DETECTION OF COGNITIVE PROCESSING SPEED EFFECTS ON EXECUTIVE FUNCTIONS USING FUNCTIONAL AND STRUCTURAL MRI

by

SPENCER W. LIEBEL

(Under the Direction of LAWRENCE H. SWEET)

ABSTRACT

Cognitive processing speed (CPS) has been shown to be a sensitive behavioral marker of cognitive decline prior to the onset of disease or the aging process. Together with white matter volume, CPS influences the successful completion of working memory (WM), yet it remains unclear to what extent neural activation during a WM paradigm is resultant of these variables in a healthy, non-aging sample. The present study employed an FMRI WM paradigm to examine neural response (*i.e.*, overactivations) in four key regions of interest to quantify potential compensatory activation after controlling for WM performance. Results did not support CPS as an index of compensatory activation during the FMRI WM paradigm. White matter volume also did not significantly influence FMRI WM activations. Findings suggest that the *processing speed model* of aging does not extend to healthy, non-aged individuals and that possible latent factors account for FMR WM brain activity.

INDEX WORDS: Cognitive processing speed; working memory; FMRI; white matter volume; compensatory activation

DECTECTION OF COGNITIVE PROCESSING SPEED EFFECTS ON EXECUTIVE FUNCTIONS USING FUNCTIONAL AND STRUCTURAL MRI

by

SPENCER W. LIEBEL

BS, BRIGHAM YOUNG UNIVERSITY, 2012

MS, UNIVERSITY OF GEORGIA, 2017

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

DOCTOR OF PHILOSOPHY

ATHENS, GEORGIA

2019

© 2019

Spencer W. Liebel

All Rights Reserved

DETECTION OF COGNITIVE PROCESSING SPEED EFFECTS ON EXECUTIVE FUNCTIONS USING FUNCTIONAL AND STRUCTURAL MRI

by

SPENCER W. LIEBEL

Major Professor:	Lawrence H. Sweet
Committee:	L. Stephen Miller
	Brian W. Haas

Electronic Version Approved:

Ron Walcott
Interim Dean of the Graduate School
The University of Georgia
December 2019

DEDICATION

To my extraordinary partner, Emily. Without her support, patience, and wisdom throughout my graduate school training achieving my academic and professional pursuits would not have been possible. She kept me focused on my goals and provided critical perspective when I struggled.

ACKNOWLEDGEMENTS

I am so very grateful to my advisor, Lawrence H. Sweet, for his kindness and genuine concern for my training. He routinely went above and beyond in his role as advisor to help me learn the necessary skills to excel as a Clinical Neuropsychologist. I will use his example to guide me when I have the opportunity to train and mentor others.

TABLE OF CONTENTS

LIST OF TABLES

Page

LIST OF FIGURES

Page

CHAPTER 1

INTRODUCTION

Cognitive Processing Speed

Performance on a wide-range of neuropsychological tests changes with age, and for this reason, raw performance scores are typically adjusted for age to guide inference. In other words, the scores obtained are compared to an age-matched normative sample. However, the biological basis for the age-related variance in different cognitive abilities is still not completely understood. Numerous theories and models, from neurophysiological perspectives to more behavioral and cognitive perspectives, have been proposed (see Cabeza, Nyberg, & Park, 2005; Reuter-Lorenz & Park, 2010, for reviews). To date, the most influential and empirically tested model is the *processing speed theory*, which implies a mediational indirect effect of such factors as age or brain injury on cognitive functioning through slowing cognitive processing speed (CPS; Salthouse, 1996). Accordingly, this generalized slowing has a detrimental effect not only on the quantitative but also the qualitative dimension of performance for a variety of cognitive skills. According to Salthouse, cognitive performance degrades because relevant, basic cognitive operations are executed too slowly and hence, slowed CPS reduces the amount of simultaneously available information needed for higher-order processing.

CPS has been a fundamental component of the scientific inquiry of cognitive differences since the inception of that field (Cattell, 1890). In clinical and laboratory settings, it is primarily measured using perceptual speed tasks, involving visual search, elementary comparison, and substitution operations. In its most complicated form, CPS is assessed using timed decision-

making tests that have been created and standardized psychometrically. Perhaps the most well-known of these have been incorporated into the Wechsler (2008) intelligence scales and are called the Coding and Symbol Search subtests. Coding, for example, requires the subject to enter a number below each simple symbol in a long series using a readily available key. Scores are based on the numbers of items completed correctly in the allotted time. Yet more basic assessments of CPS also exist and have been derived not from psychometric tests, but from cognitive-experimental psychology and psychophysics. In these instances, the item content is more simple than those described previously and the relevant completion times for items are much shorter (*i.e.*, milliseconds). These tasks typically take the form of reaction time tasks, such that the speed with which the subject performs a very simple mental operation is the measurement of CPS. Each of these types of CPS are significantly correlated with higher-order cognitive functions (Deary, Der, & Ford, 2001; Grudnik & Kranzler, 2001).

CPS exhibits one of the most rapid declines with advancing age and is among the first impairments detected in many disorders with cognitive consequences (*e.g.*, cardiovascular disease, multiple sclerosis, traumatic brain injury, psychosis; Genova, Hillary, Wylie, & Rypma, 2009; Kelleher et al., 2013; Liebel & Sweet, 2019; Mathias & Wheaton, 2007). Although age-related cognitive declines are expected in many other cognitive domains, they are usually less precipitous than CPS. This is evident among the subtests of the Wechsler Adult Intelligence Scale (WAIS), an assessment instrument that is widely recognized for its reliability, validity and excellent norms (Wechsler, 2008). Raw scores on the Symbol Search subtest, a validated measure of CPS, decline by more than 65% between the ages of 25 and 65, while performance on Matrix Reasoning, a measure of perceptual reasoning and fluid intelligence, declines by approximately 35% (Wechsler, 2008). Along these lines, extant research using both cross-

sectional (Gottsdanker, 1982; Salthouse, 2000, 2009; Tombaugh, 2004; Wilkinson & Allison, 1989) and longitudinal samples (Schaie, 2005) show that across the lifespan, CPS has a quadratic trajectory that takes the shape of an inverted U; it reaches maximum efficiency around the mid-30s then demonstrates a generally linear decline thereafter.

The fundamental importance of CPS is supported by a substantial body of research literature that has repeatedly demonstrated that CPS deficits are responsible for declines in higher-order cognitive domains such as executive functioning (EF), including working memory (Jensen, 1992; Kail & Salthouse, 1994; Liebel et al., 2017; Rypma & Prabhakaran, 2009; Salthouse, 1996; Salthouse & Ferrer-Caja, 2003; Shucard et al., 2004). The effects of slowed CPS on other cognitive domains are especially well-documented in older adults (Finkel et al., 2004; Liebel et al., 2017; MacPherson et al., 2017; Salthouse & Coon, 1993; Whiting & Smith, 1997) and in populations with specific pathologies, such as temporal lobe epilepsy (Dow, Seidenberg, & Hermann, 2004), left-hemisphere stroke (Turken et al., 2008), multiple sclerosis (Sperling et al., 2001; Kail, 1998; Swirsky-Sacchetti et al., 1992), and traumatic brain injury (Verger et al., 2001). However, declines in CPS are not solely reserved for patients with the aforementioned pathologies. Rather, slowed CPS and subsequent deficits in other cognitive domains are also observed in non-elderly adult patient populations (Albinet, Boucard, Bouquet, & Audiffren, 2012; Ebaid et al., 2017; Kelleher et al., 2013; Magistro et al., 2015; Schretlen, Pearlson, Anthony, & Aylward, 2000). For example, Kelleher and colleagues (2013) reported that adolescents with prodromal psychiatric syndromes performed worse than control subjects on multiple test of CPS.

Although most studies supporting the *processing speed theory* have employed cross-sectional designs that are unable to address within-person change and may provide biased

estimates of longitudinal mediational processes (Cole & Maxwell, 2003; Hofer, Flaherty, & Hoffman, 2006; Hofer & Sliwinski, 2001; Lindenberger & Pötter, 1998; Maxwell & Cole, 2007; Maxwell, Cole, & Mitchell, 2011), the role of CPS as a mediator of age-related change in other aspects of cognition has also been supported by a few longitudinal studies (Finkel et al., 2005, 2007; Hertzog, Dixon, Hultsch, & MacDonald, 2003; Hultsch, Hertzog, Small, McDonald-Miszczak, & Dixon, 1992; Lemke & Zimprich, 2005; MacDonald, Hultsch, Strauss, & Dixon, 2003; Sliwinski & Buschke, 1999; Sliwinski, & Buschke, 2004; Taylor, Miller, & Tinklenberg, 1992; Zimprich, 2002; Zimprich & Martin, 2002). More recent research, which utilized developments in structural equation modeling for longitudinal data, reported that time-specific variation in CPS accounted for a significant portion of the longitudinal relationship between age and cognitive functioning (Robitaille et al., 2013).

Neuroimaging techniques have been applied in both healthy individuals and clinical populations to elucidate the relationships between CPS and functional brain activity. For example, FMRI research has found a positive relationship between CPS performance and activation of fronto-parietal networks (Forn et al., 2013). Furthermore, increased CPS demands are associated with greater patterns of connectivity within fronto-parietal and fronto-occipital networks, as well as an increase in the number of functional networks involved (Forn et al., 2013).

Thus, as a fundamental cognitive process required for efficient higher-order functions, the accurate assessment of CPS may be particularly useful as a sensitive predictor of changes in these higher-order cognitive domains, and therefore, an early marker of brain dysfunction (Duering et al., 2014; Eckert, 2011; Salthouse & Ferrer-Caja, 2003; Tam, Lam, Huang, Wang, & Lee, 2015). Indeed, measures of CPS are frequently recommended for detection of cognitive

changes associated with both normal age-related and pathological changes in brain integrity that often occur in cardiovascular disease, traumatic brain injury, multiple sclerosis, and healthy aging (Cutter et al., 1999; Gronwall, 1977; Liebel & Sweet, 2019).

White Matter and CPS

White matter pathways of the brain mediate the long-range transmission of information across distributed brain networks and support the synchronization and integration of operations carried out by individual brain areas (Mesulam, 1998; Mesulam, 2000). Structural neuroimaging studies document protracted developmental maturation of bidirectional anterior-posterior white matter connections between the prefrontal cortex (PFC) and posterior parietal lobes (Giedd, 2004; Østby, Tamnes, Fjell, & Walhovd, 2011). White matter volume increases linearly through young adulthood, which yields relatively stable total brain volumes after puberty (Giedd et al., 2009). It has been shown by computer simulations of brain connectivity patterns that distributed patterns of cortical activity can be largely attributed to the patterns of interaction afforded by the white matter fiber systems (Hilgetag et al., 2000; Kötter & Sommer, 2000). Therefore, individual differences in CPS are likely to depend to a large extent on structural variations in the development of these pathways, which both constrain and facilitate the communication and coordination among cortical nodes of brain-wide networks (Magistro et al., 2015).

Long association tracts sub-serve functional integration among frontal, parietal, and temporal association cortices (Schmahmann & Pandya, 2006). The most prominent association tracts bridging frontal, temporal, and parietal regions are the superior longitudinal fasciculus, inferior longitudinal fasciculus, occipito-frontal fasciculus, and the uncinate fasciculus. Higher-order association areas in prefrontal cortex and temporal and posterior-parietal lobes are considered to have important roles in attention, working memory, and response selection

(Goldman-Rakic, 1988; Mesulam, 2000). These are brain regions that are most commonly recruited by the diverse range of cognitive tasks used in functional neuroimaging studies (Cabeza & Nyberg, 2000; Duncan & Owen, 2000; Shulman et al., 1997).

Functional and structural coupling between posterior and frontal brain regions, mediated by long-range cortico-cortical association tracts, are construed as being central for carrying out cognitive operations (Fuster, 2001; Goldman-Rakic, 1988). Studies have increasingly focused on the role of white matter as the biological basis underlying CPS (Bartzokis et al., 2007; Bucur et al., 2008; Charlton et al., 2006; Deary et al., 2006; Kennedy & Raz, 2009; Kuznetsova et al., 2016; Lu et al., 2011; Madden et al., 2009; Marner, Nyengaard, Tang, & Pakkenberg, 2003; O'Sullivan et al., 2001; Tang, Nyengaard, Pakkenberg, & Gundersen, 1997; Tuch et al., 2005; Turken et al., 2008; Vernooij et al., 2009). For example, Turken et al. (2008) found that CPS is closely associated with the structural integrity of major white matter tracts that run along the anterior-posterior axis of the brain allowing fronto-posterior network interactions. Kennedy and Raz (2009) examined relationships between imaging biomarkers in several white matter regions and cognitive tests, including CPS, in a sample of 52 subject aged between 19 and 81 years. After correcting for the effects of age, working memory and CPS remained significantly associated with white matter structure in anterior brain regions. Haász et al. (2013) further illustrated the relationship between white matter and CPS. These authors investigated links between general fluid intelligence and white matter water diffusion parameters in a cohort of 100 healthy participants aged between 49 and 80 years. Using two measures of CPS, a color-word interference test and a visuospatial attention task, they found that CPS scores contributed most towards associations with white matter structure than did other measures of fluid intelligence.

Performance on CPS measures requires these diffuse white matter systems of integrated brain networks, as disruption of white matter between these networks results in slowed CPS (Kuznetsova et al., 2016; Seiler et al., 2018). The critical role of white matter in CPS and other cognitive functions is most evident in the hallmark features of many disorders of the cerebral white matter, such as cardiovascular disease (Breteler et al., 1994), sickle cell anemia (Stotesbury et al., 2018), multiple sclerosis (Rao, 1995), and traumatic brain injury (Donders, Tulsky, & Zhu, 2001; Rao, 1996). Research on the cognitive functioning of patients with white matter diseases, such as multiple sclerosis, which leads to demyelination and wide spread damage across fiber systems, suggests that approximately 50% of patients demonstrate a cognitive disorder (Rao, 1995). Similarly, investigations of the effects of traumatic brain injury on cognition show an overall slowing of cognitive processes attributable to its effects on the cerebral white matter (Levine et al., 2006; Rao, 1996; Stotesbury et al., 2018).

There are also normal individual differences in CPS that are believed to reflect individual variation in neural efficiency and capacity (Birren & Fisher, 1995; Mendelson & Ricketts, 2001), as well as age-related changes in neural processing, including both the development and decline of axonal myelination across the lifespan (Charlton et al., 2006, 2008; Kuznetsova et al., 2016). Indeed, Lu and colleagues (2011) reported that the myelin integrity of a large sample of very healthy older adults was significantly correlated with CPS in highly vulnerable late-myelinating regions, including the prefrontal cortex and the genu of the corpus callosum.

Considered together, extant research on the relationship between white matter and CPS demonstrates a linear relationship such that CPS declines as a function of white matter integrity. This pattern is evident across healthy, neurological, and aging samples. In each of these populations, bidirectional anterior-posterior white matter connections sub-serve functional

integration among frontal, parietal, and temporal association cortices. As these distinct and intricately related brain systems perform a multitude of cognitive functions, the disruption of the white matter bridges connecting them results in subsequent cognitive decline, particularly slowed CPS.

Working Memory

While the term *working memory* (WM) was introduced into the behavioral literature more than 50 years ago (see Miller, Galanter, & Pribram, 1960), the most enduring conceptualization of WM has been that of Alan Baddeley and Graham Hitch which defines WM as a limited capacity system used to store and manipulate information in support of goal-directed behavior during a short time span (Baddeley, 1998; Diamond, 2013). It is a key component of EF (Diamond, 2013). Along with CPS, WM accounts for a substantial portion of developmental variance in global intelligence in children and adults (Conway, Kane, & Engle, 2003; Fry & Hale, 1996). Performance on WM tasks improves throughout adolescence (Conklin, Luciana, Hooper, & Yarger, 2007), and individuals vary in terms of how many pieces of information they can hold and manipulate in WM (Engle, Tuholski, Laughlin, & Conway, 1999). These individual differences have been variously associated with performance on a wide variety of academic and occupational outcomes in addition to reasoning and problem-solving (Engle, Kane, & Tuholski, 1999).

WM is a property of the brain that supports successful attainment of behavioral goals that are being carried out by any of the several systems, including sensory systems, those that underlie semantic and episodic memory, and motor systems (D'Esposito & Postle, 2015). Extant research of WM at such a systems-level has supported several neural mechanisms that likely underlie WM function, including prefrontal cortex, posterior parietal cortex, basal ganglia,

thalamic, and brainstem systems. The PFC and posterior parietal lobes are most frequently implicated in functional imaging studies of WM such that brain activation reliably scales with the amount of information required to be held in the system (Braver et al., 1997; Nee et al., 2013; Sweet et al., 2006). Meta-analyses of previous neuroimaging studies have also revealed activation of a fronto-parietal network in response to WM task demands (Curtis & D'Esposito, 2003), including lateral frontal cortex, and bilateral lateral posterior parietal cortex (Owen, McMillan, Laird, & Bullmore, 2005; Rottschy et al., 2012; Wang et al., 2019).

Another consistent finding in functional neuroimaging studies of WM is compensatory activation in order to maintain successful task performance. There is evidence that suggests certain populations (*e.g.*, carriers of the *APOE* ε4 allele, multiple sclerosis patients, individuals with Alzheimer's disease, substance-dependent patients) demonstrate overactivation of these WM-related fronto-parietal networks in the absence of behavioral differences that is thought to constitute a compensatory response (Bookheimer et al., 2000; Chariet et al., 2014; Scheller et al., 2017; Sweet et al., 2006: Sweet et al., 2010b; Trachtenberg, Filippini, Mackay, 2012; Wishart et al., 2006). Moreover, compensatory activation has been noted when stressors or increased task demands are introduced, even among healthy samples (Sweet et al., 2006; Sweet et al., 2008; Sweet, Jerskey, Aloia, 2010a; Sweet et al., 2010b).

WM and CPS

The rate at which the brain processes cognitive information (*i.e.*, CPS) is intricately related to WM (Nebes et al., 2000; Salthouse, 1994). Indeed, some researchers have argued that variability in WM directly reflects variability in CPS (Jensen, 1992; Salthouse, 1994, 1996). Researchers have also postulated that age-related changes in CPS drive developmental changes in WM function (Fry & Hale, 1996; Jensen, 1992; Salthouse, 1996; Verhaeghen & Salthouse,

1997). Fundamental to these theories are the notion that efficient processing of stimuli by the brain depends, in part, on a balance between the rate at which the incoming information can be processed and the rate at which the information decays or is displaced. Consider the Paced Auditory Serial Addition Task (PASAT; Gronwall, 1977). The PASAT is a speed-dependent task that is frequently used in clinical setting to assess WM, sustained attention, and CPS (Fisk & Archibald, 2001; Rao, Leo, Bernardin, & Unverzagt, 1991). In order to accurately perform the PASAT, one must both quickly and efficiently process incoming stimuli (*i.e.*, numbers), hold the results of this processing for subsequent manipulation, and efficiently combine these results with new incoming stimuli. Thus, the PASAT requires both CPS and WM abilities to function in concert to result in accurate performance. A breakdown of either system renders the task impossible.

In multiple sclerosis, a disorder characterized by CPS and WM deficits, two models have been proposed to explain the relationship between them. The *relative consequence model* purports that impaired CPS accounts for deficits in cognitive domains such as WM, particularly in patients with the less severe disease course (Archibald & Fisk, 2000; DeLuca et al., 2004; Lengenfelder et al., 2006). Therefore, given adequate time on WM tasks, patients with CPS deficits should perform within normal limits. Thus, an apparent deficit in WM is actually an indirect effect of a CPS deficit. The *independent consequence model* suggests that impairments in separate cognitive domains such as CPS and WM are independent, although not mutually exclusive, of each other (DeLuca et al., 2004). Accordingly, WM could be impaired independently of CPS even though CPS is an important component of WM ability.

N-back Tasks

N-back tasks have been used often in experimental studies of WM. They provide behavioral indices of simple and complex CPS and WM (Parmenter et al., 2006; Parmenter, Shucard, & Shucard, 2007). During the N-back task, participants decide whether each currently presented stimulus matches the stimulus previously presented "*n*" trials back. As *n* increases, the task difficulty increases, placing greater demand on WM. Simple CPS reflects the mental speed required to perform undemanding attentional tasks such as target detection (*e.g.*, 0-back), while complex CPS reflects the additive time required to perform the increasingly more demanding executive aspects of WM (*e.g.*, 1- and 2-back). The N-back is widely used in functional neuroimaging studies, resulting in demonstrated validity and reliability, including well-replicated activation patterns (Owen, McMillan, Laird, & Bullmore, 2005; Rottschy et al., 2012; Wang et al., 2019) across subjects (Drobyshevsky et al., 2006) and time (Caceres, Hall, Zelaya, Williams, & Mehta, 2009). In addition, there is data suggesting that the N-back may be used as a functional localizer (Drobyshevsky, Baumann, & Schneider, 2006), and it can be modified to assess multiple embedded contrasts (*e.g.*, memory load, stimulus type, error-related activity, conflict-related activity; Awh et al., 1996; Smith & Jonides, 1997; Sweet et al., 2008).

Rationale and Hypotheses

In summary, CPS is a sensitive behavioral marker of individual differences that has been shown to account for variation in higher-order EFs, such as WM, and neuroimaging indices of white matter. Previous studies have reported a positive relationship between faster CPS and larger global white matter volume (Turken et al., 2008). Therefore, it is not surprising that a positive relationship between white matter volume and WM has also been demonstrated (Darki & Klingberg, 2015; Nee et al., 2013). Because CPS measures are among the most sensitive

indicators of cognitive decline in aging and white matter disease, it is likely that CPS paradigms may also be a useful complement to functional neuroimaging studies. While behavioral CPS indices may serve as early detection of cognitive dysfunction, they are also likely to capture individual differences in brain function that may not be detected in behavioral or functional neuroimaging assessments of higher-order domains (*e.g.,* WM).

The goal of the present study was to capitalize on the sensitivity of CPS measures to reflect changes in age-related cognitive function and to take advantage of the ability of FMRI to detect individual differences in brain function before they are apparent in behavior (*e.g.,* compensatory activation). It was expected that slower CPS would be associated with smaller white matter volumes and greater brain response to a WM challenge after statistically controlling WM performance level (*i.e.,* compensatory activity). CPS performance and white matter volume were expected to provide better predictors of compensatory activation than either alone. Thus, the current study had three Aims:

1. Determine whether the substantial research literature that has demonstrated strong relationships in patient populations can be extended to a large healthy sample. Hypothesis 1: Faster CPS and larger white matter volumes will be significantly correlated with better N-back performance as measured via both reaction time and accuracy. Hypothesis 2: CPS and white matter volume will be significantly positively correlated with each other.
2. Quantify the amount of compensatory activation that may be predicted by CPS performance and/or white matter volume. Hypothesis 3: CPS performance will be positively related to compensatory activation in N-back regions on FMRI when performance is statistically controlled.

3. Examine the generalizability of the expected Aim 2 findings. Specifically, determine whether individuals with the greatest compensatory activity during the N-back exhibited evidence of lower cognitive function on another EF domain. Hypothesis 4: The magnitude of compensatory activity during the N-back will be inversely related to scores on a neuropsychological test of EF.

CHAPTER 2

METHOD

Participants

Structural and functional magnetic resonance imaging (MRI) data were collected from a community sample of 1,051 participants at Washington University in St. Louis as part of the Human Connectome Project between August 2012 and October 2015, and released in full on March 1, 2017 (see Table 1; Van Essen et al., 2013). The primary participant pools came from healthy individuals born in Missouri to families that include twins. They were recruited from the Missouri Department of Health and Senior Services Bureau of Vital Records. Additional recruiting efforts were used to insure that participants broadly reflect the ethnic and racial composition of the U.S. population as represented in the 2000 decennial census. Participants were 22-35 years old and had no significant history of psychiatric disorder, substance abuse, neurological disorder, cardiovascular disease, or Mendelian genetic disease (*e.g.,* cystic fibrosis). They also did not have any contraindications for MRI such as metal devices in the body or claustrophobia (Van Essen et al., 2012). In order to ensure that the brain activation patterns elicited during the WM FMRI paradigm (described below) were actually associated with WM cognitive processes, participants who performed the 2-Back at a below chance level (<50% correct response rate) were excluded. The final total sample following these exclusions was 1,051.

Procedures

Participants completed the structural and functional MRI scans over a total of 4 imaging sessions, each approximately one hour in duration. The neurocognitive assessment took place on the same days as the MRI scans. Participants provided written informed consent and were not monetarily compensated. The study was approved and monitored by the local Institutional Review Board and conformed to the Helsinki Declaration.

Measures

MRI Data Acquisition

Structural MRI data were collected on a 3T Siemens Skyra scanner (Siemens AG, Erlanger, Germany) with a 32-channel head coil. High-resolution T1-weighted MPRAGE structural images were acquired with a resolution of 0.7 mm^3 isotropic (FOV = 224 × 240, matrix = 320 × 320, 256 sagittal slices; TR = 2400 ms and TE = 2.14 ms). FMRI data were collected using the same scanner as structural MRI with a multi-band EPI pulse sequence that collected eight slices simultaneously. Images were acquired with a resolution of 2 mm^3 isotropic (FOV = 208 × 180 × 144, matrix = 104 × 90, 72 axial slices; TR = 720 ms and TE = 33 ms).

White Matter Volume Quantification

All structural images were reviewed by a technician immediately following acquisition to ensure scans did not have any significant artifact or exhibit substantial movement. If problems were found, structural scans were reacquired immediately. Within hours of the initial acquisition, scans were examined by quality control specialists who assessed them for image crispness, blurriness, and motion and other artifacts. Based on these factors, scans were rated on a 1 to 4 scale (poor to excellent). In all cases where structural scans were below 3 (good), new structural scans were reacquired on the participant's second day. Through this process, all subjects provided high quality structural imaging data (Marcus et al., 2013). T1 structural data were

reconstructed and preprocessed using a modified version of the Freesurfer pipeline (Dale, Fischl, & Sereno, 1999; Fischl, Sereno, Dale, 1999; Fischl, Sereno, Tootell, & Dale, 1999; Fischl et al., 2004) using FreeSurfer Image Analysis Suite version 5.3 (http://surfer.nmr.harvard.edu) and using DICOM to NIFTI conversion software (https://www.nitrc.org/projects/dcm2nii/). Among other output, this processing pipeline yields a measure of intracranial volume and whole-brain white matter volume that excludes the brainstem, cerebellum, ventricles, and cortical and subcortical gray matter. White matter volumes were converted to proportions of intracranial volume before use in hypothesis testing.

FMRI N-back

The HCP N-back task included the 0- and 2-back and both used embedded category specific stimuli presented in blocks of trials that consisted of pictures of faces, places, tools, and body parts (Barch et al., 2013). HCP investigators chose faces, places, tools, and body parts as the four categories of stimuli due to evidence that N-back versions using these stimuli reliably engage cortical regions shown to be critical for WM functioning (Downing et al., 2001; Fox, Iaria, & Barton, 2009; Peelen & Downing, 2005; Taylor, Alison, Wiggett, & Downing, 2007) and because the associated brain activations are reliable across subjects (Downing et al., 2001; Fox et al., 2009) and time (Kung, Peissig, & Tarr, 2007; Peelen & Downing, 2005).

Within each imaging run, the four different stimulus types were presented in separate blocks. One half of these blocks presented during a 2-back WM task, during which participants responded to each "target" - whenever the current stimulus was the same as the stimulus presented two before. Half of these blocks presented a 0-back active control task, during which a target cue is presented at the start of each block and the person responded to any presentation of that target during the block. Images were presented on a computer screen and participants

responded via response box in the dominant hand. A 2.5 second cue indicated the task type at the start of the block. Each of the two runs contained eight 2-Back and 0-Back task blocks (10 trials of 2.5 seconds each for 25 seconds) and four fixation blocks (15 seconds each). Each N-back stimulus was presented for 2 seconds, followed by a 2500 millisecond response period. Each block contains 10 trials, of which two were targets, and 2-3 were non-target lures (i.e., repeated items in the wrong N-back position, either 1- or 3-back). The inclusion of lures was used to ensure that participants were using an active memory approach to the task and to allow the assessment of conflict-related activity as well as error-related activity.

FMRI Analyses

Data were spatially and temporally preprocessed in a pipeline designed by HCP scientists that utilizes tools from FSL, Freesurfer, and their in-house software Workbench (Glasser et al., 2013; Smith et al., 2013). Following pre-processing, dataset processing and statistical analyses were performed using Analysis of Functional NeuroImages (AFNI; Cox, 1996). Additional quality control checks were performed to identify and remove movement artifact. Preprocessing of the functional N-back datasets included slice-time correction and registration of each volume to the third volume of the first imaging run to correct for head movement. Data from participants with head movement > 2.0 mm (one voxel) in any direction were omitted from analyses. Individual anatomical images were aligned to the volume-registered functional run, skull-stripped, and then transformed into Talairach standard stereotaxic space. The functional runs in native space were then aligned to the anatomical image in Talairach space using the concatenated transformation matrices from the volume registration, anatomical to functional alignment, and anatomical transformation into standard space. A 5-mm full-width Gaussian filter was applied

and the raw time-series was scaled to a mean of 100 to enable interpretation as a percent signal change from baseline.

The general linear model (GLM) was used to quantify condition-specific activity for each brain voxel of individual datasets. That is, a multiple regression of the temporal pattern of 2-back presentation, 0-back control task presentation, and covariates (*i.e.*, instruction screens, observed movement, linear drift) were performed using BOLD signal over time as the dependent variable. A direct GLTest of the effects of the 2-back compared to the 0-back was added to the GLM. A resulting individual activation map for each participant of 2-back versus 0-back BOLD signal was created and this brain response was expressed as voxel-wise betas. These were used to conduct group level analysis using participants' mean betas in *a priori* regions of interest as the dependent variable in analyses.

Group level activation maps were created from the individual 2-back vs 0-back contrast maps using voxel-by-voxel one sample *t*-tests versus a hypothetical mean of zero and thresholded using a two-tailed $p < .01$, corrected for multiple comparisons using AFNI's false discovery rate (FDR) procedure. Clusters with fewer than 200 voxels were excluded from the group level activation maps (Owens et al., 2018). This group summary map was used for comparison to prior literature and generation of ROIs.

Region of Interest Analyses

As N-back compensatory activation was expected in task-related regions, functionally defined regions of interest (ROI) were delineated within the larger *a priori* ROIs. Specifically, the whole brain voxel-wise analyses conducted to reveal regions that demonstrate significant WM effects in this sample were used. In order to optimize internal and external validity, we chose four task-related clusters of significant activation from our sample that fell within the four

larger *a priori* regions consistently reported in prior literature. Given the widespread use of the N-back, its activation patterns are well-documented (Owen et al., 2005; Yeo et al., 2015). We chose the four most robust regions of activation reported in this prior literature: the bilateral PFC and bilateral posterior parietal cortex (PPC). In the current study, structures anterior to the pre-motor cortex, including the lateral, dorsolateral, ventrolateral, orbitofrontal, and medial prefrontal cortices, were considered part of the PFC. The PPC included those structures posterior to the primary somatosensory cortex and included the superior and inferior parietal lobules. The overlap of these *a priori* ROI and the largest cluster of significant activation became the functional ROI within which activation was examined to test hypotheses.

In order to determine whether these 2-back task-related functional ROI responses were related to CPS at the group level, activation effects (GLM beta values) were averaged for each ROI for each participant and examined at the group level for associations with CPS and white matter volumes. As described below, group level hypothesis testing included a multiple regression analysis predicting mean activation effects from white matter volume and CPS scores after controlling N-back performance level.

NIH Toolbox Cognition Battery Tests

The NIH Toolbox Cognition Battery (NIHTB-CB; http://www.nihtoolbox.org) is one module within the larger NIH Toolbox for the Assessment of Neurological and Behavioral Function. It is a fully computerized battery that was developed to assess cognitive function across the lifespan (ages 3-85). It is available in both English and Spanish, and only requires approximately 30 minutes to administer. The Cognition Battery consists of seven tests measuring five neurocognitive domains, including CPS and EF.

CPS task. The Pattern Comparison subtest of the NIHTB-CB was used in the current study as the measure of CPS. The Pattern Comparison CPS measure was modeled directly on Salthouse's Pattern Comparison Task (Salthouse, Babcock, & Shaw, 1991). During the NIHTB-CB Pattern Comparison Test, participants were asked to identify whether two visual patterns are the "same" or "not the same" via pressing a "yes" or "no" button (Figure 1). Patterns were either identical or varied on one of three dimensions: color, adding/taking something away, or one versus many. Scores reflect the number of correct items (of a possible 130) completed in 90 seconds. The Pattern Comparison Test demonstrates strong convergent (r = .50 to r = .54, all p < .0001) and discriminant (r = .36 to r = .38, all p < .0001) validity and test-retest reliability (ICC = .73 [95% CI: .62, .81]; Carlozzi et al., 2014).

EF task. The DCCS of the NIHTB-CB is a measure of cognitive flexibility, and is similar, but more simple, than other card sorting tasks, like the Wisconsin Card Sorting Task (Heaton et al., 1993). This measure was presented on a touch-screen monitor. Target pictures were presented that vary along two dimensions: shape and color. Participants were asked to match a series of bivalent test pictures (*e.g.,* yellow balls and blue trucks) to the target pictures, first according to one dimension and then, after a number of trials, according to the other dimension (Figure 2). Switch trials were also employed, in which the participant must have changed the dimension being matched. A total of 50 mixed trials were given and scoring was based on a combination of accuracy and reaction time (see Zelazo et al., 2014 for a complete description of scoring procedures). Briefly, a two-vector scoring method combining accuracy and reaction time into one score was utilized to ensure an accurate representation of the participants' cognitive flexibility was captured. That is, both accuracy of the card sort task and the speed with which participants performed these sorts were weighted so an approach favoring

speed over accuracy (or vice versus) did not skew results. The NIHTB-CB DCCS demonstrates adequate to good convergent validity (r = .52 to r = 71, all p < .0001) and good discriminant validity (rs = .06, p = .35 to p = .37. It also shows excellent test-retest reliability (ICC = .81 to .92, all p < .0001; Zelazo et al., 2014). For Aim 3, the generalizability of functional compensatory activity was assessed to address the hypothesis that it may be a result of CPS effects on WM brain activity and other measures of EF. To do this, the relationship between measures of compensatory activity and performance on the NIHTB-CB DCCS was examined.

Statistical Analyses

Aim 1. CPS performance, as measured by the NIHTB-CB Pattern Comparison Test, and whole brain white matter volume were examined for significant correlations with FMRI 2-back accuracy and median reaction time for correct responses. Results were expected to replicate a consistent prior literature and support the premise that people with lower CPS and lower white matter volumes will find EF tasks, including the 2-back, more difficult.

A second analysis examined the correlation between CPS performance and white matter volume. These have exhibited consistent significant associations in prior literature and were used as predictors of compensatory activation in Aim 2. These yielded a preliminary understanding about whether they may serve as independent or common predictors of compensatory activation. That is, large Pearson correlation coefficients between CPS and white matter volume would suggest these indices are highly related and both must be included in statistical modeling in order to capture appropriate variance in WM 2-back brain activation that may not have been captured using just one or the other.

Aim 2. Multiple regression analyses were conducted to examine the associations between CPS performance and white matter volume (predictors) and FMRI brain response in functional

ROIs (criterion) during successful performance of the 2-back task while controlling for 2-back accuracy. The goal was to reveal compensatory effects related to CPS, an intended proxy index of effort. At the group level, overactivations (variance in activation after controlling 2-back accuracy) in the *a priori* ROIs (bilateral PFC and bilateral PPC) were expected.

Aim 3. The ΔR^2 values reflecting the amount of variance accounted for in WM 2-back activation by CPS after controlling for 2-back accuracy were used in a multiple regression model to predict participants' performance on the DCCS of the NIHTB-CB. As ΔR^2 is an effect size estimate, it was ideal for assessing how much or how little the hypothesized CPS might relate to compensatory effect of WM 2-back brain activation after controlling performance level affects and how strongly this activity relates to other EFs. It was predicted that the magnitude of the compensatory activity during WM 2-back (*i.e.,* ΔR^2 for the CPS variable) would be related to scores on the separate tests of EF.

For the Pattern Comparison Task and the DCCS of the NIHTB-CB, age-adjusted scores were used in all analyses. As such, participant age was not included in statistical models as a distinct covariate to avoid over-estimation of age effects.

Power Analyses

A statistical power analysis was performed for sample size estimation for Aims 1 and 2, based on data from Liebel et al. (2017), comparing CPS to an EF composite measure. The effect size in this study was Cohen's $d = .57$ which is considered to be a medium-to-large effect size using Cohen's (1992) criteria. With a two-tailed alpha = .05 and power = .80, the sample size needed for this effect size is approximately $N = 51$ (G*Power 3.1; Faul, Erdfelder, Buchner, & Lang, 2009). Thus, the proposed sample size of $N = 1{,}051$ was more than adequate for these hypotheses. Because of the novelty of Aim 3, there is no prior literature available on how the

relationship between CPS and N-back brain response after controlling performance level generalized to other EFs. However, this large sample size suggests that the current proposal should be able to detect very small effects ($d < .10$) given the same power and alpha parameters.

CHAPTER 3

RESULTS

Preliminary Analyses

Statistical Package for Social Sciences (SPSS 21.0 for Windows, SPSS, Chicago, IL) was used for preliminary and primary data analyses. Demographic characteristics and cognitive performance are displayed in Table 1. The study sample was comprised of adults with above average educational attainment. Pattern Comparison Test and DCCS scores were in the average range. Similarly, 2-back performance accuracy and reaction times were consistent with prior N-back literature (Braver et al., 1997; Smith & Jonides, 1997; Sweet et al., 2008). The distributions of the Pattern Comparison Test (Kolmogorov-Smirnov test: D[1051] = .02, p = .11, DCCS (D[1051] = .04, p = .09), 2-back accuracy (D[1051] = .08, p = .10), 2-back median reaction time (D[1051] = .03, p = .06), and white matter volume (D[1051] = .04, p = .07) were normally distributed.

FMRI Response

Brain response patterns associated with the 2-back at the group level are listed in Table 2 and shown in Figure 3. Results of these whole brain voxel-wise analyses across the sample revealed regions of activation consistent with prior literature, including the bilateral PFC and the bilateral PPC (Owen et al., 2005; Owens, Duda, Sweet, & MacKillop, 2018; Smith & Jonides, 1995; Sweet et al., 2008).

Aim 1

As hypothesized, Pattern Comparison Test performance was significantly correlated with both 2-back performance indices, and these relationships were found to be in the predicted directions (see Table 3). The association between the Pattern Comparison Test and 2-back accuracy was positive and significant (r[1049] = .28, p < .01), indicating that as Pattern Comparison Test performance improved so did 2-back accuracy. Pattern Comparison Test and 2-back median reaction time for correct responses were significantly, negatively related (r[1049] = -.30, p < .01), indicating that as Pattern Comparison Test performance improved the speed of accurate 2-back performance also improved (*i.e.*, reaction time went down). Participant performance on the DCCS, a separate measure of EF, was positively, significantly related to Pattern Comparison Test performance (r[1049] = .41, p < .01). DCCS was also significantly associated with 2-back accuracy (r[1049] = .31, p < .01) and 2-back median reaction time (r[1049] = -.22, p < .01). DCCS was the only measure of cognitive functioning significantly associated with white matter volume (r[1049] = .10, p < .01).

It was further hypothesized that Pattern Comparison Test performance would be significantly, positively related to white matter brain volume, as a significant body of prior research literature has reported such findings. However, results from the current study revealed that, after controlling intracranial volume, Pattern Comparison Test performance was not significantly correlated with total brain white matter volume. Of note, neither 2-back accuracy nor 2-back median reaction time was significantly associated with white matter volume (Table 3).

Aim 2

Following quantification of significant brain response to the 2-back (controlling 0-back), mean intensity effects were summarized by ROI (*i.e.*, left PFC, right PFC, left PPC, right PPC;

Table 4). Participants' mean 2-back activation effects in the left PFC were not significantly predicted by Pattern Comparison Test performance or white matter volume after controlling 2-back performance level, (R^2 = .09, F(4,1047) = .414, p = .60; Table 5). Similarly, neither Pattern Comparison Test performance nor white matter volume significantly predicted 2-back activation effects in the right PFC, (R^2 = .04, F(4,1047) = 1.20, p = .31; Table 6). Activation effects within the left PPC were not significantly predicted by Pattern Comparison Test performance or white matter volume after controlling 2-back performance level, (R^2 = .04, F(4,1047) = 1.14, p = .34; Table 7). Right PPC activation was similarly not predicted by Pattern Comparison Test performance or white matter volume, (R^2 = .00, F(4,1047) = 0.55, p = .70; Table 8).

Aim 3

As reported above, analyses revealed no significant compensatory effects of Pattern Comparison Test performance on 2-back activation. Thus, the ΔR^2 value of Pattern Comparison Test performance predicting 2-back activation were zero and their use in predicting how much or how little they contribute to the prediction of performance on another measure of EF (*i.e.*, the NIHTB-CB DCCS) was not performed.

CHAPTER 4

DISCUSSION

The present study investigated the potential roles that a behavioral measures of CPS and white matter volume play in WM performance among a very large sample of healthy adults. The experimental design capitalized on the sensitivity of CPS as a behavioral marker of individual differences in cognitive function and the use of FMRI to detect individual differences in brain function before they are apparent in behavior. It was hypothesized that CPS performance levels would reflect a compensatory effect on FMRI WM brain activation patterns after WM performance was controlled because it is an independent marker of effort needed to perform the N-back. The current study had three Aims. First, the relationships between CPS, white matter volume, and performance on the N-back WM task were measured. Second, it was predicted that CPS and white matter volume could each be used to gauge the effort required to successfully perform the N-back, and therefore might be a useful marker of compensatory brain activation during this task. Third, if evidence linking CPS or white matter volume to compensatory activation were supported, Aim 3 was to examine variance in another measure of EF to address convergent validity.

Hypothesis 1 was partially supported. Results from these analyses indicated that CPS was significantly related to WM accuracy and reaction time and these associations were in expected directions. That is, as CPS increased, the number of accurate WM responses increased and the speed of correct responses to the WM paradigm decreased, indicating more efficient and rapid decision making. These findings are consistent with a sizeable research literature that includes

similar positive relationships among several different measures of CPS and WM function in healthy adult populations (Albinet, Boucard, Bouquet, & Audiffren, 2012; Ebaid et al., 2017; Kelleher et al., 2013; Magistro et al., 2015; Schretlen, Pearlson, Anthony, & Aylward, 2000). However, white matter volume was not significantly associated with N-back performance, as had been predicted. This finding is not consistent with prior literature that has found significant, positive correlations between white matter volume and measures of WM (Takeuchi et al., 2011) and might be explained by the use of a whole brain metric of white matter volume in the current study rather than regional white matter volumes. However, the critical role of white matter volume in the performance of other aspects of EF was identified in the current study. The significant, positive relationship found between white matter volume and the DCCS, a measure of cognitive flexibility, reflects the relationship between white matter and higher-order EF more broadly. Prior research has suggested that, even among "young" adults similar in age to the current study sample, white matter volume mediates the successful performance of EF tasks (Brickman et al., 2006). Thus, current study findings and those from prior research indicate that white matter volume is integral to the successful completion of EF tasks prior to the onset of disease or aging processes.

Another possible explanation for mixed support for Hypothesis 1 is that Hypothesis 2 was not supported; the expected inverse relationship between CPS and white matter volume was not found. These findings were unexpected given the significant associations reported between these variables in previous research studies (Madden et al., 2009; Turken et al., 2008). As the current study measured CPS and white matter volume in a large sample, there was excellent statistical power to detect even small effects. A possible explanation for why there was no relationship between CPS and white matter is that this sample of young, healthy adults may

possess a distinct "CPS ability" that does not yet rely as heavily on white matter volume as occurs in aging and various disease processes.

Aim 2 was the quantification of compensatory activation during WM performance. Findings from Hypothesis 3 revealed that neither CPS nor white matter volume were associated with WM brain activation, as would be expected were they indices of effort. After statistically controlling WM performance accuracy in order to reveal unexpected compensatory response and participant education, the amount of variance explained in WM activation was virtually zero in each *a priori* ROI (see Tables 5-8). These findings suggest CPS was not responsible for the maintenance of WM abilities in this sample. Such null results are particularly surprising in the bilateral PFC *a priori* ROI. Frontal regions are especially critical in the performance of both CPS and WM, which suggests WM activation in these regions would have demonstrated an association with CPS. Because Aim 2 was not supported and effects sizes were nearly zero, Hypothesis 4 was not tested. The purpose of Aim 3 was to assess how much or how little the hypothesized compensatory activity of CPS generalized to other, non-WM, measures of EF. As noted, this Aim was not supported, as no compensatory activity was found. The DCCS task of the NIHTB-CB measures cognitive flexibility and requires rapid decision-making processes similar to some CPS tasks. It was hypothesized that CPS compensatory effects would explain a significant amount of performance variance in this measure as well. As the ΔR^2 values reflecting the amount of variance accounted for in WM N-back activation by CPS were zero (0), statistical analysis of these questions were not able to be carried out.

This was the first study to investigate potential WM compensatory activation as indexed by putative measures of difficulty and effort, specifically behavioral CPS performance and white matter volume. It was a novel attempt to determine whether the *processing speed theory*

(Salthouse 1996) might be extended to a large sample of healthy younger adults. Results do not support this extension. Indeed, the *processing speed theory* suggests that CPS should been an excellent choice for an index of compensatory WM brain activation because of the strong covariance between the two cognitive functions (Jensen, 1992; Nebes et al., 2000; Salthouse, 1994, 1996). Without the predicted compensatory effects on WM brain activation, it appears some other variable not included in the current study (*e.g.*, grey matter, another cognitive function) may assist in explaining participants' WM brain activity.

Current findings also suggest a different mechanism of action than what might be explained by the *relative consequence model* or the *independent consequence model* (DeLuca et al., 2004). Because participant performance on measures of WM and CPS were within expected ranges, neither would have inhibited nor propagated the other as suggested in these models.

A potential explanation for the lack of explanatory power of CPS may the use of age-adjusted scores. As described previously, CPS is sensitive to the effects of age and often used as a behavioral marker of cognitive change (Schaie, 2005). By controlling individual differences related to age, these known effects on the NIHTB-CB measure of CPS, one of the factors driving the effect that CPS was meant to capture may have been removed from the analyses. That is, the use of age-adjusted scores may have removed a substantial proportion of the variance responsible for compensatory activity.

Limitations

The current study requires consideration in light of several limitations. First, the study sample was young (*M*age = 28.77 years), performed the CPS, WM, and DCCS in the average range, and was well-educated, which poses potential problems with generalizability. Similarly, participants in the sample likely possessed optimal white matter volume as they were free of

germane disease processes or normal aging effects. As such, the index of white matter volume used may not have been sensitive enough or possessed sufficient variance to detect white matter effects on WM brain activation patterns. Prior research on the influence of regional white matter volume on neuropsychological functioning indicates there may exist differential effects of specific white matter regions on certain neuropsychological functions (Brickman et al., 2006). Related, the current study utilized a volumetric index of white matter that may be less sensitive to individual differences in white matter integrity than other measures, including those provided by diffusion tensor imaging.

Future Directions

The relationship between white matter volume and measures of cognitive functioning in this sample warrants additional investigation. Rather than using a single, whole-brain measure of white matter volume, future research may investigate the possible differential effects of white matter volume by hemisphere or smaller brain regions. The current study utilized mean activation intensities (expressed as beta values) to measure compensatory activation. Future research may also include volumetric quantification of significant task-related voxels in ROI to measure this construct. This approach is well-suited for examination of unexpected recruitment, rather than the compensatory increases in intensity examined in the current study.

A better understanding of factors that may influence compensatory activation processes in healthy adults may aide future research. For example, sociological and cultural factors such as education, occupational complexity, social activity, and physical exercise have been linked to maintenance of cognitive function in aging (Katzman, 1993; Stern, 2012). However, the effects of these factors on non-aged, healthy adults are, understandably, less well-known and understudied.

Future research may also include measurement of brain deactivations as a variable of interest when assessing potential compensatory effects in WM. For instance, a bilateral "default network" of anterior and posterior cortices has been described that is most active at rest and relatively deactivated during task performance, presumably because its suppression enables successful cognitive performance (Raichle et al., 2001). As the current study found no evidence of compensatory activity linked to a CPS index of ability and presumed effort, the inclusion of default network regions may capture compensatory WM N-back brain activation after performance has been controlled.

REFERENCES

Albinet, C. T., Boucard, G., Bouquet, C. A., & Audiffren, M. (2012). Processing speed and executive functions in cognitive aging: How to disentangle their mutual relationship? *Brain and Cognition, 79*, 1-11. doi:10.1016/j.bandc.2012.02.001

Awh, E., Jonides, J., Smith, E. E., Schumacher, E. H., Koeppe, R. A., & Katz, S. (1996). Dissociation of storage and rehearsal in verbal working memory: Evidence from positron emission tomography. *Psychological Science, 7*(1), 25-31. doi:10.1111/j.1467-9280.1996.tb00662.x

Baddeley, A. (1998). Working memory. *Comptes Rendus de L'Académie des Sciences-Series III-Sciences de la Vie, 321*(2-3), 167-173. doi:10.1016/S0764-4469(97)89817-4

Barch, D. M., Burgess, G. C., Harms, M. P., Petersen, S. E., Schlaggar, B. L., Corbetta, M., . . . Van Essen, D. C. (2013). Function in the human connectome: Task-fMRI and individual differences in behavior. *NeuroImage, 80*, 169-189. doi:10.1016/j.neuroimage.2013.05.033

Bartzokis, G., Lu, P. H., Geschwind, D., Tingus, K., Huang, D., Mendez, M. F., . . . Mintz, J. (2007). Apolipoprotein E affects both myelin breakdown and cognition: Implications for age-related associations of decline into dementia. *Biological Psychiatry, 62*(12), 1380-1387. doi:10.1016/j.biopsych.2007.03.024

Birren, J. E., & Fisher, L. M. (1995). Aging and speed of behavior: Possible consequences for psychological functioning. *Annual Review of Psychology, 46*, 329-353. doi:10.1146/annurev.ps.46.020195.001553

Braver, T. S., Cohen, J. D., Nystrom, L. E., Jonides, J., Smith, E. E., & Noll, D. C. (1997). A parametric study of prefrontal cortex involvement in human working memory. *NeuroImage, 5*(1), 49-62. doi:10.1006/nimg.1996.0247

Breteler, M. M. B., van Swieten, J. C., Bots, M. L., Grobbee, D. E., Claus, J. J., van den Hout, J. H. W., . . . Hofman, A. (1994). Cerebral white matter lesions, vascular risk factors, and cognitive function in a population-based study. *Neurology, 44*(7), 1246. doi:10.1212/WNL.44.7.1246

Brickman, A. M., Zimmerman, M. E., Paul, R. H., Grieve, S. M., Tate, D. F., Cohen, R. A., . . . Gordon, E. (2006). Regional white matter and neuropsychological functioning across the adult lifespan. *Biological Psychiatry, 60*(5), 444-453. doi:10.1016/j.biopsych.2006.01.011

Bookheimer, S. Y., Strojwas, M. H., Cohen, M. S., Saunders, A. M., Pericak-Vance, M. A., Mazziotta, J. C., & Small, G. W. (2000). Patterns of brain activation in people at risk for Alzheimer's disease. *New England Journal of Medicine, 34*(7), 450-456. doi:10.1056/NEJM200008173430701

Bucur, B., Madden, D. J., Spaniol, J., Provenzale, J. M., Cabeza, R., White, L. E., . . . Huettel, S. A. (2008). Age-related slowing of memory retrieval: Contributions of perceptual speed and cerebral white matter integrity. *Neurobiology of Aging, 29*(7), 1070-1079. doi:10.1016/j.neurobiolaging.2007.02.008

Cabeza, R., & Nyberg, L. (2000). Imaging cognition II: An empirical review of 275 PET and fMRI studies. *Journal of Cognitive Neuroscience, 12*(1), 1-47. doi:10.1162/08989290051137585

Cabeza, R., Nyberg, L., & Park, D. C. (2005). Cognitive neuroscience of aging: Emergence of a new discipline. In R. Cabeza, L. Nyberg, & D. Park (Eds.), *Cognitive neuroscience of aging: Linking cognitive and cerebral aging* (pp. 3-15). New York, NY: Oxford University Press.

Carlozzi, N. E., Tulsky, D. S., Chiaravalloti, N. D., Beaumont, J. L., Weintraub, S., Conway, K., & Gershon, R. C. (2014). NIH Toolbox Cognitive Battery (NIHTB-CB): The NIHTB Pattern Comparison Processing Speed Test. *Journal of the International Neuropsychological Society, 20*(6), 630-641. doi:10.1017/S1355617714000319

Cattell, J. McK. (1890). Mental tests and measurements. *Mind, 15*(59), 373-381. doi:10.1093/mind/os-XV.59.373

Chariet, K., Beck, A., Jorde, A., Wimmer, L., Vollstädt-Klein, S., Gallinat, J., . . . Heinz, A. (2014). Increased neural activity during high working memory load predicts low relapse risk in alcohol dependence. *Addiction Biology, 19*(3), 402-414. doi:10.1111/adb.12103

Charlton, R. A., Barrick, T. R., McIntyre, D. J., Shen, Y., O'Sullivan, M., Howe, F. A., . . . & Markus, H. S. (2006). White matter damage on diffusion tensor imaging correlates with age-related cognitive decline. *Neurology, 66*(2), 217-222. doi:10.1212/01.wnl.0000194256.15247.83

Charlton, R. A., Landau, S., Schiavone, F., Barrick, T. R., Clark, C. A., Markus, H. S., & Morris, R. G. (2008). A structural equation modeling investigation of age-related variance in executive function and DTI measured white matter damage. *Neurobiology of Aging, 29*(10), 1547-1555. doi:10.1016/j.neurobiolaging.2007.03.017

Cohen, J. (1992). A power primer. *Quantitative Methods in Psychology, 112*(1), 155-159.

Cole, D. A., & Maxwell, S. E. (2003). Testing mediational models with longitudinal data: Myths and tips in the use of structural equation modeling. *Journal of Abnormal Psychology, 112*, 558-577. doi:10.1037/0021-843X.112.4.558

Conklin, H. M., Luciana, M., Hooper, C. J., & Yarger, R. S. (2007). Working memory performance in typically developing children and adolescents: Behavioral evidence of protracted frontal lobe development. *Developmental Neuropsychology, 31*(1), 103-128. doi:10.1080/87565640709336889

Conway, A. R. A., Cowan, N., Bunting, M. F., Therriault, D. J., & Minkoff, S. R. B. (2002). A latent variable analysis of working memory capacity, short term memory capacity, processing speed, and general fluid intelligence. *Intelligence, 30*(2), 163-183. doi:10.1016/S0160-2896(01)00096-4

Conway, A. R., Kane, M. J., & Engle, R. W. (2003). Working memory capacity and its relation to general intelligence. *Trends in Cognitive Sciences, 7*(12), 547-552. doi:10.1016/j.tics.2003.10.005

Cox, R. W. (1996). AFNI: Software for analysis and visualization of functional magnetic resonance neuroimages. *Computational Biomedical Research, 29*(3), 162-173. doi:10.1006/cbmr.1996.0014

Curtis, C. E., & D'Esposito, M. (2003). Persistent activity in the prefrontal cortex during working memory. *Trends in Cognitive Sciences, 7*(9), 415-423. doi:10.1016/S1364-6613(03)00197-9

Cutter, G. R., Baier, M. L., Rudick, R. A., Cookfair, D. L., Fischer, J. S., Petkau, J., . . . Willoughby, E. (1999). Development of a multiple sclerosis functional composite as a clinical trial outcome measure. *Brain, 122*(5), 871-882. doi:10.1093/brain/122.5.871

Dale, A. M., Fischl, B., & Sereno, M. I. (1999). Cortical surface-based analysis: I. Segmentation and surface reconstruction. *NeuroImage, 9*(2), 179-194. doi:10.1006/nimg.1998.0395

Darki, F., & Klingberg, T. (2015). The role of fronto-parietal and fronto-striatal networks in the development of working memory: A longitudinal study. *Cerebral Cortex, 25*(6), 1587-1595. doi:10.1093/cercor/bht352

Deary, I. J., Bastin, M. E., Pattie, A., Clayden, J. D., Whalley, L. J., Starr, J. M., & Wardlaw, J. M. (2006). White matter integrity and cognition in childhood and old age. *Neurology, 66*(4), 505-512. doi:10.1212/01.wnl.0000199954.81900

Deary, I. J., Der, G., & Ford, G. (2001). Reaction times and intelligence differences: A population-based cohort study. *Intelligence, 29*(5), 389-399. doi:10.1016/S0160-2896(01)00062-9

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

Donders, J., Tulsky, D. S., & Zhu, J. (2001). Criterion validity of new WAIS-II subtest scores after traumatic brain injury. *Journal of the International Neuropsychological Society, 7*(7), 892-898.

Dow, C., Seidenberg, M., & Hermann, B. (2004). Relationship between information processing speed in temporal lobe epilepsy and white matter volume. *Epilepsy & Behavior, 5*(6), 919-925. doi:10.1016/j.yebeh.2004.08.007

Downing, P. E., Jiang, Y., Shuman, M., & Kanwisher, N. (2001). A cortical area selective for visual processing of the human body. *Science, 293*(5539), 2470-2473. doi:10.1126/science.1063414

Duering, M., Gonik, M., Malik, R., Zieren, N., Reyes, S., Jouvent, E., . . . Dichgans, M. (2013). Identification of a strategic brain network underlying processing speed deficits in vascular cognitive impairment. *Neuroimage, 66,* 177-183. doi:10.1016/j.neuroimage.2012.10.084

Duncan, J., & Owen, A. M. (2000). Common regions of the human frontal lobe recruited by diverse cognitive demands. *Trends in Neurosciences, 23*(10), 475-483. doi:10.1016/S0166-2236(00)01633-7

Ebaid, D., Crewther, S. G., MacCalman, K., Brown, A., & Crewther, D. P. (2017). Cognitive processing speed across the lifespan: Beyond the influence of motor speed. *Frontiers in Aging Neuroscience, 9*(62). doi:10.3389/fnagi.2017.00062

Eckert, M. A. (2011). Slowing down: Age-related neurobiological predictors of processing speed. *Frontiers in Neuroscience, 5*(25). doi:10.3389/fnins.2011.00025

Engle, R. W., Kane, M. J., & Tuholski, S. W. (1999). Individual differences in working memory capacity and what they tell us about controlled attention, general fluid intelligence, and functions of the prefrontal cortex. In A. Miyake & P. Shah (Eds.), *Models of Working Memory: Mechanisms of active maintenance and executive control* (pp. 102-134). Cambridge, MA: Cambridge University Press.

Engle, R. W., Tuholski, S. W., Laughlin, J. E., & Conway, A. R. A. (1999). Working memory, short-term memory, and general fluid intelligence: A latent-variable approach. *Journal of Experimental Psychology: General, 128*(3), 309-331. doi:10.1037/0096-3445.128.3.309

Faul, F., Erdfelder, E., Buchner, A., & Lang, A. -G. (2009). Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses. *Behavior Research Methods, 41*(4), 1149-1160. doi:10.3758/BRM.41.4.1149

Felleman, D. J., & Van Essen, D. C. (1991). Distributed hierarchical processing in the primate cerebral cortex. *Cerebral Cortex, 1*(1), 1-47. doi:10.1093/cercor/1.1.1

Finkel, S. I., Mintzer, J. E., Dysken, M., Krishnan, K. R. R., Burt, T., & McRae, T. (2004). A randomized, placebo-controlled study of the efficacy and safety of sertraline in the treatment of the behavioral manifestations of Alzheimer's disease in outpatients treated with donepezil. *International Journal of Geriatric Psychiatry, 19*, 9-18. doi:10.1002/gps.998

Finkel, D., Reynolds, C., McArdle, J. J., Stewart, W. F., & Schwartz, B. S. (2005). Multivariate modeling of age and retest in longitudinal studies of cognitive abilities. *Psychology and Aging, 20*, 412-422. doi:10.1037/0882-7974.20.3.412

Finkel, D., Reynolds, C. A., McArdle, J. J., & Pedersen, N. L. (2007). Age changes in processing speed as a leading indicator of cognitive aging. *Psychology and Aging, 22*, 558-568. doi:10.1037/0882-7974.22.3.558

Fischl, B., Sereno, M. I., & Dale, A. M. (1999a). Cortical surface-based analysis. II: Inflation, flattening, and a surface-based coordinate system. *NeuroImage, 9*(2), 195-207. doi:10.1006/nimg.1998.0396

Fischl, B., Sereno, M. I., Tootell, R. B., & Dale, A. M. (1999). High-resolution intersubject averaging and a coordinate system for the cortical surface. *Human Brain Mapping, 8*(4), 272-284.

Fischl, B., Salat, D. H., van der Kouwe, A. J., Makris, N., Segonne, F., Quinn, B. T., & Dale, A. M. (2004). Sequence-independent segmentation of magnetic resonance images. *NeuroImage, 23*(Suppl 1), S69-S84. doi:10.1016/j.neuroimage.2004.07.016

Forn, C., Ripolles, P., Cruz-Gomez, A. J., Belenguer, A., Gonzalez-Torre, J. A., & Avila, C. (2013). Task-load manipulation in the Symbol Digit Modalities Test: An alternative measure of information processing speed. *Brain and Cognition, 82*(2), 152-160. doi:10.1016/j.bandc.2013.04.003

Fox, C. J., Iaria, G., & Barton, J. J. S. (2009). Defining the face processing network: Optimization of the functional localizer in fMRI. *Human Brain Mapping, 30*(5), 1637-1651. doi:10.1002/hbm.20630

Fry, A. F., & Hale, S. (1996). Processing speed, working memory, and fluid intelligence: Evidence for a developmental cascade. *Psychological Science, 7*(4), 237-241. doi:10.1111/j.1467-9280.1996.tb00366.x

Fuster, J. M. (2001). The prefronal cortex—an update: Time is of the essence. *Neuron, 30*(2), 319-333. doi:10.1016/S0896-6273(01)00285-9

Genova, H. M., Hillary, F. G., Wylie, G., & Rypma, B. (2009). Examination of processing speed deficits in multiple sclerosis using functional magnetic resonance imaging. *Journal of the International Neuropsychological Society, 15*(3), 383-393. doi:10.1017/S1355617709090535

Giedd, J. N. (2004). Structural magnetic resonance imaging of the adolescent brain. *Annals of the New York Academy of Science, 1021*, 77-85. doi:10.1196/annals.1308.009

Giedd, J. N., Lalonde, F. M., Celano, M. J., White, S. L., Wallace, G. L., Lee, N. R., & Lenroot, R. K. (2009). Anatomical brain magnetic resonance imaging of typically developing children and adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry, 48*(5), 465-470. doi:10.1097/CHI.0b013e31819f2715

Glasser, M. F., Sotiropoulos, S. N., Wilson, J. A., Coalson, T. S., Fischl, B., Andersson, J. L., . . . Jenkinson, M. (2013). The minimal preprocessing pipelines for the Human Connectome Project. *NeuroImage, 80*(15), 105-124. doi:10.1016/j.neuroimage.2013.04.127

Goldman-Rakic, P. S. (1988). Topography of cognition: Parallel distributed networks in primate association cortex. *Annual Review of Neuroscience, 11*, 137-156. doi:10.1146/annurev.ne.11.030188.001033

Gottsdanker, R. (1982). Age and simple reaction time. *Journal of Gerontology, 37*(3), 342-348.

Gronwall, D. (1977). Paced Auditory Serial-Addition Task: A measure of recovery from concussion. *Perceptual and Motor Skills, 44*, 367-373.

Grudnik, J. L., & Kranzler, J. H. (2001). Meta-analysis of the relationship between intelligence and inspection time. *Intelligence, 29*(6), 523-535. doi:10.1016/S0160-2896(01)00078-2

Haász, J., Westlye, E. T., Fjaer, S., Espeseth, T., Lundervold, A., & Lundervold, A. J. (2013). General fluid-type intelligence is related to indices of white matter structure in middle-aged and old adults. *NeuroImage, 83*, 372-383. doi:10.1016/j.neuroimage.2013.06.040

Heaton, R. K., Chelune, G. J., Talley, J. L., Kay, G. G., & Curtiss, G. (1993). Wisconsin Card Sorting Test manual. Odessa, FL: Psychological Assessment Resources, Inc.

Hertzog, C., Dixon, R. A., Hultsch, D. F., & MacDonald, S. W. S. (2003). Latent change models of adult cognition: Are changes in processing speed and working memory associated with changes in episodic memory? *Psychology and Aging, 18*, 755-769. doi:10.1037/0882-7974.18.4.755

Hilgetag, C. C., Burns, G. A., O'Neill, M. A., Scannell, J. W., & Young, M. P. (2000). Anatomical connectivity defines the organization of clusters of cortical areas in the

macaque monkey and the cat. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences, 355*(1393), 91-110. doi:10.1098/rstb.2000.0551

Hofer, S., Flaherty, B. P., & Hoffman, L. (2006). Cross-sectional analysis of time-dependent data: Problems of mean-induced association in age-heterogenous samples and an alternative method based on sequential narrow age-cohorts. *Multivariate Behavioral Research, 41*, 165-187. doi:10.1207/s15327906mbr4102_4

Hofer, S. M., & Sliwinksi, M. J. (2001). Understanding ageing: An evaluation of research designs for assessing the interdependence of ageing-related changes. *Gerontology, 47*, 341-352. doi:10.1159/000052825

Hultsch, D. F., Hertzog, C., Small, B. J., McDonald-Miszczak, L., & Dixon, R. A. (1992). Short-term longitudinal change in cognitive performance in later life. *Psychology and Aging, 7*, 571-584. doi:10.1037/0882-7974.7.4.571

Jaeggi, S. M., Buschkuehl, M., Etienne, A., Ozdoba, C., Perrig, W. J., & Nirkko, A. C. (2007). On how high performers keep cool brain in situations of cognitive overload. *Cognitive, Affective, & Behavioral Neuroscience, 7*(2), 75-89. doi:10.3758/CABN.7.2.75

Jensen, A. R. (1992). The importance of intraindividual variability in reaction time. *Personality and Individual Differences, 13*(8), 869-881. doi:10.1016/0191-8869(92)90004-9

Kail, R. (1998). Speed of information processing in patients with multiple sclerosis. *Journal of Clinical and Experimental Neuropsychology, 20*(1), 98-106.

Kail, R., & Salthouse, T. A. (1994). Processing speed as a mental capacity. *Acta Psychologica, 86*(2-3), 199-225.

Katzman, R. (1993). Education and the prevalence of dementia and Alzheimer's disease. *Neurology, 43*(1), 13-20. doi:10.1212/WNL.43.1_Part_1.13

Kelleher, I., Murtagh, A., Clarke, M. C., Murphy, J., Rawdon, C., & Cannon, M. (2013). Neurocognitive performance of a community-based sample of young people at putative ultra high risk for psychosis: Support for the processing speed hypothesis. *Cognitive Neuropsychiatry, 18*(1-2), 9-25. doi:10.1080/13546805.2012.682363

Kennedy, K. M., & Raz, N. (2009). Aging white matter and cognition: Differential effects of regional variations in diffusion properties on memory, executive functions, and speed. *Neuropsychologia, 47*(3), 916-927. doi:10.1016/j.neuropsychologia.2009.01.001

Kötter, R., & Sommer, F. T. (2000). Global relationship between anatomical connectivity and activity propagation in the cerebral cortex. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences, 355*(1393), 127-134. doi:10.1098/rstb.2000.0553

Kung, C. C., & Peissig, J. J., & Tarr, M. J. (2007). Is region-of-interest overlap comparison a reliable measure of category specificity? *Journal of Cognitive Neuroscience, 19*(12), 2019-2034. doi:10.1162/jocn.2007.19.12.2019

Kuznetsova, K. A., Maniega, S. M., Ritchie, S. J., Cox, S. R., Storkey, A. J., Starr, J. M., . . . Bastin, M. E. (2016). Brain white matter structure and information processing speed in healthy older age. *Brain Structure & Function, 221*(6), 3223-3235. doi:10.1007/s00429-015-1097-5

Lemke, U., & Zimprich, D. (2005). Longitudinal changes in memory performance and processing speed in old age. *Aging, Neuropsychology, and Cognition, 12*(1), 57-77. doi:10.1080/13825580590925116

Levine, B., Fujiwara, E., O'Connor, C., Richard, N., Kovacevic, N., Mandic, M., . . . Black, S. E. (2006). In vivo characterization of traumatic brain injury neuropathology with structural

and functional neuroimaging. *Journal of Neurotrauma, 23*(10), 1396-1411. doi:10.1089/neu.2006.23.1396

Liebel, S. W., Jones, E. C., Oshri, A., Hallowell, E. S., Jerskey, B. A., Gunstad, J., & Sweet, L. H. (2017). Cognitive processing speed mediates the effects of cardiovascular disease on executive functioning. *Neuropsychology, 31*(1), 44-51. doi:10.1037/neu0000324

Liebel, S. W., & Sweet, L. H. (2019). Effects of cardiovascular disease and related risk factors on neurocognition. In R. A. Stern & M. L. Alosco (Eds.), *The Oxford Handbook of Adult Cognitive Disorders* (pp. 84-116). New York, NY: Oxford University Press.

Lindenberger, U., & Pötter, U. (1998). The complex nature of unique and shared effects in hierarchical linear regression: Consequences for cross-sectional developmental research. *Psychological Methods, 3*, 218-230. doi:10.1037/1082-989X.3.2.218

Lu, P. H., Lee, G. J., Raven, E. P., Tingus, K., Khoo, T., Thompson, P. M., & Bartzokis, G. (2011). Age-related slowing in cognitive processing speed is associated with myelin integrity in a very health elderly sample. *Journal of Clinical and Experimental Neuropsychology, 33*(10), 1059-1068. doi:10.1080/13803395.2011.595397

MacDonald, S. W. S., Hultsch, D. F., Strauss, E., & Dixon, R. A. (2003). Age-related slowing of Digit Symbol Substitution revisited: What do longitudinal age changes reflect? *The Journal of Gerontology: Series B: Psychological Sciences and Social Sciences, 58*, 187-194. doi:10.1093/geronb/58.3.P187

MacPherson, S. E., Cox, S. R., Dickie, D. A., Karama, S., Starr, J. M., Evans, A. C., . . . Deary, I. J. (2017). Processing speed and the relationship between Trail Making Test-B performance, cortical thinning and white matter microstructure in older adults. *Cortex, 95*, 92-103. doi:10.1016/j.cortex.2017.07.021

Madden, D. J., Spaniol, J., Costello, M. C., Bucur, B., White, L. E., Cabeza, R., . . . Heuttel, S. A. (2009). Cerebral white matter integrity mediates adult age differences in cognitive performance. *Journal of Cognitive Neuroscience, 21*(2), 289-302. doi:10.1162/jocn.2009.21047

Magistro, D., Takeuchi, H., Kashkouli Nejad, K., Taki, Y., Sekiguchi, A., Nouchi, R., . . . Kawashima, R. (2015). The relationship between processing speed and regional white matter volume in healthy young people. *PLoSONE, 10*(9), e0136386. doi:10.1371/journal.pone.0136386

Marcus, D. S., Harms, M. P., Snyder, A. Z., Jenkinson, M., Wilson, J. A., Glasser, M. F., . . . Van Essen, D. C. (2013). Human Connectome Project informatics: Quality control, database services, and data visualization. *NeuroImage, 80,* 202-219. doi:10.1016/j.neuroimage.2013.05.077

Marner, L., Nyengaard, J. R., Tang, Y., & Pakkenberg, B. (2003). Marked loss of myelinated nerve fibers in the human brain with age. *Journal of Comparative Neurology, 462*(2), 144-152. doi:10.1002/cne.10714

Mathias, J. L., & Wheaton, P. (2007). Changes in attention and information-processing speed following severe traumatic brain injury: A meta-analytic review. *Neuropsychology, 21*(2), 212-223. doi:10.1037/0894-4105.21.2.212

Maxwell, S. E., & Cole, D. A. (2007). Bias in cross-sectional analyses of longitudinal mediation. *Psychological Methods, 12,* 23-44. doi:10.1037/1082-989X.12.1.23

Maxwell, S. E., Cole, D. A., & Mitchell, M. A. (2011). Bias in cross-sectional analyses of longitudinal mediation: Partial and complete mediation under an autoregressive model. *Multivariate Behavioral Research, 46,* 816-841. doi:10.1080/00273171.2011.606716

Mendelson, J. R., & Ricketts, C. (2001). Age-related temporal processing speed deterioration in auditory cortex. *Hearing Research, 158*(1-2), 84-94. doi:10.1016/S0378-5955(01)00294-5

Mesulam, M. M. (1998). From sensation to cognition. *Brain, 121*(6), 1013-1052. doi:10.1093/brain/121.6.1013

Mesulam, M. M. (2000). Brain, mind, and the evolution of connectivity. *Brain and Cognition, 42*(1), 4-6. doi:10.1006/brcg.1999.1145

Miller, G. A., Galanter, E., Pribham, K. H. (1960). *Plans and the Structure of Behavior*. New York, NY: Holt, Rinehart & Winston.

Nebes, R. D., Butters, M. A., Mulsant, B. H., Pollock, B. G., Zmuda, M. D., Houck, P. R., Reynolds, C. F. (2000). Decreased working memory and processing speed mediate cognitive impairment in geriatric depression. *Psychological Medicine, 30*(3), 679-91.

Nee, D. E., Brown, J. W., Askren, M. K., Berman, M. G., Demiralp, E., Krawitz, A., & Jonides, J. (2013). A meta-analysis of executive components of working memory. *Cerebral Cortex, 23*(2), 264-282. doi:10.1093/cercor/bhs007

Neuroimaging Tools and Resources Collaboratory. (n.d.). Retrieved from https://www.nitrc.org/projects/dcm2nii/

Østby, Y., Tamnes, C. K., Fjell, A. M., & Walhovd, K. B. (2011). Morphometry and connectivity of the fronto-parietal verbal working memory network in development. *Neuropsychologia, 49*(14), 3854-3862. doi:10.1016/j.neuropsychologia.2011.10.001

O'Sullivan, M., Jones, D. K., Summers, P. E., Morris, R. G., Williams, S. C. R., & Markus, H. S. (2001). Evidence for cortical "disconnection" as a mechanism of age-related cognitive decline. *Neurology, 57*(4), 632-638. doi:10.1212/WNL.57.4.632

Owen, A. M., McMillan, K. M., Laird, A. R., & Bullmore, E. (2005). N-back working memory paradigm: A meta-analysis of normative functional neuroimaging studies. *Human Brain Mapping, 25*(1), 46-59. doi:10.1002/hbm.20131

Owens, M. M., Duda, B., Sweet, L. H., & MacKillop, J. (2018). Distinct functional and structural neural underpinnings of working memory. *NeuroImage, 174*, 463-471. doi:10.1016/j.neuroimage.2018.03.022

Parmenter, B. A., Shucard, J. L., Benedict, R. H. B., & Shucard, D. W. (2006). Working memory deficits in multiple sclerosis: Comparison between the N-back task and the Paced Auditory Serial Addition Test. *Journal of the International Neuropsychological Society, 12*(5), 677-687. doi:10.1017/S1355617706060826

Parmenter, B. A., Shucard, J. L., & Shucard, D. W., (2007). Information processing deficits in multiple sclerosis: A matter of complexity. *Journal of the International Neuropsychological Society, 13*(3), 417-423. doi:10.1017/S1355617707070580

Peelen, M. V., & Downing, P. E. (2005). Within-subject reproducibility of category-specific visual activation with functional MRI. *Human Brain Mapping, 25*(4), 402-408. doi:10.1002/hbm.20116

Stotesbury, H., Kirkham, F. J., Kolbel, M., Balfour, P., Clayden, J. D., Sahota, S., . . . Kawadler, J. M. (2018). White matter integrity and processing speed in sickle cell anemia. *Neurology, 90*(23), e2042-e2050. doi:10.1212/WNL.0000000000005644

Verhaeghen, P., Salthouse, T. A. (1997). Meta-analyses of age-cognition relations in adulthood: Estimates of linear and non-linear age effects and structural models. *Psychological Bulletin, 122*(3), 231-249. doi:10.1037/0033-2909.122.3.231

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 of the United States of America, 98*(2), 676-682. doi:10.1073/pnas.98.2.676

Rao, S. M. (1995). Neuropsychology of multiple sclerosis. *Current Opinion in Neurology, 8*(3), 216-220.

Rao, S. M. (1996). White matter disease and dementia. *Brain and Cognition, 31*(2), 250-268. doi:10.1006/brcg.1996.0044

Reuter-Lorenz, P. A. & Park, D. C. (2010). Human neuroscience and the aging mind: A new look at old problems. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences, 65B*(4), 405-415. doi:10.1093/geronb/gbq035

Robitaille, A., Piccinin, A. M., Muniz-Terrera, G., Hoffman, L., Johansson, B., Deeg, D. J. H., . . . Hofer, S. M. (2013). Longitudinal mediation of processing speed on age-related change in memory and fluid intelligence. *Psychology and Aging, 28*(4), 887-901. doi:10.1037/a0033316

Rottschy, C., Langner, R., Dogan, I., Reetz, K., Laird, A. R., Schulz, J. B., . . Eickhoff, S. B. (2012). Modelling neural correlates of working memory: A coordinate-based meta-analysis. *NeuroImage, 60*, 830-846. doi:10.1016/j.neuroimage.2011.11.050

Rypma, B., & Prabhakaran, V. (2009). When less is more and when more is more: The mediating roles of capacity and speed in brain-behavior efficiency. *Intelligence, 37*(2), 207-222. doi:10.1016/j.intell.2008.12.004

Salthouse, T. A. (1994). The aging of working memory. *Neuropsychology, 8*(4), 535-543.

Salthouse, T. A. (1996). The processing-speed theory of adult age differences in cognition. *Psychological Review, 103*(3), 403-428.

Salthouse, T. A. (2000). Aging and measures of processing speed. *Biological Psychology, 54*(1-3), 35-54. doi:10.1016/S0301-0511(00)00052-1

Salthouse, T. A. (2009). When does age-related cognitive decline begin? *Neurobiology of Aging, 30*(4), 507-514. doi:10.1016/j.neurobiolaging.2008.09.023

Salthouse, T. A., Babcock, R. L., & Shaw, R. J. (1991). Effects of adult age on structural and operational capacities in working memory. *Psychology and Aging, 6*(1), 118-127. doi:10.1037/0882-7974.6.1.118

Salthouse, T. A., & Coon, V. E. (1993). Influence of task-specific processing speed on age differences in memory. *Journal of Gerontology, 48*(5), 245-255.

Salthouse, T. A., & Ferrer-Caja, E. (2003). What needs to be explained to account for age-related effects on multiple cognitive variables? *Pyschology and Aging, 18*(1), 91-110. doi:10.1037/0882-7974.18.1.91

Schaie, K. W. (2005). What can we learn from longitudinal studies of adult development? *Research in Human Development, 2*(3), 133-158. doi:10.1207/s15427617rhd0203_4

Scheller, E., Peter, J., Schumacher, L. V., Lahr, J., Mader, I., Kaller, C. P., & Klöppel, S. (2017). APOE moderates compensatory recruitment of neuronal resources during working memory processing in healthy older adults. *Neurobiology of Aging, 56*, 127-137. doi:10.1016/j.neurobiolaging.2017.04.015

Schmahmann, J. D., & Pandya, D. N. (2006). *Fiber pathways of the brain*. New York, NY: Oxford University Press.

Schretlen, D., Pearlson, G. D., Anthony, J. C., & Aylward, E. H. (2000). Elucidating the contributions of processing speed, executive ability, and frontal lobe volume to normal

age-related differences in fluid intelligence. *Journal of the International Neuropsychological Society, 6*(1), 52-61.

Seiler, S., Fletcher, E., Hassan-Ali, K., Weinstein, M., Beiser, A., Himali, J. J., . . . Maillard, P. (2018). Cerebral tract integrity relates to white matter hyperintensities, cortex volume, and cognition. *Neurobiology of Aging, 72*, 14-22. doi:10.1016/j.neurobiolaging.2018.08.005

Shucard, J. L., Parrish, J., Shucard, D. W., McCabe, D. C., Benedict, R. H., & Ambrus, J. Jr. (2004). Working memory and processing speed deficits in systemic lupus erythematosus as measured by the paced auditory serial addition test. *Journal of International Neuropsychological Society, 10*(1), 35-45. doi:10.1017/S1355617704101057

Shulman, G. L., Corbetta, M., Buckner, R. L., Raichle, M. E., Fiez, J. A., Miezin, F. M., & Petersen, S. E. (1997). Top-down modulation of early sensory cortex. *Cerebral Cortex, 7*(3), 193-206. doi:10.1093/cercor/7.3.193

Sliwinski, M., & Buschke, H. (1999). Cross-sectional and longitudinal relationships among age, memory and processing speed. *Psychology and Aging, 14*, 18-33. doi:10.1037/0882-7974.14.1.18

Sliwinski, M., & Buschke, H. (2004). Modeling intraindividual cognitive change in aging adults: Results from Einstein Aging Studies. *Aging, Neuropsychology, and Cognition, 11*, 196-211. doi:10.1080/13825580490511080

Smith, S. M., Beckmann, C. F., Andersson, J., Auerbach, E. J., Bijsterbosch, J., Douaud, G., . . . Glasser, M. F. (2013). Resting-state fMRI in the Human Connectome Project. *NeuroImage, 80*(15), 144-168. doi:10.1016/j.neuroimage.2013.05.039

Smith, E. E., & Jonides, J. (1997). Working memory: A view from neuroimaging. *Cognitive Psychology, 33*(1), 5-42. doi:10.1006/cogp.1997.0658

Sperling, R. A., Guttmann, C. R. G., Hohol, M. J., Warfield, S. K., Jakab, M., Parente, M., . . . Weiner, H. L. (2001). Regional magnetic resonance imaging lesion burden and cognitive function in multiple sclerosis: A longitudinal study. *Archives of Neurology, 58*(1), 115-121.

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

Stotesbury, H., Kirkham, F. J., Kolbel, M., Balfour, P., Clayden, J. D., Sahota, S., . . . Kawadler, J. M. (2018). White matter integrity and processing speed in sickle cell anemia. *Neurology, 90*, e2042-e2050. doi:10.1212/WNL.0000000000005644

Sweet, L. H., Jerskey, B. A., & Aloia, M. S. (2010a). 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*, 155-163. doi:10.1007/s11682-010-9095-y

Sweet, L. H., Mulligan, R. C., Finnerty, C. E., Jerskey, B. A., David, S. P., Cohen, R. A., & Niaura, R. S. (2010b). Effects of nicotine withdrawal on verbal working memory and associated brain response. *Psychiatry Research: Neuroimaging, 183*, 69-74. doi:10.1016/j.pscychresns.2010.04.014

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*(4), 1114-1123. doi:10.1016/j.neuropsychologia.2007.10.022

Sweet, L. H., Rao, S. M., Primeau, M., Durgerian, S., & Cohen, R. A. (2006). Functional magnetic resonance imaging response to increased verbal working memory demands among patients with multiple sclerosis. *Human Brain Mapping, 27,* 28-36. doi:10.1002/hbm.20163

Swirsky-Sacchetti, T., Mitchell, D. R., Seward, J., Gonzales, C., Lublin, F., Knobler, R., & Field, H. L. (1992). Neuropsychological and structural brain lesions in multiple sclerosis: A regional analysis. *Neurology, 42*(7). doi:10.1212/WNL.42.7.1291

Takeuchi, H., Taki, Y., Sassa, Y., Hashizume, H., Sekiguchi, A., Fukushima, A., & Kawashima, R. (2011). Verbal working memory performance correlates with regional white matter structures in the frontoparietal regions. *Neuropsychologia, 49*(12), 3466-3473. doi:10.1016/j.neuropsychologia.2011.08.022

Tam, H. M. K., Lam, C. L. M., Huang, H., Wang, B., & Lee, T. M. C. (2015). Age-related difference in relationships between cognitive processing speed and general cognitive status. *Applied Neuropsychology: Adult*, *22*(2), 94-99. doi:10.1080/23279095.2013.860602

Tang, Y., Nyengaard, J. R., Pakkenberg, B., & Gundersen, H. J. (1997). Age-induced white matter changes in the human brain: A stereological investigation. *Neurobiology of Aging, 18*(6), 609-615. doi:10.1016/S0197-4580(97)00155-3

Taylor, J. L., Miller, T. P., & Tinklenberg, J. R. (1992). Correlates of memory decline: A 4-year longitudinal study of older adults with memory complaints. *Psychology and Aging, 7,* 185-193. doi:10.1037/0882-7974.7.2.185

Taylor, J. C., Wiggett, A. J., & Downing, P. E. (2007). Functional MRI analysis of body and body part representations in the extrastriate and fusiform body areas. *Journal of Neurophysiology, 98*(3), 1626-1633. doi:10.1152/jn.00012.2007

Trachtenberg, A. J., Filippini, N., & Mackay, C. E. (2012). The effects of APOE-ε4 on the BOLD response. *Neurobiology of Aging, 33*, 323-334. doi:10.1016/j.neurobiolaging.2010.03.009

Tuch, D. S., Salat, D. H., Wisco, J. J., Zaleta, A. K., Hevelope, N. D., & Rosas, H. D. (2005). Choice reaction time performance correlates with diffusion anisotropy in white matter pathways supporting visuospatial attention. *Proceedings of the National Academy of Sciences, USA, 102*(34), 12212-12217. doi:10.1073/pnas.0407259102

Turken, A., Whitfield-Gabrieli, S., Bammer, R., Baldo, J. V., Dronkers, N. F., & Gabrieli, J. D. E. (2008). Cognitive processing speed and the structure of white matter pathways: Convergent evidence from normal variation and lesion studies. *NeuroImage, 42*(2), 1032-1044. doi:10.1016/j.neuroimage.2088.03.057

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

Van Essen, D. C., Ugurbil, K., Auerbach, E., Barch, D., Behrens, T. E., Bucholz, R., . . . Yacoub, E. (2012). The Human Connectome Project: A data acquisition perspective. *NeuroImage, 62*(4), 2222-2231. doi:10.1016/j.neuroimage.2012.02.018

Verger, K., Junqué, C., Levin, H. S., Jurado, M. A., Pérez-Gómez, M., Bartrés-Faz, D., . . . Mercader, J. M. (2001). Correlation of atrophy measures on MRI with

neuropsychological sequelae in children and adolescents with traumatic brain injury. *Brain Injury, 15*(3), 211-221. doi:10.1080/02699050010004059

Vernooij, M. W., Ikram, M. A., Vrooman, H. A., Wielopolski, P. A., Krestin, G. P., Hofman, A., . . . Breteler, M. M. B. (2009). White matter microstructural integrity and cognitive function in a general elderly population. *Archives of General Psychiatry, 66*(5), 545-553. doi:10.1001/archgenpsychiatry.2009.5

Wang, H., He, W., Wu, J., Zhang, J., Jin, Z., & Li, L. (2019). A coordinate-based meta-analysis of the N-back working memory paradigm using activation likelihood estimation. *Brain and Cognition, 132*, 1-12. doi:10.1016/j.bandc.2019.01.002

Wechsler, D. (2008). *Wechsler Adult Intelligence Scale, Fourth Edition*. New York, NY: Pearson.

Whiting, W. L. IV., & Smith, A. D. (1997). Differential age-related processing limitation in recall and recognition tasks. *Psychology and Aging, 12*(2), 216-224. doi:10.1037/0882-7974.12.2.216

Wilkinson, R., & Allison, S. (1989). Age and simple reaction time: Decade differences for 5,325 subjects. *Journal of Gerontology: Psychological Sciences, 44*(2), 29-35.

Wishart, H. A., Saykin, A. J., Rabin, L. A., Santulli, R. B., Flashman, L. A., Guerin, S. J., . . . McAllister, T. W. (2006). Increased brain activation during working memory in cognitively intact adults with the APOE epsilon4 allele. *American Journal of Psychiatry, 163*(9), 1603-1610. doi:10.1176/ajp.2006.163.9.1603

Yeo, B. T. T., Krienen, F. M., Eickhoff, S. M., Yaakub, S. N., Fox, P. T., Buckner, R. L., . . . Chee, W. L. (2015). Functional specialization and flexibility in human association cortex. *Cerebral Cortex, 25*(10), 3654-3672. doi:10.1093/cercor/bhu217

Zelazo, P. D., Anderson, J. E., Richler, J., Wallner-Allen, K., Beaumont, J. L., Conway, K. P., . . . Weintraub, S. (2014). NIH Toolbox Cognition Batter (CB): Validation of executive function measures in adults. *Journal of the International Neurological Society, 20*(6), 620-629. doi:10.1017/S1355617714000472

Zimprich, D. (2002). Cross-sectionally and longitudinally balanced effects of processing speed on intellectual abilities. *Experimental Aging Research, 28,* 231-251. doi:10.1080/03610730290080290

Zimprich, D., & Martin, M. (2002). Can longitudinal changes in processing speed explain longitudinal age changes in fluid intelligence? *Psychology and Aging, 17,* 690-695. doi:10.1037/0882-7974.17.4.690

APPENDIX A

Table 1

Descriptive Information of Study Participants (N = 1,051) and Performance on Cognitive Tests

	M	*SD*	Min	Max
Age (years)	28.77	3.70	22	37
Education (years)	14.95	1.77	11	17
Handedness	66.05	44.20	-100	100
Sex				
Male	494 (46%)			
Female	580 (54%)			
CPS	103.01	19.91	45.31	149.30
WM-acc (%)	83.49	10.70	50	100
WM-rt (ms)	966.30	142.00	559.63	1477.20
DCCS	102.42	9.87	57.79	122.65

Notes. Assessment of handedness is scaled such that -100 = completely left-handed and 100 = completely right-handed. CPS = Cognitive Processing Speed measure via the NIHTB-CB Pattern Comparison Task; WM-acc = Accuracy on 2-back task; WM-rt = Median reaction time on 2-back task; DCCS = NIHTB-CB Dimensional Change Card Sort task, measure of cognitive flexibility.

Table 2

Clusters of Significant Activation Response to the 2-back Relative to the 0-back

Hemi	Region	Size in Voxels	X	Y	Z
R	Middle Frontal Gyrus	4135	-35	-26	37
B	Posterior Parietal	4109	-10	56	48
L	Middle Frontal Gyrus	3718	35	-22	36
B	Supplemental Motor Area	1710	-1	-22	45
R	Cerebellum	594	-36	61	-29
L	Cerebellum	488	26	68	-30
L	Insula	503	36	-20	1
R	Insula	484	-37	-21	1
B	Posterior Cingulate Cortex	306	-9	-48	31

Notes. B = Bilateral; L = Left; R = Right. Coordinates reported in center of mass Talairach coordinates, RAI orientation.

Table 3

Correlational Relationships of Cognitive Processing Speed, Working Memory Accuracy and Reaction Time, a Separate Measure of Executive Functioning, and White Matter Brain Volume

	1	2	3	4	5
1. CPS	--				
2. WM-acc	.28**	--			
3. WM-rt	-.30**	-.24**	--		
4. DCCS	.41**	.31**	-.22**	--	
5. White Matter Volume	-.02	-.02	-.02	.10**	--

Notes. CPS = Cognitive Processing Speed; WM-acc = Accuracy on 2-back task; WM-rt = Median reaction time on 2-back task; DCCS = NIHTB-CB Dimensional Change Card Sort task. Results of relations between neurocognitive measures and white matter volume are partial correlations controlling for the effect of intracranial volume. Values represent Pearson *r* correlation coefficients.

*$p < .05$

**$p < .01$

Table 4

Mean Intensity of Activation Effects of 2-back versus 0-back by Region of Interest

	Mean	SD
Left PFC	0.57	0.31
Right PFC	0.38	0.23
Left PPC	0.47	0.30
Right PPC	0.52	0.35

Notes. Values reflect partial beta weights. PFC = Prefrontal cortex; PPC = Posterior parietal cortex

Table 5

Multiple Regression Analyses Predicting Left Prefrontal Cortex Working Memory Brain Activation (2-back versus 0-back)

Model	Variable	B	SE_B	R^2	ΔR^2
1	Education	-.02	.04		
	WM-acc	.00	.01	.00	.00
2	Education	-.02	.04		
	WM-acc	.00	.01		
	White Matter Volume	-1.95E-.008	.00		
	CPS	.00	.00	.00	.00

Notes. WM-acc = Accuracy on 2-back WM task; CPS = Cognitive Processing Speed.

Table 6

Multiple Regression Analyses Predicting Right Prefrontal Cortex Working Memory Brain Activation (2-back versus 0-back)

Model	Variable	B	SE_B	R^2	ΔR^2
1	Education	.00	.00		
	WM-acc	.00	.00	.00	.00
2	Education	.00	.00		
	WM-acc	.00	.00		
	White Matter Volume	-3.74E-.007	.00		
	CPS	.00	.00	.01	.00

Notes. WM-acc = Accuracy on 2-back WM task; CPS = Cognitive Processing Speed.

Table 7

Multiple Regression Analyses Predicting Left Posterior Parietal Cortex Working Memory Brain Activation (2-back versus 0-back)

Model	Variable	B	SE_B	R^2	ΔR^2
1	Education	.01	.01		
	WM-acc	.00	.00	.00	.00
2	Education	.01	.01		
	WM-acc	.00	.00		
	White Matter Volume	1.802E-007	.00		
	CPS	.00	.00	.01	.00

Notes. WM-acc = Accuracy on 2-back WM task; CPS = Cognitive Processing Speed.

Table 8

Multiple Regression Analyses Predicting Right Posterior Parietal Cortex Working Memory Brain Activation (2-back versus 0-back)

Model	Variable	B	SE_B	R^2	ΔR^2
1	Education	.00	.00		
	WM-acc	.00	.00	.00	.00
2	Education	.00	.00		
	WM-acc	.00	.00		
	White Matter Volume	-1.69E-01	.00		
	CPS	.00	.00	.00	.00

Notes. WM-acc = Accuracy on 2-back WM task; CPS = Cognitive Processing Speed.

APPENDIX B

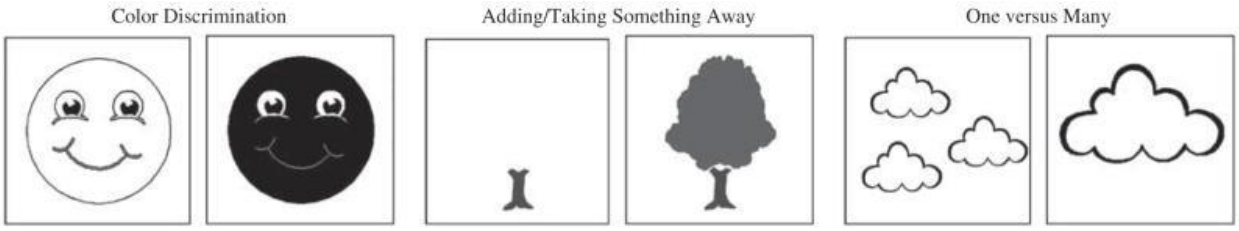

Figure 1. Example items of the NIH Toolbox-Cognition Battery Pattern Comparison Task (from Carlozzi et al., 2014).

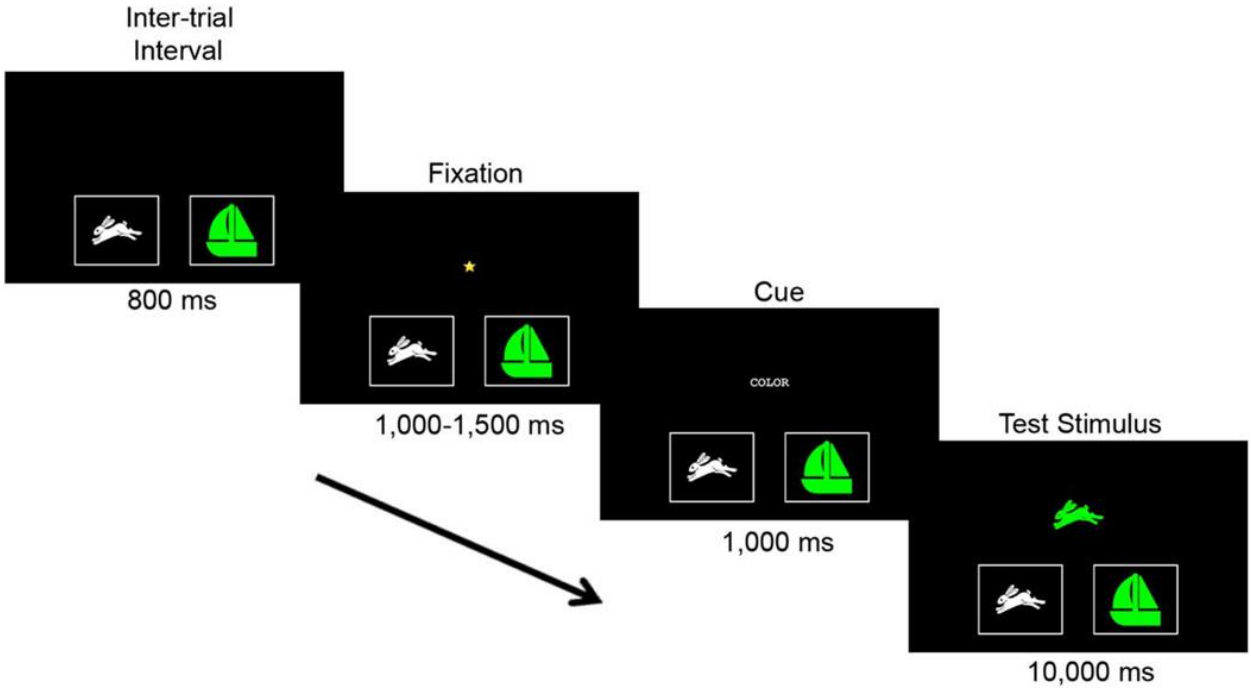

Figure 2. Example items of the NIH Toolbox-Cognition Battery Dimensional Change Card Sort task (from Zelazo et al., 2014).

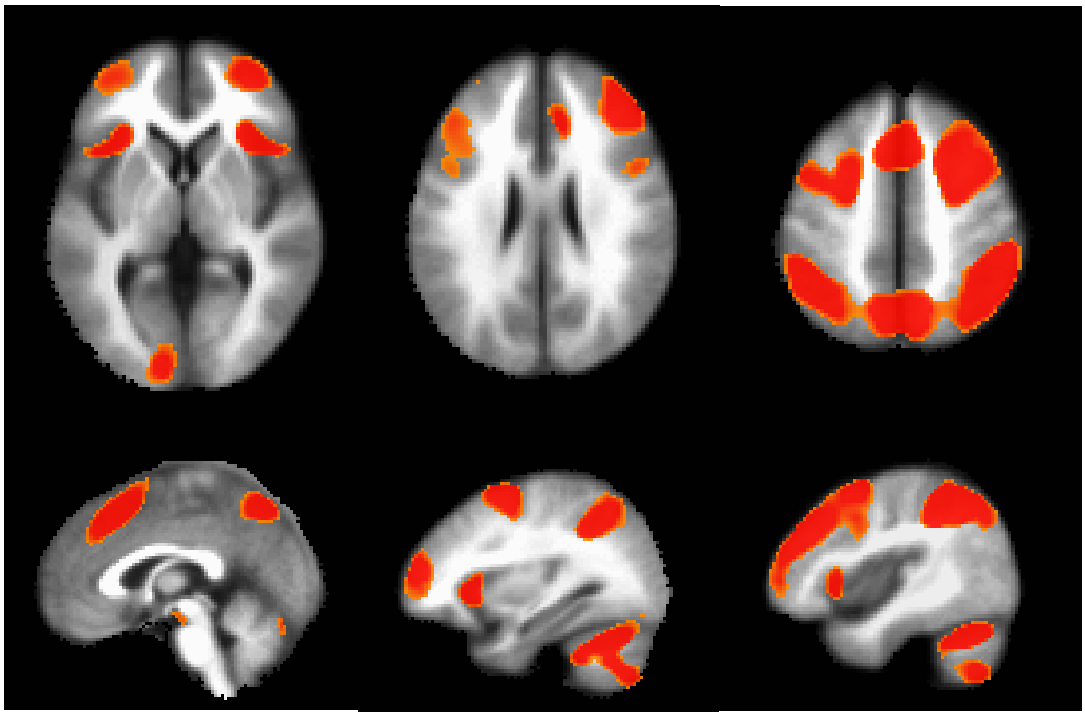

Figure 3. Clusters of significant brain response to the FMRI WM 2-back relative to 0-back

Notes. Axial view: z-plane coordinates = 2, 26, 50. Sagittal view: x-plane coordinates = -42, 0, 32.