode network during an

executive function task that required low cognitive demand. However, on a more challenging condition, age was associated with lower frontoparietal network activity. Better performance on the challenging condition was associated with lower default mode network activity and higher frontoparietal network activity. Aim #3 reported that metabolic syndrome did not accelerated age-related brain changes identified in Aim #2. The results challenge existing theories regarding the effect of age on the relationship between the brain and cognition. New lines of inquiry regarding the role of metabolic syndrome in typical aging are suggested. Lastly, the results present exciting implications for several potential interventions to prevent cognitive decline.

Table of Contents

List of Tables

List of Figures

1. BACKGROUND AND SIGNIFICANCE

1.1 Overview

Aging is associated with a number of processes that are detrimental to the body including the brain. The US population is getting older, partly due to a decrease in chronic disease mortality and an increase in life expectancy, leaving cognitive functioning in the foreground of maintaining quality of life and independence in activities of daily living during older age. Currently, epidemiological research has identified cardiovascular and metabolic disorders that develop in middle age as risk factors for cognitive decline in older age. However, little is known about the brain during midlife when the presence of these risk factors seems to play a role in establishing cognitive aging trajectories. Intervening in middle age may prove to be a critical time period for slowing and preventing cognitive decline; therefore, an understanding of brain mechanisms at play in middle age is needed.

Previous research has identified many brain markers that account for some variance of age-related cognitive changes, yet significant cognitive decline likely involves multiple processes that interact and have synergistic effects. Degradation of the white matter in the brain, which represents the physical architecture by which neurons communicate and is referred to as the structural connectivity, is one process that occurs with increasing age. Changes in the functional connectivity, which represents patterns of interactions between brain regions, on the other hand, may reorganize and moderate the relationship between structural connectivity and cognitive functioning. There is a dearth of studies that examine functional connectivity's impact on the relationship between brain structure and function in the context of aging. The proposed studies will improve our understanding of how structural and functional connectivity are associated with

cognitive functioning during middle age in order to subsequently develop interventions to prevent cognitive decline.

The goal of **Aim 1** was to examine the interplay between functional and structural connectivity and their relationships to cognitive performance in middle age. With increasing age, we hypothesized that functional connectivity in the default mode network and the frontoparietal network would moderate the relationship between white matter structure and executive function. Specifically, we hypothesized that lower functional network efficiency would strengthen the relationship between a marker of white matter degradation and lower executive function (Figure 5). **Aim 2** expanded the search for markers of early brain vulnerability in middle age by determining if functional coupling of brain networks is associated with task performance. In the face of structural brain changes, the dynamics between activation and deactivation of multiple brain networks may adapt to successfully perform tasks (Turner & Spreng, 2015). At higher cognitive load on an executive function task, we hypothesized that age will be associated with higher activity in the default mode network as a compensatory mechanism, lower activity in the frontoparietal network as a deficit, and higher coupling between the networks (Figure 7). In addition, we hypothesized that this pattern will be associated with poorer task performance. Finally, **Aim 3** evaluated the effect of metabolic syndrome on the early markers of brain and cognitive vulnerability identified in Aim 2, namely differences in brain activity and network coupling. Metabolic syndrome refers to a cluster of cardiovascular risk factors including hypertriglyceridemia, low HDL-cholesterol, abdominal obesity, hypertension and hyperglycemia (Alberti, Zimmet, Shaw, & Group, 2005). Metabolic syndrome is of interest because of its increased prevalence in recent years and evidence of its relationships with brain structure in midlife and later-life cognitive decline (Whitmer, Sidney, Selby, Johnston, & Yaffe, 2005; Yaffe, 2007).

Understanding the mechanisms of how metabolic syndrome affects cognition could help identify individuals vulnerable to age-related cognitive changes since cardiovascular health is thought to underlie some age-related brain changes. Together, the three aims expand our understanding of the relationship between the brain and cognition in midlife and the role of cardiovascular risk factors in order to identify vulnerable individuals and potential interventions.

1.2 Aging demographics, cost, and quality of life

A number of physical and cognitive changes accompany the aging process and present major challenges for public health and policy. Largely driven by an increase in life expectancy and the maturation of the baby boomer generation, the population in the United States is getting older. The proportion of the population age 65 and older was 14% in 2012 and is expected to grow to over 20% in 2030 (Ortman, Velkoff, & Hogan, 2014). Declining cognitive function in older age is of particular concern because of the adverse impact on functional independence, financial decision-making, and quality of life (Samanez-Larkin, 2013). To lessen the financial stress placed on an aging society, cognitive demands at older age consequently amplify as individuals live longer. For example, individuals will work into older ages as the U.S. Social Security Administration's full-benefit retirement age increases from 65 to 67 for those born after 1960.

Healthy aging usually refers to the deleterious aging process after parsing out pathological processes including Alzheimer's disease. In reality, normal aging and pathological aging cannot be completely separated as preclinical forms of pathological processes are present in cognitively intact older adults (Sperling et al., 2011). In addition, a body of literature argues that cognitive symptoms of Alzheimer's pathology emerge

under the presence of other neurodegenerative processes. Therefore, besides the benefit of increasing functional independence in older age, preventing cognitive decline in older age will likely impact the incidence of dementia. Essentially, individuals with more resilient brain networks in healthy aging can accumulate more brain pathology before exhibiting cognitive symptoms. Therefore, in addition to the direct benefit of increasing functional independence in older age, preventing age-related cognitive decline could delay dementia onset and reduce the considerable economic burden of dementia care (Kelley, McGarry, Gorges, & Skinner, 2015). Because of the current projections in population demographics, establishing interventions and guidelines in order to maintain cognitive function in older age is of ever-increasing importance.

1.3 Cognitive and brain aging

1.3.1 COGNITIVE AGING

A likely challenge in implementing interventions to prevent age-related cognitive decline is identifying individuals who are particularly vulnerable to target for intervention. There is a general consensus that aging affects individuals differently. Cognitive aging is not merely a function of time; it relies on a complex system of biological and genetic factors that react to environmental factors such as stress, head trauma, and cardiovascular health (Salthouse, 2009). Some are able to maintain cognitive abilities in older age while others experience significant cognitive decline (Rogalski et al., 2013; Rowe & Kahn, 1987; Wilson et al., 2002). Nevertheless, preventing typical age-related decline is thought to delay dementia onset by creating cognitive and brain reserve (Stern, 2012). Targeting vulnerable individuals would enable cost effective and more manageable interventions. In addition, if preserving cognitive function during the

normal aging process delays the onset of dementia, interventions may be targeted towards individuals who are at an increased risk for pathological processes.

The success of cognitive aging interventions will also likely depend on establishing optimal periods to intervene based on the age of onset and trajectory of cognitive decline. Studies of cognitive functions and neurobiological variables across the lifespan indicate that declines in brain and cognitive function likely begin in early adulthood and accelerate in older age (Salthouse, 2009). Interventions that target individuals in older age may have limited efficacy because the magnitude of cognitive decline and neurobiological changes may be too much to overcome. In contrast, because little change has occurred in younger adults, targeted interventions in this age group may prove impractical due to difficulty identifying vulnerable individuals to target. Intervening in middle age may prove to be the most effective at mitigating cognitive decline. Currently, little is known about the relationship between the brain and cognitive function during middle age.

To summarize, brain health and cognitive functioning in older age are of ever-increasing importance, yet interventions in older age are likely to have limited efficacy because of the overwhelming magnitude of accumulated brain degeneration. There is a need to identify brain mechanisms underlying age-related cognitive decline present in midlife in order to identify biological targets for interventions aimed at vulnerable individuals.

1.3.2 COGNITIVE ASSESSMENT

Numerous neuropsychological tests have been developed to assess various cognitive functions in different populations. Factor analysis has revealed that these tests tend to cluster into cognitive domains such as memory, cognitive speed, and language

among others (Carroll, 1993). One such domain, executive functioning, refers to a higher-order, multicomponent domain that is involved in non-routine activities (Glisky, 2007). Executive functioning is thought to direct attention and inhibit irrelevant information and is considered crucial for tasks that have not developed habitual processing. Neuroimaging studies show that the prefrontal cortex of the brain is particularly active during executive control tasks, along with reciprocally activated posterior cortical regions.

In normal aging, some cognitive domains, such as semantic knowledge, demonstrate stability (D. C. Park et al., 2002). Other cognitive domains such as processing speed and executive function consistently demonstrate declines in older age. Some argue that declines in executive function underlie age-related difficulties in other domains such as memory, which consists of executive components (Hasher & Zacks, 1988; West, 1996). In contrast to normal aging, neurodegenerative disorders demonstrate effects on different cognitive domains. For example, Alzheimer's disease particularly affects episodic memory (Buckner, 2004; Hedden & Gabrieli, 2004). Executive functioning likely provides a potent cognitive measure to study healthy aging.

In studying what is considered healthy cognitive aging, executive function needs to be measured using several tests that cover this multicomponent domain. Working memory refers to the limited capacity system that holds information in current attention and is conceptualized as an executive control task (McCabe, Roediger, McDaniel, Balota, & Hambrick, 2010). It is thought that working memory involves the synchronization of abstract representations in the prefrontal cortex, which acts as a central executive, and stimulus-specific representations in the posterior cortex (D'Esposito & Postle, 2015). Working memory differs from short-term memory in that working memory requires not only immediate retrieval of information, but the ability to actively manipulate the information being held. A classic working memory task is known as digit span, during

which individuals are asked to repeat a sequence of numbers (Wechsler, Psychological, & PsychCorp, 2008). Repeating the sequence backwards and in numerical order specifically taps into the ability to manipulate information in working memory capacity. The n-back task, during which individuals are asked if a stimulus is the same as the stimulus presented "*n"* before it, is considered a working memory task that requires divided attention (Owen, McMillan, Laird, & Bullmore, 2005). The trail-making test is a speeded graphomotor task that consists of an "A" condition that is much like numerical connect-the-dots, and a "B" condition that requires set shifting between numerical and alphabetical sequences. The A condition is thought to tap into processing speed while the set shifting in the B condition is thought to tap into executive control (Tombaugh, 2004). Subtracting A from B is thought to remove the speed component and isolate the executive component. In terms of the inhibitory control aspect of executive function, the Stroop task presents the printed name of colors in a different color ink and individuals are asked to name the color of the ink (Stroop, 1935). This task requires inhibitory control of a prepotent response, in this case the printed name.

In terms of brain networks, executive function tasks activate a group of networks that have been termed "task positive networks" because they are particularly activated during goal-directed activities that demand attention and cognitive control. Task positive networks are anticorrelated with a task negative system (i.e. the default mode network) (Fox et al., 2005). The task positive system has been subdivided into networks including the dorsal attention network, frontoparietal control network, and the cingulo-opercular control network. The dorsal attention network is thought to be responsible for selective attention of visual and spatial stimuli (Corbetta & Shulman, 2002; Fox, Corbetta, Snyder, Vincent, & Raichle, 2006). The cingulo-opercular network appears to underlie vigilance and sustained attention (Sadaghiani & D'Esposito, 2015). The frontoparietal network

appears to be sensitive to task content and is thought to be responsible for adapting attention and executive functioning, including working memory (Dosenbach et al., 2007; Wallis, Stokes, Cousijn, Woolrich, & Nobre, 2015).

In summary, executive functioning is a multicomponent cognitive domain that is particularly affected during typical aging. Previous research indicates that attention and cognitive control are associated with several systems, but executive functioning appears to be specialized in the frontoparietal control network. Since executive functioning likely affects performance in other domains, future research examining early relationships between the brain and cognitive decline in midlife should focus on executive functioning and the frontoparietal control network.

1.3.3 BRAIN AGING

One obstacle to developing interventions to maintain brain health and cognitive function is a lack of understanding regarding the relationship between brain structure and age-related cognitive decline. In general, the scientific community agrees that changes in the material brain causally relate to changes in cognitive functioning, as this is made clear in cases of frank brain insults such as the famous case of Phineas Gage (Harlow, 1848) and in advanced cases of neurodegenerative diseases. However, in typical aging, the relationship between brain markers and cognitive function is more tenuous, likely because the changes are more subtle (Raz & Rodrigue, 2006).

The brain includes a number of physical elements that are thought to give rise to cognitive functioning, including neuronal cell bodies, axonal connections, neuroglia, and neurochemicals. Generally, brain tissue is separated into two classes, gray matter and white matter. Gray matter is mostly located on the outside of the brain and contains neuronal cell bodies. White matter is located on the inside of the brain and contains

axons, which are appendages of the neuronal cell body that carry electric signals for communication between neurons.

In regards to how aging affects brain health, post-mortem studies of humans, monkeys, and rodents indicate little neuronal loss in healthy aging (O'Donnell, Rapp, & Hof, 1999; Rapp, Deroche, Mao, & Burwell, 2002; Terry, DeTeresa, & Hansen, 1987). Some suggest that neuron counts remain relatively stable because new neuron generation balances neuronal death (Eriksson et al., 1998; Gould, Reeves, Graziano, & Gross, 1999; Kornack & Rakic, 1999). In contrast, extensive neuronal loss is associated with pathological processes such as Alzheimer's disease (Morrison & Hof, 1997). In light of this evidence, reductions in gray matter volume associated with age and cognition may reflect shrinkage of large neurons (Haug, Kuhl, Mecke, Sass, & Wasner, 1984; Terry et al., 1987), loss of intralaminar myelin (Courchesne et al., 2000), and loss of dendritic arbors (Dumitriu et al., 2010; Hara et al., 2012; Jacobs, Driscoll, & Schall, 1997; Morrison & Baxter, 2012) in addition to some neuronal death (Kril, Hodges, & Halliday, 2004). Neuroimaging studies examining brain volumes report more significant changes occurring in white matter than gray matter (Raz & Rodrigue, 2006). These findings suggest that aging is more associated with changes in the connections between neurons rather than neuronal death and illustrates the need to examine white matter structure and functional connections in aging research.

As discussed above, aging exerts preferential effects on executive function and different neurological processes seem to underlie this pattern. For example, declines in vascular health preferentially impact brain regions that are located towards the ends of cerebral arteries (Raz & Rodrigue, 2006). In addition, myelin forming oligodendrocytes are thought to be especially vulnerable to aging processes (Bartzokis et al., 2004). During the aging process, multiple neurological processes are likely occurring independently and

these processes may have differential, synergistic, and interacting effects on cognitive function (Hedden et al., 2016). A study examining the cumulative effects of several regional and whole brain neuroimaging markers reported that the full set of markers explained 70-80% of age related variability in processing speed, executive functioning, and episodic memory among adults 65-to-90-years-old (Hedden et al., 2016). Yet, when examining the effect of individual markers on cognitive function domains, a majority of the variance was shared among markers. This finding raises the possibility that multiple aging processes may interact to affect cognition in older age. This study also reported that functional connectivity in the default mode and frontoparietal networks failed to explain any significant age-related cognitive decline, yet these were significantly related to cognition. Other studies suggest that in the face of physical changes, patterns of functional activation reorganize to compensate and moderate the relationship between brain structure and cognitive function (Betzel et al., 2014; Daselaar et al., 2015; Zimmermann et al., 2016). As this study was conducted among older adults, focus on midlife is needed to understand the trajectories of the relationship between brain markers and cognitive function.

1.4 White matter in aging

The idea that disconnection between brain regions could give rise to dysfunction dates back to Wernicke's hypothesis that aphasia results from a lesion disconnecting sensory and motor speech areas (Wernicke, 1874). Geschwind brought the hypothesis of "cortical disconnection" into modern neurology to explain higher order cognitive deficits (Geschwind, 1965a, 1965b). In regards to age related white matter changes, evidence from postmortem studies of nonhuman primates suggests little loss of axons in normal age (Nielsen & Peters, 2000). Rather, there is evidence of dysfunction and degradation of

myelin forming oligodendrocytes that could be responsible for age-related changes in white matter structure and function (Nielsen & Peters, 2000; Peters, 1996; Peters, Leahu, Moss, & McNally, 1994). In healthy aging, histopathology studies show myelin pallor (Kemper, 1994), loss of myelinated fibers (Marner, Nyengaard, Tang, & Pakkenberg, 2003), and myelin malformation (Peters, 2002).

In terms of testing the "disconnection" hypothesis in vivo, DTI is sensitive to white matter degeneration associated with aging and cognitive function. Fractional anisotropy (FA) is a DTI metric that reflects the amount of diffusion in the principle direction relative to the total amount of diffusion. In well-myelinated and developed white matter, water diffuses along myelin sheaths parallel to axons (Figure 1).

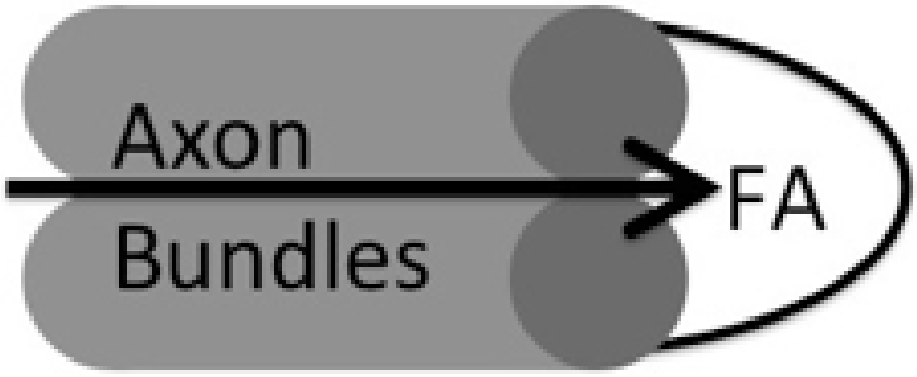

Figure 1: Schematic of fractional anisotropy.

As white matter develops, FA increases from childhood to young adulthood and slowly decreases thereafter (Barnea-Goraly et al., 2005; Bendlin et al., 2010; Betzel et al., 2014; Kochunov et al., 2011; Sullivan & Pfefferbaum, 2006). It is thought that age-related changes in DTI metrics reflect demyelination and axonal degradation resulting in more extracellular space and therefore less directional diffusion (Bennett, Madden,

Vaidya, Howard, & Howard, 2010). In regards to spatial patterns of age-related change, research suggests that anterior white matter changes are associated with normal aging, while posterior changes are associated with pathological aging (Gunning-Dixon, Brickman, Cheng, & Alexopoulos, 2009; Head et al., 2004; Yoshita et al., 2006). The mechanism behind this spatial pattern is unknown, but some have hypothesized that the less myelinated anterior fibers of the corpus callosum may be particularly sensitive to the aging process. Degradation of these corpus callosum fibers would primarily impact anterior white matter, possibly explaining the anterior to posterior gradient (Gunning-Dixon et al., 2009).

In terms of the effect on cognitive function, white matter microstructural change as measured by DTI has proven to be a predictor of age-related cognitive decline, with the largest effects in the domains of processing speed and executive functioning (Bendlin et al., 2010; Borghesani et al., 2013; Brickman et al., 2012; Haasz et al., 2013; Salami, Eriksson, Nilsson, & Nyberg, 2012; Ystad et al., 2011). With respect to potential mechanisms, cardiovascular disease is also most often associated with cognitive differences in processing speed and executive functioning (Birdsill et al., 2013; Bokura, Nagai, Oguro, Kobayashi, & Yamaguchi, 2010; Cavalieri et al., 2010; Dik et al., 2007; Roberts et al., 2010; Rouch et al., 2014; Segura, Jurado, Freixenet, Albuin, et al., 2009). In the domain of memory, there is some indication that white matter microstructure may be related to memory in Alzheimer's disease but not in healthy aging (He et al., 2012). Even when results are found that link white matter structure with cognitive differences, little variance is explained as age often mediates the relationship between white matter structure and cognitive function, rather than white matter structure mediating the relationship between age and cognitive function. The latter of which would follow

theoretical predictions that structural degradation affects cognitive function (Bennett & Madden, 2014).

To summarize, white matter structural changes measured by DTI are thought to contribute to age-related declines in processing speed and executive function. Yet, DTI measures tend to explain little variance in cognitive function. A more comprehensive understanding of how white matter structure affects the function of the brain may help elucidate the relationship with cognitive decline as reorganization of functional connectivity may moderate the relationship between white matter structure and cognitive test performance.

1.5 Resting state functional connectivity in aging

The first body of literature investigating age-related changes in the brain using MRI largely focused on regional brain structure and function using functional magnetic resonance imaging (fMRI). fMRI is an MRI modality that utilizes the magnetic difference in oxygenated hemoglobin and deoxygenated hemoglobin. When an area of the brain is active, cerebral blood flow increases to that region, however this increase is greater than the metabolic rate and therefore an abundance of oxygenated hemoglobin collects. This is referred to as the blood-oxygen-dependent level (BOLD) signal. In the last decade, focus has aptly expanded to connectivity between regions. Propelling this shift of focus from regional activity to network activity was the explosion of research using resting state fMRI (rs-fMRI). Resting state fMRI identifies correlated BOLD signal at rest and has revealed intrinsic, functional networks (Biswal, Yetkin, Haughton, & Hyde, 1995; Fox & Raichle, 2007). The default mode network is thought to support internally focused, self-generated thought and is more active during rest than during externally directed tasks (Figure 2) (Andrews-Hanna, Smallwood, & Spreng, 2014;

Ferreira et al., 2016; Mason et al., 2007). In fact, it is often anticorrelated with "task-positive" networks, such as the dorsal attention, cingulo-opercular control and frontoparietal control networks (Figure 3) (Fox et al., 2005; Raichle, 2015). Of significance to aging, the default mode network encompasses brain regions that first accumulate in Alzheimer's disease pathology, including the posterior cingulate cortex and hippocampus (Buckner, Andrews-Hanna, & Schacter, 2008; Mevel, Chetelat, Eustache, & Desgranges, 2011). Consideration of brain function in preclinical Alzheimer's disease regions is important in normal aging, as the combination of Alzheimer's disease pathology and other neurodegeneration likely produce clinically significant cognitive decline (Jagust, 2013). The potential clinical utility of rs-fMRI has been demonstrated through numerous studies that have found functionally meaningful differences and the ability to predict disease state with rs-fMRI in neurological and psychiatric conditions including Alzheimer's disease (Craddock, Holtzheimer, Hu, & Mayberg, 2009; Fox & Greicius, 2010; Sheline & Raichle, 2013).

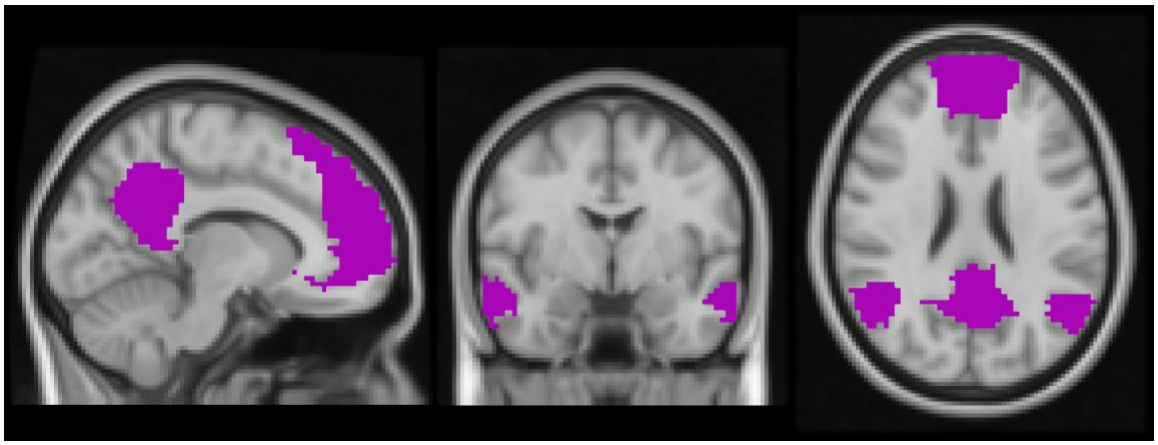

Figure 2: The default mode network.

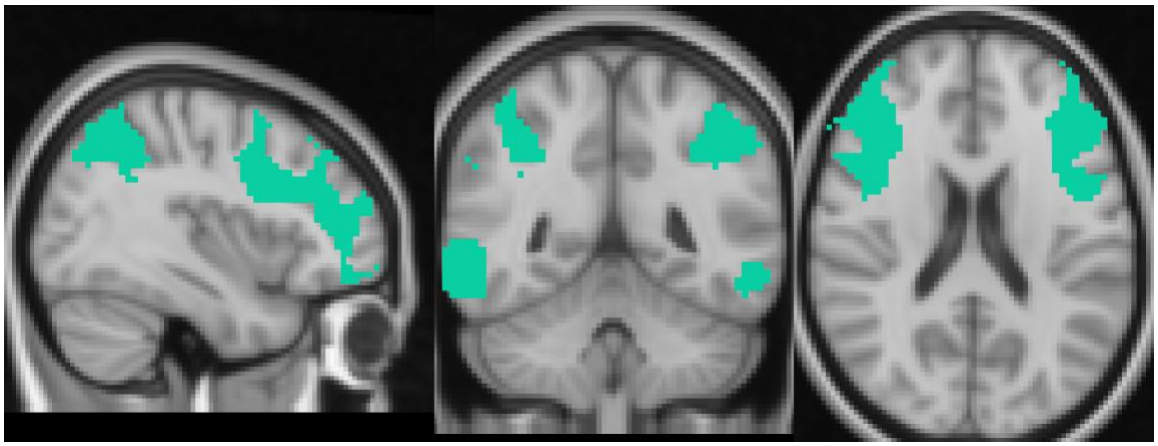

Figure 3: The frontoparietal control network.

Investigations of rs-fMRI in healthy aging most often report lower default mode network connectivity in older age (Achard & Bullmore, 2007; Bluhm et al., 2008; Esposito et al., 2008; Koch et al., 2010; Tomasi & Volkow, 2012; Wang et al., 2010). These results are not likely explained by neuronal death because they have been found independent of decreases in gray matter volume (Damoiseaux et al., 2008). To explain why default mode network connectivity decreases with age, some suggest a selective loss of long fibers or polysynaptic circuits (Tomasi & Volkow, 2012). This would fall into the hypothesis that later developing circuits are the most vulnerable in aging (Grieve, Clark, Williams, Peduto, & Gordon, 2005; Kalpouzos et al., 2009; Terribilli et al., 2011). Other whole-brain studies have shown that with increasing age, intra-network connectivity decreases and inter-network connectivity increases, indicating the possibility that other regions may become active during task in a compensatory fashion. (Chan, Park, Savalia, Petersen, & Wig, 2014; L. Geerligs, Maurits, Renken, & Lorist, 2014).

There are some limitations of rs-fMRI in aging research that should be noted. There is some evidence that younger and older adults engage in different thought patterns and that older adults “mind wonder” less (Charles & Carstensen, 2010; Hess, 2014;

Maillet & Schacter, 2016b; Mevel et al., 2013). Additional confounds related to aging include an increase in motion, changes in vascular health and changes in neurovascular coupling that could impact BOLD signal (Andrews-Hanna et al., 2007; D'Esposito, Deouell, & Gazzaley, 2003; Golestani, Kwinta, Strother, Khatamian, & Chen, 2016). Because rs-fMRI does not contrast different task conditions, it may be particularly vulnerable to these age-related confounds. Finally, there is a body of literature that suggests flexibility in functional connectivity, as networks are spatially different between rest and cognitive tasks (Bolt, Laurienti, Lyday, Morgan, & Dagenbach, 2016; DeSalvo, Douw, Takaya, Liu, & Stufflebeam, 2014; Moussa et al., 2011; Rzucidlo, Roseman, Laurienti, & Dagenbach, 2013; Sadaghiani, Poline, Kleinschmidt, & D'Esposito, 2015; Stanley, Dagenbach, Lyday, Burdette, & Laurienti, 2014). Therefore, some argue that rest should be viewed as a task in of itself and caution should be made when making cognitive inferences based on rs-fMRI. In respect to making cognitive inferences, findings using rs-fMRI are best be viewed as hypotheses to later test with task based fMRI.

To summarize, default mode network is particularly active during rest, and is of interest to aging because it is comprised of regions affected by preclinical Alzheimer's disease. Aging has been associated with lower default mode connectivity, possibly due to a loss of long axonal fibers. In addition, advancing age is associated with a decrease in intra-network connectivity and an increase in inter-network connectivity, indicating that more regions may be recruited during cognitive tasks. Yet, the relationship between age-related white matter structural changes and functional connectivity remains poorly understood. Measures that incorporate the complexity of networks and their interactions will be essential to further knowledge of brain aging.

1.6 Network graph theory and brain aging

Graph theory refers to the complex study of pairwise relationships and has been applied to functional neuroimaging data, particularly at rest, in order to better understand the complex dynamics of brain networks. As applied to neural networks, a graph is made up of nodes, which can refer to regions of interests or voxels, and edges, which represent the presence of a relationship between two regions. At opposite extremes, a network can be completely regular (i.e. lattice) or completely random. Neural networks are characterized as "small-world networks," in that there is a balance of clustering between neighboring nodes and paths between nodes (Latora & Marchiori, 2001). An efficient network combines functionally specialized clusters and integrating links.

A burgeoning number of graph theory metrics have been used to characterize brain networks (Rubinov & Sporns, 2010). In terms of characterizing the "small-worldness" architecture of a network, *global efficiency* is calculated as the inverse of the shortest path length between all nodes and is thought to represent functional integration of brain regions (Stanley et al., 2015). *Local efficiency* is calculated by identifying the neighbors of an individual node, removing the individual node, and taking the inverse of the shortest path between all neighboring nodes. Local efficiency is thought to be an indicator of functional segregation and how well information is shared among neighboring nodes. In a small-world network, local and global efficiency are both high (Figure 4). In a lattice network, local efficiency is high, but global efficiency is poor, as information must pass through a number of nodes to reach distant nodes. A random graph has high global efficiency, but low local efficiency, as paths to neighbors are lacking.

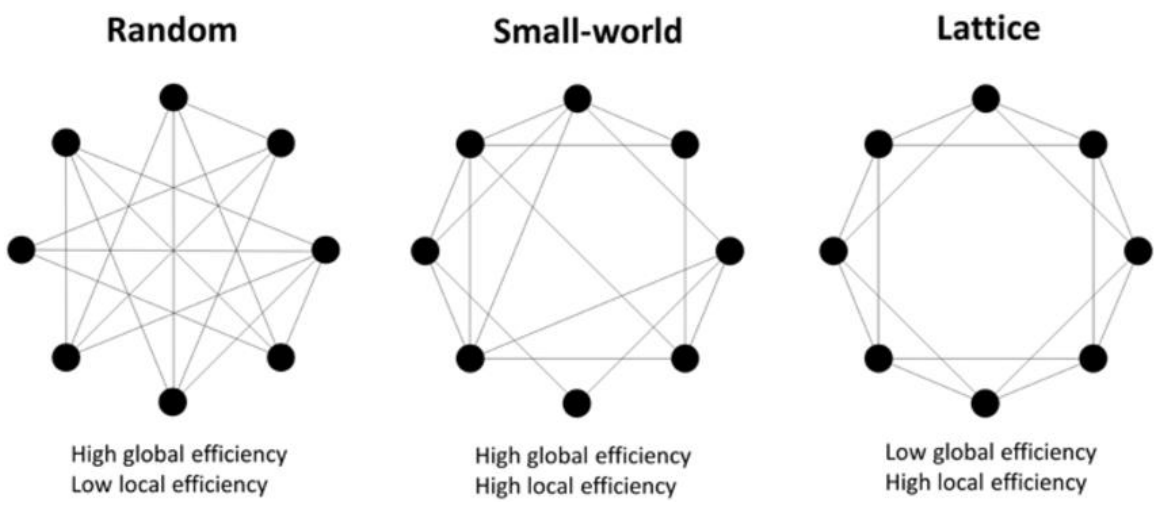

Figure 4: Schematic of networks.

Previously, local and global efficiency have been used to understand how functional brain networks change as a function of age. The hypothesis that age-related decreases in network connectivity may result from a selective loss of long fibers or polysynaptic circuits would be consistent with more robust decreases in global efficiency relative to local efficiency (Tomasi & Volkow, 2012). However, two studies have reported associations between age and local efficiency but no relationship between age and global efficiency. Geerligs et al. found that older adults had lower local efficiency compared to younger adults in default mode, cingulo-opercular and frontoparietal control networks (2015). They concluded that lower local efficiency in older age fits with the dedifferentiation hypothesis, in that lower local efficiency could reflect less modularity and less distinct activation patterns in older age. Cao et al. found that local efficiency follows an inverted U shaped curve across the lifespan from 7 to 85 years old and concluded that functionally segregated units develop in childhood, are optimal in young

adulthood, and then degenerate in older age (2014). At least one study reported decreases in global efficiency with increasing age. Archard and Bullmore compared a group of older adults to a group of younger adults and found lower local and global efficiency among 90 cortical and subcortical regions in older adults (2007). They also presented evidence of lower network efficiency after administration of a dopamine receptor antagonist and speculated that a loss of dopamine transmission may partly underlie age related decreases in network efficiency.

There are several other commonly used graph metrics that can further characterize a network by providing measures of functional segregation, centrality, and functional integration. A measure of functional segregation, *clustering coefficient* is another graph metric that is calculated as the fraction of the node's neighbors that are also neighbors of each other. High clustering coefficient reflects segregated processing in the network (Watts & Strogatz, 1998). *Degree* is a metric of centrality that is calculated as the number of links connected to a node. High degree reflects a well developed and resilient network (Rubinov & Sporns, 2010). *Betweenness centrality,* another measure of centrality, is calculated as the number of shortest paths in the network that pass-through a given node. High between centrality signals a large number of nodes that connect disparate parts of the network. *Average path length* is calculated as shortest path length between two nodes, averaged across the network. Low average path length reflects an efficient network, as information is able to quickly and easily traverse the network.

In summary, graph theory characterizes the complex dynamics of functional networks. Global and local efficiency are two graph theory metrics that are sensitive to network integration and segregation respectively. Previous research has indicated that local efficiency decreases in older age, possibly reflecting less modularity in brain networks. An age-related decrease in modularity would be consistent with the

dedifferentiation hypothesis, which posits that brain activation patterns become less distinct with increasing age. However, there are conflicting reports regarding the effect of age on global efficiency and clarifying this relationship would help determine the role of integrative network communication in aging.

1.7 Structural and functional connectivity

Unsurprisingly, the organization of neural activity into networks reflects the underlying structure of major white matter bundles (Greicius, Supekar, Menon, & Dougherty, 2009; Hagmann et al., 2008; Honey et al., 2009; Skudlarski et al., 2008). In fact, structural and functional connectivity are likely to be tightly bound through Hebbian learning. Both are believed to play a role in age-related cognitive decline (C. Grady, 2012), making it important to understand how their relationship changes with age. Given that advancing age is associated with a degeneration of the physical means by which functional connectivity propagates (Gunning-Dixon et al., 2009), changes in functional connectivity may moderate the relationship between white matter changes and cognitive functioning. Studies examining the effects of DTI on cognitive function in older age have suggested that white matter changes partially mediate age related declines in executive functioning, processing speed, and episodic memory (Correia et al., 2008; Hedden et al., 2016; Kennedy & Raz, 2009; Turken et al., 2008). If white matter degeneration affects cognitive function through a loss of neural connections, this should impact the functional activation of neural networks.

Evidence suggests that in older age, functional connectivity is related to cognitive function, but not age, while FA mediates age-related cognitive changes (Hedden et al., 2016). This finding raises the possibility that functional connectivity may moderate the effect of FA on age-related variance with cognitive function. Several other studies that

examined functional connectivity along the lifespan or in older adults compared to younger adults suggest that functional connectivity reorganizes in the face of structural changes (Betzel et al., 2014; Daselaar et al., 2015; Gallen, Turner, Adnan, & D'Esposito, 2016; Zimmermann et al., 2016). Although it is generally accepted that functional connectivity depends on the structural connectivity, it is unknown how age-related white matter degeneration affects this relationship.

In terms of cognitive effects in older age, Daselaar et al. reported that during a semantic memory task, older adults with lower executive functioning had greater activity in the prefrontal cortex (Daselaar et al., 2015). In turn, lower FA in adjacent white matter was reported. They interpreted their results to support the "less-wiring-more-firing" compensation hypothesis. Their results suggest that increased activity in the executive network contributes to successful completion of a cognitive task that is normally associated with the medial temporal lobes.

There are a few studies that have examined the direct coupling of structural and functional connectivity in advancing age. Using whole brain connectivity matrices, Zimmermann et al. reported that decreases in structural connectivity, functional connectivity, and coupling predict age in almost all regions (2016). In a separate model, they reported that coupling was uniquely predictive of age, but the relationship varied regionally. In some regions, stronger coupling predicted age while in others, weaker coupling predicted age, suggesting a more complex reorganization in the relationship between structural and functional connectivity.

To summarize, while functional and structural connectivity are both believed to play a role in cognitive aging, little is understood about how these brain markers interact across the lifespan, specifically in middle age. Given the task dependent flexibility in

functional networks, the universality and intrinsic nature of rs-fMRI may be particularly suitable for examining the impact of structural differences on functional connectivity.

1.8 Age related changes in task activation

The use of BOLD signal obtained from fMRI is generally accepted as a measurement of brain activity in aging research. Numerous studies have used fMRI to investigate age-related differences in brain activity while individuals engage in cognitive tasks. Despite an extensive literature on age related changes in task activation, a comprehensive understanding on how task activation changes with age is lacking, partly due to competing findings. Studies have shown age-related decreases in activity are usually interpreted as deficits, and increases in activity are usually interpreted as age-related compensation, a lack of efficiency, or dedifferentiation (C. Grady, 2012).

In regards to the theory of compensation, this may occur because older adults seem to engage in more reactive control while younger adults engage in more proactive control (Dew, Buchler, Dobbins, & Cabeza, 2012; Jimura & Braver, 2010). Another possible explanation for compensation is known as 'compensation-related utilization of neural circuits hypothesis' (CRUNCH)(Reuter-Lorenz & Cappell, 2008). The CRUNCH model posits that as cognitive load increases, brain activity follows a sigmoid growth curve that is shifted left for older adults. For example, older adults exhibit more brain activity at easier levels of a working memory task compared to younger adults. At more difficult levels, older adults exhibit lower activity and poorer performance (Schneider-Garces et al., 2010). This evidence suggests that neural recruitment plateaus at lower cognitive load in older adults. The CRUNCH model could potentially explain why older adults display over and under recruitment depending on the cognitive task and level of cognitive demand.

Dedifferentiation refers to the idea that older adults have less distinct and selective activation patterns as networks lose specialization and become more common to different domains. In the domains of memory, visual perception, and working memory, younger adults show more specific activation while older adults show more distributed activation (Carp, Gmeindl, & Reuter-Lorenz, 2010; Carp, Park, Polk, & Park, 2011; Dennis & Cabeza, 2011; D. C. Park et al., 2004; J. Park, Carp, Hebrank, Park, & Polk, 2010; Rieckmann, Fischer, & Backman, 2010; St-Laurent, Abdi, Burianova, & Grady, 2011). The causes of dedifferentiation are unknown but some hypothesize that dedifferentiation during memory tasks results from decreasing dopaminergic neuromodulation that leads to "noisy" information processing (Abdulrahman, Fletcher, Bullmore, & Morcom, 2017; Li, Lindenberger, & Sikstrom, 2001). Others suggest that dedifferentiation in sensory processing results from a broadening of tuning curves (J. Park et al., 2012).

To summarize, research on task-based activation using fMRI has revealed both increases and decreases in activity depending on task and cognitive load. Several theories have been proposed to explain these differences including deficits, compensation, and dedifferentiation. Competing theories suggest that age-related changes in task activation are likely complex and a comprehensive understanding is lacking.

1.9 Network coupling

The simplicity and between-study standardization of rs-fMRI likely contribute to its utility and success compared to the variability that exists in numerous iterations of cognitive tasks. Yet, evidence suggests that rs-fMRI has limited utility in predicting cognitive changes because of changes in network dynamics that occur during task. In

order to understand age-related changes in cognitive function, task based fMRI is still needed (C. L. Grady, 2016).

Previous research suggests that in older age, brain networks become dedifferentiated possibly because of a breakdown in the intrinsic architecture (Chan et al., 2014; Ferreira et al., 2016; Spreng, Stevens, Viviano, & Schacter, 2016). Over-activation that is interpreted as a compensatory mechanism may simply reflect shifting connectivity resulting from structural changes (Linda Geerligs & Tsvetanov, 2017). This raises the possibility that changes in network interactions may play a role in maintaining cognitive function through increased flexibility between networks. In addition, the CRUNCH model suggests that the relationship between activation and increasing cognitive load changes during the aging process, stressing the importance of evaluating cognitive load. Research is needed that integrates activity in multiple networks, cognitive load and performance on cognitive tasks to fully understand the neural mechanism involved in how changes in age-related activation impacts cognitive function.

It is thought that during task, internally directed processes decrease in favor of externally directed attention processes. There is some evidence that younger adults deactivate regions of the default mode network more so than older adults and this may explain differences in task performance. For example, a few studies show that in young adults, areas of the default mode network deactivate more during memory encoding for subsequently remembered trials compared to forgotten trials and this pattern is absent in older adults (Duverne, Motamedinia, & Rugg, 2009; Gutchess et al., 2005; Kukolja, Thiel, Wilms, Mirzazade, & Fink, 2009; Morcom, Good, Frackowiak, & Rugg, 2003). Turner and Spreng have proposed the default-executive coupling hypothesis of aging that posits that older adults fail to suppress the default mode network and fail to moderate lateral prefrontal cortex with increasing cognitive load during an executive function task

(Turner & Spreng, 2015). Furthermore, they report that connectivity between the frontoparietal network and default mode network increases in older adults. These results were found by comparing young adults (range = 19-27) and older adults (range = 63-78) and it is unknown if this pattern can be detected in middle age. In addition, the functional implications of this pattern are unknown. Specifically, it is unknown if this pattern is adaptive by facilitating older adults to successfully complete the task. Some speculate that increased activity in the default mode network may be the result of older adults relying on crystallized knowledge to complete a fluid task. However, in novel tasks, this strategy would likely not be beneficial.

To summarize, evidence suggests that in older age, default mode network activity fails to suppress during an executive function task, possibly to compensate for limited activation in the frontoparietal attention network. It is unknown if this difference in activation pattern is adaptive in successfully completing tasks. It is unknown if this pattern can be detected in midlife and in the presence of risk factors for cognitive decline. If it is present in midlife, it may prove useful as a marker of early brain vulnerability.

1.10 Metabolic health and later life cognitive decline

Metabolic syndrome (MetS) refers to a cluster of cardiovascular risk factors including hypertriglyceridemia, low HDL-cholesterol, abdominal obesity, hypertension and hyperglycemia (Alberti et al., 2005). A body of literature associates the midlife presence of these component factors and later life cognitive decline, likely through vascular disease, inflammation, insulin resistance, and leptin dysfunction (Gustafson, 2008; Kanaya, Barrett-Connor, Gildengorin, & Yaffe, 2004; Launer, Masaki, Petrovitch, Foley, & Havlik, 1995; Moroney et al., 1999; Qiu, Winblad, & Fratiglioni, 2005; Whitmer et al., 2008; Whitmer et al., 2005; Yaffe, Barrett-Connor, Lin, & Grady, 2002;

Yaffe, Blackwell, et al., 2004). There is some evidence that the cumulative presence of these components presents a risk for later life cognitive decline greater than the presence of individual components (Raffaitin et al., 2011; Yaffe, 2007). Yet, Creavin et al. suggests that midlife cognitive decline is associated with diabetes and hypertension, but not metabolic syndrome (Creavin et al., 2012). There is also some evidence that these components interact. For example, McEvoy et al. reported that MetS is associated with decline in executive function only among women with diabetes (McEvoy et al., 2012). In regards to the effect on cognitive function, MetS seems to impact domains that have been associated with vascular disease, namely executive functioning and processing speed (Birdsill et al., 2013; Bokura et al., 2010; Cavalieri et al., 2010; Dik et al., 2007; Roberts et al., 2010; Rouch et al., 2014; Segura, Jurado, Freixenet, Albuin, et al., 2009). To date, the brain mechanisms responsible for the association between cognitive decline and metabolic syndrome are unknown.

1.11 Midlife metabolic health and the brain

Neuroimaging markers hold promise in understanding neural mechanisms associated with MetS, identifying vulnerable individuals, and identifying therapeutic targets. Studies have suggested that MetS is associated with markers of brain health including cerebral blood flow (Birdsill et al., 2013; Pasha, Birdsill, Oleson, Haley, & Tanaka, 2017), alterations in BOLD fMRI during cognitive tasks (Hoth et al., 2011; Shigaeff et al., 2017), neurochemistry (Haley et al., 2010; Haley, Gonzales, Tarumi, & Tanaka, 2012) and white matter microstructure (K. Park et al., 2008; Segura, Jurado, Freixenet, Falcon, et al., 2009; Shimoji et al., 2013). Hoth et al. reported that metabolic syndrome was associated with lower activation in a working memory task despite equivalent task performance in midlife. This result was interpreted as early brain

vulnerability, although this interpretation is seemingly at odds with literature demonstrating a compensatory increase in frontal activity in older age. This difference may indicate that the effects of metabolic syndrome on the brain differ from age effects. Another possibility is that despite lower activation in frontoparietal regions, higher activation in the default mode network may be compensatory, as has been found in older adults (Turner & Spreng, 2015). This hypothesis would be consistent with early age-related brain vulnerability and lend support to the hypothesis that metabolic syndrome may underlie age related changes in the brain. Currently, it is unknown if metabolic syndrome affects brain health to increase vulnerability to separate age-related changes, or if metabolic syndrome effects underlie aging effects.

1.12 General summary and overview

In conclusion, examining the relationship between structural connectivity, functional connectivity, and coupling of brain networks in midlife may elucidate the gap between brain structure and cognitive functioning in healthy aging during a time that may prove crucial in preventing and delaying cognitive decline. Furthermore, applying these markers of early brain vulnerability to metabolic syndrome may help clarify the implications that midlife cardiovascular risk factors have on future cognitive decline. Understanding the relationship these risk factors have on the aging brain and cognitive functioning is vital considering the confluence of an aging population and an increase in the prevalence of these risk factors over the past few decades. Early markers of vulnerability such as differences in the structure and function of the brain may reveal mechanisms behind midlife risk factors and present opportunities for early interventions.

2. SPECIFIC AIM #1

2.1 Introduction

Aim #1 was to determine the relationship between white matter structure and intrinsic functional connectivity in midlife. Previous research suggests that increasing age is related to lower FA and lower network efficiency. It is believed that white matter dysfunction contributes to age related cognitive decline and that rs-fMRI is sensitive to cognitive disorders. Research is lacking that simultaneously links white matter structure, functional connectivity, and cognitive function in aging.

The dedifferentiation hypothesis posits that regions become less specialized with increasing age, while the compensation hypothesis posits that cognitive tasks may recruit regions that do not show increased activity in young adults. With increasing age, we hypothesized that changes in network efficiency would moderate the relationship between FA and executive function, in that lower network efficiency would strengthen the relationship between lower FA and lower executive function (Figure 5). We proposed that lower network efficiency would decrease the ability for compensation by default mode network regions during executive function tasks.

The domain of executive function was chosen because decreases are consistently reported in normal aging. In addition, changes in activation patterns during an executive function task have differentiated younger and older adults and executive functioning tasks are thought to require local processing as well as integrating functional units. Whole brain FA was used as a measure of white matter structure as this was previously reported to mediate age-related variance in executive function (Hedden et al., 2016). Local and global efficiency from the default mode network and frontoparietal network were used as measures of intrinsic functional connectivity. These networks were chosen because

changes in activity patterns within and between these networks have been implicated in age related changes in executive functioning.

Exploratory analyses were conducted using additional graph networks including betweenness centrality, average path length, clustering, and degree in order to further characterize network relationships with age, FA and executive functioning.

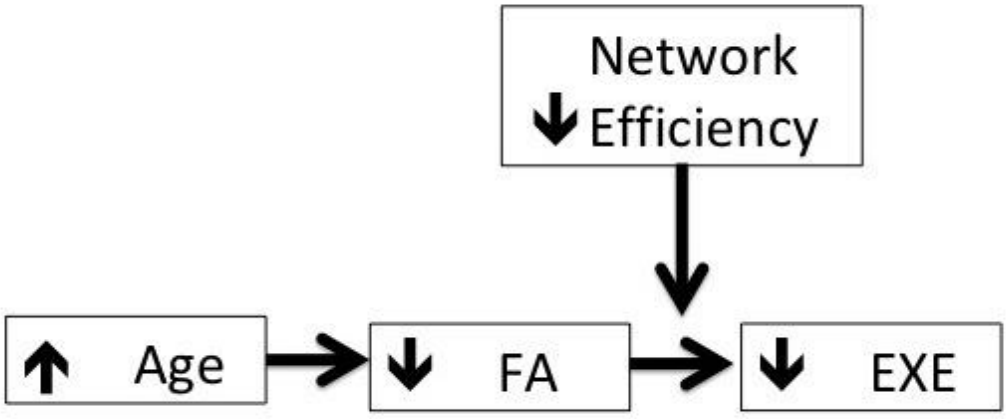

Figure 5: Hypothesized model for Aim 1. Network efficiency moderates the relationship between FA and executive function (EXE).

2.2 Methods

2.2.1 PARTICIPANTS

Aim 1 included 207 participants from whom DTI, resting state fMRI, and cognitive testing was collected as part of a study previously collected. This dataset included apparently healthy adults between the ages of 40 and 62 years old recruited from the Austin, Texas community through flyers, newspaper advertisements, and Craigslist. Participants with histories of cardiovascular disease (e.g., coronary artery disease, angina

pectoris, myocardial infarction), neurological disease (e.g., Parkinson's disease, clinically significant traumatic brain injury), major psychiatric illness (e.g., schizophrenia), substance abuse, smoking, or contraindications of MRI were excluded. Participants with cognitive performance 2 standard deviations below the mean in the executive functioning domain were excluded (n = 3) yielding 204 participants included in the final analysis.

All participants underwent a medical history interview, general health assessment, and brain imaging. All participants gave written informed consent for all study procedures and the institutional review board at the University of Texas at Austin approved all procedures.

2.2.2 Executive Function

Executive function domain scores were calculated as the average Z-score from the following neuropsychological tests: digit span, Stroop interference, and Trails B minus Trails A.

2.2.3 Diffusion Tensor Imaging

MRI was performed using a 3T Siemens Skyra system (Siemens Medical Solutions, Malvern, PA) with a 32-channel head coil. A diffusion-weighted, spin-echo, echo planar imaging pulse sequence was used to acquire images in 64 directions at b=700 s/mm. The encoding directions spanned the entire sphere. One image with b=0 was collected for a non-diffusion weighted reference image. Contiguous 2mm slices with voxel resolution of 2 x 2 x 2 mm were collected from anterior to posterior with the following parameters: FOV = 256mm, TR = 9600ms, TE = 84ms, GRAPPA 2. Advanced shimming was performed before diffusion weighted imaging in order to optimize the homogeneity of the magnetic field across the brain and to minimize EPI distortions. All

images were visually inspected and 4 images deemed poor quality were not included in the analysis (n = 200).

Processing diffusion-weighted images included high dimensional registration to a study specific template using DTI-TK (http://www.nitrc.org/projects/dtitk/). Preprocessing included correction for motion and eddy current distortions with affine transformations using the eddy tool in FSL (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012). Non-brain signal was remove using FSL's brain extraction tool (Smith, 2002). Tensor fitting was performed using FSL's dtifit function.

Normalization was achieved using the full tensor, instead of tensor-derived indices such as FA, based on the methods of Hui Zhang et al. (2007). A study-specific template was created using iterative rigid, affine, and diffeomorphic alignments of the full tensor in DTI-TK. Each participant's tensor map was normalized to the study-specific template using one warp that combined affine and diffeomorphic alignments with final isotropic $1mm^3$ resolution. FA was calculated with DTI-TK's TVtool in subject space. Whole brain FA was calculated by averaging FA values after applying a threshold of 0.2 in order to remove non-white matter.

2.2.4 STRUCTURAL MRI

Structural images were collected and used for fMRI registration and normalization to MNI space. The structural images spanned the entire brain and were collected in the sagittal plane using a high-resolution magnetization prepared rapid gradient echo (MPRAGE) sequence (256 × 256 matrix, flip angle = 7°, FOV = 24 × 24 cm^2, 1 mm slice thickness, 0 gap).

2.2.5 RESTING STATE FMRI

Six minutes of continuous rs-fMRI was collected during which participants were instructed to keep their eyes open and fixated on a crosshair. A whole brain echo-planar imaging (EPI) sequence with the following parameters was used: TR=3000ms, TE=30ms, FOV=24 x 24cm^2, 64 x 64 matrix, 42 axial slices, 3 mm slice thickness, 0.3 mm gap. The default preprocessing pipeline of the Conn toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2012) implemented with SPM12 for ROI-to-ROI analysis was used for rs-fMRI analysis.

Preprocessing included functional realignment and unwarping, slice-timing correction, structural segmentation and normalization, functional normalization, outlier detection, and smoothing. Outlier detection utilized Artifact Detection Tools (https://www.nitrc.org/projects/artifact_detect) with default thresholds (z = 9 for global signal; 2 mm motion). First level within-subject analysis utilized the general linear model consisting of realignment and scrubbing. The band-pass filter was set to [0.008 0.09] Hz. Denoising was performed and covariates included linear and quadratic effects of white matter and CSF BOLD timeseries, all first-level covariates, and rest. Nodes were defined using a previously validated atlas that included 264 nodes organized into functional networks (Power et al., 2011). Nodes corresponding to the default mode network and the frontoparietal control network were included in calculating graph metrics. Edges were defined using an absolute correlation coefficient threshold of r = 0.60, which allowed for joint maximization of local and global efficiency for the sample (Figure 6).

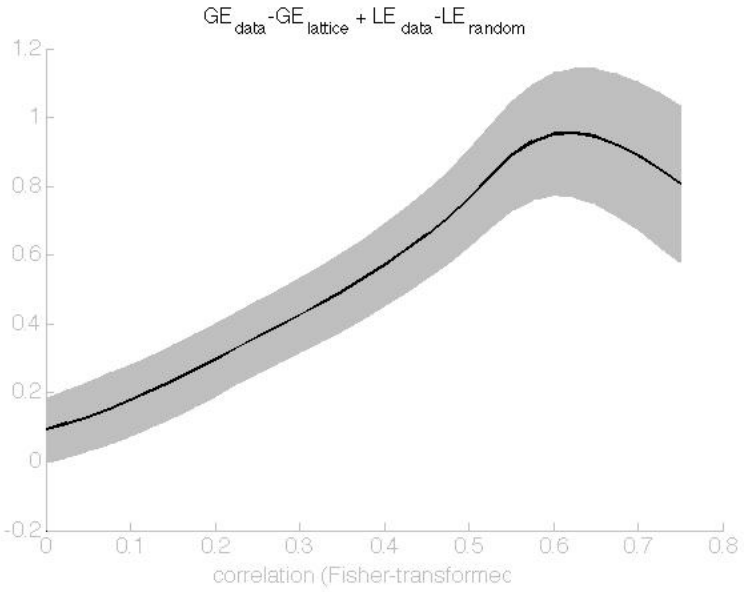

Figure 6: Graph showing the combined differences between (1) global efficiency of the data and global efficiency of a lattice graph and (2) local efficiency of the data and local efficiency of a random graph.

2.2.6 STATISTICAL ANALYSES

All statistical analyses were conducted using IBM SPSS Statistics Version 25. To test for the main effects of age on FA and network efficiency, linear regression was used with age as the independent variable and network efficiency as the dependent variable. Sex was entered as a covariate. Separate models were run for local and global efficiency. Years of education was added as an additional covariate when testing the main effect of age on executive functioning.

To test the main effect of FA on network efficiency, linear regression was used with FA as the independent variable and network efficiency as the dependent variable. Sex was entered as a covariate. Separate models were run for local and global efficiency. To test the main effects of network efficiency and FA on executive functioning, three models were run with local efficiency, global efficiency, and FA entered into separate

models. For each model, executive functioning was entered as the dependent variable and sex and education were entered as covariates.

To test if network efficiency moderates the relationship between FA and executive function, linear regression was used. FA, network efficiency, and the interaction term were entered as the independent variables and executive function as the dependent variable. Sex and education were controlled for. Separate models were run for local efficiency and global efficiency.

Exploratory analyses used the same models described above, but replaced local and global efficiency with other graph theory metrics. .

2.3 Results

2.3.1 DEMOGRAPHICS

Analysis of Aim #1 used a sample representative of the community and included: 59% Caucasian, 21% Latino, 9% African American, 5% Asian, and 7% other or no response. The sample consisted of 116 women (58%) and 84 men (42%). Participant ages ranged from 40 to 62 (M = 48.86, SD = 6.34). Participants in the sample received 10 to 20 years of education (M = 16.22, SD = 2.40)

2.3.2 AGE EFFECTS

Linear regression was used to predict global efficiency based on age and sex. This model resulted in a non-significant regression equation, R^2 = .01, F(2,197) = .63, p = .54. Neither age (β = -.02, p = .82), nor sex (β = -.08, p = .27) were found to have an effect on global efficiency.

Linear regression was used to predict local efficiency based on age and sex. This model resulted in a non-significant regression equation, R^2 = .01, F(2,197) = 1.19, p =

.31. Neither age (β = .11, p = .13), nor sex (β = -.02, p = .78) were found to have an effect on local efficiency.

Linear regression was used to predict FA based on age and sex. This model resulted in a significant regression equation, R^2 = .03, F(2,197) = 2.95, p = .05. While age was found to predict FA (β = -.15, p = .03), sex was found to not have an effect (β = -.08, p = .28).

Linear regression was used to predict executive function based on age, sex, and years of education. This model resulted in a non-significant regression equation, R^2 = .04, F(3,196) = 2.55, p = .06). Education was found to predict executive functioning (β = .19, p = .01). Neither age (β = -.04, p = .58), nor sex (β = .01, p = .92) were found to have an effect on executive functioning.

2.3.3 Main effects between FA, network efficiency and executive functioning

Linear regression was used to predict global efficiency based on FA and sex. This model resulted in a significant regression equation, R^2 = .03, F(2,197) = 3.18, p = .04. While FA was found to predict global efficiency (β = .16, p = .03), sex was found to not have an effect (β = -.07, p = .35). Linear regression was used to predict local efficiency based on FA and sex. This model resulted in a non-significant regression equation, R^2 = .02, F(2,197) = 2.10, p = .13. While FA was found to predict local efficiency (β = .14, p = .04), sex was found to not have an effect (β = -.01, p = .87).

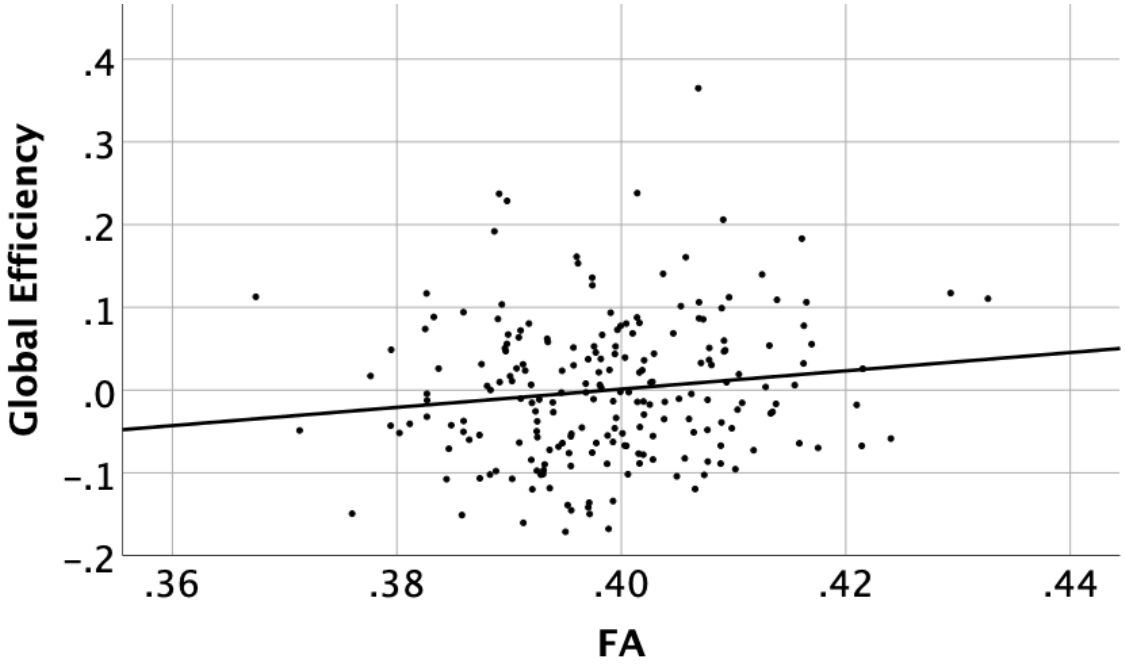

Figure 7: Scatter plot of FA and global efficiency residuals (effect of sex removed).

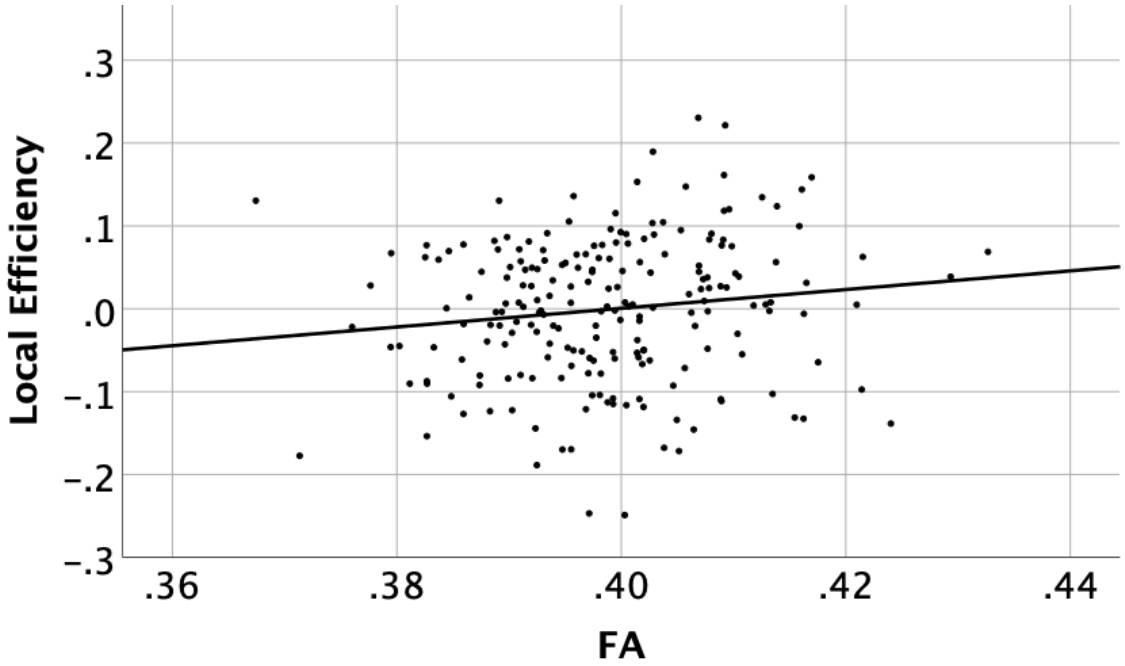

Figure 8: Scatter plot of FA and local efficiency residuals (effect of sex removed).

Linear regression was used to predict executive functioning based on global efficiency, sex, and years of education. This model resulted in a significant regression equation, R^2 = .05, F(3,196) = 3.56, p = .02. While years of education was found to predict executive functioning (β = .19, p = .01), neither sex (β = .02, p = .80) nor global efficiency (β = .13, p = .07) were found to have an effect. Linear regression was used to predict executive functioning based on local efficiency, sex, and years of education. This model resulted in a non-significant regression equation, R^2 = .04, F(3,196) = 2.50, p = .06. While years of education was found to predict executive functioning (β = .19, p = .01), neither sex (β = .01, p = .91) nor local efficiency (β = .02, p = .81) were found to have an effect.

Linear regression was used to predict executive functioning based on FA, sex, and years of education. This model resulted in a significant regression equation, R^2 = .05, F(3,196) = 3.42, p = .02. While years of education was found to predict executive functioning (β = .18, p = .01), neither sex (β = .02, p = .83) nor FA (β = .12, p = .10) were found to have an effect.

2.3.4 MODERATING EFFECT

A hierarchical multiple regression was used to test the interaction between FA and network efficiency on executive functioning. Sex and years of education were added to the models as covariates. For global efficiency, the inclusion of the interaction term did not explain a significant amount of additional variance, ΔR^2 = .001, ΔF(1,194) = .12, p = .73. There was not a moderating effect of global efficiency on the relationship between FA and executive functioning, as evidenced by the interaction term, B = -22.36, 95% CI [-152.20, 107.48]. For local efficiency, the inclusion of the interaction term did not explain a significant amount of additional variance, ΔR^2 = .004, ΔF(1,194) = .88, p = .35.

There was not a moderating effect of local efficiency on the relationship between FA and executive functioning, as evidenced by the interaction term, *B* = -58.40, 95% *CI* [-180.95, 64.16].

2.3.5 EXPLORATORY ANALYSES

In order to better characterize the network's relation to age, FA, and executive functioning and to guide further hypotheses, several other network connectivity metrics to were tested using the same statistical strategy used with network efficiency. As shown in Table 1, FA significantly predicted network degree and betweenness centrality was found to significantly predict executive functioning.

	Age		FA		Exe. Func.		Moderation	
	Beta	*p*	*Beta*	*p*	*Beta*	*p*	*B*	*95% CI*
Betweenness Centrality	-0.13	0.07	-0.02	0.77	0.19	0.01	1189	-133, 2511
Avg. Path Length	-0.10	0.51	-0.12	0.11	0.11	0.11	9.54	-3.77, 22.86
Clustering	0.13	0.07	0.13	0.07	-0.02	0.77	-83.86	-235, 67
Degree	0.02	0.79	0.17	0.02	0.03	0.71	-2.81	-6.95, 1.34
Covariates	Sex		Sex		Sex, Education		Sex, Education	

Table 1. Exploratory analyses with additional network metrics.

2.4 Discussion

The main goal of the current study was to characterize the relationship between white matter structure and functional connectivity in midlife, in order to identify early brain changes that may indicate vulnerability to age-related declines in executive functioning. The default mode network and frontoparietal networks were chosen because changes in activity patterns within and between these networks have been implicated in age related changes in executive functioning. The results reported that FA, a metric that is considered sensitive to white matter health, is positively associated with local and global

network efficiency within the default and frontoparietal networks. Exploratory analyses also revealed a positive association between FA and degree across the networks. Although a relationship between FA and executive functioning was not found in the current study, several others have reported such a relationship (Bendlin et al., 2010; Borghesani et al., 2013; Brickman et al., 2012; Haasz et al., 2013; Salami et al., 2012; Ystad et al., 2011). Exploratory analyses found that executive functioning was related to betweenness centrality, a measure of hub-like nodes. Nevertheless, we hypothesized that network efficiency may enable compensatory mechanisms and therefore reveal a relationship between FA and executive functioning. However, such a moderating effect was not found. Taken together, the results further strengthen the importance of maintaining white matter health to independently preserve functional networks and cognitive functioning.

The current results found that FA is positively associated with network degree, local efficiency, and global efficiency in the frontoparietal and default mode networks. This finding is consistent with several previous studies that report a similar relationship between white matter structure and functional connectivity in older age (Betzel et al., 2014; Daselaar et al., 2015; Zimmermann et al., 2016). Comparing the relative effects of FA on local and global efficiency could help illuminate the reorganization of brain networks that occurs during aging. For example, some have speculated that long fibers and polysynaptic circuits are selectively impaired with increasing age, which would likely have a greater impact on global efficiency (Tomasi & Volkow, 2012). Others have suggested that greater age-related decreases in local efficiency may underlie decreases in modularity and promote dedifferentiation (L. Geerligs et al., 2015). In the current study, local and global efficiency were found to be similarly associated with FA, indicating that white matter structure is associated with the function of modular units and connections

between units during middle age. It is possible that the results may reflect the baseline influence of white matter structure on functional networks, especially considering that the results offered no evidence that age was associated with network efficiency or executive functioning. However, in addition to network efficiency, FA was associated with age, indicating that the current sample captured some age-related structural decline that in turn, may have impacted network efficiency even though an age effect on network efficiency was not found. At least one other study also failed to find an association between functional connectivity and age, albeit among adults 65 to 90 years old (Hedden et al., 2016). They reported that functional connectivity in default mode and frontoparietal networks were associated with cognition, independent of age, and speculated that more regionally specific measures may reveal an association with age-related variance in cognitive functioning.

In the current study, we were expressly interested in detecting early changes in cognitive functioning and brain health that occur during middle age, which may be too early to detect age-related differences in network efficiency, and executive functioning. Previous studies reported such effects in samples among older adults, who may have accelerated brain and cognitive changes, or by comparing older adults with younger adults, which offers a greater range of variability. It should also be noted that the current sample was relatively well educated and mechanisms related to cognitive reserve may mask age-related changes in structure-function relationships. While the biological mechanisms are not well understood, it is thought that cognitive reserve works in part by increasing the robustness of functional networks and the ability to recruit new resources (Steffener, Reuben, Rakitin, & Stern, 2011).

In an effort to better understand how functional networks may play a role in preventing cognitive decline due to structural changes—a proposed mechanism of

cognitive reserve—the current study failed to find evidence for a moderating effect of network efficiency on the relationship between FA and executive functioning. We hypothesized that network reorganization may mask differences in executive functioning being driven by white matter degeneration. Supporting this hypothesis, others have reported that strong functional connections can exist in the absence of direct structural connections through indirect paths in young adults (Honey et al., 2009). In fact, case studies have reported interhemispheric functional connectivity measured by rs-fMRI in corpus callostomey patients through indirect paths (Johnston et al., 2008; Uddin et al., 2008). These dramatic examples highlight the possibility of robust functional networks to preserve cognitive function during structural changes. According to previous research investigating older adults, functional connectivity is related to cognitive function, but not age, while FA mediates age-related cognitive changes (Hedden et al., 2016). In contrast, the present results suggest that in midlife, FA is related to age and functional connectivity, while functional connectivity is not related to age. While efficiency of the frontoparietal and default mode network was selected apriori because it was previously identified as a possible compensatory mechanism for age-related declines in executive functioning, other networks and mechanisms might be playing a role in sustaining executive function. In this study, rs-fMRI was used as a measure of intrinsic functional connectivity because it is thought to have a high correspondence to structural connectivity and such a relationship was observed in these results. However, intrinsic connectivity may be a better measure of the ability to process predictable input and less of a measure of the ability to adjust network dynamics in response to rich input, such as when performing a challenging executive function task (H. J. Park & Friston, 2013).

Exploratory analyses found that betweenness centrality was significantly related with executive functioning, indicating the importance of hub properties within the

frontoparietal and default mode networks in supporting executive functioning. A previous study reported that executive functioning was related to betweenness centrality in medial aspects of the frontoparietal network and cuneus among young adults (Reineberg & Banich, 2016). However, that study also found that executive functioning was also related to lower clustering coefficient, a measure of functional segregation, in frontoparietal regions. Future research that examines regionally specific differences in network metrics within the frontoparietal and default mode networks may provide more provide further information regarding age-related functional reorganization.

In summary, the results affirm that white matter structure during middle age plays a role in rs-fMRI functional connectivity which in turn is related to executive functioning. The lack of a moderating effect of intrinsic network efficiency on the relationship between FA and executive functioning implicates other mechanisms that may play such a role. Mechanisms of cognitive compensation that occur in the face of age-related structural changes may rely on dynamics between networks that must be measured during task performance. These results also highlight the need to understand health factors that impact white matter structure and therefore functional connectivity and executive functioning. Vascular and metabolic factors have been implicated in age-related changes in white matter health and their contribution toward changes in functional networks that may underlie age-related cognitive changes warrants further investigation.

The current study offers several strengths to note. It utilizes a large sample—especially necessary for detecting moderating effects—representative of the community. The study focuses on adults between the ages of 40 to 62, an age period that is understudied, yet could prove to be an optimal time to implement interventions. The study also collected multimodal imaging and cognitive testing simultaneously, which enable direct relationships between different brain factors and cognitive functioning to be

tested. Among weaknesses to note, the study was cross-sectional and therefore caution should be taken in interpreting these results as age-related changes.

3. SPECIFIC AIM #2

3.1 Introduction

Aim #2 was to determine coupling between default mode network and frontoparietal control network in midlife during an executive function task. Aim #1 established the relationship between structure and functional connectivity during rest. Aim #2 extended this by determining the coupling of the default mode and frontoparietal networks during an executive function task. Changes in the coupling between these networks have previously been reported in older age (Spreng et al., 2016; Turner & Spreng, 2015). At lower cognitive load, we hypothesized that age would be associated with higher coupling between the networks. At higher cognitive load, we hypothesized that age would be associated with higher activity in the default mode network, lower activity in the frontoparietal network, and higher coupling between the networks. In addition, we hypothesized that this pattern would be associated with poorer task performance. This pattern was previously observed comparing younger and older adults (Turner & Spreng, 2015). If this pattern emerges in midlife, it may serve as a possible marker of early brain vulnerability.

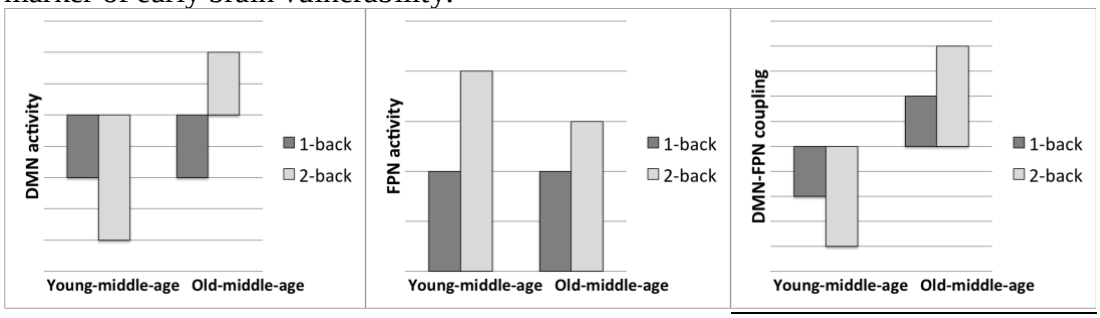

Figure 9: Graphs depicting the hypothesized effects of age on default mode network (DMN) activity, frontoparietal network activity (FPN), and coupling during an executive function task of low cognitive load (1-back) and high cognitive load (2-back).

3.2 Methods

3.2.1 PARTICIPANTS

Aim #2 was conducted from a dataset previously collected and included 205 participants from whom task fMRI was collected. This dataset included apparently healthy adults between the ages of 40 and 62 years old recruited from the Austin, Texas community through flyers, newspaper advertisements, and Craigslist. Participants with histories of cardiovascular disease (e.g., coronary artery disease, angina pectoris, myocardial infarction), neurological disease (e.g., Parkinson's disease, clinically significant traumatic brain injury), major psychiatric illness (e.g., schizophrenia), substance abuse, smoking, or contraindications of MRI were excluded. Participants scoring less than 50% accuracy (n = 16) were excluded. Accuracy was calculated as the sum of correct hits and correct misses, divided by the number of trials. Participants were also excluded if they showed movement greater than 3 mm during the scan (n = 12). The final sampled yielded 177 participants.

All participants underwent a medical history interview, general health assessment, and brain imaging. All participants gave written informed consent for all study procedures and the institutional review board at the University of Texas at Austin approved all procedures.

3.2.2 STRUCTURAL MRI

Structural images were collected to be used for fMRI registration and normalization to MNI space. The structural images spanned the entire brain and were collected in the sagittal plane using a high-resolution magnetization prepared rapid gradient echo (MPRAGE) sequence (256 × 256 matrix, flip angle = 7°, FOV = 24 × 24 cm^2, 1 mm slice thickness, 0 gap).

3.2.3 TASK FMRI

Task fMRI was collected using a whole brain echo-planer imaging (EPI) sequence (TR = 3000 ms, TE = 30 ms, flip angle = 90°, FOV = 24 × 24 cm^2, 64 × 64 matrix, 42 axial slices, 3 mm slice thickness, 0.3 mm gap).

The verbal n-back task used in the current study included visual presentation of letters (500 ms) followed by a crosshair (2500 ms), during which the participant was to respond based on the demands of three alternating conditions. During the 0-back condition, participants were asked to respond yes/no if the stimulus was the letter "H". During the 1-back condition, participants were asked to respond yes/no if the stimulus was identical to the stimulus immediately preceding. During the 2-back task, participants were asked to respond yes/no if the stimulus was identical to the stimulus preceding 2 before it. All responses were given using a two-button box. One run of the n-Back task consisted of three alternating 0-Back, 1-Back, and 2-Back blocks. Each block included the presentation of random constant letters: twelve for the 0-Back condition, or fifteen for the 1-Back and 2-Back conditions. Therefore, each run consisted of 36 0-back trials, 45 1-back trials, and 45 2-back trials. Targets made up 33% of each block. E-Prime software (Psychology Software Tools, Inc., Pittsburgh, PA) was used to program and display the task, as well as record responses and reaction times. The task was back-projected onto a screen located behind the participant, and was viewed through a double-mirror fixed to the head coil. All participants practiced the task before the scan in order to ensure comprehension of task instructions.

Data was processed using tools from FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Preprocessing consisted of MCFLIRT for motion correction, BET for removal of non-brain structures, FILM prewhitening, high-pass filtering with a cut-off of 100 seconds, and 5 mm full width half maximum Gaussian

kernel spatial smoothing. Functional images were aligned to high-resolution anatomical images using a 7-parameter affine transformation with FLIRT. These images were then registered to MNI space using FLIRT. First level data analysis used a general linear model implemented in the FSL tool Feat. Regressors for the model included the block events (1-Back, 2-Back) against a baseline condition (0-Back), following convolution with a double-gamma hemodynamic response function. Covariates included reaction time, missed trials, motion parameters, and the temporal derivatives of all regressors. Contrast of interest included 1-Back > 0-Back and 2-Back > 0-Back. The second level analysis combined task runs using a fixed effects design. The mean 1-Back > 0-Back and 2-Back > 0-Back BOLD response were extracted from each network and percent signal change was computed. Each network mask was created using a previously published consensus atlas (Power et al., 2011).

3.2.4 COUPLING

To calculate coupling, psychophysiological interactions (PPI) analysis was used (O'Reilly, Woolrich, Behrens, Smith, & Johansen-Berg, 2012). Briefly, the time course from the frontoparietal network was extracted and entered in as a regressor in the same model used in the preceding section. Other regressors included the block events (1-back, 2-back), reaction time, missed trials, motion parameters, and the temporal derivatives of all regressors. The interaction terms between the frontoparietal network times series and the block events were entered into the model. These interaction terms identify any change in the relationship between frontoparietal network activity and other brain regions that occurs between 0-back and 1-back, and between 0-back and 2-back. The regression coefficient was extracted and averaged from all voxels included in the default mode network mask. A higher regression coefficient for this task by network interaction term

would mean that activity between the two regions was more strongly correlated during the respective task.

3.2.5 Statistical Analyses

All statistical analyses were conducted using IBM SPSS Statistics Version 25. To test age-related differences during midlife in default mode network activity and frontoparietal network activity during an executive function task, linear regression models were used with default mode network and frontoparietal network percent signal change as dependent variables and age as the independent variable. Sex was entered as a covariate. To test age-related differences during midlife in coupling between the networks, linear regression was used with coupling between the networks as the dependent variable and age as the independent variable. Sex was entered as a covariate. Linear regression was also used to examine the relationship between task performance (dependent variable) and default mode network activity, frontoparietal network activity and network coupling (independent variables). Accuracy was calculated as the sum of correct hits and correct misses, divided by the number of trials.

3.3 Results

3.3.1 Demographics

Analysis of Aim #2 used a sample representative of the community and included: 63% Caucasian, 19% Latino, 8% African American, 5% Asian, and 11% other or no response. The sample consisted of 107 women (60.5%) and 70 men (39.5%). Participant ages ranged from 40 to 61 (M = 49.15, SD = 6.13). Years of education ranged from 10 to 20 (M = 16.23, SD = 2.33)

3.3.2 AGE EFFECT ON NETWORK ACTIVITY DURING TASK

Linear regression was used to predict default mode network activity during the 1-back task. Age and sex were entered in the model as independent variables. This model resulted in a non-significant regression equation, $R^2 = .03$, $F(2,174) = 2.34$, $p = .10$. Age was found to be a predictor of default mode network activity during the 1-backs task ($\beta = 0.16$, $p = 0.04$), while sex was found to not have an effect ($\beta = 0.04$, $p = 0.58$).

Linear regression was used to predict frontoparietal network activity during the 1-back task. Age and sex were entered in the model as independent variables. This model resulted in a non-significant regression equation, $R^2 = .00$, $F(2,174) = 0.36$, $p = .70$. Neither age ($\beta = 0.03$, $p = 0.75$), nor sex ($\beta = -.06$, $p = 0.44$) were found to be predictors of frontoparietal network activity during the 1-backs task.

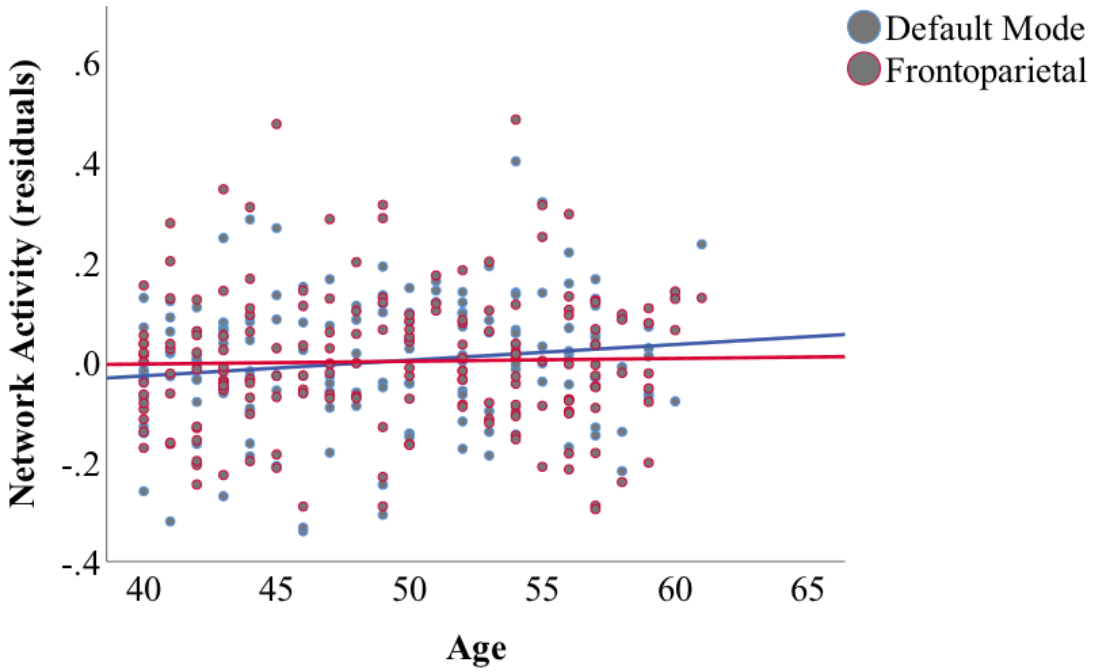

Figure 10: Scatter plot of age and network activity residuals (effect of sex removed) during the 1-back condition.

Linear regression was used to predict default mode network activity during the 2-back task. Age and sex were entered in the model as independent variables. This model resulted in a non-significant regression equation, $R^2 < .01$, $F(2,174) = 0.05$, $p = .95$. Neither age ($\beta = 0.01$, $p = 0.93$), nor sex ($\beta = .02$, $p = 0.77$) were found to be predictors of default mode network activity during the 2-back task.

Linear regression was used to predict default mode network activity during the 2-back task. Age and sex were entered in the model as independent variables. This model resulted in a significant regression equation, $R^2 = .08$, $F(2,174) = 7.82$, $p = .001$. Age was found to be a predictor of default mode network activity during the 2-back task ($\beta = -0.26$, $p = 0.001$), while sex was found to not have an effect ($\beta = -.13$, $p = 0.08$).

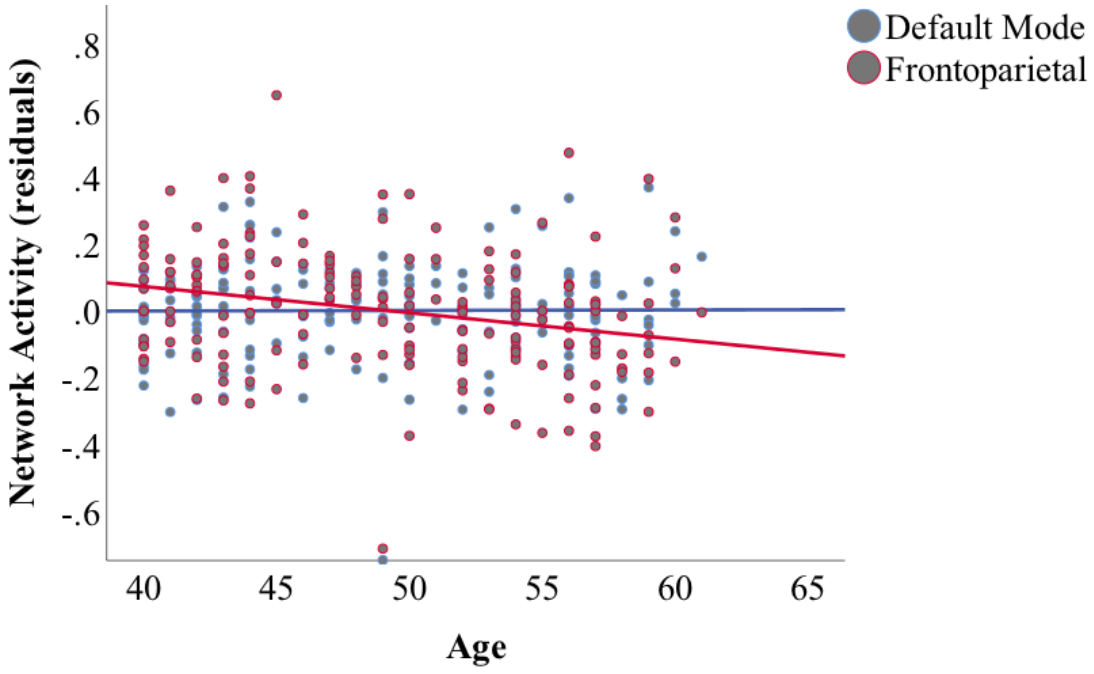

Figure 11: Scatter plot of age and network activity residuals (effect of sex removed) during the 2-back condition.

3.3.3 COUPLING OF NETWORKS DURING TASK

Linear regression was used to predict coupling between the default mode and frontoparietal networks during the 1-back task. Age and sex were entered in the model as independent variables. This model resulted in a non-significant regression equation, R^2 = .01, $F(2,174) = 0.45$, $p = .64$. Neither age ($\beta = .03$, $p = 0.65$), nor sex ($\beta = .06$, $p = 0.41$) were found to be predictors of coupling during the 1-back task.

Linear regression was used to predict coupling between the default mode and frontoparietal networks during the 2-back task. Age and sex were entered in the model as independent variables. This model resulted in a non-significant regression equation, R^2 = .00, $F(2,174) = 0.04$, $p = .96$. Neither age ($\beta = -.02$, $p = 0.81$), nor sex ($\beta = .01$, $p = 0.87$) were found to be predictors of coupling during the 2-back task.

3.3.4 TASK ACCURACY

Accuracy was calculated as the sum of correct hits and correct misses, divided by the number of trials. The average accuracy on the 0-back task was 97.10 ($SD = 5.13$). For the 1-back task, average accuracy was 92.76 ($SD = 9.65$). Average accuracy on the 2-back task was 78.26% ($SD = 11.01$). Bivariate correlations were used to determine the relationship between age and accuracy. There was no statistically significant correlation between age and accuracy on the 0-back condition, $r(175) = -.12$, $p = .11$. However, there were statistically significant correlations between age and accuracy on the 1-back condition, $r(175) = -.20$, $p = .007$, and 2-back condition, $r(175) = -.25$, $p = .001$.

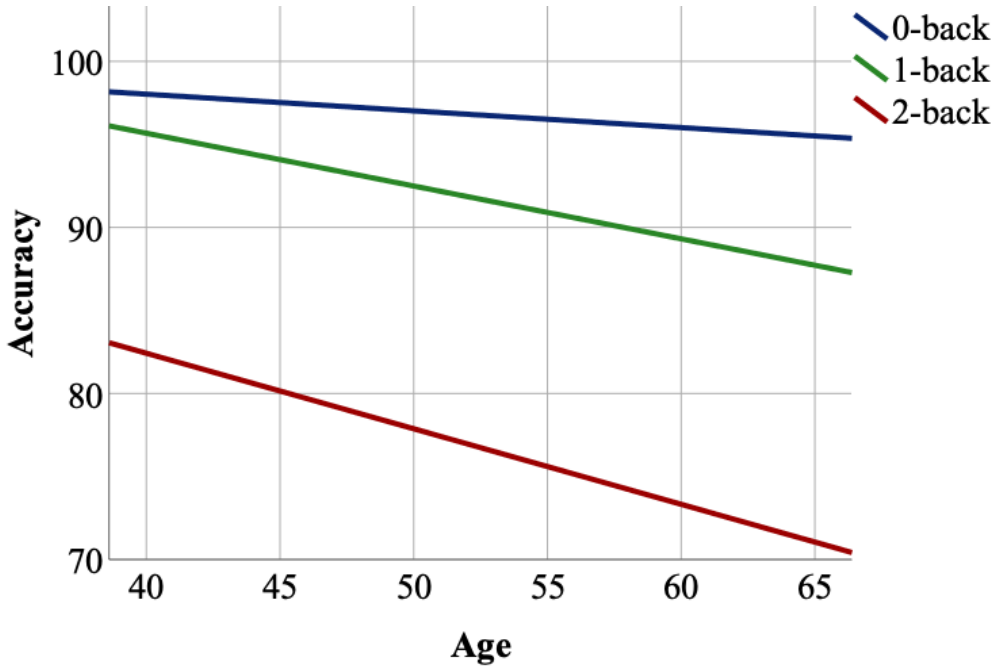

Figure 12: Best fit lines are displayed for the correlation between age and accuracy by condition.

Because the distributions of 0-back and 1-back accuracies were negatively skewed, only 2-back accuracy was examined in relation with network activity. Linear regression was used to predict 2-back accuracy with default mode network activity, frontoparietal network activity, network coupling and sex as independent variables, resulting in a significant regression equation, $R^2 = .27$, $F(4,172) = 15.82$, $p < .001$. Higher accuracy was predicted by lower default mode network activity ($\beta = -.46$, $p < .001$) and higher frontoparietal network activity ($\beta = 0.61$, $p < 0.001$). Coupling ($\beta = -.01$, $p < 0.90$) and sex ($\beta = -.06$, $p = .36$), were not significant predictors of 2-back accuracy.

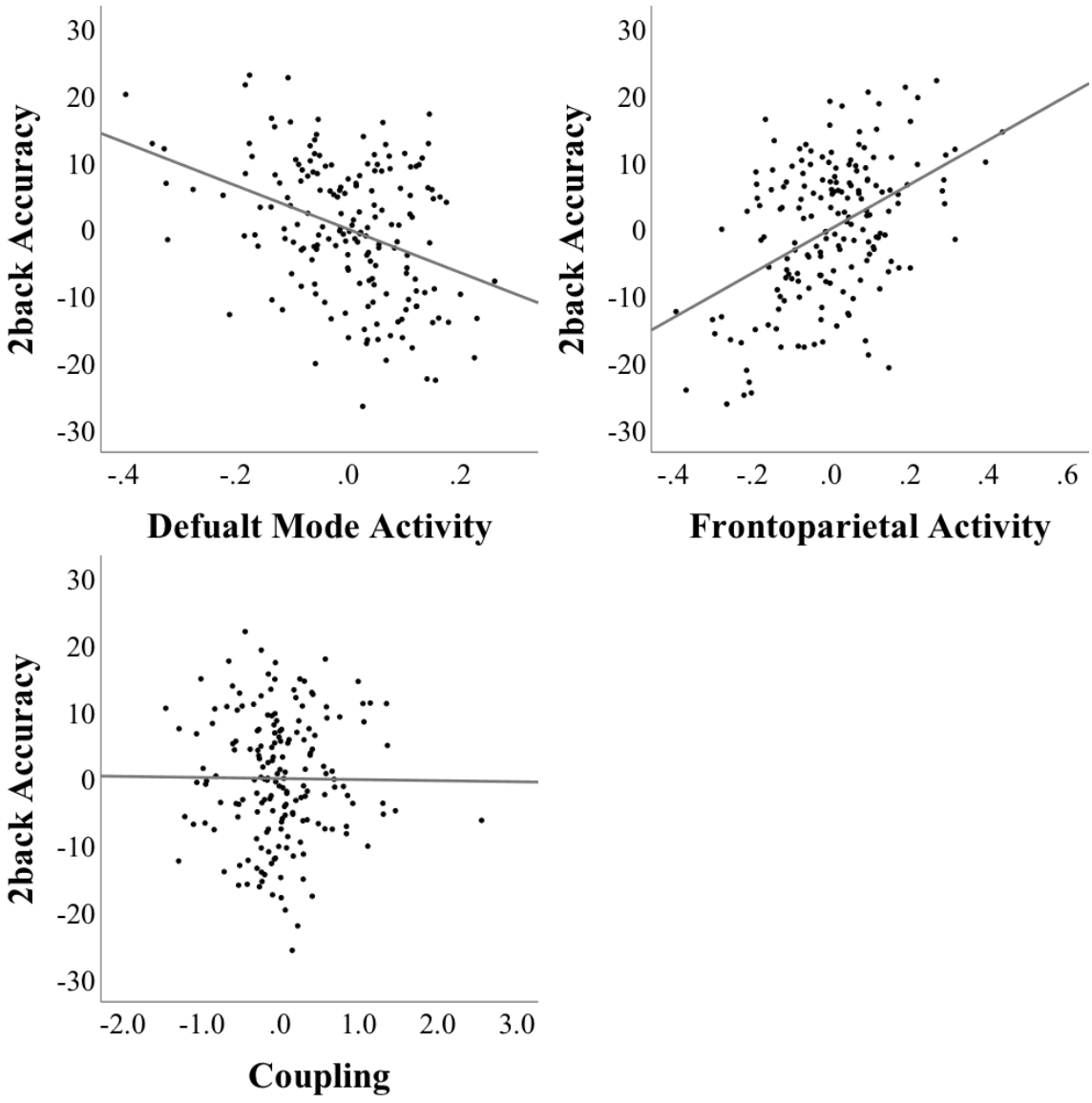

Figure 13: Scatter plots of 2-back task accuracy residuals (effect of sex removed) and default mode network activity, frontoparietal network activity, and coupling of the two networks.

3.4 Discussion

Little is understood about the compensatory mechanisms that preserve cognitive functioning relative to age related changes in brain structure. Aim #1 found that network

efficiency measured at rest exhibited no such moderating effect. However, network dynamics while performing a task may play a role in moderating the negative impact of age-related structural changes. The primary goal of Aim #2 was to determine the coupling between the default mode and frontoparietal control networks during an executive function task in middle age. We hypothesized that coupling between the networks may serve as an early marker of age-related brain vulnerability. We found that age was related to higher default mode network activity during a low demand executive functioning task (1-back). On a high demand executive function task (2-back), we found that age was related to lower frontoparietal network activity. Age was not related to coupling between the networks. Lastly, we found that better accuracy on the high demand task was related to lower default mode activity and higher frontoparietal activity. These results raise the possibility that differences in network activation during tasks may serve as an early marker of brain vulnerability and have important implications for developing prevention strategies and intervention.

Previous research has reported failure of default mode network inhibition in older age (over 60 years-old) when performing a task, potentially recruiting additional neural resources as a compensatory mechanism (Maillet & Schacter, 2016a) . The current study extends the current literature by reporting that age was associated with a failure to inhibit the default mode network during middle age. However, it was previously reported that older adults exhibit reduced default mode network inhibition with greater task difficulty (Turner & Spreng, 2015). In contrast, the current study reported that default mode network inhibition was similar during the high demand task and subtle failures to inhibit occurred during the low demand task. This discrepancy may have resulted from the many pitfalls of cross-sectional research, but there may also be an interaction between age and task difficulty that affects default mode network inhibition. Regardless, the current results

suggest that subtle failures to inhibit default mode network activity during low demand tasks may be an early marker of age-related decline.

The dissociation between network and task difficulty with increasing age may indicate difficulty modulating network activity with task demands. In the current study, lower frontoparietal network activity was associated with older age and lower performance accuracy during the 2-back task, suggesting that age related deficits in the frontoparietal network may adversely impact cognitive performance. As for higher activity of the default mode network during the 1-back task, this could be interpreted as compensation or dedifferentiation.

In terms of compensation, it could be that higher default mode activity reflects the recruitment of more neural resources, improving cognition. Conversely, higher activity could also reflect less efficiency or a lack of network inhibition that could impair performance. The literature has suggested both positive and negative effects of compensatory activity on cognitive function that appear to be task specific (C. Grady, 2012). On the 2-back, the default mode network was inversely associated with performance, suggesting that higher default mode network activity may have a negative impact on cognitive performance. Previous research has suggested that increased default mode network is adaptive only when it allows access to stored representations that are congruent with the task (Spreng et al., 2014). Specifically, Spreng et al. found that default mode network activity was helpful when performing a 2-back task with famous faces, but not with anonymous faces. Considering that access to stored representations would likely not be helpful in performing the *n*-back task, default mode network activity was likely not beneficial. Regarding the mechanisms of compensation, others have implicated age-related changes in the temporal dynamics of brain activity in response to cognitive tasks.

For example, older adults appear to engage more reactive control instead of proactive control (Dew et al., 2012; Jimura & Braver, 2010).

When the task requires more cognitive resources, we found that older adults' ability to engage the frontoparietal network is limited. These results offer some support to the CRUNCH model in that at lower cognitive load, more resources are active, while at higher cognitive load, activity is lower because the system is at or beyond capacity (Schneider-Garces et al., 2010). However, consistent with the CRUNCH model, others have reported that older adults should exhibit distinct brain activity with low task demand and dedifferentiated activity with higher demand (Carp et al., 2010). We report the opposite pattern: increasing age was associated with more dedifferentiation at low cognitive load. Furthermore, an interpretation that is consistent with the CRUNCH model would suggest that higher default mode network activity—a recruitment of domain general cognitive resources—would be associated with greater performance at low cognitive demand. In this study, accuracy on the low cognitive demand task was heavily skewed, reflecting the ease of the task and making it difficult to interpret. Yet, it seems unlikely that default mode network activity would be helpful at lower cognitive load when it is associated with poorer performance at higher cognitive load.

We hypothesized that coupling between the default mode and frontoparietal networks would increase with age, particularly during the more challenging task. This hypothesis is consistent with previous research that found an effect of coupling when comparing young adults (range = 19-27) and older adults (range = 63-78) (Spreng et al., 2016; Turner & Spreng, 2015). The current study found no such evidence of coupling related to age in either the 1-back or 2-back conditions. A simple interpretation for this is that the current study examined midlife and a coupling effect may emerge in older age. Others have hypothesized that coupling may result from greater activation of executive

control in the face of internal distractors from default mode network activity (Chadick & Gazzaley, 2011). However, there is a growing literature to suggest that older adults experience less internal distractors than younger adults (Maillet & Schacter, 2016b). It should also be noted that to our knowledge, only one study has investigated age-related coupling of the default and frontoparietal networks.

Acute stress while performing the n-back task could potentially explain the observed results. Previous research has demonstrated that acute stress can decrease performance on the n-back task (Het, Rohleder, Schoofs, Kirschbaum, & Wolf, 2009). Furthermore, acute stress many decrease activity in the frontoparietal network and increase activity in the default mode network during a working memory task (Qin, Hermans, van Marle, Luo, & Fernandez, 2009). Failure to inhibit default mode network activation may result from the introduction of stress-related internal distractors, while decreases in frontoparietal network activation may result from stress-related catecholamine modulation (Arnsten & Li, 2005). However, it is unknown if the response to stress while performing the n-back task changes with age. A physiological stress response that impairs prefrontal activity may result from a stereotype threat in older adults, who expect to do poorly on a challenging working memory task (Angelidis, Solis, Lautenbach, van der Does, & Putman, 2019; Schmader, Johns, & Forbes, 2008). However, some have suggested that older adults are less susceptible to executive functioning impairment in response to acute stress, possibly because of a reduction in glucocorticoid activity (Perlman, Webster, Herman, Kleinman, & Weickert, 2007; Pulopulos et al., 2015). Further research directly testing stress as a mediator of age-related changes in network activation during an executive functioning task is needed.

In summary, Aim #2 suggests that subtle failures to inhibit default mode network during low demand executive function tasks and decreases in frontoparietal network

activation during high demand tasks may serve as an early marker of brain vulnerability to cognitive decline. Future research is needed that identifies the specific mechanisms that may underlie these early changes in order to develop targeted interventions and prevention strategies to prevent cognitive decline.

4. SPECIFIC AIM #3

4.1 Introduction

Aim #3 was to determine if metabolic syndrome (MetS) accelerates age-related brain changes identified in Aim 2. The results of Aim #2 suggest that subtle failures to inhibit default mode network during low demand executive function tasks and decreases in frontoparietal network activation during high demand tasks may serve as an early marker of brain vulnerability to cognitive decline. Metabolic syndrome has been identified as a risk factor for age-related cognitive decline yet the brain mechanisms involved are unknown. Relating metabolic syndrome to these markers may provide insights into age-related brain mechanisms and indicate possible avenues for intervention to prevent cognitive decline. We hypothesized that during an executive function task, metabolic syndrome would moderate age-related variance in frontoparietal attention network activity, default mode network activity, and coupling between the networks. Specifically, we expected that metabolic syndrome would accelerate age-related differences in these brain markers.

4.2 Methods

4.2.1 PARTICIPANTS

Aims #3 was conducted from a dataset previously collected and included 177 participants from whom task fMRI was collected. This dataset included apparently healthy adults between the ages of 40 and 62 years old recruited from the Austin, Texas community through flyers, newspaper advertisements, and Craigslist. Participants with histories of cardiovascular disease (e.g., coronary artery disease, angina pectoris,

myocardial infarction), neurological disease (e.g., Parkinson's disease, clinically significant traumatic brain injury), major psychiatric illness (e.g., schizophrenia), substance abuse, smoking, or contraindications of MRI were excluded.

All participants underwent a medical history interview, general health assessment, and brain imaging. All participants gave written informed consent for all study procedures and the institutional review board at the University of Texas at Austin approved all procedures.

4.2.2 General Health Assessment

Body mass index and waist circumference were measured as indices of global and abdominal obesity. A blood sample was collected from the antecubital vein by venipuncture after an 8-hour fast. Standard enzymatic techniques were used to quantify plasma concentrations of glucose, HDL-cholesterol, and triglycerides. Brachial blood pressure was determined after 15 minutes of supine rest using a semi-automated device (VP-1000plus, Omron Healthcare, Bannockburn, IL).

4.2.3 Metabolic Syndrome

MetS was defined according to consensus criteria published in 2009 (Alberti et al., 2009). The criteria included the following: waist circumference >102 cm for men, >88 cm for women; triglycerides ≥150 mg/dL; HDL cholesterol < 40 mg/dL in men, and < 50 mg/DL in women; blood pressure ≥ 130/85 mmHg; fasting glucose ≥ 100 mg/dL. The use of medication to treat high blood pressure, elevated triglycerides, elevated glucose or low HDL indicated the presence of the respective MetS factor. Participants who exceeded criteria on three or more factors were included in the MetS group, whereas the rest of the sample were considered controls.

4.2.4 STATISTICAL ANALYSES

All statistical analyses were conducted using IBM SPSS Statistics Version 25. To test if metabolic syndrome moderates age-related difference during midlife identified in Aim 2, age, sex, metabolic syndrome status, and interaction term were entered as the independent variable and age-related changes in Aim 2 as dependent variables. The interaction term was calculated as the product

4.3 Results

4.3.1 DEMOGRAPHICS

Analysis of Aim #2 used a sample representative of the community and included: 63% Caucasian, 19% Latino, 8% African American, 5% Asian, and 11% other or no response. The sample consisted of 107 women (60.5%) and 70 men (39.5%).

	range	*m*	*SD*
Age (years)	40-61	49.2	6.1
Education (years)	10-20	16.2	2.3
BMI (kg/m²)	17-53	29.8	6.7
Waist circumference (cm)	68-154	97.7	16
HDL-cholesterol (mg/dL)	21-100	52.6	16
Systolic blood pressure (mmHg)	91-166	123.7	14
Triglycerides (mg/dL)	46-340	116.8	63
Fasting Glucose (mg/dL)	65-268	97.8	24

Table 2: Sample demographics for Aim #3.

The sample included 55 participants who classified with having metabolic syndrome and 122 who were not. The sample included 36 participants who were taking

medication for blood pressure, 20 who were taking medication for diabetes, and 24 who were taking medication for cholesterol. Differences between the groups are displayed in Table 3. There were no significant differences between groups found with age, $t(175) = -.37$, $p = .71$, years of education , $t(175) = -.98$, $p = .33$, or 2-back accuracy, $t(175) = 1.82$, $p = .07$. No significant differences between groups were also found with sex, $\chi^2(1, N = 177) = 3.04$, $p = .08$.

	Non-Mets $n = 122$		Mets $n = 55$	
	m	*SD*	*m*	*SD*
Age	49.03	5.99	49.4	6.49
% Female	64.75	-	50.90	-
Education	16.34	2.26	15.97	2.46
2-Back Accuracy	79.27	10.54	76.03	11.79

Table 3: Group demographics for Aim #3.

4.3.2 MAIN EFFECT OF METS

Linear regression was used to predict default mode network activity during the 1-back task, with MetS status and sex entered as independent variables. This model resulted in a non-significant regression equation, $R^2 = .01$, $F(2,174) = 0.47$, $p = .62$. Neither MetS ($\beta = .06$, $p = 0.43$), nor sex ($\beta = .5$, $p = 0.51$) were found to be predictors of default mode network activity during the 1-back task.

Linear regression was used to predict frontoparietal network activity during the 2-back task, with MetS status and sex entered as independent variables. This model resulted in a non-significant regression equation, $R^2 = .02$, $F(2,174) = 2.01$, $p = .13$. Neither MetS ($\beta = -.09$, $p = 0.26$), nor sex ($\beta = -.14$, $p = 0.07$) were found to be predictors of frontoparietal network activity during the 2-back task.

4.3.3 METS BY AGE INTERACTION

A hierarchical multiple regression was used to test the interaction between age and MetS on default mode network activity during the 1-back task. Age, sex, and MetS status was entered as independent variables. The inclusion of the interaction term did not explain a significant amount of additional variance, ΔR^2 <.01, $\Delta F(1,172) = .02$, $p = .80$, and there was not a moderating effect of MetS on the relationship between age and default mode network activity, as evidenced by the interaction term, $B = .001$, 95% *CI* [-.005, .007].

A hierarchical multiple regression was used to test the interaction between age and MetS on default mode network activity during the 1-back task. Age, sex, and MetS status was entered as independent variables. The inclusion of the interaction term did not explain a significant amount of additional variance, $\Delta R^2 = .01$, $\Delta F(1,172) = 2.37$, $p = .13$, and there was not a moderating effect of MetS on the relationship between age and default mode network activity, as evidenced by the interaction term, $B = -.007$, 95% *CI* [-.016, .002].

4.4 Discussion

The process of brain aging is thought to be a function of time, genetics, and the environment. Research has implicated MetS, a cluster of cardiovascular risk factors, in negatively affecting brain structure and function and leading to poor aging outcomes (Yaffe, Kanaya, et al., 2004). Previous research indicates that MetS has a deleterious effect on cerebral blood flow (Birdsill et al., 2013; Pasha et al., 2017), alterations in BOLD fMRI during cognitive tasks (Hoth et al., 2011; Shigaeff et al., 2017), neurochemistry (Haley et al., 2010; Haley et al., 2012) and white matter microstructure (K. Park et al., 2008; Segura, Jurado, Freixenet, Falcon, et al., 2009; Shimoji et al., 2013).

However, little is known about how the physical alterations in brain structure associated with MetS, subsequently impacts cognitive function. We hypothesized that MetS would accelerate age related differences identified in Aim #2, namely higher default mode network activity during the 1-back task and lower frontoparietal activity during the 2-back task. Yet, the current study found no such interacting effect of MetS and age on network activation.

The lack of findings in the current study may reflect a more complicated picture of how MetS affects the brain, especially during midlife. A recent meta-analysis of longitudinal studies reported that MetS was a risk factor for vascular dementia and conversion of mild cognitive impairment to dementia, but exerted a protective effect on the incidence of Alzheimer's disease (Atti et al., 2019). One possibility is that the accumulation of Alzheimer's disease pathology, which occurs decades before amnestic symptoms, may decrease adiposity, a driver of MetS. Muller et al. reported that BMI began to decrease 17.8 years before symptom onset in autosomal dominant Alzheimer's disease (Muller et al., 2017). If a similar effect is present in sporadic Alzheimer's disease, individuals in the preclinical stage may present with a lower burden of MetS in midlife, yet exhibit early dysfunction in brain networks, particularly in the default mode network, which is preferentially affected in Alzheimer's disease. Therefore, the lack of results in the current study could be caused by the inclusion of preclinical Alzheimer's in the sample. Future research utilizing Alzheimer's biomarkers, such as amyloid imaging, may help determine if MetS interacts with Alzheimer's pathology in affecting brain networks.

Furthermore, the effect of MetS on the brain is etiologically complex and some have proposed independent pathways that exert competing effects on the brain that are regionally specific (Schwarz et al., 2018; Verstynen et al., 2013). Specifically, blood pressure has been reported to be positively associated with regional white matter structure

(Verstynen et al., 2013) and cortical thickness (Schwarz et al., 2018), possibly because of increased perfusion. If MetS encompasses competing mechanisms, any effects on brain networks may become null. Although beyond the hypotheses of this study, future analyses should investigate the effects of individual MetS component.

Another possible explanation for the failure to detect an interaction between MetS and age on network activation is that MetS may have yet to exert a detectable effect on functional connectivity in middle age. Although aging mechanisms such as oxidative stress, inflammation, and disturbances in metabolism are all thought to be associated with MetS, a potential accelerating effect of MetS may only become apparent in later life.

In conclusion, the results suggest that MetS does not accelerate age related differences in default mode and frontoparietal network activation. However, MetS components may exert competing effects and the presence of preclinical Alzheimer's pathology may weaken the overall effect of MetS in this sample. Further research exploring the role of individual components and integrating Alzheimer's imaging markers may help reveal a potential role that MetS may have on age related brain differences in midlife.

5. SYNTHESIS

5.1 Background and Significance

The proportion of older adults is increasing as people live longer, projecting a financial burden on society because of retirement and care costs (Ortman et al., 2014). Cognitive functioning is a critical factor in functional independence and quality of life in older age (Samanez-Larkin, 2013). Although several theories explaining the relationship between brain aging and cognitive decline have been proposed, a unified understanding is lacking. The overarching goal of the current Aims was to better characterize age related brain and cognitive changes in midlife in order to identify targets for future interventions. Before an overwhelming accumulation of pathology, midlife likely offers an optimal time for interventions that prevent or delay cognitive decline.

Together, the Aims identified age related changes in the brain, the effect on cognitive functioning, and examined potential mechanisms. Aim #1 determined the relationship between white matter structure, intrinsic functional connectivity, and executive functioning in midlife. Aim #2 examined the dynamics of the default mode and frontoparietal networks during an executive function task. Aim #3 determined if MetS accelerated age-related brain changes identified in Aim #2. The results suggest new lines of inquiry regarding the role of MetS in typical aging and have implications for several potential interventions to prevent cognitive decline.

5.2 Effects of age

Determining age-related effects associated with brain health was a primary goal of the Aims. The results of Aim #1 offered no evidence that age was associated with network efficiency or executive functioning in the sample. We were expressly interested

in detecting early changes in cognitive functioning and brain health that occur during middle age, which may be too early to detect age-related differences. Previous studies reported such effects in samples among older adults, who may demonstrate accelerated brain and cognitive changes, or by comparing older adults with younger adults, which offers a greater range of variability.

Regarding age related differences in task activation, Aim # 2 found that age was related to higher default mode network activity during a low demand executive functioning task (1-back). On a high demand executive function task (2-back), age was related to lower frontoparietal network activity. Age was not related to coupling between the networks. The results suggest that failure to modulate network activity based on task demands may be an early sign of brain dysfunction. In contrast to other theories of brain aging (i.e. compensation, dedifferentiation, CRUNCH), which suggest greater activation of general neural resources (i.e. default mode network) at higher cognitive loads, we found greater activation at lower cognitive loads. These results offer the possibility that dedifferentiation may begin at lower cognitive load in midlife and become more pronounced at high cognitive load in later life. Research has suggested distinct patterns of network degradation that differentiates typical aging and Alzheimer's disease. The presence of preclinical Alzheimer's disease, which becomes more common in older age and is associated with degradation of within network connections, may explain why the current results differ from other aging hypotheses.

Taken together, the results of these two Aims suggest that differences in brain network activation as a function of task demands may serve as an early indicator of age-related brain changes. Interventions that modulate brain activation to resemble younger activation patterns may prove fruitful in preventing cognitive decline.

5.3 Cognitive functioning

Aim #1 did not find a relationship between FA and executive function, despite previous literature that has found such an effect (Bendlin et al., 2010; Borghesani et al., 2013; Brickman et al., 2012; Haasz et al., 2013; Salami et al., 2012; Ystad et al., 2011). Particularly in middle age, executive function may be associated with FA in isolated regions, rather than whole brain FA. In regards to age related increases in activation during tasks, the literature has suggested both positive and negative effects on cognitive function that appear to be task specific (C. Grady, 2012). Aim #2 found that better accuracy on the high demand executive function task was related to lower default mode activity and higher frontoparietal activity. The finding that higher default mode activity was associated with worse performance argues against the compensation hypothesis, which posits that higher default mode activity represents the beneficial recruitment of additional neural resources. Instead, the results argue that a higher default mode network activity may represent a failure to modulate brain networks that subsequently harms cognitive performance. In conclusions, the results of suggest that white matter structure may support the inhibition of the default mode network and the activation of the frontoparietal network as a function of cognitive load during executive function tasks.

5.4 Proposed mechanisms

Several mechanisms have been identified that appear to underlie age related changes in the brain, including genetic, inflammation, oxidative stress, and infarcts related to microvascular changes. MetS is known to amplify many of these same mechanisms that have been associated with typical aging. We therefore hypothesized that the presence of MetS would accelerate age-related changes. Aim #3 found that during an executive function task, MetS did not moderate age-related variance in frontoparietal

attention network activity or default mode network activity between the networks. While these results may suggest that MetS does not underlie age-related differences in network activation, it is also possible that different individual components of MetS may exert competing pathways and therefore mask any overall effects. Others have reported such a relationship between MetS components and brain markers of cortical thickness and white matter health (Schwarz et al., 2018; Verstynen et al., 2013).

Taken together, the Aims identified markers of early age-related brain changes. Specifically, the results report that age is related to white matter structure and network activation during task. A unifying mechanism between age related structural and functional changes is still unknown.

5.5 Future directions

The current Aims raise several interesting new lines of investigation. Exploring the role of individual MetS components on age-related brain markers may help elucidate more specific mechanisms. It should also be noted that the current Aims all utilized cross-sectional studies and longitudinal follow-up would help clarify the role of age by removing cohort effects. Although typical aging is currently inextricably linked with Alzheimer's pathology, the accumulation of such pathology may confound the results of this current aims given that Alzheimer's may be linked to a reduction in obesity decades before clinical symptoms. Incorporating markers of Alzheimer's pathology, such and amyloid and tau imaging, may help separate the effects of age and preclinical Alzheimer's disease.

The emergence of neuromodulation, especially noninvasive technologies such as real-time fMRI, transcranial low-level laser therapy and transmagnetic stimulation, in clinical practice and research, offers exciting possibilities that such technologies may be

used to treat and prevent cognitive decline in the future (Lewis, Thomson, Rosenfeld, & Fitzgerald, 2016; Rojas, Bruchey, & Gonzalez-Lima, 2012). With the identification of changes in brain networks that underlie age-related cognitive decline, neuromodulation could potentially be used to suppress default mode network activity or promote frontoparietal network activity during cognitive training. Although the efficacy has yet to be proven, the results of the current Aims may help further the goal of decreasing the burden of cognitive decline in the future.

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