REDUCED NEURAL NETWORK COHERENCE AND EXECUTIVE FUNCTION AMONG OLDER ADULTS AT-RISK OF STROKE

by

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(Under the Direction of Lawrence Sweet)

ABSTRACT

Age-related reductions in executive functions and the brain networks that support them, such as the frontoparietal network (FPN) and default mode network (DMN), have been well-documented. Less well known, however, are the cognitive and neural consequences of mild cerebrovascular disease. The present study sought to employ a revised stroke risk classification system (CHA_2DS_2-VASc) to validate its utility as a predictor of working memory performance in a sample of 45 healthy older adults and determine if this relationship is related to coherence of the FPN and DMN. Results validated CHA_2DS_2-VASc as a predictor of age-related working memory decline, and connectivity of FPN and DMN regions; while their mean coherence did not significantly influence this relationship, connectivity of the left dorsolateral prefrontal and right posterior parietal cortices mediated the relation between CHA_2DS_2-VASc and working memory. Findings identified CHA_2DS_2-VASc as an early marker of stroke risk in healthy older adults and a potential mechanistic basis for age-related working memory in two prominent FPN nodes.

INDEX WORDS: Aging, Stroke risk, Functional Connectivity, Mediation, Working memory

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CHAPTER 1

INTRODUCTION

Advancements in healthcare have contributed to a worldwide increase in lifespan. The number of individuals aged 65 or older is projected to exceed 1.5 billion in 2050 (National Institute on Aging & World Health Organization, 2011) and will comprise approximately 30% of the population by 2060 (FUTURAGE project, 2011). This demographic shift suggests that there will be higher prevalence of age associated disorders, such as heart disease, stroke, and dementia. It is estimated that 47 million individuals worldwide are currently affected by Alzheimer's disease, which is recognized as a leading cause of death and the most prevalent dementia (World Health Organization, 2017). While aging has been identified as the strongest risk factor for dementia, its two most common etiologies remain difficult to classify (Gorelick et al., 2011; Alzheimer's association, 2016), as reflected by broad prevalence estimates of Alzheimer's disease (AD) and cerebrovascular disease, and a limited understanding of their comorbidity and etiologies (O'Brien & Thomas, 2015; Iadecola, 2013). In addition to the significant difficulties associated with dementia, the rapidly growing non-demented OA population will also present considerable challenges. Healthy aging has been consistently linked with reduced cognitive function, and importantly, decline in functional status (IADL; Roy et al., 2016; Duda, Puente, & Miller, 2014). These mechanisms are also not completely understood. However, it is well-documented that common physical disorders that increase in prevalence with aging, such as hypertension, arrhythmia, and other cardiovascular diseases, also lead to cognitive decline independent of age. The mechanism for accelerated cognitive decline appears to be the

breakdown of the blood brain barrier that leads to recognized and unrecognized stroke and small vessel disease (Liebel and Sweet, in press). Therefore, efforts to identify both risk and protective factors among the rapidly growing OA population are critical for improving our current classification of stroke risk and facilitating development of effective interventions that may ultimately forestall cognitive and functional decline.

Consequences of Typical Aging

It has been well-documented, at least since the beginning of formal intelligence testing, that non-demented older adults have exhibited patterns of neurocognitive decline over time (Wechsler, 1939; Cattell, 1943; Wechsler, 1945). Decline in aspects of attention and memory are frequently reported; healthy OAs have demonstrated lower scores on tests of episodic memory (Buckner, 2004; Hedden & Gabrieli, 2004), explicit memory (Davis et al., 2003; Grady et al., 2006), and processing speed (Charness, 2008; Salthouse, 1996). Moreover, complex cognitive tasks that rely on executive functions (EFs), such as working memory (Balota, Dolan, & Duchek, 2000; Zacks, Hasher, & Li, 2000), selective attention (Barr & Gambria, 2000; Madden, 1990), and task-switching (Kray & Lindenberger, 2002; 2000), appear to be particularly susceptible to the aging process (Glisky, 2007).

Neurobiological changes in aging. Consistent with cognitive findings, neuroimaging studies have identified patterns of neural changes in non-demented OAs. In structural neuroimaging studies, OAs have exhibited reduced white matter integrity (i.e., reduced functional anisotropy found using diffusion tensor imaging) in subcortical prefrontal (PFC) and parietal regions (Persson et al., 2006; Grady, 2012), and reduced gray matter volume within the hippocampus and PFC (Raz et al., 2004; Haug & Eggers, 1991). Functional neuroimaging studies, using positron emission tomography (PET) and functional magnetic resonance (fMRI),

have revealed both age-related increases and decreases in brain activity. These findings were initially thought to reflect poorer brain function (i.e., reduced blood flow) underlying observations of worse performance associated with cognitive decline. Specifically, decreases in brain activity have been interpreted as reflecting a reduced allocation of neural resources; in contrast, observations of increases in brain activity, coupled with worse performance in aging, have been interpreted as reduced efficiency and selectivity of neural responses, referred to as *dedifferentiation* (see Grady, 2008 for review).

Functional Connectivity and Aging

Functional connectivity is a neuroimaging analysis method that has been increasingly used to assess the integration of neural activity across distant brain regions, irrespective of their structural connectivity (Schölvinck et al., 2010). Various methods have been developed to measure this type of functional synchronization, or *coherence*, which is most frequently assessed using fMRI in a method commonly referred to as "functional connectivity MRI" (fcMRI; Van Dikj, Sabuncu, & Buckner, 2012). A variety of fcMRI methods have been developed; however, a fundamental common feature is the assessment of correlations between the blood oxygenation level dependent (BOLD) time-series at the voxel level with a BOLD time course in *a priori* seed voxels or seed regions (Biswal et al., 1995), or by empirically driven approaches, such as independent component analyses (Dennis & Thompson, 2014). While this BOLD signal is typically acquired during a "resting state," fcMRI analyses can also be conducted using data acquired while an individual is engaged in a task. Due to increased vulnerability to movement artifact, band-pass frequency filtering is used to exclude extraneous high frequency patterns associated with physiological processes (< 0.01 Hz; e.g., heart rate) and low-frequency

fluctuations (>0.1 Hz; e.g., head movement, linear drift) before conducting correlational analyses.

More than 20 years ago, the initial development of this method linking cerebral and cerebellar motor regions (Biswal et al., 1995) has since fueled the discovery of a number of other temporally coherent networks that are robust and reliable across groups (Honey et al., 2009; Meindl et al., 2010; Shehzad et al., 2009; Van Dijk et al., 2010; Zuo et al., 2010; Damoiseaux et al., 2006; Fox et al., 2005; Beckmann et al., 2005). The two most common methods of assessing functional connectivity in older adults have been resting state *seed region based analysis* and *independent components analysis (ICA)*.

In a *seed-based* approach, the researcher selects a "seed" of interest – such as a single brain voxel or cluster of voxels – and extracts the time course of activation in that seed. When seed regions are used, the temporal course of the BOLD signal is typically averaged across the region at each time point (i.e., each brain volume acquired). This time course is then tested for temporal associations with the time courses of the rest of the voxels of the brain using correlational techniques that range from simple Pearson's r-values to more complicated GLM models with covariates (Fox and Raichle, 2007; Chen, Adleman, Saad, Leibenluft, & Cox, 2014). Those regions that show a high degree of positive correlation with the seed are said to be *functionally coupled*. Brain regions that are negatively correlated with each other are thought to belong to opposing networks, whose functions switch.

By contrast, ICA is a model free approach (i.e., *a priori* seed regions are not required) in which a four-dimensional fMRI (3D plus time) dataset can be decomposed into time courses and then spatial maps, describing the temporal and spatial characteristics of the components making up the data (Beckmann et al., 2005; Dennis & Thompson, 2014). Both seed-based and ICA

approaches tend to reveal the same networks if the number of seeds or components are similar, although each method has advantages and disadvantages. Seed-based analyses are preferred when *a priori* regions are examined. Statistical analyses are less complicated and generally yield less variation than components identified by ICA. On the other hand, the ICA method is more data-driven and not "biased" by the investigator's choice of seed (Dennis & Thompson, 2014). This method relies on post-hoc determination of which components are important to the research question. Pertinent to the present study, both methods have been used successfully to identify age-related alterations in both task-positive networks and the task-negative default mode network.

Task-positive network coherence. With an increasing body of research employing fcMRI analyses, multiple functional neural networks have been identified (Power et al., 2011). One well-studied brain network that appears to be affected by aging, the “frontoparietal network” (FPN), includes portions of the lateral prefrontal and posterior parietal cortex (Ptak et al., 2012). The FPN has been identified as a system involved in a wide variety of tasks, particularly by initiating and modulating “cognitive control” (Dosenbach et al., 2008). Specific cognitive control functions mediated by the FPN include several attention-executive processes, such as attention selection, shifting, and vigilance (Mackie, Dam, & Fame, 2013; Naghavi & Nyberg, 2005; Giuliano, Karns, Neville, & Hillyard, 2014; Moisala et al., 2015; Chun & Turk-Browne, 2007), attention-shifting (Xu, Calhoun, Pearlson, & Potenza, 2014;), sustained attention (Langner & Eikhoff, 2013; Moisala et al., 2015; Sarter, Givens, & Bruno, 2001), and working memory (Barnes, Nobre, Woolrich, Baker, & Astle, 2016; Giuliano et al., 2014; Darki & Klingberg, 2015; Chun & Turk-Browne, 2007; Naghavi & Nyberg, 2005). In addition to flexible attentional processing and higher-order cognitive functioning, evidence suggests that the FPN

may also modulate several other multimodal perception systems (e.g., visual, limbic, motor; Cole et al., 2013; Zanto & Gazzaley, 2008).

Altered patterns of FPN function have been demonstrated in older adults. Specifically, evidence suggests that older adults show a well-established pattern of greater activity within regions of the FPN, relative to their younger counterparts, during successful performance of different cognitive tasks (e.g., working memory) that may reflect an over-recruitment neurocompensatory process (Grady et al., 1994; Cabeza et al. 1997). However, a growing number of studies suggest that as attentional demands increase, older adults are less able to rally additional resources to meet the increasing load, and also show reduced efficiency or selectivity of responses (i.e., dedifferentiation) within FPN regions with reduced EF performance (Reuter-Lorenz & Cappell, 2008; Nagel et al., 2009; Carp, Gmeindle, & Reuter-Lorenz, 2010; Madden et al., 2010; Hidden et al., 2011).

Age-related fcMRI reductions of the FPN have been identified using multiple functional connectivity methods (Goh, 2011), including both seed-region analyses (Campbell et al., 2012) and a comprehensive machine-learning ICA technique (i.e., graph theory analysis; Geerligs et al., 2014). Several of these studies have also identified a significant relation between age-related FPN coherence and declines in higher order cognitive abilities, including EFs such as task-switching (Gold et al., 2010; Madden et al. 2010) working memory (Nyberg, Dahlin, Neely, & Backman, 2009), and attentional inhibition (Campbell et al., 2012).

Task-negative network coherence. The most frequently studied brain network at rest is the default mode network (DMN; Andrews-Hanna, Smallwood, & Spreng, 2014). The DMN is a system of interacting brain regions that include posterior and anterior midline cortices (e.g., posterior cingulate cortex, medial prefrontal cortex). Raichle and others (Raichle et al., 2001;

Fair et al., 2007) have proposed that these regions support active baseline processes during conscious rest with low external attentional demands, which is abandoned to successfully perform more effortful externally driven cognitive tasks.

The DMN has been found to be a highly compromised system in aging (Sala-Llonch, Bartes-Fax, & Junque, 2015). Older adults affected by neurodegenerative processes have demonstrated alterations of DMN functioning, commonly with reduced connectivity of DMN nodes, including OAs diagnosed with mild cognitive impairment (MCI; Agosta et al., 2012; Bai et al., 2008; Binnewijzend et al., 2011; Rombouts, Barkhof, Goekoop, Stam, & Scheltens, 2005; Zhou et al., 2008; Petrella et al., 2011), and AD (Buckner et al., 2005; Rombouts et al., 2005; Grecious, Srivastava, Reiss, & Menon, 2003; Binnewijzend et al., 2011; Koch et al., 2010; Zhou et al., 2008; Petrella et al., 2011). In addition, maladaptive neural alterations in DMN coherence among individuals with MCI and AD have demonstrated associated cognitive dysfunction in multiple domains, including immediate and delayed memory (Celone et al., 2006; Binnewijzend et al., 2011).

A growing body of empirical evidence suggests that functional connectivity of the DMN reduces with healthy aging as well (Klaassens et al., 2017; Spreng, Stevens, Viviano, Schacter, 2016; Andrews-Hanna et al., 2007; Sheline et al., 2010; Rombouts et al., 2005) and is inversely associated with processing speed (Ng et al., 2016), working memory (Grady et al., 2010; Hampson, Driesen, Skudlarski, Gore, & Constable, 2006), associative learning (Miller et al., 2008), and executive control performance (Turner & Spreng, 2015). Relatedly, healthy aging has also been associated with reduced and altered patterns of suppression of baseline DMN function with reduced performance during task-based fMRI (i.e., observed as relative deactivations), which occur when individuals abandon unconstrained processes, such as

attending to external environmental stimuli, monitoring one's internal state, and autobiographical memory processing (Persson et al., 2007). Moreover, a shift from task-independent suppression to neurocompensatory overactivation has been speculated to reflect declining task-related neural resources, reduced efficiency in the allocation of resources, or both (Grady, Springer, Hongwanishkul, McIntosh, & Winocur, 2006; Sweet, Rao, Primeau, Durgerian, & Cohen, 2006; Sweet, Jerskey, & Aloia, 2010; Sweet et al., 2008). This notion has been supported by several studies that have linked inverse relationships between the coherence of task-dependent networks and the DMN to cognitive performance in aging (Spreng et al., 2016; Ng et al., 2016; Avelar-Pereira, Backman, Wahlin, Nyberg, & Salami, 2017).

Network coherence and age-related cognitive decline. Accumulating evidence has identified the coherence of brain networks as a causal mechanism of the relation between age-related neuropathological changes and deterioration of cognitive performance (Barulli & Stern, 2013; Stern, 2017); See Figure 1, as presented in Stern, 2017. These findings have included investigations of several task-positive networks as well as the task-negative DMN. For example, using a multivariate linear modeling technique, Gazes et al., (2015; 2012) reported that the functional coherence of a large-scale, task-positive brain network mediated the inverse effects of age and the performance of a challenging task-switching paradigm. Using a similar approach to quantify the coherence of large-scale, task-positive brain networks, Steffener et al. (2014) identified reductions in the strength of correlations between several regions (e.g., middle frontal, subcortical, and occipital gyri) that partially mediated the relation between age and working memory performance. While not causal in nature, Andrew-Hannah et al. (2007) identified a significant, positive relation between reduced coherence of the DMN and performance measured by composite scores of EF, memory, and processing speed. In addition, using an ICA approach,

Sambataro et al., (2010) reported a significant, inverse relationship between reduced DMN coherence and age-related decline in working memory (i.e., 2-Back) performance. Moreover, reduced functional connectivity between the dorsolateral and medial prefrontal cortices, post-central gyrus, and anterior cingulate cortex has been associated with worse performance during the challenging Paced Audition Serial Addition Task (PASAT) in multiple sclerosis (MS) patients (Duong et al., 2005). Conversely, results of a computerized cognitive rehabilitation program for individuals affected by MS revealed an increase in the functional coherence of the DMN that was associated with EF performance (Bonavita et al., 2014). Taken together, these findings provide evidence of brain network coherence as a mechanism of age-related cognitive decline. However, this literature is in its nascent stages with significant variability across studies, and would therefore benefit from further investigation (Barulli & Stern, 2013; Stern, 2017). For example, age-related declines in health, such as cardiovascular risk factors, may support further growth and clarification within this literature.

Cardiovascular Disease and Age-related Cognitive Decline

Cardiovascular disease (CVD) is a diagnosis that has been used to describe all congenital and acquired diseases of the circulatory system (International Classification of Diseases-10 Codes I00-I99). Prevalence is highly related to age, with more than 80% of men and 90% of women over the age of 80 experiencing some form of CVD (Mozaffarian et al., 2016). Approximately one in three of all American adults have some type of CVD, affecting approximately 44 million people over the age of 60 (Mozaffarian et al., 2016), and resulting in approximately 610,000 deaths each year (Center for Disease Control, 2013). This is particularly troubling given the rapidly expanding OA population. With improved survival from acute cardiac events, older adults are often faced with the prospect of living with CVD, which has been

shown to cause significant psychological, social, and economic hardship (Haan et al., 1997; Mangano, 1995; Miller & Missov, 2001; Rich, 1997; Smith & Mensah, 2003). Research literature has consistently demonstrated age-related impairments in cognitive functioning associated with CVD (Cannon et al., 2017; DeRight, Jorgensen, & Cabral, 2015; Eggermont et al., 2012; Newman et al., 2005; Rusanen et al., 2014; Stephan et al., 2017). Given the link between various types of CVD and small vessel disease (e.g., heart failure, hypertension) and related cognitive decline, it is reasonable to conclude that small vessel disease may account for cognitive dysfunction in pathological aging (Leibel & Sweet, 2017).

$CHADS_2$-VASc and risk of stroke. Recent efforts have been made to improve our understanding of the mechanisms of stroke and small vessel disease. In this vein, a classification system referred to as "$CHADS_2$" was developed to improve the predictive ability of stroke among CVD researchers (Gage et al., 2001). Since its inception, the $CHADS_2$ system has been validated by many studies and gained widespread use as clinical prediction rules for the estimation of stroke risk in CVD patients with atrial fibrillation (Lee et al., 2010; Winkle et al., 2013; Uehara et al., 2014; Boriani et al., 2011; Chen et al., 2013; Olesen & Torp-Pedersen, 2015; Letsas et al., 2013; Odum et al., 2012; Pieri et al., 2011; Perini et al., 2013; Palm, 2012; Zhu et al., 2015; Zuo et al., 2013; Komatsu et al., 2014; Giralt-Steinhauer et al., 2012), and other heart conditions, such as acute ischemic stroke, other arrhythmia, interatrial block, flutter, and hypertension (Ntaios et al., 2013; Lip et al., 2013; Tu et al., 2013; Wasmer et al., 2013; Perini et al., 2013). Given the large-scale consequences of CVD and the rapidly expanding OA population, research on the cognitive and neuropathological effects among OAs with pre-clinical subtypes of CVD is of great importance. The $CHADS_2$ classification system offers a well-validated option for such research that would also benefit from validation among healthy OAs.

The original $CHADS_2$ score (scored as 1 point each for congestive heart failure, hypertension, diabetes mellitus, or age ≥75 years, and 2 points each for past stroke or transient ischemic attack) has been used to tailored initiation of antithrombotic treatments for stroke risk reduction (Lip, Tse, & Lane, 2012; Puwanant et al., 2009). Recently, the CHA_2DS_2-VASc score (scored as 1 point each for congestive heart failure, hypertension, diabetes mellitus, vascular disease, age 65 to 75 years, or female sex, and 2 points each for age ≥75 years or past stroke/transient ischemic attack) was developed to improve the precision of risk stratification by including other important predictive factors. These newer scores have been reported to improve the accuracy of the $CHADS_2$ score in estimating the risk of stroke in older adults with several cardiac conditions (Lip et al., 2010; Piccini et al., 2013).

Due to its inclusion of additional common stroke risk factors, the CHA_2DS_2-VASc has begun to supersede its original $CHADS_2$ version in clinical use, and it offers a very practical tool for identifying stroke risk in older adults, as well as estimating negative consequences of stroke (e.g., cognitive outcomes) and other cardiac complications (Tabata et al., 2017). This is an important advancement due to its target risk factors' effect on deficits in cognitive function and brain health. Older adults with cardiac conditions (e.g., atrial fibrillation, acute stroke patients) and $CHADS_2$ elevations have demonstrated significantly lower global cognitive functioning (Washida et al., 2017; Cerit et al., 2016; Meyre et al., 2017; Graff-Radford et al., 2016) as well as increased risk of mild cognitive impairment (Graff-Radford, 2016; Yaneva-Sirakova et al., 2013; Shaw et al., 2016) relative to their healthy counterparts.

Originally validated to aid in the decision whether or not to treat heart arrhythmia patients with anticoagulant medication due to the elevated risk of thromboembolic stroke, the validity of $CHADS_2$ and CHA_2DS_2-VASc scales have been extended to other stroke vulnerable populations,

such as patients with other cardiovascular diseases. A novel purpose of this proposal is to test the hypothesis that CHA_2DS_2-VASc validity will extend to older adult cognitive performance as assessed by the PASAT, a behavioral measure that has demonstrated sensitivity to white matter pathology.

CHA_2DS_2-VASc components.

Congestive heart failure. As a common disease complicating many other cardiac pathologies, heart failure (HF) is defined as the heart's inability to produce an adequate flow of blood at a pressure low enough to prevent pulmonary edema (Yancy et al., 2013). Despite advancements in treatment, an estimated 5.7 million Americans have HF, and its prevalence is projected to increase nearly 50% by 2030 (Heidenreich et al., 2013). HF is also the costliest CVD in the United States, with estimates over $30 billion in 2012 (Mozaffaria et al., 2016). Importantly, individuals with HF are much more likely to experience personal challenges, as well, including heightened risk of disability, death, emotional distress and lower quality of life (Mozaffarian et al., 2016; Pena et al., 2011; Gowrishankar, 2011).

Research efforts have identified several forms of cognitive dysfunction and neuropathology among individuals affected by HF. Executive functioning appears to be the cognitive domain most frequently impaired in HF patients (Alosco et al., 2014; Hajduk et al., 2013; Bauer et al., 2012), particularly WM (Arslanian-Engoren et al., 2014; Callegari et al., 2002; Grubb et al., 2000; Morys et al., 2016; Vogels et al., 2007b). Numerous studies have also reported lower functioning in the domains of global cognition (Gallagher et al., 2013; Garcia et al., 2011), attention (Miller et al., 2012; Morys et al., 2016), and delayed memory (Almeida et al., 2012; Athilingam et al., 2011). The neuropathological mechanisms associated with these cognitive deficits in HF continue to be investigated. It has been well documented that cerebral

blood flow is significantly compromised in HF (Gruhn et al., 2001; Rajagopalan, Raine, Cooper, & Ledingham, 1984), which presumably leads to both gray and white matter damage (Almeida et al., 2012; Kumar et al., 2011). Structural changes can be diffuse or localized and may relate to specific neurocognitive impairments (Pan et al., 2013; Vogels et al., 2007). Almeida et al. (2012) found that HF patients exhibit gray matter loss in several frontal regions, the right middle temporal gyrus, occipital-parietal regions, including the precuneus, and the left caudate nucleus that were associated with deficits in immediate and delayed memory and CPS.

Hypertension. Hypertension (HTN) is sustained elevation in blood pressure (BP), and over 90% of cases are classified as primary (i.e., essential), denoting uncertain cause. In the United States, the overall prevalence of HTN reaches 65% among people over the age of 60 (Nwankwo et al., 2013), and in 2014, over 30,000 deaths were attributed to HTN alone (Kochanek et al., 2016). HTN has been identified as a significant risk factor for other CVDs and has also been estimated to account for half of all strokes (Rapsomaniki et al., 2014). Given the relationship between stroke and dementia (Pendlebury & Rothwell, 2009), it is clear that the relationship between hypertension and stroke also makes it a risk factor for dementia. Age is the greatest risk factor for hypertension and has been recognized as a moderator in several studies of neurocognitive impairment (Qui et al., 2009; Shang et al., 2016).

HTN has been linked to reduced neurocognitive function across several domains. The most frequently studied effects have used global cognitive assessment measures. Most studies have reported inverse relationships between current or historical BP and MMSE scores (Haring et al., 2016; Obisesan et al., 2008). Similarly, studies have found an association between HTN and basic auditory or visual attention (Nishtala et al., 2015; Waldstein et al., 2005). A high rate of significant effects of HTN across several EFs suggests an elevated risk in this domain as well,

including verbal fluency (Gottesman et al., 2017; Nishtala et al., 2015) and cognitive flexibility (Alosco et al., 2012; Debette et al., 2011) skills. Pathophysiological effects of HTN have also been identified. Structural brain changes found to correlate with HTN have included reduced gray matter volume (Strassburger et al., 1997), including prefrontal cortex volume (Raz, Rodrigue, & Acker, 2003). Regarding functional brain changes, HTN has also been primarily associated with reduced blood flow throughout the brain (Friedman et al., 2014), including hippocampal and prefrontal regions (Efimova et al., 2008; Jennings et al., 2005).

Diabetes mellitus. Diabetes is a complex and heterogenous metabolic disorder that typically begins with insulin resistance, which is linked with physical inactivity and obesity (Stumvoll, Goldstein, & van Haeften, 2005). Type 2 diabetes (T2D) is highly prevalent among older adults, with an estimated 25%+ of older adults in the United States affected by T2D (Center for Disease Control and Prevention, 2011). Consistent with the CVDs, as the population ages, the prevalence of T2D increases (Center for Disease Control and Prevention, 2014), and the life expectancy for people with T2D extends. It is well-established that long-term complications of T2D include microvascular and macrovascular disease throughout the body, including ischemic stroke in the brain (American Diabetes Association, 2014). Results from a recent meta-analysis of 19 longitudinal cohort studies suggested that older adults with T2D, compared to those without, have more than double the risk of developing vascular dementia, and the relative risk of developing AD, MCI and any dementia were 1.46, 1.21, and 1.51, respectively (Gheng, Huang, Deng, & Wang, 2012). Therefore, understanding the epidemiology of geriatric outcomes, including cognitive decline and dementia among individuals with T2D, is very important.

Cross-sectional studies generally report modestly lower cognitive function among people with T2D compared to people without (see Van den Berg et al, 2009 for review). Many studies have reported an association between T2D and decline in one or more domains, but across studies, there has not been a consistent associated between T2D and decline in individual domains. For example, many studies have reported an association between T2D and accelerated decline in processing speed (Yaffe et al., 2012; Gregg et al., 2000), aspects of memory (Spauwen et al., 2013; Comijs et al., 2009), and EF (Gregg et al., 2000; Debette et al., 2011), while other studies have not (Comijs et al., 2009; Knopman, Mosley, Catellier, & Coker, 2009; Van den Berg et al., 2006). Neuroimaging studies have also identified pathophysiological effects of T2D (Mayeda, Whitmer, & Yaffe, 2015). Structural MRI studies have consistently reported an association between T2D and cortical and subcortical cerebral atrophy among older adults (Espeland et al., 2013; Moran et al., 2013; Falvey et al., 2013). Cerebral infarcts associated with T2D have been found relatively consistently, while white matter intensities, as a marker of microvascular cerebral damage, has been inconsistent (Manschot et al., 2006; van Harten et al., 2006; Saczynski et al., 2009).

Stroke or transient ischemic accident. Along with AD, stroke has one of the largest morbidity burdens in older populations (Lopez, Mathers, Ezzati, Jamison, & Murray, 2006). It is well-establish that stroke significantly increases the risk of dementia (Desmond, Moroney, Sano, & Stern, 2002; Ivan et al., 2004; Pendlebury & Rothwell, 2009; Gamaldo et al., 2006). Vascular dementia has been estimated to account for approximately 15% of dementia cases (O'Brien & Thomas, 2015). In community-based studies, the prevalence of post-stroke dementia in stroke survivors is about 30%, and the incidence of new onset dementia after stroke increases considerably over time (Leys, Henon, Mackowiak-Cordoliani, & Pasquier, 2005). Stroke causes

cognitive impairment through several mechanisms, including lacunar infarcts, ischemic white matter disease, cerebral hypoperfusion, amyloid burden, and neuroinflammation (Thiel et al., 2014; Rockwood, Bowler, Erkinjuntti, Hachinski, & Wallin, 1999; Yao et al., 1992; Henon et al., 2001).

While cognitive deficits following stroke are highly variable, based in part upon the type of stroke, region(s) affected, and severity, and moderating risk factors (Kaffashian et al., 2014). Individuals often exhibit several risk factors of stroke, such as obesity, smoking, HTN, and hypercholesterolemia, that may act in an additive or synergistic manner (Kivipelto et al., 2005). Using this information, several early detection tools, such as the CHA_2DS_2-VASc, have been developed and validated to clinically assess for risk in a practical and effective manner (Gage et al., 2001; Lip et al., 2010; Kaffashian et al., 2014). In addition to these early detection endeavors, several behavioral intervention modalities have proven to be effective in reducing the risk of stroke in older adults, such as the Mediterranean diet (Psaltopoulou et al., 2013) and physical activity (Schmidt, Endres, Dimeo, & Jungehulsing, 2013). Moreover, behavioral intervention strategies have also shown efficacy in preventing cognitive decline following stroke, including multimodal approaches (Ihle-hansen et al., 2012) and community exercise therapy (Moore et al., 2014). Given the value of stroke risk assessment in clinical populations, increased efforts to assist researchers and clinicians in improving upon stroke risk among healthy OAs is paramount for effective health management of the rapidly growing older adult population.

PASAT, aging, and cardiovascular health. Given the pattern of EF declines associated with cardiovascular health and aging, identification of a neuropsychological task that significantly challenges EFs would be ideal for assessing stroke risk in community dwelling OAs, and the PASAT may offer such utility. In a follow-up to Gronwall and Sampson's (1974)

original clinical study of the PASAT, Gronwall (1977) identified increased variability in PASAT performance related to age, which was supported by later studies that identified an inverse relationship between PASAT performance and age in adults (Baird, 2004, Brittain et al., 1991, Crawford et al., 1998, Diehr et al., 2003; Diehr, Heaton, Miller, & Grant, 1998; Fluck, Fernandes, & File, 2001; Roman et al., 1991; Stuss, Stethem, & Poirier, 1987; Wiens et al., 1997). Due to the PASAT's well-established sensitivity to white matter disease, the PASAT may also be sensitive to white matter changes related to cardiovascular burden (e.g., small vessel disease). For example, a significantly greater decline in PASAT performance, relative to tests across several other cognitive domains, was revealed in 177 subacute ischemic infarct patients (Jaillard et al., 2009). Patients with T2D have also been shown to perform worse on the PASAT than age-matched pre-diabetic patients (Nazaribadie et al., 2014). Recently, generally healthy OAs diagnosed with MCI and DM have also shown reduced PASAT performance at baseline of a cognitive intervention study (Umegaki et al., 2017). Thus, the PASAT appears to be an optimal candidate to help researchers increase our understanding of cognitive declines associated with stroke risk.

Mechanistic role of network coherence. Increasing efforts within neuroimaging literature have broadly focused on the identification of neural mechanisms that mediate cognitive functions as potential foci for intervention. Accumulating evidence has identified the coherence of brain networks as a causal mechanism (i.e., mediator) of the relation between age-related neuropathological changes (such as cerebrovascular disease) and deterioration of cognitive performance (Barulli & Stern, 2013; Stern, 2017); See Figure 1, as presented in Stern, 2017. These findings have included investigations of several task-positive networks as well as the task-negative DMN (Gazes et al., 2015; 2012; Steffener et al., 2014). Moreover, the DMN and FPN

have proven particularly useful for the study of mechanistic bases to cognition due to their robustness and reliability (Andrews-Hanna et al., 2014; Honey et al., 2009); moreover, they are particularly strong candidates relative to the current study, as they have both demonstrated age-related reductions in coherence (Goh, 2011; Klaassens et al., 2017), and modulation of EF functions in OAs, including WM (Nyberg et al., 2009; Grady et al., 2010). Furthermore, reduced coherence of FPN regions have been associated with reduced PASAT performance in MS patients (Duong et al., 2005). Age-related declines in health, such as CVD risk factors that also cause white matter disease, may support further growth and clarification within this literature. Thus, the DMN and FPN are ideal candidates for examination of mechanistic basis that support the expected relation between stroke risk and WM performance in OAs.

Aims and Hypotheses

The present study examined the relationship between OAs' risk of stroke and performance on a challenging WM task (i.e., PASAT) that has demonstrated sensitivity in patients with white matter disease (Gronwall, 1977; Rao, 1991). Consistent with modern models of brain reserve (Stern, 2017), the potential indirect effect of network coherence on the relation between stroke risk and WM performance was assessed. It is specifically hypothesized that (1) CHA_2DS_2-VASc would exhibit a significant inverse correlation with PASAT performance, such that increasing risk of stroke would negatively correlate with EF performance. Next, it was hypothesized that CHA_2DS_2-VASc score would be inversely correlated with coherence strength of the FPN (2), as well as the DMN (3). Contingent upon these findings, it was hypothesized that (4) the strength of FPN coherence would mediate the relation between CHA_2DS_2-VASc and PASAT performance, and that, (5) similarly, strength of DMN coherence would mediate the relation between CHA_2DS_2-VASc and PASAT performance. Results in support of these findings may

have practical and theoretical implications: (a) validation of a stroke-risk index for community-dwelling OAs would provide quantitative support for the utility of extending its use, (b) identification of a mechanistic basis for CVD-related cognitive decline would provide support for the modern models of clinical neuropsychology that predict network coherence mediates the cognitive consequences of brain pathology, and offers foci for the continued development of interventions, including cognitive training programs and pharmacotherapies.

CHAPTER 2

METHODS

Participants

Participants included 45 community-dwelling, right handed, and English-speaking men and women over the age of 50 (29 female, age range 53-86, *M* age = 65.06 years, *SD* = 8.81) who participated in a study of cardiovascular disease. Although they were recruited from both the community and cardiology clinics in the Providence, RI area, heart health status was not an exclusionary criterion. For each participant, a risk of stroke estimation was calculated according to the CHA_2DS_2-VASc criteria. Participants were well-educated (*M* = 16.30, *SD* = 2.17). See Table 1 for descriptive statistics of the sample. Exclusion criteria included left-hand dominance, corrected visual acuity poorer than 20:40, low global cognitive function (> 1.5 *SD*s below the sample population on the MMSE), or any MRI contraindications (e.g., metal implants). Significant medical (e.g., endocrine disorders), neurological (i.e., multiple sclerosis, traumatic brain injury with loss of consciousness), and psychiatric problems (e.g., substance abuse with hospitalization, diagnosis of any current or chronic psychiatric illness) were exclusion criteria that were assessed by interview, physical examination, review of medical records and self-report questionnaires.

Procedure

The current study was conducted using data from a parent study intended to examine the behavioral and neural effects of CVD in aging. Quantification of fcMRI and CHA_2DS_2-VASc

and all statistical analyses used in the present study were conducted independent of the parent study.

All participants underwent telephone screening and provided written informed consent. Assessments were conducted over three visits that spanned approximately six weeks. They included a comprehensive neuropsychological battery, a cardiology assessment (e.g., echocardiogram), and an MRI scanning session. The three-hour neuropsychological assessment was supervised by a licensed clinical neuropsychologist. Echocardiogram assessments were conducted by a licensed cardiologist in order to measure the absence or presence and severity of CVD and related risk factors. At a subsequent visit, a one-hour MRI assessment was conducted using a Siemen's 3T TIM Trio scanner. The scanning session included the acquisition of T1-weighted structural and echoplanar functional images during a working memory task and resting state (i.e., fixated on a "+"). Participants were compensated for their participation. The study was approved and monitored by the university and hospital institutional review boards (IRB) where the research took place and conformed to the Helsinki Declaration on human subjects' protection.

Measures

Three primary assessments were used to address the aims of this study. These included a quantification of stroke risk, behavioral assessment of EFs, and fcMRI.

Assessment of executive function. The Paced Auditory Serial Addition Test (PASAT) was administered using 3 second interstimulus intervals. The PASAT is a clinical assessment instrument that has been frequently used by neuropsychologists to assess attention and EFs (Tombaugh, 2006; Gronwall & Sampson, 1974). It has demonstrated sensitivity to detect cognitive impairment and functional impairment in patient populations with white mater disease

and executive deficits, including traumatic brain injury (Gronwall, 1977) and multiple sclerosis (Rao, 1995; Fischer et al., 1999). Administration of the PASAT involves presenting a series of single digit numbers where the two most recent digits must be summed. For example, if the digits "3", "6", and "2" were presented, the participant would respond with correct sums, "9" and then "8." The participant must respond prior to the presentation of the next digit to be scored as correct. The PASAT is conceptualized as a multifactorial test because it requires the successful completion of numerous executive and other cognitive functions. Cicerone (1997) observed that the PASAT has two components: 1) cognitive ability required to complete the task, and 2) speed of information processing. Since then, several specific EFs have been identified as necessary for the successful completion of the PASAT, including selective and sustained attention, working memory, and divided attention (Madigan et al., 2000). The PASAT has demonstrated good psychometric properties, such as high levels of internal consistency, test-retest reliability, and sensitivity to executive deficits in patients with known white matter disease (Tombaugh, 2006; Rao, 1995; Fischer et al., 1999; Gronwall & Sampson, 1974). For the present study, the raw score of the PASAT (3 second interval) served as the dependent variable.

$CHADS_2$ classification. The CHA_2DS_2-VASc is a system for quantifying an individual's stroke risk. (Gage et al., 2001). It is based on an earlier $CHAD_2$ version, which determined scores by adding one point for each congestive heart failure, hypertension, age over 75, and diabetes mellitus. CHA_2DS_2-VASc was developed to improve the precision of risk stratification by including other important predictive factors (scored as 1 point each for congestive heart failure, hypertension, diabetes mellitus, vascular disease, age 65 to 75 years, or female sex, and 2 points each for age ≥75 years or past stroke/transient ischemic attack). These newer scores have been reported to improve the accuracy of the $CHADS_2$ score in estimating the risk of stroke in

heart arrhythmia patients (Lip et al., 2010; Piccini et al., 2013). Due to its inclusion of additional common stroke risk factors, the CHA_2DS_2-VASc has begun to supersede its original version in clinical use and offers a very practical tool for identifying stroke risk even in older adults with mild neuropathology (Tabata et al., 2017).

Neuroimaging.

Data acquisition. Whole-brain echoplanar fMRI was conducted using a Siemen's TIM Trio 3 tesla scanner (TR = 2500 ms, TE = 28 ms, FOV = 192^2, matrix size = 64^2, in 42 3-mm-thick axial slices). The resting state acquisition yielded 116 whole-brain volumes for each of the one 4-min imaging runs, yielding a spatial resolution of $3mm^3$ per voxel. Whole-brain high-resolution T1 images were also acquired in the sagittal plane for anatomical reference (TR = 1900 ms, TE = 2.98 ms, FOV = 256^2 mm, matrix size 256^2). A fixation crosshair was presented using E-prime (Psychology Software Tools, Sharpsburg, USA) and back-projected onto a screen visible to the participant via a mirror mounted to the head coil.

Data processing. fcMRI dataset processing and statistical analyses were performed with the CONN v1.2 software: A functional connectivity toolbox for correlated and anticorrelated brain networks (Whitfield-Gabrieli & Castanon, 2012). After defining our raw functional (i.e, resting state) and structural data, CONN's default Montreal Neurological Institute (MNI) preprocessing pipeline was used to correct for artifact and prepare for connectivity analyses. Preprocessing steps included functional realignment and unwarping, slice-timing correction, structural segmentation and normalization, outlier detection, and smoothing (8-mm FWHM Gaussian filter) using SPM default parameter choices. Anatomical volumes were segmented into gray matter, white matter, and CSF areas, and the resulting masks were eroded (one voxel erosion, isotopic 2-mm voxel size) to minimize partial volume effects. The temporal time series

characterizing the estimated subject motion (three-rotation and three-translation parameters, plus another 6 parameters representing their first-order temporal derivatives), as well as the BOLD time series within the single-participant-specific white matter mask and CSF mask, were used as temporal covariates and removed from BOLD functional data using linear regression. Due to the heightened sensitivity to head motion artifact to fcMRI analysis (Dijk, Sabuncu, & Buckner, 2011), the resulting residual BOLD time series were band-pass filtered using CONN's default threshold (0.008 – 0.09 Hz).

Region of Interest definition.

Four distinct regions of interest (ROI) were chosen to characterize each network. Using the CONN fMRI functional connectivity toolbox (Whitfield-Gabrieli & Castanon, 2012), we selected the default bilateral regions offered by the software for each of these well-established networks, with coordinates listed in MNI space, and surrounded by a 5 mm radius sphere. As depicted in Figure 3, the task-positive FPN was defined by relations among the following ROIs: left lateral prefrontal cortex (L PFC; -43, 33, 28); left posterior parietal cortex (L PPC; -46, -58, 49); right lateral prefrontal cortex (R PFC; 41, 38, 30); right posterior parietal cortex (R PPC; 52, -52, 45). As depicted in Figure 4, the task-negative DMN was defined by relations among the following ROIs: medial prefrontal cortex (mPFC; 1, 55, -3); left lateral parietal cortex (LPC; -39, -77, 33); right lateral parietal cortex (RPC; 47, -67, 29); posterior cingulate cortex (PCC; 1, -61, 38). CONN's default ROIs for each network were found to be consistent with prior literature of regions that define the FPN (Ptak et al., 2012) and DMN (Raichle et al., 2001; Fair et al., 2007), and they were also validated using the publicly available Neurosynth software (http://neurosynth.org/analyses/terms/), a platform for large-scale, automated synthesis of fMRI data using pooled meta-analytic data published in peer-reviewed journals.

Functional connectivity analysis.

Using the CONN toolbox (Whitefield-Gabrieli & Castanon, 2012), we used the ROI-to-ROI connectivity (bivariate correlation measures) analyses to test our hypotheses. Each of the 4 ROIs selected for the FPN and DMN, respectively, served as a seed and a target region. For each participant, residual BOLD activity in each region was averaged at each time point to create a mean waveform for that ROI over time, and the four mean waveforms each became an independent measure that predicted the residual BOLD signal over time (i.e., the DV) in separate whole-brain voxel-wise GLM analyses. CONN converted each of the resulting beta values to z-scores using Fischer's transformation. To adjust for multiple corrections, results were thresholded using an FDR-corrected p-value ($q = .05$). To provide one metric of DMN and FPN connectivity for each individual, the z-values in each voxel of each ROI were averaged to produce one mean z-score representing the connectivity among all four DMN nodes (i.e., a "coherence" value"). This procedure was repeated using the four nodes of the FPN to generate one mean z-score per person relative to the entire network. At the group level, each subject had a total "coherence" value for each of the two networks, and these values were used as a continuous variable (the mediator) in the 2 multiple regression models. Lastly, we used the same four seeds from each network to conduct two separate seed-to-voxel connectivity analyses (in order to ensure that primary nodes of each network were appreciated, thus validating the results of our ROI-to-ROI fcMRI analyses). To accomplish this, the average BOLD time-series of each seed region (ROI) were tested for significant relations with each voxel of the brain, and results were thresholded using FDR corrected p-values by a combination of height (voxel-level) and extent (cluster-level) thresholds of $q = 1.0 \times 10^{-8}$.

Multiple Regression and Mediation Analyses. Before conducting behavioral analyses, assumptions of multiple linear regression were examined, including homoscedasticity, independence of residuals, and normality of residuals (Cohen, Cohen, West, & Aiken, 2003). In addition, multicollinearity between the independent variable and the mediator were reduced through the use of variable centering (Aiken & West, 1991). For mediation analyses, the publicly-available PROCESS SPSS macro plug-in (http://afhayes.com/introduction-to-mediation-moderation-and-conditional-process-analysis.html; Hayes, 2012) was applied to examine the data within a multiple regression framework. Following a test of multiple linear regression assumptions, the model (4) designated for mediation analyses was run to examine the mediation effect of functional network coherence (FPN and DMN, respectively) on the relation between CHA_2DS_2-VASc and PASAT.

PROCESS provides a structured framework for assessing both complete and partial mediation effects. The formal heuristic analysis that is often used to detect mediation effects follows from the definition of a mediator provided by the multi-step process described by Baron and Kenny (1986). Variable *M* is considered a mediator if (1) *X* significantly predicts *Y* (i.e., $c \neq 0$), (2) *X* significantly predicts *M* (i.e., $a \neq 0$), and (3) *M* significantly predicts *Y* controlling for *X* ($b \neq 0$). While useful, Baron and Kenny's rule-driven analysis is limited, and Hayes (2012) developed the PROCESS macro to provide a more data-driven and flexible approach. In the simple mediation model, the relationship between *X* and *Y* is often referred to as the *total effect*, and this is denoted as ***c***, which is distinguished (by subtraction) from ***c'***, which denotes the *direct effect* of *X* on *Y* after controlling for *M* (Preacher & Hayes, 2004). The resulting value is compared (and should be equivalent to) the *indirect effect* of *M* on the relation between *X* and *Y*, which is the interaction term of path A (*M* regressed on *X)* * path B (*Y* regressed on *M* in the

presence of *X).* A bootstrapping method is then used to test the *indirect effect* for statistical significance, as revealed by 95% CIs that do not contain zero.

With appreciation for the current sample size, we adopted the requirement of Baron and Kenny (1986) stating that a significant bivariate correlation between *X* and *Y* and/or *Y* and *C* must be observed to conduct a mediation analysis. Using the PROCESS macro, we sought to test the *indirect effect* of the mediator (FPN/DMN coherence) on the significant and inverse relation between *X* (CHA_2DS_2-VASc) and *Y* (PASAT performance).

It was hypothesized that: **(1)** the *total effect* would reveal a significant and inverse relation between CHA_2DS_2-VASc and PASAT performance; **(2)** the *direct effect* would reveal a non-significant relation between CHA_2DS_2-VASc and PASAT performance, controlling for FPN/DMN coherence, that significantly differed from the *total effect* (i.e., $c - c' \neq 0$); and **(3)** an significant *indirect effect* of the mediator (FPN/DMN coherence) would be identified; this finding would be characterized by **(3a)** a significant and negative relation between CHA_2DS_2-VASc and FPN/DMN coherence, and (**3b**) a significant and positive relation between FPN/DMN coherence and PASAT performance.

Power Analyses. Power analyses were conducted with the G*Power software package (Erdfelder, Faul, & Buchner, 1996) to ensure that the current sample size was adequate to detect the hypothesized effects. Power analyses indicated that a total sample of 41 participants would be needed to detect medium effects (i.e., r = .20) of the linear multiple regression and mediation analyses with .70 power using a two-tailed alpha of .05.

CHAPTER 3

RESULTS

Preliminary Statistics

Preliminary data analyses were conducted using the Statistical Package for Social Sciences (SPSS 21.0 for Windows, SPSS, Chicago, IL). Sample characteristics and cognitive performance are displayed in Table 1. The study sample was comprised of older adults with above average intellectual functioning and educational attainment. Stroke risk status among the study sample, as measured by CHA_2DS_2-VASc, was generally consistent with known distributions among OAs affected by atrial fibrillation and coronary artery disease with and without atrial fibrillation (Zuo et al., 2013; Tabata et al., 2017; see Table 1). Performance on a task challenging the working memory, attention, and calculation systems was consistent with prior PASAT literature (Buitenweg, van de Ven, Prinssen, Murre, & Ridderinkhof, 2017; Brittain, La Marche, Reeder, Roth, & Boll, 1991).

CHA_2DS_2-VASc and Executive Function. CHA_2DS_2-VASc and PASAT performance were inversely correlated, indicating that increased risk of stroke was significantly and negatively associated with reduced working memory functioning (r = -.32, p = .03). However, CHA_2DS_2-VASc was not found to significantly correlate with mean coherence values of the FPN (r = -.06, p = .72) or the DMN (r = .04, p = .81) ROIs. Correlation analyses also pertinent to hierarchical regression and mediation analyses are presented in Table 2.

Functional Connectivity Analyses. Results of the ROI-to-ROI and seed-to-voxel functional analyses that were conducted for each network are discussed below.

Frontoparietal network: Group level ROI-to-ROI analyses revealed significant connectivity among all four nodes of the FPN. As expected, and illustrated in Table 3, each FPN node exhibited statistically significant associations with the rest of the network, as identified by CONN with global-network intensity values: L PFC (t = 20.11; p-*FDR* < .01), L PPC (t = 26.35; p-*FDR* < .01), R PFC (t = 20.58; p-*FDR* < .01), R PPC (t = 25.10; p-*FDR* < .01).

CONN also computes a correlation value for all ROI relationships in the network (6 in this case). The strongest relation between two nodes of the FPN was identified between the L PPC and R PPC (t = 11.25; p < .01), followed by the relation between the L PFC and L PPC (t = 10.30; p < .01), the R PFC and R PPC (t = 9.91; p < .01), the L PFC and R PFC (t = 5.86; p < .01), the L PPC and R PFC (t = 4.81; p < .01), and L PFC and R PPC (t = 3.95; p < .01). Using the effect size (*r)* from each ROI-to-ROI relation at the individual level, we computed a mean "coherence" value for the FPN network (z = .05; *SD* = .04; range = .27) at the group level to be used for hierarchical multiple regression and mediation analyses. Figure 5 uses a color bar to provide a visual representation of the strength of each FPN connection.

The seeds chosen for the whole-brain, seed-to-voxel connectivity analyses were the four hubs of the FPN: the left PFC, the right PFC, the left PPC, and the right PPC. Results of the seed-to-voxel connectivity analysis revealed statistically significant clusters in the bilateral dorsolateral PFC, bilateral posterior/inferior parietal cortex, bilateral precuneus/PPC, and bilateral middle temporal gyrus (Table 5; Figure 7).

Default mode network: Group level ROI-to-ROI analyses revealed significant connectivity among all four nodes of the DMN. As illustrated in Table 3, each DMN node exhibited statistically significant associations with the overall network, as identified by CONN

with global-network intensity values: L LPC (t = 30.89; p-*FDR* < .01), R LPC (t = 29.77; p-*FDR* < .01), B PCC (t = 22.89; p-*FDR* < .01), B mPFC (t = 20.20; p-*FDR* < .01).

CONN also computes a correlation value for all ROI relationships in the DMN network. The strongest relation between two nodes of the DMN was identified between the L LPC and R LPC (t = 13.55; p <. 01), followed by the relation between the R LPC and PCC (t = 9.42; p < .01), the L LPC and PCC (t = 8.71; p < .01), the mPFC and L LPC (t = 8.63; p < .01), the mPFC and R LPC (t = 6.81; p < .01), and mPFC and R LPC (t = 6.81; p < .01). Using the effect size (*r)* from each ROI-to-ROI relation at the individual level, we computed a mean "coherence" value for the DMN network (z = .05; SD = .04; range = .27) at the group level to be used for hierarchical multiple regression and mediation analyses. Figure 6 uses a color bar to provide a visual representation of the strength of each DMN connection.

The seeds chosen for the whole-brain, seed-to-voxel connectivity analyses were the four hubs of the DMN: the left LPC, the right LPC, the bilateral PCC, and the bilateral mPFC. A seed-to-voxel connectivity analysis revealed statistically significant clusters in the bilateral PPC/posterior parietal cortex, bilateral mPFC/ACC, bilateral middle temporal gyrus, bilateral inferior frontal gyrus, and R superior frontal cortex (Table 6; Figure 8).

Multiple Regression and Mediation Analyses

Despite the significant correlation found between CHA_2DS_2-VASc and PASAT performance (r = -.31, p = .04), CHA_2DS_2-VASc did not significantly correlate with functional coherence values of the FPN (r = -.01, p = .96) or DMN (r = .10, p = .54). In addition, PASAT performance did not significantly correlate with coherence of the FPN (r = .14, p = .36) or DMN (r = -.09, p = .57). Due to the absence of the two most common effects of a correlation between the IV and DV, and/or the mediator and DV, no further explorations of mediation effects relative

to the FPN and DMN coherence values were made. Upon review of the correlation matrix of all study variables (Table 2), however, the coherence of FPN node 1 (i.e., L PFC) and FPN node 4 (i.e., R PPC), hereafter referred to as "$FPN_{1\text{-}4}$ coherence," was significantly and inversely correlated with CHA_2DS_2-VASc (r = -.40, p = .01) and significantly and positively correlated with PASAT performance (r = .35, p = .02). Therefore, a post-hoc mediation analysis was conducted to examine the proposed mechanism of $FPN_{1\text{-}4}$ coherence as a mediator between CHA_2DS_2-VASc and PASAT performance.

As proposed, the mediation model was tested using bootstrapped resampling methods with the PROCESS macros (Hayes, 2012). The overall model fit and total effect were significant (R^2 = .10, F(3,44) = 4.80, B = -2.04, *SE* = .93, t = -2.19, p = .03). Unstandardized direct and indirect effects were computed for 1000 bootstrapped samples at the 95% confidence interval. The direct effect of CHA_2DS_2-VASc on PASAT performance, controlling for FPN_{14} coherence, revealed a and non-significant relation (B = -1.40, *SE* = .98, t = 1-1.42, p = .16, 95% CI [-3.38, .59]). The indirect effect of CHA_2DS_2-VASc on PASAT performance through the mediator, $FPN_{1\text{-}4}$ coherence, revealed an inverse and significant relation (B = -.64, Boot *SE* =.41, 95% CI [-1.69, -.10]). This indirect effect was further characterized by an inverse and significant relation between CHA_2DS_2-VASc and $FPN_{1\text{-}4}$ coherence (B = -.01, *SE* = .00, t = -2.66, p = .01), and a positive but non-significant relation between $FPN_{1\text{-}4}$ coherence and PASAT performance, controlling for CHA_2DS_2-VASc (B = 50.25, *SE* = 25.19, t = 1.72, p = .09). Results of the mediation analysis are displayed in Figure 2.

CHAPTER 4

DISCUSSION

The present study examined the influence of network coherence of the FPN and DMN on the hypothesized relation between a stroke risk classification system (CHA_2DS_2-VASc) and an age-sensitive, challenging EF task (PASAT). It was first determined whether stroke risk classification inversely correlated with EF performance (Hypothesis 1), and then if mean FPN and DMN coherence values were mediating this relation (Hypothesis 2). This was the first examination of the utility of CHA_2DS_2-VASc classification system for healthy OAs, and an assessment of neural network coherence as a mediator of age-related pathology and potentially cognitive decline, consistent with modern brain reserve models (Stern, 2017; see Figure 1). Findings revealed support for Hypothesis 1; stroke risk classification significantly and inversely correlated with performance on a challenging WM task. Hypothesis 2 was not directly supported; since CHA_2DS_2-VASc and PASAT scores did not significantly correlate with mean coherence values of the FPN or DMN, mediation analyses were not conducted. However, because a significant inverse correlation between two FPN nodes (L PFC_1 and R PPC_4) and PASAT performance provided limited support for Hypothesis 1, a hierarchical regression analysis was conducted, which revealed that coherence of FPN_{1-4} significantly mediated the relation between stroke risk and EF. Results suggest that CHA_2DS_2-VASc may also be used as a valid estimation of stroke risk in healthy OAs, as it was linked to two markers of white matter integrity, PASAT performance and functional connectivity within the FPN. FPN connectivity of

the L PFC and R PPC may be particularly sensitive to white matter changes associated with CVD burden (e.g., SVD) and WM function in OAs.

Behavioral Validation of CHA_2DS_2-VASc in Healthy Older Adults

The significant and inverse correlation between stroke risk classification and performance on a challenging WM task supports extension of the validity of CHA_2DS_2-VASc to healthy community-dwelling OAs. Therefore, the characteristics of the sample used in the current study provide support for a wider and more generalized use of CHA_2DS_2-VASc with OAs. For example, the statistical distribution of stroke risk classification shown by our sample was consistent with that of other samples used to validate CHA_2DS_2-VASc, including OAs affected by atrial fibrillation (Zuo et al., 2013), as well as CAD with and without atrial fibrillation (Tabata et al., 2017; see Table 1). Similarly, the distribution of scores on the PASAT were also consistent with several other studies that measured performance in OAs (Buitenweg et al., 2017; Brittain et al., 1991). According to sample and statistic considerations, therefore, the current study was well-equipped to assess the utility of using CHA_2DS_2-VASc with healthy OAs.

Validation of the CHA_2DS_2-VASc classification system in a sample of healthy, community-dwelling OAs has many both practical and theoretical implications. From a practical standpoint, a validated classification system like CHA_2DS_2-VASc is easy to use and can be computed before or during a routine office visit by a healthcare provider, with several ensuing benefits to the patient and other providers, including (a) improved consistency and organization of medical history for a team of providers, (b) an opportunity to direct feedback provided to the patient, and (c) a more preventative approach to patient healthcare. These applications and their related potential to improve healthcare, however, should be balanced with misuse of the CHA_2DS_2-VASc or unrealistic expectations. While promising, research findings are not adequate to provide

specific prognostic indicators (e.g., percent chance of a stroke) based on a patient's score relative to cut-offs. Further research is recommended to advance the tool's utility, including replication studies to further validate its utility for generally healthy OAs, and extension to validation studies for all candidate populations.

Results suggest that the CHA_2DS_2-VASc classification system is sensitive to stroke risk factors that compromise white matter integrity and coincide with EF decline in healthy OAs (Buitenweg et al., 2017; Barnes et al., 2016; Darki & Klingberg, 2015). This is an important finding due to the prevalence and significant consequences of CVD, as CVD has been found to account for nearly 50% of all dementia incidence (Shibuya, Costa Leite, & Lucato, 2017). While some of these neurophysiological effects can be identified and treated (e.g., hypertension), many are not well understood or detected (Rosenberg et al., 2016); for example, it remains difficult to differentiate vascular cognitive impairment from AD, as they often coexist, and MRI studies that might differentiate them remain limited (Gorelick et al., 2011; Iadecola et al., 2013). Moreover, it is difficult to determine how even common radiological findings (e.g., lacunes, perivascular spaces, white matter hyperintensities) pertain to cognitive impairments (Shibuya et al., 2017; Rosenberg et al., 2016). In this context, our identification of a significant inverse relation between CHA_2DS_2-VASc and PASAT performance in healthy OAs may inform future studies of cerebrovascular risks and patterns of cognitive decline.

Neural Network Coherence and Validation of CHA_2DS_2-VASc in Healthy Older Adults

Consistent with studies of neural network coherence in aging, our ROI-to-ROI fcMRI analyses revealed highly significant correlations among the four assessed nodes of the DMN, including the medial PFC, PCC, R LPC, and L LPC (Raichle et al., 2001; Fair et al., 2007) and the four assessed nodes of the FPN, including the L PFC, R PFC, L PPC, and R PPC (Ptak et al.,

2012; Dosenbach et al., 2008). Seed-to-voxel fcMRI analyses were conducted to validate findings from the ROI-to-ROI analyses, and as expected, they confirmed these four nodes were the prominent "hubs" of each network.

Counter to hypothesis 2, the mean FPN and DMN coherence values did not significantly correlate with stroke risk classification nor working memory performance (therefore mediation analyses were not conducted as originally proposed). Several reasons may account for this. For example, descriptive statistics indicate that the range of the DMN coherence value was considerably smaller than the range the node-to-node coherence values (Table 4); however, this was not the case for the FPN, discounting limited variability to detect findings as a standalone explanation for both networks. In addition, CHA_2DS_2-VASc may better predict node to node connectivity, which may be more susceptible to stroke, than the entire networks. Our findings revealed differences in intensity of coherence between individual nodes (Table 4; Figures 5 and 6). Averaging these intensity values by participant to create mean coherence values may have "washed out" some effects, as supported by the observation that FPN intensity values were significantly different for the L PPC and R PPC ($t = 11.25$) and the L PFC and R PPC ($t = 3.95$), with only the latter significantly correlated with CHA_2DS_2-VASc and PASAT scores. The observation that CHA_2DS_2-VASc score was inversely related to $FPN_{1\text{-}4}$ coherence is consistent with evidence of robust age-related alterations in the DMN (Bai et al., 2008; Andrews-Hanna et al., 2007) that may also apply to the FPN. For example, Campbell et al. (2012) reported an age-related reduction in coherence of the FPN network as a whole, with the exception of stronger coherence among the left rostral PFC connections.

Thus, several factors likely contributed to the lack of a significant finding between stroke risk classification and mean network coherence values. Future studies of the FPN with larger

samples might examine total and partial network correlations to determine whether the FPN_{1-4} coherence finding can be replicated and if the null total network finding is a small effect obscured by insufficient statistical power.

Hierarchical regression and mediation analysis. Although FPN and DMN coherence values did not satisfy our *a priori* requirements to for the use of mediation analyses, the coherence between two nodes of the FPN; FPN_{1-4} coherence (i.e., L PFC and R PPC) did meet criteria. Strength of coherence between the L PFC and R PPC demonstrated a significant inverse correlation with CHA_2DS_2-VASc and a significant and positive correlation with PASAT performance. Results of the mediational analysis revealed a significant overall model fit, a significant and inverse direct effect between CHA_2DS_2-VASc and PASAT performance, and a significant and negative mediation (indirect effect) of FPN_{14} coherence. These findings suggest that the coherence of FPN nodes L PFC and R PPC are a mechanistic basis for the significant and inverse relation between stroke risk classification and performance on the PASAT measure that is particularly susceptible to white matter changes.

Reduced FPN coherence and executive functions. In a recent experiment by Schaeffer et al. (2014), OAs with early SVD evidenced fcMRI decreases in FPN hubs, as well as reduction in eigenvector centrality of the vPFC and superior parietal lobule (i.e., nodes that were connected to fewer of the nodes that contributed most to the network) that was consistent with prior work (Yi et al., 2012). Relative increases in FC also extended from the cerebellum to FPN regions, suggestive of FC changes. In addition, the PFC coherence effects inversely correlated with performance on Trail-Making-Test A (Tombaugh, 2004) and the Stroop Test (Howieson, Lezak, & Loring, 2004), suggestive of mild psychomotor slowing commonly associated with SVD (Selnes & Vinters, 2006; Schroeter et al., 2007). Greater white matter lesions were also

identified in FPN pathways, providing further evidence of FPN disruption in SVD (Schroeter et al., 2007; Cummings, 1995). Overall, findings from Schaeffer et al. (2014) suggest that aging and mild SVD are associated with decreased FPN coherence and related declines in EFs. Moreover, these findings were validated by the identification of reduced white matter integrity in FPN pathways.

Literature focused on age-related changes in structural connectivity (e.g., white matter integrity) and EF appear complement findings from fcMRI studies, as the latter are bound by the anatomical structures of the brain, including working memory pathways (Honey et al., 2009). Consistent with the results reported by Schaeffer et al. (2014), healthy OAs have shown structural connectivity changes on multiple neuroimaging measures. For example, using diffusion tensor imaging (DTI) to examine SVD-related changes in white matter connectivity, Lawrence et al. (2010) observed reduced white matter density among bilateral PFC and parietal cortices, and an indicator of network efficiency (e.g., white matter integrity) was found to mediate the significant and inverse relation between DTI measures (i.e., functional anisotropy, mean diffusivity) and numerous EFs. Gold et al. (2010) used a combination of fMRI and DTI to examine age-related slowing on EF tasks. Results of this study revealed age-related decreased spatial extent of activation; consistent with this finding, DTI analyses showed an inverse relation between task switching cost (reaction time) and reduced fractional anisotropy in white matter integrity of the FPN (Gold et al., 2010). White matter pathways supporting the FPN thus appear to be particularly susceptible to increased lesion load and reduced efficiency associated with poorer EF performance, and these findings are generally consistent with functional FPN changes observed in OAs.

Several studies have used a combination of fcMRI measures to assess the presence of age-related changes in FPN function coherence, and these changes have often been linked to reductions in performance on tasks that engage EF systems. For example, a recent study employed resting state fcMRI and DTI measures to characterize FPN changes and associated cognitive decline in patients diagnosed with hypertension. As measured by fcMRI and analyzed using independent components analysis, the hypertension patients showed altered patterns of FPN coherence (i.e., inferior parietal lobe, left inferior frontal lobe, and precuneus), reduced EF and attention skills, and significantly reduced white matter integrity the bilateral superior longitudinal fasciculus. Most important to the current study, fcMRI of the FPN significantly mediated the impact of white matter integrity on EF performance in the hypertensive group (Li et al., 2016). In another study that used fcMRI and DTI to measure age-related changes in FPN coherence, OAs that were diagnosed with white matter lesions evidenced a significant reduction in functional FPN coherence between the right MFG and dorsolateral PFC, as well as the bilateral superior parietal cortex and right MFG. Consistent with the above findings, these reduced connections were significantly correlated with decreases in EF (Liang et al., 2016). Thus, studies that have combined measures of fcMRI and DTI to examine age-related changes in the FPN have revealed support for a common decline in both FPN structure and function.

Overall, there appears to be a growing body of research that examines functional connectivity changes in the FPN among the aging population, with an interest in both healthy OAs (Liang et al., 2016; Campbell et al., 2012; Gold et al. 2010; Andrews-Hanna et al., 2007) and those that have been diagnosed with a range of cerebrovascular risk factors, including SVD, hypertension, chronic obstructive pulmonary disease, etc. (Li et al., 2016; Schaeffer et al., 2014; Lawrence et al., 2010; Dodd & van den Broek, 2012). While there is variability across studies

with respect to methodology and outcome measures used, fcMRI measures used to study FPN connectivity and cognitive outcome are consistently indicative of reduced functional FPN coherence that has been associated with poorer performance on tasks of EF, such as cognitive flexibility and working memory. These findings have been further validated by reductions in the white matter integrity, as an indicator of the underlying structural connectivity supporting functional FPN coherence (Honey et al., 2009). Furthermore, consistent with the present result and recent theoretical considerations about the neural mechanisms that influence the relation between age-related brain pathology (e.g., SVD) and cognitive decline (Stern et al., 2017; see Figure 1) suggest that functional FPN coherence may serve as a causal mechanism of cerebrovascular risk factors and associated EF decline in community-dwelling OAs.

Limitations

The sample of the present study was relatively limited (n = 45) and young with respect to the aging literature (range = 50-83; mean = 66; SD = 10), as researchers often sample OA populations from 65 years and beyond due to general trends in age-related cognitive decline. Interpretation of study findings are also limited by a relatively small sample size (i.e., not adequately powered to detect smaller mediation effects). The majority of the sample were also intelligent (WTAR range = 88 – 134, mean = 111, SD = 7), well-educated (range = 7 – 25 years; mean = 16; SD = 2) and of Caucasian ethnicity (96%), which poses potential problems with generalizability.

Second, the significant and inverse relation between stroke risk classification and performance on a challenging task of EF represents, to our knowledge, the first evidence of CHA_2DS_2-VASc's validity for use in healthy OAs and has several practical implications. However, its application should be balanced with the potential for misuse of CHA_2DS_2-VASc.

The current literature does not appear adequate for its use as a specific prognostic indicator (e.g., percent chance of a stroke), which is a relatively common issue related to the development of risk classification systems. For example, the risk calculator for research in prodromal psychosis has shown some efficacy, though many researchers have cautioned for its current use beyond continued study of prodromal psychosis (Cannon et al., 2013).

The indirect effect of functional FPN coherence is an interesting finding that is consistent with recent fcMRI literature of the FPN and proposed theoretical models offered for the study of neural network measures as mechanistic bases for age-related brain pathology and EF function. However, approaches to interpretation of mediation analysis results are occasionally inconsistent in the literature and have elicited some debate among researchers. For example, researchers ascribed to the Baron & Kenny method (1986) for many years which has prompted the development of more data-driven and flexible approaches (Hayes, 2012). However, these new methods present unique challenges as well. MacKinnon, Krull, & Lockwood (2000) have described statistical similarities among mediation, confounding, and suppression effects, with identical statistical output of mediation and confounding effects that can be distinguished only on conceptual grounds. Therefore, results of the current study should be carefully considered in the context of modern theories about neural mechanisms bases of age-related cognitive changes (Stern et al., 2017; Figure 1).

Future Directions

As the first investigation of a stroke risk classification system in healthy OAs, and neural network coherence as a mediator of stroke risk classification and EF, findings of the current investigation are promising but also warrant replication. Future studies and providers would benefit from validation studies of CHA_2DS_2-VASc with a more generalized sample of OAs.

Given the use of a single outcome measure of EF (i.e., PASAT performance), it would also be beneficial to test the risk classification system's utility as a predictor of decline on other measures. Given the pattern of EF decline associated with cerebrovascular effects (e.g., SVD) on the elderly brain (Pantoni, 2010; Wardlaw et al., 2013; Prins et al., 2005), measures of that are particularly challenging to EFs that engage frontal-subcortical systems are recommended (e.g., Trail Making Test, Verbal Fluency, Stroop Task); these tests may also extend to other functions as well, such as tests of memory with considerable EF demands (e.g., time-limited encoding, non-contextualized word learning).

Several considerations should be made in the development of future studies of neural network coherence as a proposed mediator of age-related pathological processes of the brain (e.g., SVD) and cognitive function. As recommended for future validation studies of stroke risk classification, incorporation of other measures used to quantify cognitive function associated with age-related brain pathology may further clarify the disease processes of the brain and identify targets for interventions (e.g., cognitive training programs). This is an important step to future studies of age-related neuropathology. For example, despite the prevalence of SVD in OAs, differences in terminology and neuroimaging methods used for its diagnosis have limited our understanding of the disease, which has prompted researchers to develop well-defined neuroimaging standards for diagnostic considerations (Wardlaw et al., 2013). Informed selection of cognitive measures used to study the correlates of neuropathology may consider several factors, such as the neural systems engaged by neuropsychological tests and common difficulties demonstrated by the population of interest.

The development of statistical models (e.g., path analysis) offer promising means for future examination of the neural mechanisms associated with age-related neuropathology and

cognitive outcomes. Several challenges are inherent in this work as well, though, such as limited power to detect generally smaller effects seen in hierarchical multiple regression models (e.g., moderation, mediation), the complexity of both statistical models used to test hypotheses as well as the theoretical models that inform the experiments. Inconsistency in the way results of complex statistical models are interpreted presents ongoing challenges in statistical modeling as well; for example, statistical similarities among mediation, confounding, and suppression effects may frequently challenge experimental results (MacKinnon et al., 2000). Mediation results reported in the current study, for example, may represent an incomplete picture of the relation between stroke risk and EF through the indirect effect of FPN coherence. Future studies would benefit from consideration of other variables that may clarify this relationship, as deemed statistically appropriate (e.g., statistical power). For example, it may be that a fourth variable moderates our observed mediation effect, such that stroke risk leads to reduced FPN coherence, which then leads to decreases in EF performance among healthy OAs that have lower levels of a protective factor such as cognitive reserve (e.g., educational attainment). Given that mediation effects cannot be statistically parsed from confounding effects, therefore, future studies would benefit from developing hypotheses and statistical models with a strong appreciation for the current theoretical framework (Hayes, 2012; MacKinnon et al., 2000).

CHAPTER 5

REFERENCES

Aiken, L., & West, S. (1991). *Testing and interpreting interactions*. Newbury Park, CA: Sage Publications.

Almeida, O. P., Garrido, G. J., Beer, C., Lautenschlager, N. T., Arnolda, L., & Flicker, L. (2012). Cognitive and brain changes associated with ischaemic heart disease and heart failure. *European Heart Journal, 33,* 1769-1776. doi:10.1093/eurheartj/ehr467

Alosco, M. L., Brickman, A. M., Spitznagel, M. B., van Dulmen, M., Raz, N., Cohen, R., . . . Gunstad J. (2012). The independent association of hypertension with cognitive function among older adults with heart failure. *Journal of the Neurological Sciences, 323*(1-2), 216-220. doi:10.1016/j.jns.2012.09.019.

Alosco, M. L., Spitznagel, M. B., Raz, N., Cohen, R., Sweet, L. H., Colbert, L. H., . . . Gunstad, J. (2014). Executive dysfunction is independently associated with reduced functional Independence in heart failure. *Journal of Clinical Nursing, 23*(5-6), 829-836. doi:10.1111/jocn.12214

Alzheimer's Association. (2016). *2016 Alzheimer's Disease Facts and Figures: Includes a Special Report on the Personal Financial Impact of Alzheimer on Families*. Alzheimer's Association.

American Diabetes Association. (2014). Diagnosis and classification of diabetes mellitus. *Diabetes Care, 37*(Supplement 1), S81-S90.

Andrews-Hanna, J. R., Smallwood, J., & Spreng, R. N. (2014). The default network and self-generated thought: Component processes, dynamic control, and clinical relevance. *Annals of the New York Academy of Sciences, 1316*(1), 29-52.

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

Arslanian-Engoren, C., Giordani, B. J., Algase, D., Schuh, A., Lee, C., & Moser, D. K. (2014). Cognitive dysfunction in older adults hospitalized for acute heart failure. *Journal of Cardiac Failure, 20*(9), 669-678. doi:10.1016/j.cardfail.2014.06.003

Athilingam, P., King, K. B., Burgin, S. W., Ackerman, M., Cushman, L. A., & Chen, L. (2011). Montreal Cognitive Assessment and Mini-Mental Status Examination compared as cognitive screening tools in heart failure. *Heart & Lung, 40*(6), 521-529. doi:10.1016/j.hrtlng.2010.11.002

Avelar-Pereira, B., Bäckman, L., Wåhlin, A., Nyberg, L., & Salami, A. (2017). Age-related differences in dynamic interactions among default mode, frontoparietal control, and dorsal attention networks during resting-state and interference resolution. *Frontiers in Aging Neuroscience, 9*.

Bai, F., Zhang, Z., Yu, H., Shi, Y., Yuan, Y., Zhu, W., ... & Qian, Y. (2008). Default-mode network activity distinguishes amnestic type mild cognitive impairment from healthy aging: A combined structural and resting-state functional MRI study. *Neuroscience Letters, 438*(1), 111-115.

Baird, B. J., Tombaugh, T. N., & Francis, M. (2007). The effects of practice on speed of information processing using the Adjusting-Paced Serial Addition Test (Adjusting-

PSAT) and the Computerized Tests of Information Processing (CTIP). *Applied Neuropsychology*, *14*(2), 88-100.

Balota, D. A., Dolan, P. O., & Duchek, J. M. (2000). Memory changes in healthy older adults. *The Oxford handbook of memory*, 395-409.

Barnes, J. J., Nobre, A. C., Woolrich, M. W., Baker, K., & Astle, D. E. (2016). Training working memory in childhood enhances coupling between frontoparietal control network and task-related regions. *Journal of Neuroscience*, *36*(34), 9001-9011.

Baron, R. M., & Kenny, D. A. (1986). The moderator-mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. *Journal of Personality and Social Psychology, 51,* 1173–1182. doi:10.1037//0022-3514.51.6.1173.

Barr, R, & Giambra, L. (2000). Age-related decrement in auditory selective attention. *Psychology of Aging, 5*(4), 597-599.

Barulli, D., & Stern, Y. (2013). Efficiency, capacity, compensation, maintenance, plasticity: Emerging concepts in cognitive reserve. *Trends in Cognitive Sciences, 17,* 502–509.

Bauer, L., Pozehl, B., Hertzog, M., Johnson, J., Zimmerman, L., & Filipi, M. (2012). A brief neuropsychological battery for use in the chronic heart failure population. *European Journal of Cardiovascular Nursing*, *11*(2), 223-230. doi:10.1016/j.ejcnurse.2011.03.007

Beckmann, C. F., DeLuca, M., Devlin, J. T., & Smith, S. M. (2005). Investigations into resting-state connectivity using independent component analysis. *Philosophical Transactions of the Royal Society of London B: Biological Sciences*, *360*(1457), 1001-1013.

Binnewijzend, M. A., Schoonheim, M. M., Sanz-Arigita, E., Wink, A. M., van der Flier, W. M., Tolboom, N., ... & Barkhof, F. (2012). Resting-state fMRI changes in Alzheimer's disease and mild cognitive impairment. *Neurobiology of Aging*, *33*(9), 2018-2028.

Biswal, B., Zerrin Yetkin, F., Haughton, V. M., & Hyde, J. S. (1995). Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magnetic Resonance in Medicine*, *34*(4), 537-541.

Boriani, G., Botto, G. L., Padeletti, L., Santini, M., Capucci, A., Gulizia, M., ... & Lip, G. Y. (2011). Improving stroke risk stratification using the CHADS2 and CHA2DS2-VASc risk scores in patients with paroxysmal atrial fibrillation by continuous arrhythmia burden monitoring. *Stroke*, *42*(6), 1768-1770.

Brittain, J. L., La Marche, J. A., Reeder, K. P., Roth, D. L., & Boll, T. J. (1991). Effects of age and IQ on paced auditory serial addition task (PASAT) performance. *The Clinical Neuropsychologist*, *5*(2), 163-175.

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

Buitenweg, J. I., van de Ven, R. M., Prinssen, S., Murre, J. M., & Ridderinkhof, K. R. (2017). Cognitive Flexibility Training: A Large-Scale Multimodal Adaptive Active-Control Intervention Study in Healthy Older Adults. *Frontiers in Human Neuroscience*, *11*, 529.

Cabeza, R., Grady, C., Nyberg, L., McIntosh, A., Tulving, E., Kapur, S… Craik, F. (1997). Age-related differences in neural activity during memory encoding and retrieval: A position emission tomography study. *Journal of Neuroscience, 17*(1), 391-400.

Cabeza, R., Mangels, J., Nyberg, L., Habib, R., Houle, S., McIntosh, A.R… Tulving, E. (1997). Brain regions differentially involved in remembering what and when: A PET study. *Neuron 19,* 863-870.

Callegari, S., Majani, G., Giardini, A., Pierobon, A., Opasich, C., Cobelli, F., & Tavazzi, L. (2002). Relationship between cognitive impairment and clinical status in chronic heart failure patients. *Monaldi Archives for Chest Disease, 58*(1), 19-25.

Campbell, K. L., Grady, C. L., Ng, C., & Hasher, L. (2012). Age differences in the frontoparietal cognitive control network: implications for distractibility. *Neuropsychologia*, *50*(9), 2212-2223.

Cannon, T. D., Yu, C., Addington, J., Bearden, C. E., Cadenhead, K. S., Cornblatt, B. A., ... & Perkins, D. O. (2016). An individualized risk calculator for research in prodromal psychosis. *American Journal of Psychiatry*, *173*(10), 980-988.

Cannon, J. A., Moffitt, P., Perez-Moreno, A. C., Walter, M. R., Broomfield, N. M., McMurray, J. J. V., & Quinn, T. J. (2017). Cognitive impairment and heart failure: Systematic review and meta-analysis. *Journal of Cardiac Failure, 23*(6), 464-475. doi:10.1016/j.cardfail.2017.04.007.

Carp, J., Gmeindl, L., & Reuter-Lorenz, P. A. (2010). Age differences in the neural representation of working memory revealed by multi-voxel pattern analysis. *Frontiers in Human Neuroscience*, *4*.

Cattell, R. B. (1943). The measurement of adult intelligence. *Psychological Bulletin*, *40*(3), 153.

Celone, K. A., Calhoun, V. D., Dickerson, B. C., Atri, A., Chua, E. F., Miller, S. L., ... & Albert, M. S. (2006). Alterations in memory networks in mild cognitive impairment and

Alzheimer's disease: an independent component analysis. *Journal of Neuroscience*, *26*(40), 10222-10231.

Centers for Disease Control and Prevention. (2013). *The state of aging and health in America.* Atlanta, GA: Centers for Disease Control and Prevention, US Dept. of Health and Human Services.

Centers for Disease Control and Prevention. (2014). National diabetes statistics report: Estimates of diabetes and its burden in the United States, 2014. *Atlanta, GA: US Department of Health and Human Services*, *2014*.

Cerit, L., Kemal, H., Günsel, A., & Duygu, H. (2016). Double-edged blind, hemorrhagic or cardioembolic cognitive impairment. *Journal of Geriatric Cardiology*, *13*(8), 724.

Charness, N. (2008). Aging and human performance. *Human Factors*, *50*(3), 548-555.

Chen, G., Adleman, N. E., Saad, Z. S., Leibenluft, E., & Cox, R. W. (2014). Applications of multivariate modeling to neuroimaging group analysis: A comprehensive alternative to univariate general linear model. *NeuroImage*, *99*, 571-588.

Chen, J. Y., Zhang, A. D., Lu, H. Y., Guo, J., Wang, F. F., & Li, Z. C. (2013). CHADS2 versus CHA2DS2-VASc score in assessing the stroke and thromboembolism risk stratification in patients with atrial fibrillation: a systematic review and meta-analysis. *Journal of Geriatric Cardiology*, *10*(3), 258.

Chun, M. M., & Turk-Browne, N. B. (2007). Interactions between attention and memory. *Current Opinion in Neurobiology*, *17*(2), 177-184.

Cicerone, K. D. (1997). Clinical sensitivity of four measures of attention to mild traumatic brain injury. *The Clinical Neuropsychologist*, *11*(3), 266-272.

Cohen, J., Cohen, P., West, S. G., & Aiken, L. S. (2003). *Applied multiple regression/correlation analysis for the behavioral sciences* (3rd ed.). Mahwah, NJ: Erlbaum.

Cole, M. W., Reynolds, J. R., Power, J. D., Repovs, G., Anticevic, A., & Braver, T. S. (2013). Multi-task connectivity reveals flexible hubs for adaptive task control. N*ature Neuroscience, 16*(9), 1348-1355.

Comijs, H. C., Kriegsman, D. M., Dik, M. G., Deeg, D. J., Jonker, C., & Stalman, W. A. (2009). Somatic chronic diseases and 6-year change in cognitive functioning among older persons. *Archives of Gerontology and Geriatrics*, *48*(2), 191-196.

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

Crawford, J. R., Obonsawin, M. C., & Allan, K. M. (1998). PASAT and components of WAIS-R performance: Convergent and discriminant validity. *Neuropsychological Rehabilitation*, *8*(3), 255-272.

Damoiseaux, J. S., Rombouts, S. A. R. B., Barkhof, F., Scheltens, P., Stam, C. J., Smith, S. M., & Beckmann, C. F. (2006). Consistent resting-state networks across healthy subjects. P*roceedings of the National Academy of Sciences*, *103*(37), 13848-13853.

Darki, F., & Klingberg, T. (2014). The role of fronto-parietal and fronto-striatal networks in the development of working memory: A longitudinal study. *Cerebral Cortex, 25*(6), 1587-1595.

Davis, H. P., Small, S. A., Stern, Y., Mayeux, R., Feldstein, S. N., & Keller, F. R. (2003). Acquisition, recall, and forgetting of verbal information in long-term memory by young, middle-aged, and elderly individuals. *Cortex, 39*(4), 1063-1091.

Debette, S., Seshadri, S., Beiser, A., Au, R., Himali, J. J., Palumbo, C., . . . DeCarli, C. (2011).

Midlife vascular risk factor exposure accelerates structural brain aging and cognitive decline. *Neurology*, *77*(5), 461-468. doi:10.1212/WNL.0b013e318227b227

Dennis, E. L., & Thompson, P. M. (2014). Functional brain connectivity using fMRI in aging and Alzheimer's disease. *Neuropsychology Review*, *24*(1), 49-62.

DeRight, J., Jorgensen, R. S., & Cabral, M. J. (2015). Composite cardiovascular risk scores and neuropsychological functioning: A meta-analytic review. *Annals of Behavioral Medicine*, *49*(3), 344-357. doi:10.1007/s12160-014-9681-0

Desmond, D. W., Moroney, J. T., Sano, M., & Stern, Y. (2002). Incidence of dementia after ischemic stroke. *Stroke*, *33*(9), 2254-2262.

Diehr, M. C., Cherner, M., Wolfson, T. J., Miller, S. W., Grant, I., Heaton, R. K., & HIV Neurobehavioral Research Center, T. (2003). The 50 and 100-item short forms of the Paced Auditory Serial Addition Task (PASAT): Demographically corrected norms and comparisons with the full PASAT in normal and clinical samples. *Journal of Clinical and Experimental Neuropsychology*, *25*(4), 571-585.

Diehr, M. C., Heaton, R. K., Miller, W., & Grant, I. (1998). The Paced Auditory Serial Addition Task (PASAT): Norms for age, education, and ethnicity. *Assessment*, *5*(4), 375-387.

Dodd, J. W., Chung, A. W., van den Broek, M. D., Barrick, T. R., Charlton, R. A., & Jones, P. W. (2012). Brain structure and function in chronic obstructive pulmonary disease: A multimodal cranial magnetic resonance imaging study. *American Journal of Respiratory and Critical Care Medicine*, *186*(3), 240-245.

Dosenbach, N. U., Fair, D. A., Cohen, A. L., Schlaggar, B. L., & Petersen, S. E. (2008). A dual-networks architecture of top-down control. *Trends in cognitive sciences*, *12*(3), 99-105.

Duda, B., Puente, A. N., & Miller, L. S. (2014). Cognitive reserve moderates relation between global cognition and functional status in older adults. *Journal of Clinical and Experimental Neuropsychology, 36*(4), 368–78. doi:10.1080/13803395.2014.892916.

Duong, M. V. A., Audoin, B., Boulanouar, K., Ibarrola, D., Malikova, I., Confort-Gouny, S., ... & Ranjeva, J. P. (2005). Altered functional connectivity related to white matter changes inside the working memory network at the very early stage of MS. *Journal of Cerebral Blood Flow & Metabolism*, *25*(10), 1245-1253.

Efimova, I. Y., Efimova, N. Y., Triss, S. V., & Lishmanov, Y. B. (2008). Brain perfusion and cognitive function changes in hypertensive patients. *Hypertension Research*, *31*(4), 673-678. Eggermont, L. H. P., de Boer, K., Muller, M., Jaschke, A. C., Kamp, O., & Scherder, E. J. A. (2012). Cardiac disease and cognitive impairment: A systematic review. *Heart, 98*(18), 1334-1340. doi:10.1136/heartjnl-2012-301682

Erdfelder, E., & Buchner, A. (1996). GPOWER: A general power analysis program. *Behavior Research Methods, Instruments, & Computers*, *28*(1), 1–11.

Espeland, M. A., Bryan, R. N., Goveas, J. S., Robinson, J. G., Siddiqui, M. S., Liu, S., ... & Masaki, K. (2013). Influence of type 2 diabetes on brain volumes and changes in brain volumes. *Diabetes Care*, *36*(1), 90-97.

Fagioli, S., & Macaluso, E. (2016). Neural correlates of divided attention in natural scenes. *Journal of Cognitive Neuroscience*.agot-Campagna, A., Pettitt, D. J., Engelgau, M. M., Burrows, N. R., Geiss, L. S., Valdez, R., ... & Narayan, K. V. (2000). Type 2 diabetes among North adolescents: An epidemiologic health perspective. *The Journal of Pediatrics*, *136*(5), 664-672.

Fair, D.A., Schlaggar, B.L., Cohen, A.L., Miezin, F.M., Dosenbach, N.U., Wenger, K.K…

Petersen, S.E. (2007). A method for using blocked and event-related fMRI data to study ‘‘resting state’’ functional connectivity. *Neuroimage, 35*, 396-405.

Falvey, C. M., Rosano, C., Simonsick, E. M., Harris, T., Strotmeyer, E. S., Satterfield, S., & Yaffe, K. (2013). Macro-and microstructural magnetic resonance imaging indices associated with diabetes among community-dwelling older adults. *Diabetes Care*, *36*(3), 677-682.

Fischer, J. S., Rudick, R. A., Cutter, G. R., Reingold, S. C., & National MS Society Clinical Outcomes Assessment Task Force. (1999). The Multiple Sclerosis Functional Composite measure (MSFC): An integrated approach to MS clinical outcome assessment. *Multiple Sclerosis Journal*, *5*(4), 244-250.

Fluck, E., Fernandes, C., & File, S. E. (2001). Are lorazepam-induced deficits in attention similar to those resulting from aging?. *Journal of Clinical Psychopharmacology*, *21*(2), 126-130.

Fox, M. D., & Raichle, M. E. (2007). Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nature Reviews Neuroscience*, *8*(9), 700-711.

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

Friedman, D. I., McDermott, M. P., Kieburtz, K., Kupersmith, M., Stoutenburg, A., Keltner, J. L., ... & NORDIC IIHTT Study Group. (2014). The idiopathic intracranial hypertension treatment trial: Design considerations and methods. *Journal of Neuro-ophthalmology*, *34*(2), 107-117.

Gage, B. F., Waterman, A. D., Shannon, W., Boechler, M., Rich, M. W., & Radford, M. J. (2001). Validation of clinical classification schemes for predicting stroke: Results from the National Registry of Atrial Fibrillation. *Journal of the American Medical Association, 285*(22), 2864-2870.

Gage, B. F., Waterman, A. D., Shannon, W., Boechler, M., Rich, M. W., & Radford, M. J. (2001). Validation of clinical classification schemes for predicting stroke: Results from the National Registry of Atrial Fibrillation. *Journal of the American Medical Association, 285*(22), 2864-2870.

Gallagher, R., Sullivan, A., Burke, R., Hales, S., Gillies, G., Cameron, J., & Saliba, B. (2013). Mild cognitive impairment, screening, and patient perceptions in heart failure patients. *Journal of Cardiac Failure, 19*(9), 641-646. doi:10.1016/j.cardfail.2013.08.001

Gamaldo, A., Moghekar, A., Kilada, S., Resnick, S. M., Zonderman, A. B., & O'Brien, R. (2006). Effect of a clinical stroke on the risk of dementia in a prospective cohort. *Neurology*, *67*(8), 1363-1369.

Garcia, S., Spitznagel, M. B., Cohen, R., Raz, N., Sweet, L. H., Colbert, L., . . . Gunstad, J. (2011). Depression is associated with cognitive dysfunction in older adults with heart failure. *Cardiovascular Psychiatry and Neurology*, *2011*(368324). doi:10.1155/2011/368324

Geerligs, L., Renken, R. J., Saliasi, E., Maurits, N. M., & Lorist, M. M. (2014). A brain-wide study of age-related changes in functional connectivity. *Cerebral Cortex*, *25*(7), 1987-1999.

Cheng, G., Huang, C., Deng, H., & Wang, H. (2012). Diabetes as a risk factor for dementia and mild cognitive impairment: A meta-analysis of longitudinal studies. *Internal Medicine*

Journal, *42*(5), 484-491.

Giuliano, R. J., Karns, C. M., Neville, H. J., & Hillyard, S. A. (2014). Early auditory evoked potential is modulated by selective attention and related to individual differences in visual working memory capacity. *Journal of Cognitive Neuroscience, 26*(12), 2682-2690.

Glisky, E. L. (2007). Changes in cognitive function in human aging. *Brain aging: Models, Methods, and Mechanisms*, 3-20.

Goh, J. O. (2011). Functional dedifferentiation and altered connectivity in older adults: Neural accounts of cognitive aging. *Aging and Disease*, *2*(1), 30.

Gold, B. T., Powell, D. K., Xuan, L., Jicha, G. A., & Smith, C. D. (2010). Age-related slowing of task switching is associated with decreased integrity of frontoparietal white matter. *Neurobiology of Aging*, *31*(3), 512-522.

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

Gruhn, N., Larsen, F. S., Boesgaard, S., Knudsen, G. M., Mortensen, S. A., Thomsen, G., & Aldershvile, J. (2001). Cerebral blood flow in patients with chronic heart failure before and after heart transplantation. *Stroke, 32*(11), 2530-2533. doi:10.1161/hs1101.098360

Giralt-Steinhauer, E., Cuadrado-Godia, E., Ois, A., Jiménez-Conde, J., Rodríguez-Campello, A., Soriano, C., & Roquer, J. (2013). Comparison between CHADS2 and CHA2DS2-VASc score in a stroke cohort with atrial fibrillation. *European Journal of Neurology, 20*(4), 623-628.

Gnanasekaran, G. (2011). Epidemiology of depression in heart failure. *Heart Failure Clinics*,

7(1), 1-10.

Gold, B. T., Powell, D. K., Xuan, L., Jicha, G. A., & Smith, C. D. (2010). Age-related slowing of task switching is associated with decreased integrity of frontoparietal white matter. *Neurobiology of Aging*, *31*(3), 512-522.

Gorelick, P. B., Scuteri, A., Black, S. E., DeCarli, C., Greenberg, S. M., Iadecola, C., ... & Petersen, R. C. (2011). Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*, *42*(9), 2672-2713.

Gottesman, R. F., Albert, M. S., Alonso, A., Coker, L. H., Coresh, J., Davis, S. M., . . . Knopman, D. S. (2017). Associations between midlife vascular risk factors and 25-year incident dementia in the Atherosclerosis Risk in Communities (ARIC) Cohort. *Journal of the American Medical Association: Neurology*. doi:10.1001/jamaneurol.2017.1658

Grady, C. (2012). The cognitive neuroscience of ageing. *Nature Reviews Neuroscience*, *13*(7), 491–505. doi:10.1038/nrn3256.

Grady, C. L. (2008). Cognitive neuroscience of aging. *Annals of the New York Academy of Sciences*, *1124*(1), 127-144.

Grady, C. L., Springer, M. V., Hongwanishkul, D., McIntosh, A. R., & Winocur, G. (2006). Age-related changes in brain activity across the adult lifespan. *Journal of Cognitive Neuroscience*, *18*(2), 227-241.

Grady, C.L., Maisog, J.M., Horwitz, B., Ungerleider, L.G., Mentis, M.J., Salerno, J.A…, Haxby, J.V. (1994) Age-related changes in cortical blood flow activation during visual processing of faces and location. *Journal of Neuroscience, 14*, 1450-1462.

Graff-Radford, J., Madhavan, M., Vemuri, P., Rabinstein, A. A., Cha, R. H., Mielke, M. M., ... & Knopman, D. S. (2016). Atrial fibrillation, cognitive impairment, and neuroimaging. *Alzheimer's & Dementia*, *12*(4), 391-398.

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

Gronwall, D. M. A. (1977). Paced auditory serial-addition task: a measure of recovery from concussion. *Perceptual and Motor Skills*, *44*(2), 367-373.

Gronwall, D. M., & Sampson, H. (1974). The psychological effects of concussion.

Grubb, N. R., Simpson, C., & Fox, K. A. A. (2000). Memory function in patients with stable, moderate to severe cardiac failure. *American Heart Journal*, *140*(1), 2A-6A. doi:10.1067/mhj.2000.106647

Haan, M. N., Selby, J. V., Quesenberry, C. P. Jr., Schmittdiel, J. A., Fireman, B. H., & Rice, D. P. (1997). The impact of aging and chronic disease on use of hospital and outpatient services in large HMO: 1971-1991. *Journal of the American Geriatrics Society*, *45*(6), 667-674. doi:10.1111/j.1532-5415.1997.tb01468.x

Hajduk, A. M., Lemon, S. C., McManus, D. D., Lessard, D. M., Gurwitz, J. H., Spencer, F. A., . . . Saczynski, J. S. (2013). Cognitive impairment and self-care in heart failure. *Clinical Epidemiology*, *5*, 407-416. doi:10.2147/CLEP.S44560

Hampson, M., Driesen, N. R., Skudlarski, P., Gore, J. C., & Constable, R. T. (2006). Brain connectivity related to working memory performance. *Journal of Neuroscience*, *26*(51), 13338-13343.

Hansen, C., Angot, E., Bergström, A. L., Steiner, J. A., Pieri, L., Paul, G., ... & Li, J. Y. (2011). α-Synuclein propagates from mouse brain to grafted dopaminergic neurons and seeds aggregation in cultured human cells. *The Journal of Clinical Investigation, 121*(2), 715.

Haring, B., Wu, C., Coker, L. H., Seth, A., Snetselaar, L., Manson, J. E., . . . Wassertheil-Smoller, S. (2016). Hypertension, dietary sodium, and cognitive decline: Results from the Women's Health Initiative Memory Study. *American Journal of Hypertension, 29*(2), 202-216. doi:10.1093/ajh/hpv081

Haug, H., & Eggers, R. (1991). Morphometry of the human cortex cerebri and corpus striatum during aging. *Neurobiology of Aging, 12*(4), 336-338.

Hayes, A.F. (2012). PROCESS: A versatile computational tool for observed variable mediation, moderation, and conditional process modeling. Retrieved from http://www.afhayes.com/public/process2012.pdf.

Hayes, A. F., & Rockwood, N. J. (2017). Regression-based statistical mediation and moderation analysis in clinical research: Observations, recommendations, and implementation. *Behaviour Research and Therapy, 98*, 39-57.

Hedden, T., & Gabrieli, J. D. (2004). Insights into the ageing mind: A view from cognitive neuroscience. *Nature Reviews Neuroscience, 5*(2), 87-96.

Heidenreich, P. A., Albert, N. M., Allen, L. A., Bluemke, D. A., Butler, J., Fonarow, G. C., ... & Nichol, G. (2013). Forecasting the impact of heart failure in the United States. *Circulation: Heart Failure, 6*(3), 606-619.

Henon, H., Durieu, I., Guerouaou, D., Lebert, F., Pasquier, F., & Leys, D. (2001). Poststroke dementia incidence and relationship to prestroke cognitive decline. *Neurology, 57*(7), 1216-1222.

Holmes, A. J., Chew, Y. V., Colakoglu, F., Cliff, J. B., Klaassens, E., Read, M. N., ... & Raubenheimer, D. (2017). Diet-microbiome interactions in health are controlled by intestinal nitrogen source constraints. *Cell Metabolism*, *25*(1), 140-151.

Honey, C. J., Sporns, O., Cammoun, L., Gigandet, X., Thiran, J. P., Meuli, R., & Hagmann, P. (2009). Predicting human resting-state functional connectivity from structural connectivity. *Proceedings of the National Academy of Sciences*, *106*(6), 2035-2040.

Iadecola, C. (2013). The pathobiology of vascular dementia. *Neuron*, *80*(4), 844-866.

Ihle-Hansen, H., Thommessen, B., Wyller, T. B., Engedal, K., & Fure, B. (2012). Risk factors for and incidence of subtypes of ischemic stroke. *Functional Neurology*, *27*(1), 35.

Ivan, C. S., Seshadri, S., Beiser, A., Au, R., Kase, C. S., Kelly-Hayes, M., & Wolf, P. A. (2004). Dementia after stroke. *Stroke*, *35*(6), 1264-1268.

Jaillard, A., Naegele, B., Trabucco-Miguel, S., LeBas, J. F., & Hommel, M. (2009). Hidden dysfunctioning in subacute stroke. *Stroke*.

Jennings, J. R., Muldoon, M. F., Ryan, C., Price, J. C., Greer, P., Sutton-Tyrrell, K., ... & Meltzer, C. C. (2005). Reduced cerebral blood flow response and compensation among patients with untreated hypertension. *Neurology*, *64*(8), 1358-1365.

Kaffashian, S., Dugravot, A., Elbaz, A., Shipley, M. J., Sabia, S., Kivimäki, M., & Singh-Manoux, A. (2013). Predicting cognitive decline: A dementia risk score vs the Framingham vascular risk scores. *Neurology*, *80*(14), 1300-1306.

Kivipelto, M., Ngandu, T., Fratiglioni, L., Viitanen, M., Kåreholt, I., Winblad, B., ... & Nissinen, A. (2005). Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease. *Archives of Neurology*, *62*(10), 1556-1560.

Klaassens, B. L., van Gerven, J., van der Grond, J., de Vos, F., Möller, C., & Rombouts, S. A.

(2017). Diminished posterior precuneus connectivity with the default mode network differentiates normal aging from Alzheimer's disease. *Frontiers in Aging Neuroscience, 9*, 97.

Knopman, D. S., Mosley, T. H., Catellier, D. J., & Coker, L. H. (2009). Fourteen-year longitudinal study of vascular risk factors, APOE genotype, and cognition: The ARIC MRI Study. *Alzheimer's & Dementia, 5*(3), 207-214.

Koch, W., Teipel, S., Mueller, S., Benninghoff, J., Wagner, M., Bokde, A. L., ... & Meindl, T. (2012). Diagnostic power of default mode network resting state fMRI in the detection of Alzheimer's disease. *Neurobiology of Aging*, *33*(3), 466-478.

Kochanek, K. D., Murphy, S. L., Xu, J., & Tejada-Vera, B. (2016). Deaths: Final data for 2014. *National Vital Statistics System,* 65(4), 1-122.

Komatsu, T., Sato, Y., Ozawa, M., Kunugita, F., Yoshizawa, R., Morino, Y., & Nakamura, M. (2014). Comparison between CHADS2 and CHA2DS2-VASc score for risk stratification of ischemic stroke in Japanese patients with non-valvular paroxysmal atrial fibrillation not receiving anticoagulant therapy. *International Heart Journal, 55*(2), 119-125.

Kray, J., Li, K. Z., & Lindenberger, U. (2002). Age-related changes in task-switching components: The role of task uncertainty. *Brain and Cognition, 49*(3), 363-381.

Kray, J., & Lindenberger, U. (2000). Adult age differences in task switching. *Psychology and Aging, 15*(1), 126.

Kumar, R., Woo, M. A., Macey, P. M., Fonarow, G. C., Hamilton, M. A., & Harper, R. M. (2011). Brain axonal and myelin evaluation in heart failure. *Journal of Neurological Sciences, 307*(1-2), 106-113. doi:10.1016/j.jns.2011.04.028

Langner, R., & Eickhoff, S. B. (2013). Sustaining attention to simple tasks: A meta-analytic review of the neural mechanisms of vigilant attention. *Psychological Bulletin*, *139*(4), 870.

Lawrence, A. J., Chung, A. W., Morris, R. G., Markus, H. S., & Barrick, T. R. (2014). Structural network efficiency is associated with cognitive impairment in small-vessel disease. *Neurology*, 10-1212.

Lee, B. H., Park, J. S., Park, J. H., Park, J. S., Kwak, J. J., Hwang, E. S., ... & PAK, H. N. (2010). The effect and safety of the antithrombotic therapies in patients with atrial fibrillation and CHADS2 score 1. *Journal of Cardiovascular Electrophysiology*, *21*(5), 501-507.

Letsas, K. P., Efremidis, M., Giannopoulos, G., Deftereos, S., Lioni, L., Korantzopoulos, P., ... & Sideris, A. (2013). CHADS2 and CHA2DS2-VASc scores as predictors of left atrial ablation outcomes for paroxysmal atrial fibrillation. *Europace*, *16*(2), 202-207.

Leys, D., Hénon, H., Mackowiak-Cordoliani, M. A., & Pasquier, F. (2005). Poststroke dementia. *The Lancet Neurology*, *4*(11), 752-759.

Lezak, M. D., Howieson, D. B., Loring, D. W., & Fischer, J. S. (2004). *Neuropsychological assessment*. Oxford University Press, USA.

Li, X., Liang, Y., Chen, Y., Zhang, J., Wei, D., Chen, K., ... & Zhang, Z. (2015). Disrupted frontoparietal network mediates white matter structure dysfunction associated with cognitive decline in hypertension patients. *Journal of Neuroscience*, *35*(27), 10015-10024.

Lip, G. Y. (2010). Anticoagulation therapy and the risk of stroke in patients with atrial fibrillation at'moderate risk'[CHADS2 score= 1]: simplifying stroke risk assessment and

thromboprophylaxis in real-life clinical practice. *Thrombosis & Haemostasis*, *103*(4), 683.

Lip, G. Y., Nieuwlaat, R., Pisters, R., Lane, D. A., & Crijns, H. J. (2010). Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: The euro heart survey on atrial fibrillation. *Chest Journal*, *137*(2), 263-272.

Lip, G.Y., Tse, H.F., Lane, D.A. (2012). Atrial Fibrillation. *Lancet 379*(9816), 648-61.

Lloyd-Jones, D., Adams, R. J., Brown, T. M., Carnethon, M., Dai, S., De Simone, G., ... & Go, A. (2010). Heart disease and stroke statistics—2010 update. *Circulation*, *121*(7), e46-e215.

Lopez, A. D., Mathers, C. D., Ezzati, M., Jamison, D. T., & Murray, C. J. (2006). Global and regional burden of disease and risk factors, 2001: Systematic analysis of population health data. *The Lancet*, *367*(9524), 1747-1757.

Lutz, W., Sanderson, W., & Scherbov, S. (2008). The coming acceleration of global population ageing. *Nature*, *451*(7179), 716-719.

MacKinnon, D. P., Krull, J. L., & Lockwood, C. M. (2000). Equivalence of the mediation, confounding and suppression effect. *Prevention Science*, *1*(4), 173-181.

Madden, D. J. (1990). Adult age differences in the time course of visual attention. *Journal of Gerontology*, *45*(1), P9-P16.

Madden, D. J., Costello, M. C., Dennis, N. A., Davis, S. W., Shepler, A. M., Spaniol, J., ... & Cabeza, R. (2010). Adult age differences in functional connectivity during executive control. *NeuroImage*, *52*(2), 643-657.

Madigan, N. K., DeLuca, J., Diamond, B. J., Tramontano, G., & Averill, A. (2000). Speed of Information Processing in Traumatic Brain Injury: Modality-Specific Factors. *The Journal of Head Trauma Rehabilitation*, *15*(3), 943-956.

Mangano, D. T. (1995). Cardiovascular morbidity and CABG surgery—a perspective: Epidemiology, costs, and potential therapeutic solutions. *Journal of Cardiac Surgery*, *10*(s4), 366-368.

Manschot, S. M., Biessels, G. J., De Valk, H., Algra, A., Rutten, G. E. H. M., Van Der Grond, J., ... & Utrecht Diabetic Encephalopathy Study Group. (2007). Metabolic and vascular determinants of impaired cognitive performance and abnormalities on brain magnetic resonance imaging in patients with type 2 diabetes. *Diabetologia*, *50*(11), 2388-2397.

Mayeda, E. R., Whitmer, R. A., & Yaffe, K. (2015). Diabetes and cognition. *Clinics in Geriatric Medicine*, *31*(1), 101.

Meindl, T., Teipel, S., Elmouden, R., Mueller, S., Koch, W., Dietrich, O., ... & Glaser, C. (2010). Test–retest reproducibility of the default-mode network in healthy individuals. *Human Brain Mapping*, *31*(2), 237-246.

Meyre, P., Eggimann, L., Beer, J. H., Bonati, L. H., Di Valentino, M., Kuehne, M., ... & Sticherling, C. (2017). Cognitive function correlates with CHA2DS2-VASc score in patients with atrial fibrillation: The Swiss atrial fibrillation cohort study. *European Heart Journal*, *38*, 983.

Miller, L. W., & Missov, E. D. (2001). Epidemiology of Heart Failure. *Cardiology Clinics*, *19*(4), 547-555.

Miller, S. L., Celone, K., DePeau, K., Diamond, E., Dickerson, B. C., Rentz, D., ... & Sperling, R. A. (2008). Age-related memory impairment associated with loss of parietal

deactivation but preserved hippocampal activation. *Proceedings of the National Academy of Sciences*, *105*(6), 2181-2186.

Miller, L. A., Spitznagel, M. B., Alosco, M. L., Cohen, R. A., Raz, N., Sweet, L. H., . . . Gunstad, J. (2012). Cognitive profiles in heart failure: A cluster analystic approach. *Journal of Clinical and Experimental Neuropsychology, 34*(5), 509-520. doi:10.1080/13803395.2012.663344

Moisala, M., Salmela, V., Salo, E., Carlson, S., Vuontela, V., Salonen, O., & Alho, K. (2015). Brain activity during divided and selective attention to auditory and visual sentence comprehension tasks. *Frontiers in Human Neuroscience*, *9*, 86.

Moore, S. A., Hallsworth, K., Jakovljevic, D. G., Blamire, A. M., He, J., Ford, G. A., ... & Trenell, M. I. (2015). Effects of community exercise therapy on metabolic, brain, physical, and cognitive function following stroke: A randomized controlled pilot trial. *Neurorehabilitation and Neural Repair, 29*(7), 623-635.

Moran, C., Phan, T. G., Chen, J., Blizzard, L., Beare, R., Venn, A., ... & Pearson, S. (2013). Brain Atrophy in Type 2 Diabetes. *Diabetes Care*, *36*(12), 4036-4042.

Morys, J. M., Pachalska, M., Bellwon, J., & Gruchala, M. (2016). Cognitive impairment, symptoms of depression, and health-related quality of life in patients with severe stable heart failure. *International Journal of Clinical and Health Psychology*, *16*, 230-238. doi:10.1016/j.ijchp.2016.03.002

Mozaffarian, D., Benjamin, E. J., Go, A. S., Arnett, D. K., Blaha, M. J., Cushman, M., ... & Howard, V. J. (2016). Heart disease and stroke statistics—2016 update. *Circulation*, *133*(4), e38-e360.

Nazaribadie, M., Amini, M., Ahmadpanah, M., Asgari, K., Jamlipaghale, S., & Nazaribadie, S. (2014). Executive functions and information processing in patients with type 2 diabetes in comparison to pre-diabetic patients. *Journal of Diabetes & Metabolic Disorders, 13*(1), 27.

Nagel, I. E., Preuschhof, C., Li, S. C., Nyberg, L., Bäckman, L., Lindenberger, U., & Heekeren, H. R. (2009). Performance level modulates adult age differences in brain activation during spatial working memory. *Proceedings of the National Academy of Sciences, 106*(52), 22552-22557.

Naghavi, H. R., & Nyberg, L. (2005). Common fronto-parietal activity in attention, memory, and consciousness: Shared demands on integration?. *Consciousness and Cognition, 14*(2), 390-425.s

National Institute on Aging & World Health Organization. (2011). *Global Health and Aging.* Retrieved from http://www.nia.nih.gov/research/publication/global-health-and-aging/humanity's-aging.

Newman, A. B., Fitzpatrick, A. L., Lopez, O., Jackson, S., Lyketsos, C., Ives, D., . . . Kuller, L. H. (2005). Dementia and Alzheimer's disease incidence in relationship to cardiovascular disease in the Cardiovascular Disease Study cohort. *Journal of the American Geriatrics Society, 53*(7), 1101-1107. doi:10.1111/j.1532-5415.2005.53360.x

Ng, K. K., Lo, J. C., Lim, J. K., Chee, M. W., & Zhou, J. (2016). Reduced functional segregation between the default mode network and the executive control network in healthy older adults: A longitudinal study. *NeuroImage, 133*, 321-330.

Nishtala, A., Himali, J. J., Beiser, A., Murabito, J. M., Seshadri, S., Wolf, P. A., & Au, R. (2015). Midlife hypertension risk and cognition in the non-demented oldest old:

Framingham Heart Study. *Journal of Alzheimer's Disease, 47*(1), 197-204. doi:10.3233/JAD-141881

Ntaios, G., Lip, G. Y., Makaritsis, K., Papavasileiou, V., Vemmou, A., Koroboki, E., ... & Vemmos, K. (2013). CHADS2, CHA2DS2-VASc, and long-term stroke outcome in patients without atrial fibrillation. *Neurology*, *80*(11), 1009-1017.

Nwankwo, T., Yoon, S. S., Burt, V., & Gu, Q. (2013). Hypertension among adults in the United States: National health and nutrition examination survey, 2011–2012. *NCHS Data Brief*, 133, 1-8.

Nyberg, L., Dahlin, E., Stigsdotter Neely, A., & Bäckman, L. (2009). Neural correlates of variable working memory load across adult age and skill: Dissociative patterns within the fronto-parietal network. *Scandinavian Journal of Psychology*, *50*(1), 41-46.

Obisesan, T. O., Obisesan, O. A., Martins, S., Alamgir, L., Bond, V., Maxwell, C., & Gillum, R. F. (2008). High blood pressure, hypertension, and high pulse pressure are associated with poorer cognitive function in persons aged 60 and older: The Third National Health and Nutrition Examination Survey. *Journal of the American Geriatrics Society*, *56*(3), 501-509. doi:10.1111/j.1532-5415.2007.01592.x

O'Brien, J., & Thomas, A. (2015). Vascular dementia. *The Lancet*, *386*(10004), 1698-1706.

Odum, L. E., Cochran, K. A., Aistrope, D. S., & Snella, K. A. (2012). The CHADS2 versus the New CHA2DS2-VASc Scoring Systems for Guiding Antithrombotic Treatment of Patients with Atrial Fibrillation: Review of the Literature and Recommendations for Use. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*, *32*(3), 285-296.

Olesen, J. B., & Torp-Pedersen, C. (2015). Stroke risk in atrial fibrillation: do we anticoagulate CHADS2 or CHA2DS2-VASc≥ 1, or higher?. *Thrombosis and Haemostasis*, *113*(6), 1165-1169.

Palm, F., Kleemann, T., Dos Santos, M., Urbanek, C., Buggle, F., Safer, A., ... & Grau, A. J. (2013). Stroke due to atrial fibrillation in a population-based stroke registry (Ludwigshafen Stroke Study) CHADS2, CHA2DS2-VASc score, underuse of oral anticoagulation, and implications for preventive measures. *European Journal of Neurology*, *20*(1), 117-123.

Pan, A., Kumar, R., Macey, P. M., Fonarow, G. C., Harper, R. M., Woo, M. A. (2013). Visual assessment of brain magnetic resonance imaging detects injury to cognitive regulatory sites in patients with heart failure. *Journal of Cardiac Failure*, *19*(2), 94-100. doi:10.1016/j.cardfail.2012.12.001

Pantoni, L. (2010). Cerebral small vessel disease: From pathogenesis and clinical characteristics to therapeutic challenges. *The Lancet Neurology*, *9*(7), 689-701.

Paoletti Perini, A., Bartolini, S., Pieragnoli, P., Ricciardi, G., Perrotta, L., Valleggi, A., ... & Mascioli, G. (2013). CHADS2 and CHA2DS2-VASc scores to predict morbidity and mortality in heart failure patients candidates to cardiac resynchronization therapy. *Europace*, *16*(1), 71-80.

Pena, F. M., de Faria Modenesi, R., Piraciaba, M. C. T., Marins, R. M., de Souza, L. B. M., Barcelos, A. F., & da Silva Soares, J. (2011). Prevalence and variables predictive of depressive symptoms in patients hospitalized for heart failure. *Cardiology Journal*, *18*(1), 18-25.

Pendlebury, S. T., & Rothwell, P. M. (2009). Prevalence, incidence, and factors associated with

pre-stroke and post-stroke dementia: A systematic review and meta-analysis. *The Lancet Neurology, 8*(11), 1006-1018. doi:10.1016/S1474-4422(09)70236-4

Persson, J., Lind, J., Larsson, A., Ingvar, M., Cruts, M., Van Broeckhoven, C., ... & Nyberg, L. (2006). Altered brain white matter integrity in healthy carriers of the APOE ε4 allele A risk for AD?. *Neurology*, *66*(7), 1029-1033.

Persson, J., Lustig, C., Nelson, J. K., & Reuter-Lorenz, P. A. (2007). Age differences in deactivation: A link to cognitive control?. *Journal of Cognitive Neuroscience, 19*(6), 1021-1032.

Petrella, J. R., Sheldon, F. C., Prince, S. E., Calhoun, V. D., & Doraiswamy, P. M. (2011). Default mode network connectivity in stable vs progressive mild cognitive impairment. *Neurology*, *76*(6), 511-517.

Piccini, J. P., Stevens, S. R., Lokhnygina, Y., Patel, M. R., Halperin, J. L., Singer, D. E., ... & Mahaffey, K. W. (2013). Outcomes after cardioversion and atrial fibrillation ablation in patients treated with rivaroxaban and warfarin in the ROCKET AF trial. *Journal of the American College of Cardiology*, *61*(19), 1998-2006.

Power, J. D., Cohen, A. L., Nelson, S. M., Wig, G. S., Barnes, K. A., Church, J. A., ... & Petersen, S. E. (2011). Functional network organization of the human brain. *Neuron*, *72*(4), 665-678.

Power, J. D., Mitra, A., Laumann, T. O., Snyder, A. Z., Schlaggar, B. L., & Petersen, S. E. (2014). Methods to detect, characterize, and remove motion artifact in resting state fMRI. *NeuroImage*, *84*, 320-341.

Preacher, K. J., & Hayes, A. F. (2004). SPSS and SAS procedures for estimating indirect effects in simple mediation models. *Behavior Research Methods, Instruments, & Computers, 36*(4), 717-731

Prins, N. D., van Dijk, E. J., den Heijer, T., Vermeer, S. E., Jolles, J., Koudstaal, P. J., ... & Breteler, M. M. (2005). Cerebral small-vessel disease and decline in information processing speed, executive function and memory. *Brain, 128*(9), 2034-2041.

Psaltopoulou, T., Sergentanis, T. N., Panagiotakos, D. B., Sergentanis, I. N., Kosti, R., & Scarmeas, N. (2013). Mediterranean diet, stroke, cognitive impairment, and depression: A meta-analysis. *Annals of Neurology, 74*(4), 580-591.

Ptak, R., & Müri, R. M. (2013). The parietal cortex and saccade planning: lessons from human lesion studies. *Frontiers in Human Neuroscience, 7*.

Puwanant, S., Varr, B. C., Shrestha, K., Hussain, S. K., Tang, W. W., Gabriel, R. S., ... & Lindsay, B. D. (2009). Role of the CHADS 2 score in the evaluation of thromboembolic risk in patients with atrial fibrillation undergoing transesophageal echocardiography before pulmonary vein isolation. *Journal of the American College of Cardiology*, *54*(22), 2032-2039.

Qiu, C., Winblad, B., & Fratiglioni, L. (2009). Low diastolic pressure and risk of dementia in very old people: A longitudinal study. *Dementia and Geriatric Cognitive Disorders, 28*(3), 213-219. doi:10.1159/000236913

Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers,W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. *Proceedings of the National Academy of Sciences, USA, 98*, 676–682. doi: 10.1073/pnas.98.2.676.

Rajagopalan, B., Raine, A. E. G., Cooper, R., & Ledingham, J. G. G. (1984). Changes in cerebral blood flow in patients with severe congestive cardiac failure before and after captopril treatment. *The American Journal of Medicine, 76*(5, part B), 86-90. doi:10.1016/0002-9343(84)90891-X

Rao, S. M., Leo, G. J., Ellington, L., Nauertz, T., Bernardin, L., & Unverzagt, F. (1991). Cognitive dysfunction in multiple sclerosis. II. Impact on employment and social functioning. *Neurology*, *41*(5), 692-696.

Rapsomaniki, E., Timmis, A., George, J., Pujades-Rodriquez, M., Shah, A. D., Denaxas, S., . . . Hemingway, H. (2014). Blood pressure and incidence of twelve cardiovascular diseases: Lifetime risks, healthy life-years lost, and age-specific associations in 1.25 million people. *The Lancet, 383*(9932), 1899-1911. doi:10.1016/S0140-6736(14)60685-1

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

Raz, N., Rodrigue, K. M., & Acker, J. D. (2003). Hypertension and the brain: Vulnerability of the prefrontal regions and executive functions. *Behavioral Neuroscience*, *117*(6), 1169.

Reuter-Lorenz, P. A., and Cappell, K. A. (2008). Neurocognitive aging and the compensation hypothesis. *Current Directions in Psychological Science. 17*, 177–182. doi: 10.1111/j.1467-8721.2008.00570.x.

Rich, M. W. (1997). Epidemiology, pathophysiology, and etiology of congestive heart failure in older adults. *Journal of the American Geriatrics Society*, *45*(8), 968-974.

Rockwood, K., Bowler, J., Erkinjuntti, T., Hachinski, V., & Wallin, A. (1999). Subtypes of vascular dementia. *Alzheimer Disease & Associated Disorders*, *13*, S59-S65.

Roman, D. D., Edwall, G. E., Buchanan, R. J., & Patton, J. H. (1991). Extended norms for the paced auditory serial addition task. *The Clinical Neuropsychologist*, *5*(1), 33-40.

Rombouts, S. A., Barkhof, F., Goekoop, R., Stam, C. J., & Scheltens, P. (2005). Altered resting state networks in mild cognitive impairment and mild Alzheimer's disease: an fMRI study. *Human Brain Mapping*, *26*(4), 231-239.

Saczynski, J. S., Andrade, S. E., Harrold, L. R., Tjia, J., Cutrona, S. L., Dodd, K. S., ... & Gurwitz, J. H. (2012). A systematic review of validated methods for identifying heart failure using administrative data. *Pharmacoepidemiology and Drug Safety*, *21*(S1), 129-140.

Sala-Llonch, R., Bartrés-Faz, D., & Junqué, C. (2015). Reorganization of brain networks in aging: A review of functional connectivity studies. *Frontiers in Psychology*, *6*.

Salthouse, T.A. (1996). The processing-speed theory of adult age differences in cognition. *Psychological Review*, *103*, 403–428.

Sambataro, F., Murty, V. P., Callicott, J. H., Tan, H. Y., Das, S., Weinberger, D. R., & Mattay, V. S. (2010). Age-related alterations in default mode network: impact on working memory performance. *Neurobiology of Aging*, *31*(5), 839-852.

Sarter, M., Givens, B., & Bruno, J. P. (2001). The cognitive neuroscience of sustained attention: Where top-down meets bottom-up. *Brain Research Reviews*, *35*(2), 146-160.

Schaefer, A., Quinque, E. M., Kipping, J. A., Arélin, K., Roggenhofer, E., Frisch, S., ... & Schroeter, M. L. (2014). Early small vessel disease affects frontoparietal and cerebellar hubs in close correlation with clinical symptoms—a resting-state fMRI study. *Journal of Cerebral Blood Flow & Metabolism*, *34*(7), 1091-1095.

Schmidt, W., Endres, M., Dimeo, F., & Jungehulsing, G. J. (2013). Train the vessel, gain the brain: physical activity and vessel function and the impact on stroke prevention and outcome in cerebrovascular disease. *Cerebrovascular diseases*, *35*(4), 303-312.

Schomaker, S., Warner, R., Bock, J., Johnson, K., Potter, D., Van Winkle, J., & Aubrecht, J. (2013). Assessment of emerging biomarkers of liver injury in human subjects. *Toxicological Sciences*, *132*(2), 276-283.

Schölvinck, M. L., Maier, A., Frank, Q. Y., Duyn, J. H., & Leopold, D. A. (2010). Neural basis of global resting-state fMRI activity. *Proceedings of the National Academy of Sciences*, *107*(22), 10238-10243.

Schroeter, M. L., Raczka, K., Neumann, J., & Von Cramon, D. Y. (2007). Towards a nosology for frontotemporal lobar degenerations—a meta-analysis involving 267 subjects. *NeuroImage*, *36*(3), 497-510.

Selnes, O. A., & Vinters, H. V. (2006). Vascular cognitive impairment. *Nature Reviews Neurology*, *2*(10), 538.

Shah, A. D., Merchant, F. M., & Delurgio, D. B. (2016). Atrial fibrillation and risk of dementia/cognitive decline. *Journal of Atrial Fibrillation*, *8*(5).

Shehzad, Z., Kelly, A. C., Reiss, P. T., Gee, D. G., Gotimer, K., Uddin, L. Q., ... & Petkova, E. (2009). The resting brain: Unconstrained yet reliable. *Cerebral Cortex*, *19*(10), 2209-2229.

Sheline, Y. I., Raichle, M. E., Snyder, A. Z., Morris, J. C., Head, D., Wang, S., & Mintun, M. A. (2010). Amyloid plaques disrupt resting state default mode network connectivity in cognitively normal elderly. *Biological Psychiatry*, *67*(6), 584-587.

Shibuya, M., Leite, C. D. C., & Lucato, L. T. (2017). Neuroimaging in cerebral small vessel

disease: Update and new concepts. *Dementia & Neuropsychologia, 11*(4), 336-342.

Smith, S. M., & Mensah, G. A. (2003). Population aging and implications for epidemic cardiovascular disease in Sub-Saharan Africa. *Ethnicity and Disease, 13*(2; SUPP/2), S2-77.

Spauwen, P. J., Köhler, S., Verhey, F. R., Stehouwer, C. D., & van Boxtel, M. P. (2013). Effects of type 2 diabetes on 12-year cognitive change. *Diabetes Care, 36*(6), 1554-1561.

Spreng, R. N., Stevens, W. D., Viviano, J. D., & Schacter, D. L. (2016). Attenuated anticorrelation between the default and dorsal attention networks with aging: evidence from task and rest. *Neurobiology of Aging, 45*, 149-160.

Stephan, B. C. M., Harrison, S. L., Keage, H. A. D., Babateen, A., Robinson, L., & Siervo, M. (2017). Cardiovascular disease, the nitric oxide pathway and risk of cognitive impairment and dementia. *Current Cardiology Reports, 19*(9). doi:10.1007/s11886-017-0898-y

Steffener, J., Barulli, D., Habeck, C., O'Shea, D., Razlighi, Q., & Stern, Y. (2014). The role of education and verbal abilities in altering the effect of age-related gray matter differences on cognition. *PloS One*, *9*(3), e91196.

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

Stern, Y. (2009). Cognitive reserve. *Neuropsychologia*, *47*, 2015–2028.

Stern, Y. (2017). An approach to studying the neural correlates of reserve. *Brain Imaging and Behavior, 11*(2), 410-416.

Strassburger, T. L., Lee, H. C., Daly, E. M., Szczepanik, J., Krasuski, J. S., Mentis, M. J., ... & Alexander, G. E. (1997). Interactive effects of age and hypertension on volumes of brain

structures. *Stroke, 28*(7), 1410-1417.

Stumvoll, M., Goldstein, B. J., & van Haeften, T. W. (2005). Type 2 diabetes: Principles of pathogenesis and therapy. *The Lancet, 365*(9467), 1333-1346.

Stuss, D. T., Stethem, L. L., & Poirier, C. A. (1987). Comparison of three tests of attention and rapid information processing across six age groups. *The Clinical Neuropsychologist, 1*(2), 139-152.

Suchy, Y., Kraybill, M. L., & Franchow, E. (2011). Instrumental activities of daily living among community-dwelling older adults: Discrepancies between self-report and performance are mediated by cognitive reserve. *Journal of Clinical and Experimental Neuropsychology, 33*(1), 92–100. doi: 10.1080/13803395.2010.493148.

Sweet, L. H., Jerskey, B. A., & Aloia, M. S. (2010). Default network response to a working memory challenge after withdrawal of continuous positive airway pressure treatment for obstructive sleep apnea. *Brain Imaging and Behavior, 4*(2), 155-163.

Sweet, L. H., Rao, S. M., Primeau, M., Durgerian, S., & Cohen, R. A. (2006). FMRI response to increased working memory demands among patients with multiple sclerosis. *Human Brain Mapping, 27*(1), 28–36.

Sweet, L.H., Paskavitz, J.F., Haley, A.P., Gunstad, J.J., Mulligan, R.C., Nyalakanti, P.K., Cohen, R.A. (2008). Imaging phonological similarity effects on verbal working memory. *Neuropsychologia, 46*, 1114-1123.

Tabata, N., Yamamoto, E., Hokimoto, S., Yamashita, T., Sueta, D., Takashio, S., … Kumamoto Intervention Conference Study (KICS) Investigators. (2017). Prognostic Value of the CHADS2 Score for Adverse Cardiovascular Events in Coronary Artery Disease Patients Without Atrial Fibrillation—A Multi-Center Observational Cohort Study. *Journal of the*

American Heart Association: Cardiovascular and Cerebrovascular Disease, *6*(8), e006355. http://doi.org/10.1161/JAHA.117.006355

Thiel, A., Cechetto, D. F., Heiss, W. D., Hachinski, V., & Whitehead, S. N. (2014). Amyloid burden, neuroinflammation, and links to cognitive decline after ischemic stroke. *Stroke*, *45*(9), 2825-2829.

Tombaugh, T. N. (2004). Trail Making Test A and B: normative data stratified by age and education. *Archives of Clinical Neuropsychology*, *19*(2), 203-214.

Tombaugh, T. N. (2006). A comprehensive review of the paced auditory serial addition test (PASAT). *Archives of Clinical Neuropsychology*, *21*(1), 53-76.

Tu, H. T., Campbell, B. C., Meretoja, A., Churilov, L., Lees, K. R., Donnan, G. A., ... & VISTA collaborators. (2013). Pre-stroke CHADS2 and CHA2DS2-VASc scores are useful in stratifying three-month outcomes in patients with and without atrial fibrillation. *Cerebrovascular Diseases*, *36*(4), 273-280.

Turner, G. R., & Spreng, R. N. (2015). Prefrontal engagement and reduced default network suppression co-occur and are dynamically coupled in older adults: The default–executive coupling hypothesis of aging. *Journal of Cognitive Neuroscience*, *27*(12), 2462-2476.

Uehara, M., Funabashi, N., Takaoka, H., Ozawa, K., Kushida, S., Kanda, J., ... & Kobayashi, Y. (2014). CHA2DS2-VASc score is a useful-predictor of not prognosis but coronary-arteriosclerosis in chronic atrial-fibrillation compared with CHADS2 score: A two-center study of 320-slice CT, part 2. *International Journal of Cardiology*, *177*(2), 368-373.

Uehara, M., Funabashi, N., Takaoka, H., Ozawa, K., Kushida, S., Kanda, J., ... & Kobayashi, Y. (2014). CHA2DS2-VASc score is a useful-predictor of not prognosis but coronary-

arteriosclerosis in chronic atrial-fibrillation compared with CHADS2 score: A two-center study of 320-slice CT, part 2. *International Journal of Cardiology, 177*(2), 368-373.

Van den Berg, E., De Craen, A. J. M., Biessels, G. J., Gussekloo, J., & Westendorp, R. G. J. (2006). The impact of diabetes mellitus on cognitive decline in the oldest of the old: A prospective population-based study. *Diabetologia, 49*(9), 2015-2023.

Van Dijk, K. R., Hedden, T., Venkataraman, A., Evans, K. C., Lazar, S. W., & Buckner, R. L. (2010). Intrinsic functional connectivity as a tool for human connectomics: Theory, properties, and optimization. *Journal of Neurophysiology, 103*(1), 297-321.

Van Dijk, K. R., Sabuncu, M. R., & Buckner, R. L. (2012). The influence of head motion on intrinsic functional connectivity MRI. *NeuroImage, 59*(1), 431-438.

Vogels, R. L. C., Oosterman, J. M., van Harten, B., Gouw, A. A., Schroeder-Tanka, J. M., Scheltens, P., . . . Weinstein, H. C. (2007a). Neuroimaging and correlates of cognitive function among patients with heart failure. *Dementia and Geriatric Cognitive Disorders, 24*(6), 418-423. doi:10.1159/0000109811

Vogels, R. L. C., Oosterman, J. M., van Harten, B., Scheltens, P., van der Flier, W. M., Schroeder-Tanka, J. M., & Weinstein, H. C. (2007b). Profile of cognitive impairment in chronic heart failure. *Journal of the American Geriatrics Society, 55*(11), 1764-1770. doi:10.1111/j.1532-5415.2007.01395.x

Waldstein, S. R., Giggey, P. P., Thayer, J. F., & Zonderman, A. B. (2005). Nonlinear relations of blood pressure to cognitive function: The Baltimore Longitudinal Study of Aging. *Hypertension, 45*(3), 374–379.

Wardlaw, J. M., Smith, E. E., Biessels, G. J., Cordonnier, C., Fazekas, F., Frayne, R., ... & Black, S. E. (2013). Neuroimaging standards for research into small vessel disease and its

contribution to ageing and neurodegeneration. *The Lancet Neurology*, *12*(8), 822-838.

Washida, K., Kowa, H., Hamaguchi, H., Kanda, F., & Toda, T. (2017). Validation of the R2CHADS2 and CHADS2 Scores for Predicting Post-stroke Cognitive Impairment. *Internal Medicine*, *56*(20), 2719-2725.

Wasmer, K., Köbe, J., Dechering, D., Milberg, P., Pott, C., Vogler, J., ... & Eckardt, L. (2013). CHADS2 and CHA2DS2-VASc score of patients with atrial fibrillation or flutter and newly detected left atrial thrombus. *Clinical Research in Cardiology*, *102*(2), 139-144.

Wechsler, D. (1939). The measurement of adult intelligence.

Wechsler, D. (1945). A standardized memory scale for clinical use. *The Journal of Psychology*, *19*(1), 87-95.

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

Wiens, A. N., Fuller, K. H., & Crossen, J. R. (1997). Paced Auditory Serial Addition Test: adult norms and moderator variables. *Journal of Clinical and Experimental Neuropsychology*, *19*(4), 473-483.

Winkle, R. A., Mead, R. H., Engel, G., Kong, M. H., & Patrawala, R. A. (2013). Comparison of CHADS2 and CHA2DS2-VASC anticoagulation recommendations: Evaluation in a cohort of atrial fibrillation ablation patients. *Europace*, *16*(2), 195-201.

World Health Organization. (2017). *Global Health and Aging.* Retrieved from http://www.who.int/ageing/publications/global_health.pdf

Van Harten, B., de Leeuw, F. E., Weinstein, H. C., Scheltens, P., & Biessels, G. J. (2006). Brain imaging in patients with diabetes. *Diabetes Care*, *29*(11), 2539-2548.

Yaffe, K., Falvey, C., Hamilton, N., Schwartz, A. V., Simonsick, E. M., Satterfield, S., ... & Harris, T. B. (2012). Diabetes, glucose control, and 9-year cognitive decline among older adults without dementia. *Archives of Neurology*, *69*(9), 1170-1175.

Yancy, C. W., Jessup, M., Bozkurt, B., Butler, J., Casey, D. E., Drazner, M. H., ... & Johnson, M. R. (2013). 2013 ACCF/AHA guideline for the management of heart failure. *Circulation*, CIR-0b013e31829e8776.

Yaneva-Sirakova, T., Tarnovska-Kadreva, R., & Traykov, L. (2013). Atrial fibrillation and mild cognitive impairment. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *9*(4), P771.

Yao, H., Sadoshima, S., Ibayashi, S., Kuwabara, Y., Ichiya, Y., & Fujishima, M. (1992). Leukoaraiosis and dementia in hypertensive patients. *Stroke*, *23*(11), 1673-1677.

Zacks, R. T., Hasher, L., & Li, K. Z. H.(2000). Human memory. *The Handbook of Aging and Cognition*, 293-357.

Zanto, T. P., & Gazzaley, A. (2009). Neural suppression of irrelevant information underlies optimal working memory performance. *Journal of Neuroscience*, *29*(10), 3059-3066.

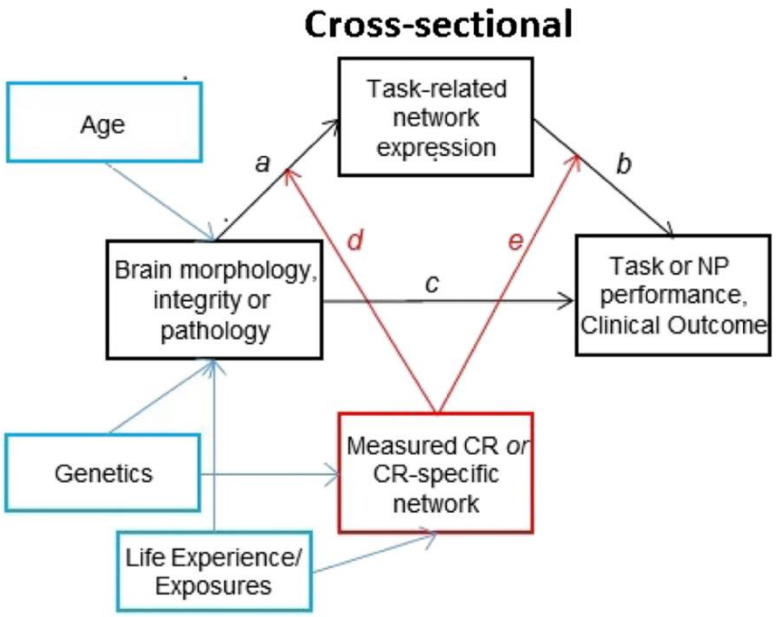
Zhu, W. G., Xiong, Q. M., & Hong, K. (2015). Meta-analysis of CHADS2 versus CHA2DS2-VASc for predicting stroke and thromboembolism in atrial fibrillation patients independent of anticoagulation. *Texas Heart Institute Journal*, *42*(1), 6-15.

Zuo, X. N., Di Martino, A., Kelly, C., Shehzad, Z. E., Gee, D. G., Klein, D. F., ... & Milham, M. P. (2010). The oscillating brain: Complex and reliable. *Neuroimage*, *49*(2), 1432-1445.

Zuo, M. L., Liu, S., Chan, K. H., Lau, K. K., Chong, B. H., Lam, K. F., ... & Tse, H. F. (2013). The CHADS2 and CHA2DS2–VASc scores predict new occurrence of atrial fibrillation and ischemic stroke. *Journal of Interventional Cardiac Electrophysiology*, *37*(1), 47-54.

FIGURE 1

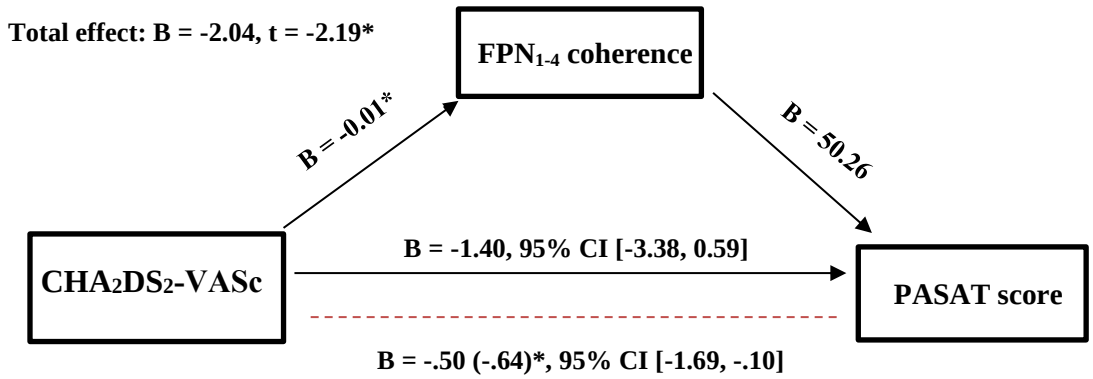
Model of Brain Pathology, Functional Connectivity, and Cognitive Outcome



Note: Model presented in Stern, 2017. Most relevant to the current study is the mediational effect of "network expression" on the relation between brain integrity (CHA_2DS_2-VASc) and task performance (Paced Auditory Serial Addition Test), following paths a → b → c).

FIGURE 2

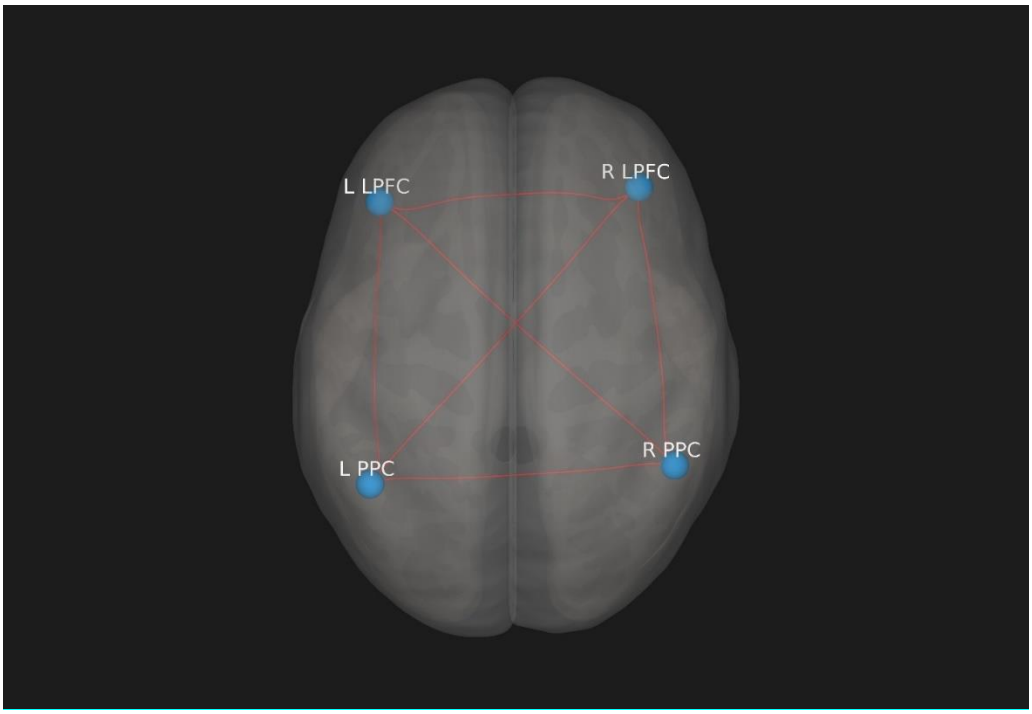
Frontoparietal Network Coherence as a Mediator of Stroke Risk and Working Memory



Note: $*p < .05$. Bootstrapped CI's based on 1000 samples. CHA_2DS_2-VASc = stroke risk classification system that is derived from an individual's status relative to age, congestive heart failure, hypertension, diabetes mellitus, vascular disease, age, sex, and past stroke. FPN_{1-4} coherence = frontoparietal network coherence value of the left prefrontal cortex and right posterior parietal cortex. PASAT score = Paced Auditory Serial Addition Test.

FIGURE 3

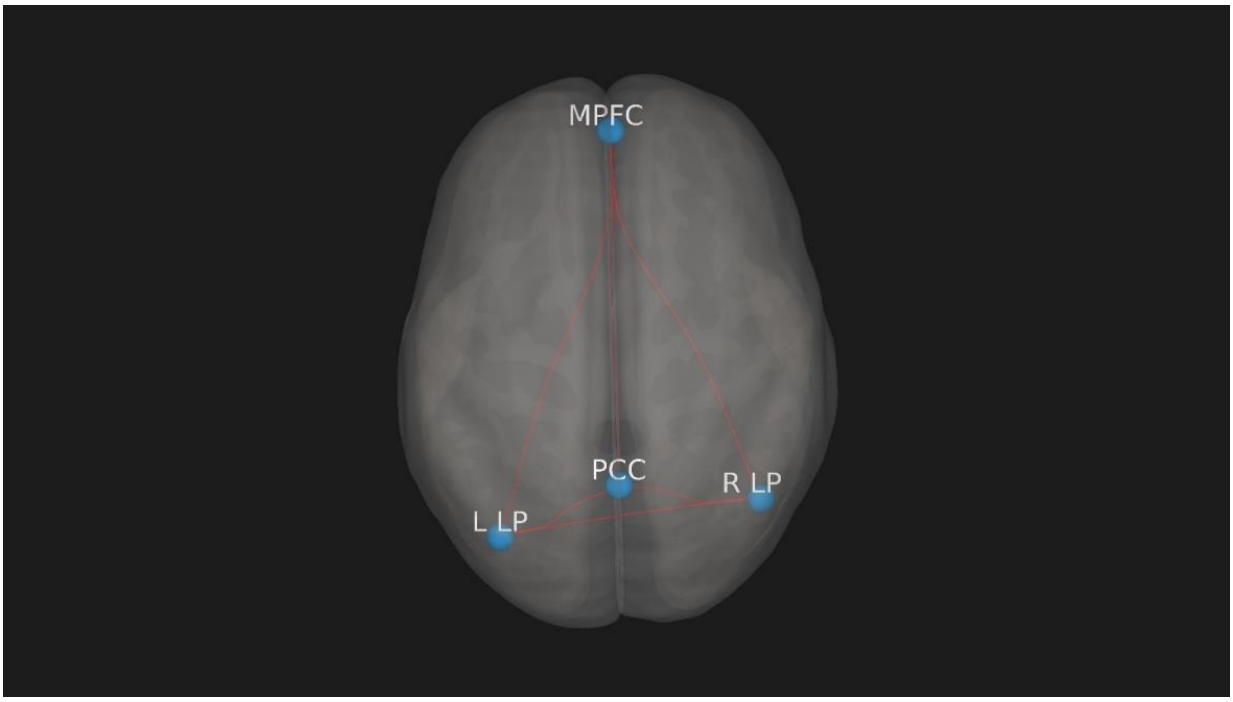
Regions of Interest Used to Quantify the Frontoparietal Network



Notes: (1) L LPFC = left lateral prefrontal cortex; (2) R LPFC = right lateral prefrontal cortex; (3) L PCC = left posterior parietal cortex; (4) R PPC = right posterior parietal cortex.

FIGURE 4

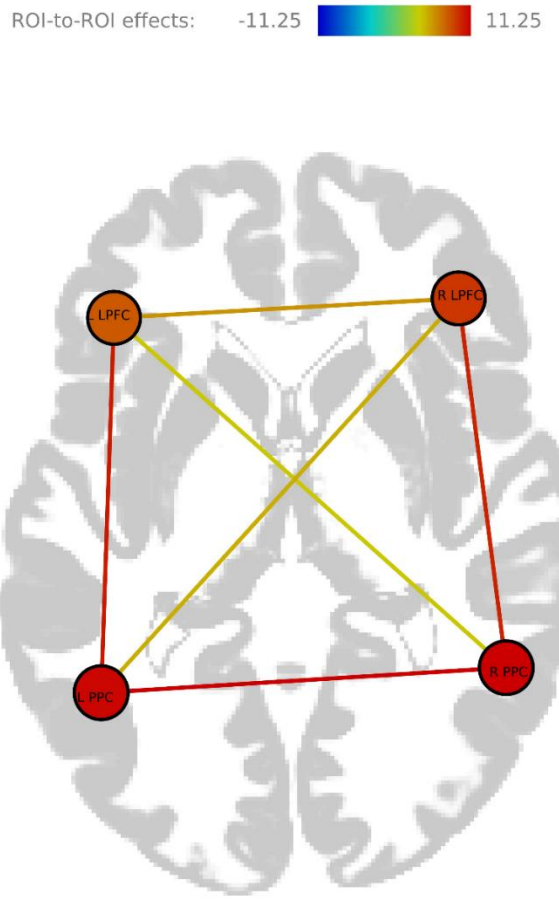
Regions of Interest Used to Quantify the Default Mode Network



Notes: (1) MPFC = medial prefrontal cortex; (2) PCC = posterior cingulate cortex; (3) L LP = left lateral parietal cortex; (4) R LP = right lateral parietal cortex.

FIGURE 5

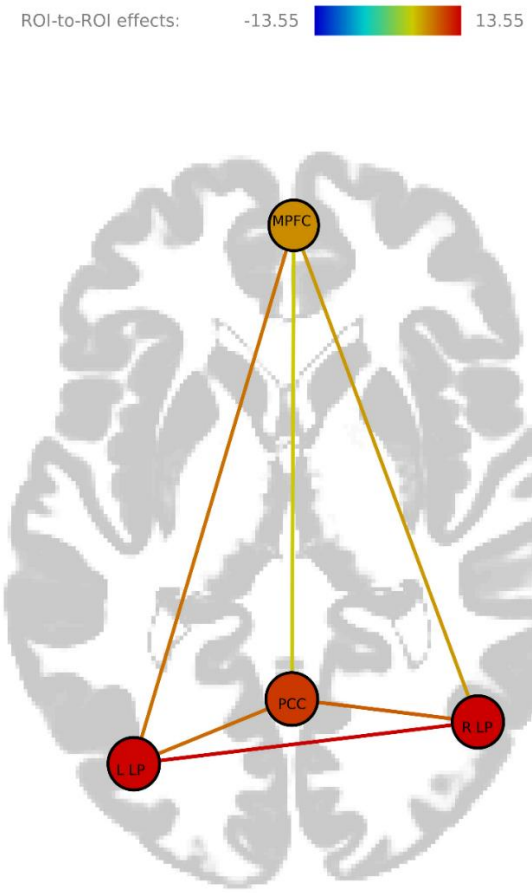
ROI-to-ROI Functional Connectivity of the Frontoparietal Network



Notes: The color bar range extends from t-values of -11.25 to 11.25. In reference to the color bar, the colors of the connectivity lines depict the strength of the seed-level correlations. L LPFC = left lateral prefrontal cortex; R LPFC = right lateral prefrontal cortex; L PPC = left posterior parietal cortex; R PPC = right posterior parietal cortex.

FIGURE 6

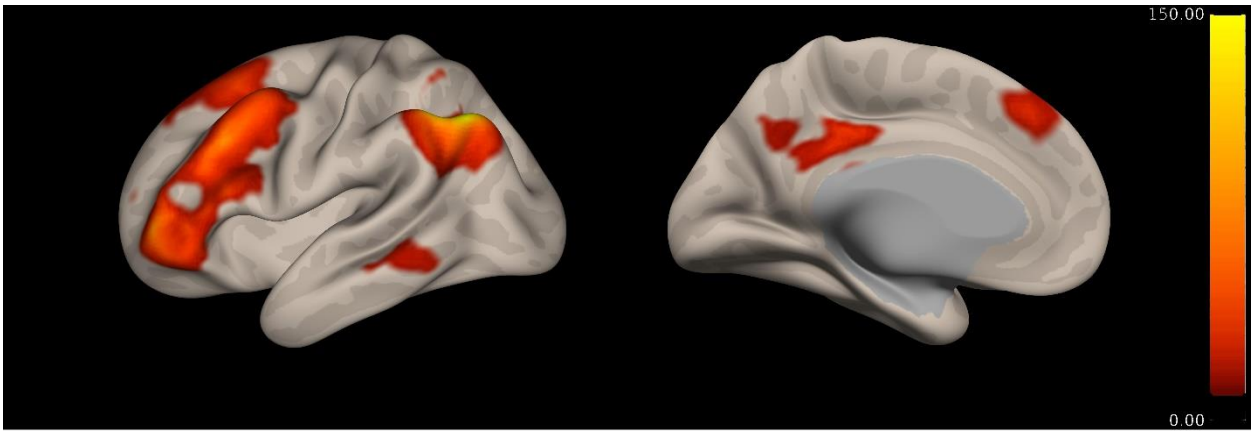
ROI-to-ROI Functional Connectivity of the Default Mode Network



Notes: The color bar range extends from t-values of -13.55 to 13.55. In reference to the color bar, the colors of the connectivity lines depict the strength of the seed-level correlations. L LPFC = left lateral prefrontal cortex; R LPFC = right lateral prefrontal cortex; L PCC = left posterior parietal cortex; R PPC = right posterior parietal cortex.

FIGURE 7

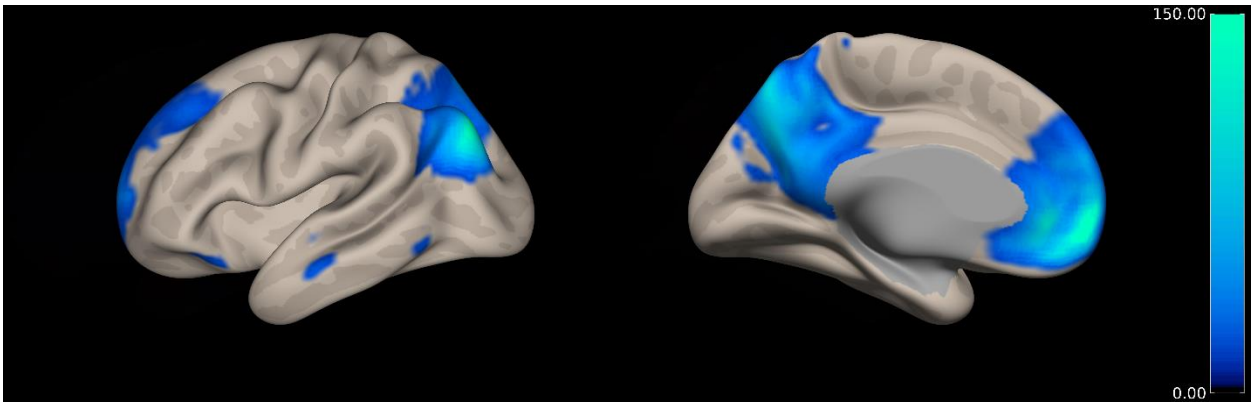
Seed-to-Voxel Functional Connectivity of the Frontoparietal Network



Note: Four seed regions were selected from pre-defined Frontoparietal Network regions of interest provided by the CONN toolbox (L lateral PFC, R lateral PFC, L posterior parietal cortex, R posterior parietal cortex). The average BOLD time-series of each seed region (ROI) were tested for significant relations with each voxel of the brain. Results were thresholded using FDR corrected p-values by a combination of height (voxel-level) and extent (cluster-level) thresholds of $q = 1.0 \times 10^{-8}$. The color bar (right) displays the strength of correlations using a t-value range of 0 to 150. Peak coordinates of each cluster are listed in Table 5.

FIGURE 8

Seed-to-Voxel Functional Connectivity of the Default Mode Network



Note: Four seed regions were selected from pre-defined Default Mode Network regions of interest provided by the CONN toolbox (mPFC, PCC, L lateral parietal cortex, R lateral parietal cortex). The average BOLD time-series of each seed region (ROI) were tested for significant relations with each voxel of the brain. Results were thresholded using FDR corrected p-values by a combination of height (voxel-level) and extent (cluster-level) thresholds of $q = 1.0 \times 10^{-8}$. The color bar (right) displays the strength of correlations using a t-value range of 0 to 150. Peak coordinates of each cluster are listed in Table 6.

TABLE 1

Demographic and Mean Summary Data

Variable	Mean	SD	Min-Max
Demographic			
Age	66.0	9.5	50-86
Sex (F)	0.55	0.5	0-1
Education	16.4	2.2	11-21
Cognitive			
MMSE	29.1	1.5	19-30
WTAR SS	111.3	6.6	80-125
PASAT	48.3	8.7	18-60
Stroke Risk			
Congestive HF	0.1	0.3	0-1
Hypertension	0.4	0.5	0-1
Diabetes	0.1	0.3	0-1
Vascular Disease	0.2	0.4	0-1
CHA_2DS_2-VASc	2.0	1.4	0-6

Note: Education = years of formal education attained. MMSE = Mini Mental Status Examination raw score. WTAR SS = Wechsler Test of Adult Reading standard score. PASAT = Paced Auditory Serial Addition Test (3 sec condition) raw score. HF = Heart failure.

TABLE 2

Correlation Matrix of Study Variables

(presented on next page)

	CHADS	PASAT	DMN_C	FPN_C	DMN_{1-2}	DMN_{1-3}	DMN_{1-4}	DMN_{2-3}	DMN_{2-4}	DMN_{3-4}	FPN_{1-2}	FPN_{1-3}	FPN_{1-4}	FPN_{2-3}	FPN_{2-4}	FPN_{3-4}
CHADS	1	-0.32*	0.04	-0.06	-0.18	-0.04	0.01	-0.06	0.17	0.18	-0.13	-0.04	-0.38*	0.19	0.04	0.01
PASAT		1	-0.09	0.14	0.1	0.04	-0.11	0	-0.11	-0.2	0.08	0.1	0.35*	0.12	0.1	0.02
DMN_C			1	.76**	.38*	.76**	.60**	.54**	.55**	0.08	.58**	.71**	-0.01	.52**	.58**	.66**
FPN_C				1	.68**	.82**	0.2	.70**	0.13	-.39**	.75**	.91**	.44**	.47**	.54**	.91**
DMN_{1-2}					1	.71**	-0.3	.86**	-.50**	-.83**	.64**	.69**	.66*	-0.13	-0.02	.73**
DMN_{1-3}						1	0.21	.73**	0.01	-.45**	.64**	.80**	.33*	0.23	0.25	.87**
DMN_{1-4}							1	-0.22	.77**	.54**	0.9	0.16	-.45**	.45**	.49**	0.11
DMN_{2-3}								1	-.32*	-.65**	-.58**	-.74**	.55**	0.01	0.06	.72**
DMN_{2-4}									1	.75**	-0.01	0.08	-.57**	.59**	.59**	-0.03
DMN_{3-4}										1	-.35*	-.47**	-.69**	.38*	.34*	-.53**
FPN_{1-2}											1	.59**	0.29	0.25	.30*	.67**
FPN_{1-3}												1	.38*	0.27	.33*	.87**
FPN_{1-4}													1	-0.15	-0.07	.40**
FPN_{2-3}														1	.67**	0.23
FPN_{2-4}															1	0.27
FPN_{3-4}																1

Note: *p < .05; **p < .01.

TABLE 3

Descriptive Data and Strength of Individual Seed Intensity

	Frontoparietal Network	x	y	z	Intensity (t)	p-FDR
1	L lateral prefrontal cortex	-43	33	28	20.11	<.01
2	L posterior parietal cortex	-46	-58	49	26.35	<.01
3	R lateral prefrontal cortex	41	38	30	20.58	<.01
4	R posterior parietal cortex	52	-52	45	25.10	<.01

	Default Mode Network	x	y	z	Intensity (t)	p-FDR
1	B medial prefrontal cortex	1	55	-3	20.20	<.01
2	L posterior parietal cortex	-39	-77	33	30.89	<.01
3	R posterior parietal cortex	47	-67	29	29.77	<.01
4	B posterior cingulate cortex	1	-61	38	22.89	<.01

Note: L = left, R = right, and B = bilateral. Intensity value for each seed represents the strength of its overall contribution to the network at large, measured via relations with other seeds (as t-scores). To adjust for multiple comparisons, results were thresholded using FDR-corrected p-values (q = .05).

TABLE 4

Group-Level Seed Correlations and Related Network Coherence Scores

	Default Mode Network	Mean (z)	SD	Range	Intensity (t)	p-FDR
1-2	Medial PFC: L LPC	0.05	0.10	0.71	8.63	<.01
1-3	Medial PFC: R LPC	0.04	0.07	0.36	6.81	<.01
1-4	Medial PFC: PCC	0.02	0.05	0.33	4.76	<.01
2-3	L LPC: R LPC	0.09	0.10	0.61	13.55	<.01
2-4	L LPC: PCC	0.05	0.11	0.45	8.71	<.01
3-4	R LPC: PCC	0.04	0.09	0.63	9.42	<.01
$\bar{X}$	Mean coherence	0.05	0.04	0.27		

	Frontoparietal Network	Mean (z)	SD	Range	Intensity (t)	p-FDR
1-2	L PFC: L PPC	0.06	0.05	0.24	10.30	<.01
1-3	L PFC: R PFC	0.03	0.10	0.59	5.86	<.01
1-4	L PFC: R PPC	0.00	0.05	0.28	3.95	<.01
2-3	L PPC: R PFC	0.00	0.05	0.26	4.81	<.01
2-4	L PPC: R PPC	0.07	0.05	0.34	11.25	<.01
3-4	R PFC: R PPC	0.08	0.11	0.57	9.91	<.01
$\bar{X}$	Mean coherence	0.04	0.05	0.28		

Note: Mean, SD, and Range represent group-level statistics (Fisher's z values) of the correlations among seed regions. Intensity represents the strength of each seed-to-seed correlation as a t-value, and p-FDR indicates the statistical significance of each relation following FDR correction (q = .05) for multiple comparisons. Default Mode network acronyms: L = left; R = right; PFC = prefrontal cortex; LPC = lateral parietal cortex; PCC = posterior cingulate cortex. Frontoparietal network acronyms: PFC = prefrontal cortex; PPC = posterior parietal cortex. Network coherence scores were computed by averaging the mean (z-values) correlations among within-network seeds.

TABLE 5

Frontoparietal Network Clusters Derived from Seed-to-Voxel Connectivity Analysis

Regions	Voxels	x	y	z
L dorsolateral PFC / frontal pole	7094	-42	54	4
R dorsolateral PFC / frontal pole	6983	36	58	14
L posterior/inferior parietal cortex	3438	-44	-64	46
R posterior/inferior parietal cortex	3122	52	-50	48
B precuneus/posterior cingulate cortex	1225	0	-34	38
L middle temporal gyrus	158	-58	-46	-8
R middle temporal gyrus	104	68	-32	-10

Note: L = Left; R = Right; B = Bilateral. Peak-voxel locations (mm) are reported in MNI space (LPI orientation). PFC = prefrontal cortex. These clusters are shown in Figure 7.

TABLE 6

Default Mode Network Clusters Derived from Seed-to-Voxel Connectivity Analysis

Regions	Voxels	x	y	z
B PCC / precuneus / lateral parietal cortex	18975	-38	-78	38
B medial PFC / ACC / frontal pole	8214	0	54	-4
R middle temporal gyrus	196	60	-6	-20
L middle temporal gyrus	173	-64	-12	-18
L inferior/middle temporal gyrus	105	-54	-58	-12
L inferior frontal gyrus	97	-34	24	-20
R inferior frontal gyrus	53	34	30	-14
R superior frontal cortex	49	22	32	38

Note: L = Left; R = Right; B = Bilateral. Peak-voxel locations (mm) are reported in MNI space (LPI orientation). PCC = posterior cingulate cortex; PFC = prefrontal cortex; ACC = anterior cingulate cortex. These clusters are shown in Figure 8.