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Within-Individual Neural Variability in the N-Back Task: Relation to Neuropsychological Assessments of Executive Function, Reading, and Language

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by

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Under the Direction of Tricia Z. King, Ph.D.

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ABSTRACT

This study investigated fMRI Blood Oxygen Level-Dependent signal variability within individuals (within-individual neural variability; WINV) during a letter n-back task, and examined the relationship between WINV and cognitive abilities in healthy adults ($N = 48$). WINV in frontoparietal brain regions was modulated during vigilance and working memory (WM) trials of the n-back task, and was related to neuropsychological measures of vigilance and WM. WINV across the n-back task influenced n-back task performance; in this study, the inferior frontal junction exhibited a behavioral double dissociation between flexibility and stability at the region of interest level. A reading and language network was also queried to determine the influence of vigilance and WM on reading and language skills. As hypothesized, ROI and cluster-based variability in the n-back task was related to performance on assessments of WM, vigilance, reading, and language. Understanding WINV in these domains will inform research about WINV in clinical populations.

INDEX WORDS: Working memory, Vigilance, Attention, Language, Reading, Within-individual BOLD signal variability, Functional magnetic resonance imaging

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DEDICATION

This thesis is dedicated to my friends and family, especially to my mother, father, and sister, for their continuous support throughout my education. I am grateful for their never-ending love and encouragement. Without them, all of my accomplishments would not be possible.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 INTRODUCTION

Functional magnetic resonance imaging (fMRI) emerged in the 1990s as a way to investigate structure-function relationships of the human brain due to its non-invasive nature, relatively low cost, and good spatial resolution (Glover, 2011). Within fMRI research, most literature has focused on drawing conclusions from average brain activation patterns (Garrett et al., 2010). This approach – that is, computing average signal across a given time course to capture average brain activation during a task – is widely accepted, based on the statistical assumption that a measure of central tendency (the mean) is most reflective of a distribution (Garrett et al., 2010). In this context, the mean activation level is computed to extract "signal" from "noise" in the acquired imaging data. Neural noise is conceptualized as the intrinsic stochastic fluctuation in brain activity (Faisal et al., 2008; Misic et al., 2010), whereas signal is defined as localized changes in brain blood flow and blood oxygenation, which are coupled to underlying neuronal activity that occurs during a specific task (Hillman, 2014).

Though identifying mean activation has become a scientific tradition (Garrett et al., 2010), it is important to note that the brain's natural state is inherently variable (Arieli et al., 1996; Faisal et al., 2008; Garrett et al., 2010; McIntosh et al., 2008; Miller et al., 2002; Neumann et al., 2003). Research within the past two decades has demonstrated that considerable within-subject variability in the blood oxygen level-dependent (BOLD) signal exists within and across task conditions. This within-subject variability, defined as intrinsic moment-to-moment fluctuations in the engagement of brain regions within a single individual (Dinstein et al., 2015; Malins et al., 2018; Nomi et al., 2017), is typically overlooked as "noise," and is attributed to issues with a task, issues with image acquisition and preprocessing, and other neuroimaging-

related complications (Aguirre et al., 1998; Garrett et al., 2010; Jones et al., 2008; Neumann et al., 2003; Smith et al., 2005; Uddin, 2020).

However, in the current era of medical and psychological science, which emphasizes the importance of precision medicine and individualization of diagnosis and treatment plans, research has started to focus on the unique functionality of within-individual neural variability (Garrett et al., 2011; Garrett et al., 2010; Malins et al., 2018; Misic et al., 2010; Roalf et al., 2014; Van Horn et al., 2008; Waschke et al., 2021). The rationale for this line of work is that considering within-individual neural variability may allow clinicians and practitioners to be better able to understand and to predict important phenomena relevant to specific individuals, especially in the realm of cognitive abilities (Faisal et al., 2008; MacDonald et al., 2009; MacDonald, Nyberg, & Backman, 2006; Stein et al., 2005; Seghier & Price, 2018; Waschke et al., 2021).

Because the notion of within-individual neural variability has only recently become a promising area of research, only a few studies have deviated from typical average BOLD signal based methodology and analysis to examine within-individual neural variability. Existing research that has explored the topic of within-individual neural variability has been conducted in the realm of developmentally normal aging (Boylan et al., 2020; Garrett et al., 2010; Grady & Garrett, 2014; Huettel et al., 2001; Hultsch et al., 2008; MacDonald et al., 2009; Schmiedek et al., 2009), creativity and divergent thinking (Roberts et al., 2020), and reading development in children (Malins et al., 2018). The methodology to explore intrinsic within-individual neural variability has the potential to be applied to many other domains of performance, such as to components of executive functioning. Executive functioning is an umbrella term that comprises a set of skills that encompass a variety of constructs, domains, and behaviors. Executive

functioning is important for adequate daily functioning, as well as for enabling one to learn and to adapt to novel situations; as a result, it is important to assess these abilities in both healthy and clinical populations.

Working memory, or one's ability to maintain, monitor, and manipulate information in the short-term, is a main facet of executive functioning and is an essential component for higher-order cognitive processes in humans (Baddeley, 2012; Diamond, 2012; Smith & Jonides, 1997, 1998). Working memory is associated with cognitive flexibility, defined as the ability to effectively switch between tasks (Miyake et al., 2000). Working memory is a domain that has been extensively studied using neuroimaging (fMRI) in both healthy and clinical populations. Compared to healthy individuals, those with varied clinical conditions perform more poorly in tasks that measure working memory; one particular population of interest that has been found to be deficient in working memory (based on neuropsychological measures) is survivors of pediatric brain tumors (Edelstein et al., 2011; King et al., 2017; Nagel et al., 2006). However, the existing neuroimaging research has relied on mean activation to draw conclusions, rather than on within-individual neural variability calculations.

Research has also demonstrated that working memory requires attention. The term "attention" comprises different functions along two dimensions: "intensity" and "selectivity." The "intensity" dimension is divided into "alertness" and "sustained attention" (Gottwald et al., 2003). Vigilance is defined as sustained attention to a task for a period of time (Oken et al., 2010), and is physiologically associated with the sleep-wake arousal system (Oken et al., 2010). Because the brain regions associated with arousal, and thus vigilance (e.g., thalamus, hypothalamus, raphe nuclei, locus coeruleus; Oken et al., 2010), are distinct from brain regions involved in working memory (dorsolateral prefrontal cortex (dlPFC), ventrolateral prefrontal

cortex (vlPFC), anterior cingulate cortex (ACC), and parietal lobes), these two constructs can be considered disparate, but connected processes. Vigilance is important in healthy individuals and is often disrupted in clinical conditions. Specifically, treatments associated with pediatric brain tumors are linked to difficulties with sustained attention (Raghubar et al., 2017).

Research has suggested that vigilance and working memory are connected to skills such as phonetic coding and phonemic segmentation, which are important to the development of language and reading skills (Levy & Hobbes, 1989). Working memory has also been shown to be a predictor of verbal fluency (Daneman, 1991; Daneman & Carpenter, 1980), as well as of reading comprehension, alongside other executive function components such as attention, decoding, and linguistic fluency (Sesma et al., 2009). Additionally, reading skill is positively related to within-individual neural variability in response to print stimuli (Malins et al., 2018). Taken together, this research identifies the importance of examining working memory, vigilance, language, and reading skills and their relation to within-individual neural variability.

The present study investigates within-individual neural variability in healthy individuals, and evaluates the relationship between within-individual neural variability and neurocognitive performance on behavioral and neuropsychological tasks. Neuroimaging data was obtained during an fMRI scan in which participants completed a letter n-back task, a commonly used task to examine working memory and vigilance. AFNI (Automated Functional Neuroimaging) software (Cox, 1996) was used to perform appropriate analyses to evaluate within-individual neural variability during the letter n-back task, and to link within-individual neural variability to performance on the n-back task and to performance on standard neuropsychological measures of working memory, vigilance, and reading and language skills. A greater understanding of within-

individual neural variability in healthy individuals will help to inform future research pertaining to within-individual neural variability in diverse clinical populations.

1.1 Working Memory, Vigilance, and Connection to Language in Healthy Individuals

Working memory is defined as one's ability to maintain and manipulate information over a short period of time. Working memory also contributes to elements of moment-to-moment functioning from language comprehension to deductive reasoning (Baddeley, 1992). Working memory can be understood as a three-part system for storing and manipulating information that is comprised of a "phonological loop" containing a phonological store and articulatory rehearsal system, a "visuospatial sketchpad" that allows for the maintenance and manipulation of visuospatial information, and a "central executive" component that influences the functions of the other two (Baddeley & Hitch, 1974). This triarchic system highlights the notion that attention, or vigilance, as well as language-related processes, are implicated in working memory.

Specifically, verbal working memory involves the ability to temporarily hold in mind information that can be verbalized, such as letters, words, or nameable objects (Koziol et al., 2015). Verbal working memory relies on the "phonological loop," which may have evolved from primitive vocal sounds as phonemes were combined to create meaning. This conceptualization of working memory implies that it may have evolved alongside language, highlighting its importance in language abilities (Aboitiz et al., 2006; Baddeley et al., 1998; Koziol et al., 2015).

1.2 Working Memory, Vigilance, and Connection to Reading in Healthy Individuals

In addition to the importance of working memory and vigilance in language abilities, these cognitive domains are recognized as playing a role in reading abilities (Biotteau et al., 2019; Walcott et al., 2009). A lot of research in the reading field is focused on children and

adults with attention-deficit/hyperactivity disorder (ADHD). However, children and adults with impaired sustained attention, but who do not necessarily meet criteria for ADHD, have also shown problems with reading (Dally, 2006; Walcott et al., 2009). Therefore, sustained attention abilities are important to consider when examining reading abilities.

The "phonological loop" component of working memory, identified by Baddeley and Hitch (1974), plays an important role in learning to read. A relevant study that performed a hierarchical multiple regression to examine the unique contributions of phonological analysis and verbal working memory to predict reading ability found that phonological analysis and working memory skills share a substantial amount of common variance (Hansen & Bowey, 1994), suggesting that working memory may underlie phonological skills important for reading.

1.3 Brain Regions Associated with Working Memory, Vigilance, and Language

Numerous reviews indicate an increase in BOLD signal that occurs in the dorsolateral prefrontal cortex (dlPFC) during 2-back and 3-back trials of letter n-back tasks, generally considered measures of working memory, compared to 0-back and 1-back trials, generally considered measures of attention and vigilance (Carpenter et al., 2000; Owen et al., 2005; Smith & Jonides, 1998). Evidence has suggested that the right and left hemispheres tend to exhibit different activation patterns depending on whether the task is spatial or verbal. Anatomical and functional research has implicated the left hemisphere in language, and the right hemisphere in spatial reasoning (Wager & Smith, 2003). Therefore, a letter n-back task, relying on language processing, will likely engage left lateralized frontal and parietal brain regions (Emch et al., 2019).

The dlPFC and vlPFC have been implicated in numerous elements of working memory including encoding, maintenance, and retrieval (Dove et al., 2001; Owen et al., 2005; Owen,

1997). Additionally, in healthy populations, activity in the ACC tends to increase as task load increases (Botvinick et al., 2004; Kolling et al., 2016). Furthermore, the parietal lobes are often implicated in working memory abilities, and are thought to play roles in both rehearsal and storage (Jonides et al., 1998; Owen et al., 2005; Wager & Smith, 2003). A functional dissociation within the inferior parietal cortex during a verbal n-back task was found, such that dorsal inferior parietal cortex (DIPC) is affected by load or effort (Ravizza et al., 2004). Based on this, it is reasonable to expect greater activation in the DIPC during 2- and 3-back trials of the letter n-back task compared to during 0- and 1-back trials. The same study indicated that the ventral inferior parietal cortex (VIPC) may support phonological encoding-recoding processes that are central to a variety of language tasks (Ravizza et al., 2004), suggesting that this region may be important when considering language fluency.

Regarding the verbal fluency aspect within the language domain, neuroimaging studies of category fluency have shown increased activation in the anterior/ventral left inferior frontal gyrus (IFG), whereas letter fluency has been associated with activation in the posterior/dorsal IFG (Shao et al., 2014). Tasks of verbal fluency may also include task switching, which is considered a component of executive control (Miyake et al., 2000). A study assessing verbal fluency task switching identified the importance of the superior posterior parietal cortex (Gurd et al., 2002).

Additionally, research has identified particular frontal and parietal regions involved in vigilance processes. In particular, the rostral prefrontal cortex, ACC, and medial and lateral posterior parietal cortex have been identified as regions comprising a frontoparietal attention network (Gottwald et al., 2003; Sheremata et al., 2018).

1.4 Brain Regions Involved in Reading

In addition to relevant brain regions supporting working memory and vigilance, this study will examine relevant brain regions supporting reading skills. A meta-analysis of brain regions involved in reading in adults identified the left IFG, left occipito-temporal regions, and left posterior parietal regions, in addition to a region in the right cerebellum (Martin et al., 2015). Another study (Aboud et al., 2016) assessed functional connectivity in regions involved in word-level processing and in extracting meaning from text, both important abilities required for skilled reading. Left-lateralized regions involved in semantic processing and working memory demonstrated task-dependent connectivity patterns: during word processing, a functional connection was identified with the left occipito-temporal region, whereas during extraction of meaning from text, a functional connection was identified with the left angular gyrus. The left angular gyrus is involved in semantic memory and assembling information into a cohesive whole (Aboud et al., 2016). Additional research has determined that print reading skill is positively associated with within-individual neural variability in the left inferior frontal gyrus pars triangularis (Malins et al., 2018).

1.5 Working Memory, Vigilance, Language, Reading, and the Cerebellum

Though the cerebellum is typically associated with motor coordination and balance, over recent years, the cerebellum has rapidly gained attention as a critically important structure for cognitive functioning. Anatomical findings suggest that the cerebellum has diffuse connections to virtually all areas of the neocortex (Buckner, 2013; Clark et al., 2021; Middleton & Strick, 1998; Steinberg et al., 2020). Specifically, anatomically distinct functional modules have been identified for motor (anterior and inferior posterior cerebellum) and cognitive (lateral and superior posterior cerebellum) processes (Stoodley & Schmahmann, 2009, 2010). A triple

representation for working memory, language, and social/emotional processing within the cerebellum has identified lobule VI, Crus I/II, and lobules IX-X (Guell et al., 2018). In addition, meta-analytic connectivity modeling has suggested functional co-activation of posterior cerebellar regions with frontal and parietal cortical regions (Balsters et al., 2014). Based on this research, the lateral posterior regions of the cerebellum can be understood to be involved in overall cognitive processing.

Specifically, research examining cerebellar involvement in working memory has identified that a cerebellar-frontal network is implicated in the phonological loop, articulatory rehearsal, and mental subvocalizations required for verbal working memory (Ailion et al., 2020). Working memory engages cerebellar lobule VI and Crus I (Koziol et al., 2015). Importantly, when verbalizable content, such as letters presented during the letter n-back task, is visually presented, activity levels in lobule VI increase during the encoding phase (Chein & Fiez, 2001; Chen & Desmond, 2005), and remain elevated during manipulation of the content (i.e., remembering the order of letter presentation). As a result, it is likely that cerebellar activation in lobule VI will be present during the letter n-back task, and variability in this activation may have implications for working memory performance in both healthy and clinical populations (Koziol et al., 2015).

Because prefrontal and posterior parietal circuitry is essential for sustained attention, the anatomical connections from these regions to the cerebellum are relevant when examining vigilance (Gottwald et al., 2003). Early studies in non-human primates found that association areas of the posterior parietal cortex and prefrontal areas, both critical for focused attention, have connections via the ventral pontine nuclei to the posterior cerebellum (Schmahmann & Pandya,

1997). As a result, it is possible that the letter n-back task, requiring elements of working memory and vigilance, will elicit activation in the posterior cerebellum.

The cerebellum has intricate connections to regions of the cortex involved in language. The primary target of the phylogenetically newer portion of the dentate, the neodentate, is the frontal lobe, where Broca's area is located. In the general population, the primary language centers of the brain (i.e., Broca's area and Wernicke's area) are typically located in the left cerebral hemisphere. Although lesions of both cerebellar hemispheres can influence linguistic abilities, right cerebellar lesions are more likely to do so (Steinberg et al., 2020). More recent research has identified specific locations in the right cerebellum that may influence language capabilities. From this research, posterior lobules VI and VII, and Crus I and II in the right cerebellar hemisphere, and some structures of the vermis, have been associated with language (Argyropoulos, 2016; Booth et al., 2007; Marien & Beaton, 2014; Runnqvist et al., 2016). Additionally, the concept of a "lateralized linguistic cerebellum" has been postulated, asserting that the right hemisphere of the cerebellum is substantially involved in the subsystem of working memory that contributes to a variety of linguistic processes implicated in semantic and phonological word retrieval, in syntactic processing, and in the dynamics of language processing (Marien et al., 2001).

Finally, the cerebellum is also believed to play a role in reading. In addition to recruiting left-hemisphere cortical regions involved in language processing, learning to read may depend on other, more implicit learning, perceptual, and cognitive processes. Automatization of phonological processing may be partly supported by the cerebellum (Vlachos et al., 2007); this notion is consistent with research that has proposed that the cerebellum facilitates "cognitive efficiency" (Koziol et al., 2015). Imaging research has demonstrated that the cerebellum is one

of the most consistent locations for structural differences between dyslexic and healthy individuals (Eckert et al., 2003). In addition to structural differences in the cerebellum pertaining to reading abilities, a functional neuroimaging study of neurologically normal adults found that specific regions in the posterior cerebellum activate in response to phonological and semantic tasks. For example, in phonologic assembly, cerebellar activation was observed in lobule VI, in the semilunar lobule, and in the posterior simple lobule, whereas during semantic processing, activation was observed in the inferior vermis (Fulbright et al., 1999; Vlachos et al., 2007). Together, these findings suggest there is significant support for the role of the cerebellum in reading.

Table 1. Brain regions of interest for relevant domains

Domain	Brain regions
Working memory	**Left dorsolateral prefrontal cortex** **Ventrolateral prefrontal cortex** **Anterior cingulate cortex** **Dorsal inferior parietal cortex** Cerebellum - Lobule VI - Crus I
Vigilance	Frontoparietal attention network - Rostral prefrontal cortex - Anterior cingulate cortex - **Medial and lateral posterior parietal cortex** Posterior cerebellum
Reading	**Left inferior frontal gyrus** **Left occipito-temporal cortex** Left posterior parietal cortex Left angular gyrus Right cerebellum - Lobule VI - Semilunar lobule (lobule VII) - Simple lobule - Vermis
Verbal fluency	Ventral inferior parietal cortex Left inferior frontal gyrus **Right cerebellum** - **Posterior lobules VI and VII** - **Crus I**
Category fluency	Left inferior frontal gyrus Right cerebellum - Posterior lobules VI and VII - Crus I
Task switching	**Inferior frontal junction** Superior posterior parietal cortex Right cerebellum - Posterior lobules VI and VII - Crus I

*Regions in bold are identified regions for ROI analyses; coordinates are listed in Table 2.

Table 2. Coordinates for identified regions of interest in MNI space (LPI orientation)

Domain	Region	*x*	*y*	*z*	#
Working memory	Left dorsolateral prefrontal cortex (left dlPFC)	-36 -44	44 18	20 22	1
	Ventrolateral prefrontal cortex (vlPFC)	-30	18	6	2
	Anterior cingulate cortex (ACC)	4	32	42	3
	Dorsal inferior parietal cortex (DIPC)	-36 -44	-50 -55	40 44	4
Vigilance	Medial posterior parietal cortex (medialPPC)	10	-66	48	5
	Lateral posterior parietal cortex (lateralPPC)	-20	-74	38	6
Reading	Left inferior frontal gyrus (left IFG)	-52 -52	20 18	18 14	7
	Left occipito-temporal cortex	-44 -48	-74 -62	-4 -20	8
Verbal fluency and Category fluency	Right cerebellum, posterior lobules VI, VII (right CB)	24	-60	-44	9
Task switching	Inferior frontal junction (IFJ)	-34 -42	6 12	40 40	10

(Armbruster-Genc et al., 2016; Kolling et al., 2016; Martin et al., 2015; Owen et al., 2005; Ravizza et al., 2004; Sheremata et al., 2018)

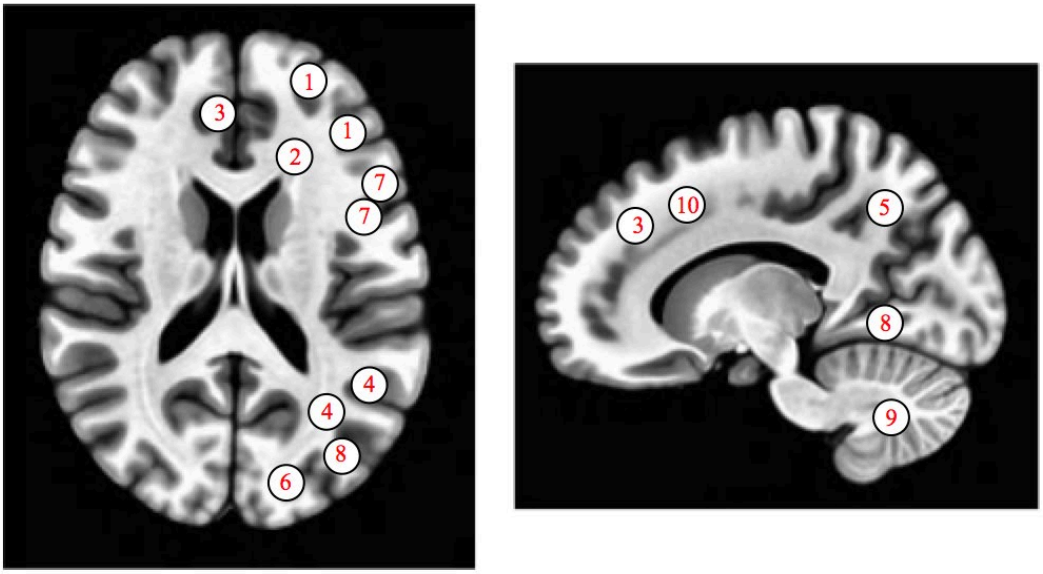

Figure 1. ROI coordinates visualized in AFNI

1.6 Within-Individual Blood Oxygen Level-Dependent (BOLD) Signal Variability

Blood oxygen level-dependent (BOLD) signal variability within individuals (within-individual neural variability) has recently been touted as an important feature in fMRI data, rather than as solely unwanted noise in the acquired signal, because it may provide information that is not captured by more classic neuroimaging methods and analyses that focus on the average level of brain activation (Garrett et al., 2011; Garrett et al., 2010; Malins et al., 2018). The inherent variability in the human brain may be functional (Armbruster-Genc et al., 2016; Deco et al., 2009; Faisal et al., 2008; Garrett et al., 2013; Stein et al., 2005). Moment-to-moment neural variability results from many neurophysiological mechanisms (Dinstein et al., 2015; Uddin, 2020). Identifying the amount of neural variability in the face of these physiological sources of variability in humans is challenging; however, it is possible to use neuroimaging to decompose neural variability into variability that appears in different parts of the stimulus/task evoked response, and into variability that is specific to local brain areas versus variability that is shared across the entire brain (Dinstein et al., 2015).

When estimating within-individual neural variability in humans using neuroimaging techniques such as fMRI, it is important to measure and control external (non-neural) sources of variability when attempting to examine trial-to-trial neural variability (e.g., head movement; Dinstein et al., 2015; Uddin, 2020). In this study, to ensure that analyses accounted for physiological sources of noise and head motion, regression of white matter, cerebrospinal fluid, and head motion parameters was done at the individual subject level during processing when creating neural variability maps.

1.7 Cognitive Flexibility and Cognitive Stability, Within-Individual Neural Variability, and Behavioral Performance

Research has demonstrated that intrinsic within-individual neural variability in the human brain may have advantageous effects in certain cognitive domains, such as cognitive flexibility, defined as the ability to effectively switch between tasks, and disadvantageous effects in others, such as cognitive stability, defined as the ability to maintain a task goal in the presence of irrelevant distractors (Armbruster-Genc et al., 2016; Armbruster-Genc et al., 2012).

Cognitive flexibility, or effective switching between tasks, is highly related with working memory (Miyake et al., 2000), and is useful for language fluency and task-switching involving language (Deak, 2003; de Paula et al., 2015). As a result, it is reasonable to suggest that variability will result in better performance on a letter n-back task, and be associated with performance on measures of language fluency and language task-switching. Within-individual neural variability has also been postulated to have some involvement in measures of vigilance; however, research pertaining to within-individual neural variability and vigilance is scarce (Arazi et al., 2019; MacDonald, Hultsch, & Bunce, 2006). Because cognitive stability is necessary to maintain a goal in the presence of distractors, it is plausible that cognitive stability would be useful for vigilance, or sustained attention, tasks. Finally, in terms of reading, previous research by Malins et al. (2018) has identified a positive relationship between within-individual neural variability and reading ability, as measured by the Letter-Word Identification subtest of the Woodcock-Johnson Tests of Achievement (WJ-III ACH). This relationship may suggest that because variability was beneficial, reading may depend on cognitive flexibility. It is noteworthy that this effect was seen in the IFG, a higher-order region, and in children with dyslexia, a decoding-based reading disorder, and that similar patterns may not hold in a sample of healthy

adults. For example, the "neural noise" hypothesis of dyslexia suggests that neural noise (perhaps synonymous with variability) can negatively impact lower-level perceptual processes involved in reading, such as phonological awareness (Hancock et al., 2017), and thus may impact reading comprehension abilities. Consequently, these different findings motivate further research into the intriguing relationship between within-individual neural variability and reading.

A double dissociation between cognitive flexibility and cognitive stability has been observed in the inferior frontal junction (IFJ; Armbruster-Genc et al., 2016), a brain region involved in three component processes of cognitive control: working memory, task switching, and inhibitory control (Derrfuss et al., 2005; Sundermann & Pfleiderer, 2012). Functional connectivity analyses have provided evidence for connectivity between the IFJ and identified regions involved in working memory (dlPFC, vlPFC), vigilance (posterior parietal cortex), and reading (occipito-temporal regions), as well as language areas (Sundermann & Pfleiderer, 2012). As a result, the IFJ is of interest in the current study.

Additionally, greater within-individual neural variability is associated with more accurate performance on complex tasks, defined by reduced error rates (Armbruster-Genc et al., 2016), and faster reaction times (Garrett et al., 2011). Notably, excessive levels of within-individual neural variability are present in individuals with different clinical disorders, and this may reveal important insights regarding neuropathology in these populations (Dinstein et al., 2015). It is speculated that behavioral variability in clinical populations may be the consequence of within-individual neural variability patterns; however, the relationship between within-individual neural variability and cognitive performance in clinical populations has been underexplored (Dinstein et al., 2015). Understanding within-individual neural variability patterns in relation to working memory (the ability to mentally maintain and manipulate information over a short period of

time), vigilance (sustained attention to a task for a period of time), and reading and language skills in healthy individuals will help inform future research on within-individual neural variability patterns in these domains in clinical populations.

1.8 Aims of the Proposed Study

The current study examined within-individual neural variability and its associations with neurocognitive processes (working memory, vigilance, and reading and language skills) within a sample of Georgia State University undergraduates, their friends, and members of the community, all of whom were neurotypical individuals. Vigilance and working memory were assessed via a letter n-back task that took place while participants were in an MRI scanner, and traditional contrast analyses (crosshair *versus* 0-back, 0-back *versus* 1-back, 1-back *versus* 2-back, and 2-back *versus* 3-back) were conducted to provide stepwise information about variability patterns throughout the n-back task. To assess variability patterns pertaining to vigilance, we conducted separate 0-back *versus* crosshair and 1-back *versus* crosshair contrasts, and followed this with a conjunction approach (0-back *versus* crosshair AND 1-back *versus* crosshair) to identify overlapping regions. Conjunction analyses are used to find common activation patterns across groups, or trial types, by examining voxels that are statistically significant across two or more contrasts. Similarly, 2-back *versus* 0-back and 3-back *versus* 0-back contrasts were conducted to evaluate working memory, followed by a conjunction approach (2-back *versus* 0-back AND 3-back *versus* 0-back) to identify regions of overlap. Within-individual neural variability was measured using a customized pipeline in AFNI using a priori regions of interest (ROIs) identified in previous meta-analytic and experimental research related to working memory (Emch et al., 2019; Owen et al., 2005; Ravizza et al., 2004), vigilance (Gottwald et al., 2003), and reading and language (Martin et al., 2015; Shao et al., 2014) in

addition to appropriate cluster-based analyses. Finally, partial least squares (PLS) regression analysis was employed to examine relationships between within-individual neural variability and neuropsychological performance on standardized measures of working memory, vigilance, and reading and language abilities.

1.8.1 Specific Aim 1

We aimed to identify areas of within-individual neural variability in a sample of healthy individuals during the vigilance (0- and 1-back) and working memory (2- and 3-back) trials of the letter n-back task using a priori ROIs from pre-existing meta-analyses. Cortical and subcortical regions were included in analyses. We tested these ROIs to determine specific relationships between within-individual neural variability in the vigilance and working memory trials of the letter n-back task and behavioral performance on neuropsychological measures of vigilance and working memory.

Hypothesis 1a: Contrasts assessing working memory (2-back *versus* 0-back; 3-back *versus* 0-back; 2-back *versus* 0-back AND 3-back *versus* 0-back) will show increased cortical variability in the left dlPFC and vlPFC, ACC, and inferior parietal cortex. Contrasts assessing vigilance (0-back *versus* crosshair; 1-back *versus* crosshair; 0-back *versus* crosshair AND 1-back *versus* crosshair) will show increased cortical variability in all of the identified PFC regions, ACC, and medial and lateral posterior parietal cortex.

Hypothesis 1b: Sub-cortical regions of increased variability during the vigilance (0- and 1-back) and working memory (2- and 3-back) trials will include lobule VI and Crus I in the posterior cerebellum, as these regions are implicated in reciprocal cerebello-cortical circuitry pertaining to working memory and vigilance.

Hypothesis 1c: Performance on neuropsychological measures of working memory (Auditory Consonant Trigrams and Digit Span Backwards) and vigilance (Digit Span Forward) will be related to within-individual neural variability during the n-back task in the dlPFC, vlPFC, ACC, dorsal inferior parietal cortex, and medial and lateral parietal cortex, such that greater within-individual neural variability will be associated with higher working memory scores and lower vigilance scores.

1.8.2 Specific Aim 2

We aimed to use a whole-brain cluster-wise analysis to investigate the relationship between within-individual neural variability and performance on the letter n-back task, measured via reaction time and accuracy.

Hypothesis 2: Because the letter n-back task is a complex task, we expect that overall, the brain regions identified will show a positive relationship between within-individual neural activity and behavioral performance, but in particular, some regions such as the IFJ might show a more nuanced relationship, such that greater within-individual neural variability in the IFJ will be related to enhanced working memory task performance, defined by faster reaction times and fewer errors for the 2- and 3-back trials, as working memory involves cognitive flexibility. In contrast, greater within-individual neural variability in the IFJ will reduce vigilance task performance, operationalized as slower reaction times and greater errors in the 0- and 1-back trials, as vigilance relies on cognitive stability.

1.8.3 Specific Aim 3

We aimed to use a combined ROI and whole-brain analysis to investigate the relationship between within-individual neural variability and performance on standard neuropsychological assessments of working memory and vigilance, beyond the previously identified ROIs, and to further probe the association between within-individual neural variability and reading and language.

Hypothesis 3a: Performance on measures of working memory (Auditory Consonant Trigrams and Digit Span Backwards) and vigilance (Digit Span Forward) when combined with measures of reading and language may also be related to within-individual neural variability in the IFJ, such that greater within-individual neural variability will be associated with higher working memory scores and lower vigilance scores.

Hypothesis 3b: Higher scores on measures of verbal fluency (Delis-Kaplan Executive Functioning System (D-KEFS) Letter Fluency, D-KEFS Category Fluency, D-KEFS Color-Word Inhibition/Switching) will be related to greater within-individual neural variability during the n-back task in the left IFG, posterior parietal cortex, and IFJ.

Hypothesis 3c: Lower scores on measures of reading (WJ-III Letter-Word Identification, WJ-III Passage Comprehension) will be related to greater within-individual neural variability during the n-back task in regions of the reading network (IFG, occipito-temporal cortex, posterior parietal cortex), consistent with the neural noise hypothesis of dyslexia.

2 METHODS

2.1 Procedures

2.1.1 Participant Recruitment and Screening

Participants were healthy undergraduate students attending Georgia State University, friends of these students, and community members in Atlanta, Georgia (see Table 3). Participants were compensated for their time with psychological class credit, monetary compensation, or both. The sample of undergraduate participants was recruited via Georgia State University's undergraduate psychological research participant pool (SONA). Friends and community members were recruited via word of mouth.

Participants were screened for a history of (as well as current) psychopathology with the Structured Clinical Interview for DSM-IV-TR Axis 1 (SCID-I; First & Gibbon, 2004; First et al., 2002; First et al., 1997). The SCID-I is broken down into separate modules corresponding to categories of diagnoses. For all diagnoses, symptoms are determined as present, subthreshold, or absent. Moderate to excellent inter-rater reliability has been established in inpatient, outpatient, and non-patient control samples on Axis I disorders (Lobbestael et al., 2011). A graduate student member of the study staff administered this measure via a phone interview.

Participants were excluded if English was not their first language, and/or if they currently met criteria for any screened item on the SCID-I (e.g., ADHD, alcohol abuse, non-alcoholic dependence) to ensure that the sample represented a healthy group. Participants with low levels of adaptive functioning, defined as scores below 70 on the Scales of Independent Behavior – Revised (SIB-R) were also excluded to ensure that the sample was healthy. Participants who had metal implants that could not be removed were also excluded because these may be dangerous while in the MRI scanner and are likely to cause an artifact on the images acquired.

Table 3. Participant demographic information

N (Number of participants)	48
	37 undergraduate students 2 friends 9 community members
Number of females	25 (52.1%)
Race	22 Caucasian (45.8%) 12 African-American (25%) 8 Asian (16.7%) 4 Hispanic (8.3%) 1 Other (2.1%) 1 not reported (2.1%)
Age at examination Mean years (SD)	22.41 (4.47)
Mean years of education (SD)	14.56 (1.79)
Mother's level of education (SES proxy measurement)	2 Junior High School (4.2%) 17 High School or Partial High School (35.5%) 25 College Graduate or Some College (52.1%) 2 Graduate Degree (4.2%) 2 not reported (4.2%)
Mean scaled score for intelligence – WASI-II (SD)	110.69 (10.31)
Occupation	39 student (81.3%) 8 employed (16.7%) 1 unemployed (2.1%)
Handedness	42 right-handed (87.5%) 3 left-handed (6.25%) 3 not reported (6.25%)

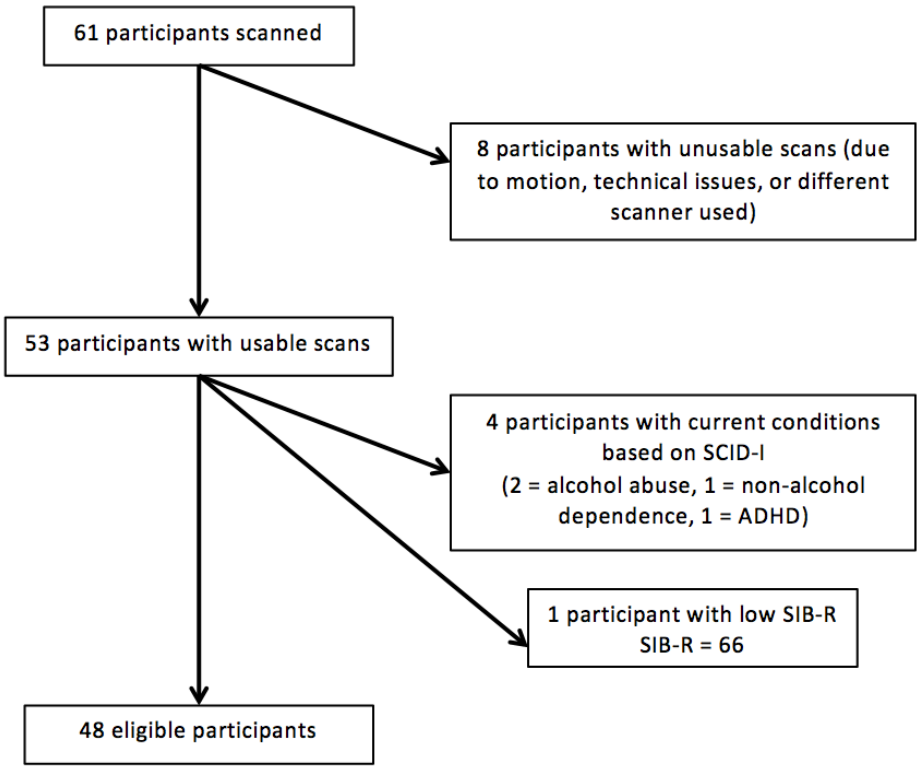

Figure 2. Participant exclusion tree

2.1.2 Letter n-back task

A widely recognized measure to assess working memory is the n-back task (Meule, 2017; Owen et al., 2005; Yaple et al., 2019). In this type of task, participants are instructed to attend to a series of stimuli and to respond when a presented stimulus is the same as the one presented n-trials previously. Functional volumes were acquired at the GSU/GaTech Joint Center for Advanced Brain Imaging (CABI) while participants completed a letter n-back task in which they were asked to monitor a series of letters and respond yes or no with their index finger on a button box if an item was presented n-items before (ranging from 1 to 3 letters back; Gevins & Cutillo, 1993). A higher "n" value (i.e., 2-back and 3-back) represents greater cognitive load due to higher monitoring, updating, and manipulating demands (Jonides et al., 1998), which has been demonstrated across ages (Bopp & Verhaeghen, 2018; Gajewski et al., 2018). On the other hand, n-values of 0 and 1 are measures of vigilance (King et al., 2015). In 0-back trials, a participant is first presented with a screen identifying a target (e.g., "Target = B"), and then would be expected to indicate "yes" with a button box when the target is subsequently presented, irrespective of letter case (e.g., for the sequence "b, a, B, c, D," the target "B/b" is presented on the first and third displays). In 1-back trials, the participant responds yes or no if the letter repeats itself from the stimulus directly before it. In 2- and 3-back trials, the participant responds yes or no if the letter repeats itself from the stimulus presented 2 or 3 items before it, respectively. N-values of 2- and 3-back are considered measures of working memory.

The n-back task was a block design paradigm with a total of 5 runs. E-prime software (version 2.0.8) was used for stimulus presentation and acquisition of accuracy and response time data. Each of the five runs consisted of 5 different blocks (crosshair, 0-, 1-, 2-, and 3-back blocks) and a fixation period, during which a crosshair was presented in the center of the screen.

Blocks were counterbalanced between separate runs to minimize order effects. Each block contained 15 letters. Written instructions for the task were presented on the stimulus presentation screen for 3000ms and preceded each block. Each letter stimulus was presented for 500ms with an interstimulus interval (ISI) of 2500ms between each letter presentation. Each run of the n-back task lasted approximately 5 minutes, yielding a total task time of approximately 20 minutes for all 5 runs (King et al., 2015).

To evaluate vigilance and set a basis for later evaluations of working memory, we analyzed the 0-back and 1-back data. Specifically, analyses used a 0-back *versus* crosshair contrast and a 1-back *versus* crosshair contrast to identify brain regions associated with vigilance. The crosshair block included in these contrasts is meant to identify regions involved in basic visual processing; thus, this contrast will subtract out activation not pertaining to vigilance. Additionally, we conducted a conjunction analysis [0-back *versus* crosshair AND 1-back *versus* crosshair] to identify regions of overlap among the contrasts. To assess working memory, we used 2-back *versus* 0-back and 3-back *versus* 0-back contrasts, followed by a [2-back *versus* 0-back AND 3-back *versus* 0-back] conjunction analysis to identify overlapping regions. Working memory performance was defined as the average percent correct for the 2-back and 3-back conditions across all five runs, whereas vigilance performance was defined as the average percent correct for the 0-back and 1-back conditions across all five runs.

To ensure that participants were familiar with the n-back task paradigm and had the opportunity to ask any questions, participants were first trained on an untimed, paper version of the task, and the researcher provided corrective feedback if a mistake was made. Subsequently, participants completed a timed version of the task on a laptop connected to a button box before

entering the scanner for the formal task (King et al., 2015). Participants were in the scanner for approximately 45 minutes.

2.1.3 Neuropsychological measures

2.1.3.1 Assessment of Intelligence

The four-subtest version of the Wechsler Abbreviated Scale of Intelligence (WASI-II), including the Block Design, Vocabulary, Matrix Reasoning, and Similarities subtests, was used to estimate full-scale intelligence quotients from four index scores (FSIQ; Wechsler, 2011), to ensure that the individuals included in the sample were neurotypical (FSIQs within 2 standard deviations of the mean). For the Block Design subtest, participants completed a series of two-color patterns using blocks. For the Vocabulary subtest, participants defined words presented orally and in print. Next, the Matrix Reasoning subtest prompted participants to view matrices and apply inductive reasoning to select a correct response. On the Similarities subtest, participants described how common items or concepts are alike (Irby & Floyd, 2013). WASI-II norms are based on a national sample of approximately 2,300 individuals aged 6 to 90 years and 11 months. The WASI-II has a very high test-retest reliability at .97 (Irby & Floyd, 2013).

2.1.3.2 Assessment of Working Memory and Vigilance

Participants were administered the Auditory Consonant Trigrams (ACT) test (Brown, 1958; Peterson & Peterson, 1959; Stuss et al., 1988) as an out-of-scanner behavioral measure of working memory. Participants were asked to remember three consonants (e.g., B-D-T) that were read by the examiner at a pace of one letter per second. Participants were asked to count backward from a given number to prevent immediate rehearsal of the consonant list. After 9, 18, or 36 seconds, the examiner knocked on the table to signal to the participant to stop counting,

and participants were asked to recall the three consonants. There are 20 items in total. Total scores are calculated by summing the number of letters correctly produced in each trial after 9, 18, or 36 seconds. Total raw scores for 9, 18, and 36 second trials were converted to standardized z-scores for analyses. The ACT is normed and validated from a population of 90 subjects ages 16-69. The total score on the ACT demonstrates good reliability (Chronbach's alpha = .79; Shura et al., 2016). The ACT has a high test-retest reliability at .71 (Shura et al., 2016).

Additionally, the Digit Span subtest from the Wechsler Memory Scale, Third Edition (Wechsler, 1997) was also used as a measure of working memory and vigilance. In Digit Span Forward, participants are asked to immediately repeat a sequence of numbers of increasing difficulty until two consecutive failed sequences are obtained. The highest number of digits repeated accurately within a sequence was used to represent vigilance ability; Digit Span Forward and Digit Span Backward represent different constructs and should not be combined (Ailion et al., 2020; Rosenthal et al., 2006). Specifically, Digit Span Forward is a measure of attention span (Lawlor-Savage & Goghari, 2016), and Digit Span Backward measures working memory. In addition to the summary normative scaled score, the maximum number of digits recalled in the forward and backward conditions were recorded and standardized into z-scores for analysis. This procedure allowed for differential association with the constructs of attention/vigilance (measured by the forward condition) and working memory (measured by the backward condition) within the task. Age-based means and standard deviations are provided for individual forward and backward spans, based on a normative population of 1,250 adults, age range 16-89 years (Hall et al., 2010). The test-retest reliability for the Digit Span Forward and Backward is high at .83 for both (Waters & Caplan, 2003; Wechsler, 1997).

2.1.3.3 Assessment of Reading Ability

The Letter-Word Identification (LW-ID) subtest from the Woodcock-Johnson III Tests of Achievement (WJ-III ACH) is a widely used measure for the assessment of reading decoding abilities (Woodcock et al., 2001). To perform this task, one must recruit cognitive processes of feature detection and analysis of letters and recognition of visual word forms. Individuals are presented with a list of words and are instructed to read and pronounce the words to the best of their ability without a time limit, which separates this subtest from subtests measuring reading fluency, which do measure response time.

The Passage Comprehension subtest from the WJ-III ACH is a widely used measure for the assessment of reading comprehension (Woodcock et al., 2001). For this subtest, an individual must read a written text passage silently, understand the information, and decide what word is needed to fill in a blank to complete the sentence (Schrank et al., 2001). Raw scores from both the LW-ID and Passage Comprehension subtests were converted to appropriate z-scores for analyses. The WJ-III ACH was normed on 8,818 individuals aged 24 months to 90+ years from over 100 geographically diverse communities in the United States (Schrank et al., 2001). The median reliability coefficient for the LW-ID subtest is .94, and the median reliability coefficient for the Passage Comprehension subtest is .88, indicating strong reliabilities for the individual subtests (Schrank et al., 2001).

2.1.3.4 Assessment of Language Ability

The Verbal Fluency subtest from the Delis-Kaplan Executive Function System (D-KEFS) was used to examine letter and category fluency. In letter fluency, individuals are presented with a letter and are given 60 seconds to produce as many words (excepting proper nouns and numbers) as they can. In category fluency, individuals are presented with a category (e.g.,

animals, boys' names) and are given 60 seconds to produce as many words associated with that category as possible. Letter fluency and category fluency raw scores were converted to standardized z-scores for analyses.

The D-KEFS Color-Word Interference subtest measures an individual's ability to inhibit a dominant and automatic verbal response. This measure consists of four different trials that differentiate between word reading, color naming, inhibitory control, and cognitive flexibility. Participants were asked to name the colors of square blocks on a page (Trial 1, Color Naming), read color words that are printed in black ink (Trial 2, Word Reading), name the color of the ink in which the word is printed (Trial 3, Inhibition), and to switch between naming the color of the ink in which the word is printed and reading the actual word based on a rule (Trial 4, Inhibition/Switching; Delis et al., 2001). The raw scores for the Inhibition/Switching trial were converted to z-scores for analyses. The D-KEFS subtests are normed on over 1,500 individuals demographically and regionally matched with the U.S. population for ages 8-89.

The Color-Word Interference subtest and Verbal Fluency subtests measure cognitive flexibility, and thus may be related to neural variability levels (Armbruster-Genc et al., 2016). The test-retest correlation for the Inhibition/Switching trial of the Color-Word Interference Test (Trial 4) is in the moderate range (r = .65; Na et al., 2018).

2.1.4 Imaging Parameters

All participants were scanned using a 3 Tesla (3T) Siemens Trio MRI scanner. Participants were outfitted with protective earplugs to reduce scanner noise. Task-dependent image series were collected using a gradient-recalled T2*-weighted echo-planar-imaging (EPI) sequence based on BOLD contrast. The primary imaging parameters for the BOLD contrast included: 40 slices, 3mm slice thickness and 0mm slice gap, repetition time (TR) = 2130ms,

echo time (TE) = 30ms, flip angle = 90 degrees, nominal resolution = 3 × 3 × 3 mm^3. For anatomical co-registration, high-resolution T1-weighted structural images were acquired with a three-dimensional (3D) magnetization prepared rapid gradient echo (3D MPRAGE) sequence using the following parameters: 176 sagittal slices, field of view = 256mm × 256mm, 1mm^3 voxel size, TR = 2250ms, TE = 3.98ms, inversion time TI = 850ms, flip angle = 9 degrees (King et al., 2015).

2.1.5 Image Processing

Data were analyzed using AFNI software (Cox, 1996). Functional images were preprocessed by first correcting for slice acquisition time (*3dTshift*). After this, functional images were aligned with anatomical images, corrected for motion (*3dvolreg*) by registering all functional volumes to the first volume across the time series, and normalized to the MNI152 brain using a non-linear transform (*@SSwarper*, which calls on *3dNwarpApply*). The MNI152 atlas was used because the meta-analyses chosen for ROI selection reported coordinates either in or converted to MNI space. All images were smoothed (*3dmerge*) using a Gaussian kernel with a full width at half maximum of 5mm. Finally, data were masked (*3dAutomask*), and time series for white matter (corpus callosum) and cerebrospinal fluid (CSF; left and right ventricles) for the unsmoothed images were regressed out (Garrett et al., 2011), along with six motion parameters (x, y, z translations and rotations). When performing the GLM, TRs were censored if they exceeded the thresholds of .3mm Euclidean movement and/or greater than 10% were outlier voxels. The AFNI default of polynomial regression was turned off because we accounted for changes in signal and drift in other steps, and we did not wish to potentially overcorrect and thereby diminish our ability to detect variability.

To calculate neural variability, which we operationalized as the standard deviation (SD) of the BOLD signal, we first extracted TRs that corresponded with task run and stimulus type, and then removed any TRs censored for excessive motion and/or outliers, so they would not be included in mean and SD calculations. We then identified the block onset for each specific voxel, and expressed each voxel value as signal change from the block onset (*3dcalc*; ((specific voxel value – onset voxel value)/onset voxel value) x 100)). To calculate SD of the signal, we clipped based on a maximum value across runs and stimulus types based on each individual participant's data distribution, and removed negative values. We then normalized all runs such that the overall 4D mean across brain and time series was 1 for each run, which corrects for potential low frequency drift (*3dBrickStat;* see Garrett et al., 2011). For each voxel, we then subtracted each respective run mean (*3dTstat*) prior to concatenating across all runs for each stimulus type (*3dTcat*; see Garrett et al., 2010). Finally, we calculated the SD of the concatenated runs for each stimulus type (*3dTstat*). In addition to calculating voxel SDs across this mean-run corrected time series to determine BOLD signal variability, we computed mean BOLD signal across the mean-run corrected time series for supplemental analyses (see Section 2.2.4). This was done by first computing the average (mean) percent change for each run and stimulus type prior to normalization (*3dTstat*), and then calculating the average signal across all runs for each stimulus type (*3dcalc*).

2.2 Data Analytic Plan

For Aim 1, hypotheses 1a and 1b, and for Specific Aim 2, a post hoc power analysis was conducted using *G*Power 3.1* (Faul et al., 2009) to determine the power that can be achieved with different effect sizes. Based on this power analysis, using a linear multiple regression with a fixed model with two predictors (a within-subjects variable of stimulus type, either trial type on

the n-back task (Aim 1), or cluster (Aim 2), and a between-subjects variable of head motion), an alpha level of .05, and a sample size of 48, an f^2 effect size of .25 will produce a power above .8. The estimated effect size is justified based on prior research that examined within-individual neural variability and its relation to reaction time (a behavioral variable) and identified an effect size of .25 (Garrett et al., 2011). This suggests that our sample size has sufficient power to detect significant effects with a medium effect size.

For analyses containing a partial least squares (PLS) regression (Aim 1, hypothesis 1c; Aim 3, hypotheses 3a-3d) a post hoc power analysis was conducted using *G*Power 3.1* (Faul et al., 2009) to determine the power that can be achieved with different effect sizes. Similarly, a linear multiple regression with a fixed model with two predictors (a brain variable and a behavioral variable), an alpha level of .05, and a sample size of 48, an effect size of $\eta^2_p = .41$, converted to a *G*Power* f^2 effect size of .21 (equation presented in Lakens, 2013) will produce a power of .78. The estimated effect size is based on PLS analysis of within-individual variability and reaction time (Garrett et al., 2011). This suggests that our sample size may produce slightly underpowered results with a medium effect size.

2.2.1 Analyses for Specific Aim 1

The first and second hypotheses for Specific Aim 1 outline the expected regions of within-individual neural variability during the letter n-back task, which involves working memory (cognitive flexibility) and vigilance (cognitive stability).

Meta-analyses evaluating the localization of working memory processes in the brain have suggested the involvement of the left dlPFC, vlPFC, ACC, and inferior parietal cortex, as primary regions involved in working memory (Alvarez & Emory, 2006; Daniel et al., 2016; Owen et al., 2005; Yaple et al., 2019). Additionally, the cerebellum has been postulated to be

involved in working memory, specifically cerebellar lobule VI and Crus I (Chein & Fiez, 2001; Chen & Desmond, 2005; Koziol et al., 2015; Kuper et al., 2016). In terms of vigilance, regions involved in a frontoparietal network are of interest: rostral PFC, ACC, medial and lateral posterior cortex, and posterior cerebellum (Gottwald et al., 2003; Schmahmann & Pandya, 1997). Masks were created for each identified ROI by creating 6mm spheres centered on the coordinates for the regions identified above and in Table 2 (*3dUndump*). For the vigilance contrasts (0-back *versus* crosshair, 1-back *versus* crosshair, [0-back *versus* crosshair AND 1-back *versus* crosshair]) and working memory contrasts (2-back *versus* 0-back, 3-back *versus* 0-back, [2-back *versus* 0-back AND 3-back *versus* 0-back]), and within each ROI, we extracted mean and SD values for every subject and stimulus type (*3dROIstats*). ROI analyses were conducted in R.

The third hypothesis of Aim 1 pertains to how within-individual variability in the identified ROIs may relate to behavioral performance on standardized neuropsychological measures of vigilance and working memory. We examined the relationship between within-individual neural variability in these specific ROIs and performance on neurocognitive measures of vigilance and working memory using PLS regression (McIntosh et al., 1996). We did a combined PLS regression for the working memory measures (ACT and Digit Span Backwards) and the vigilance measure (Digit Span Forward) at the whole-brain level, as well as with a mask containing the relevant working memory or vigilance ROIs. This type of analysis begins with a correlation matrix for each domain between the variables of interest and the signal from the whole-brain or relevant ROIs to calculate correlations across subjects. The correlation matrix is broken down using singular value decomposition to produce latent variables, consisting of correlation strength and a weighted pattern across brain voxels that optimally expresses the

correlation. For this PLS regression we obtained one predominant pair of latent variables for brain and behavior.

2.2.2 Analyses for Specific Aim 2

The hypothesis for Specific Aim 2 states that greater within-individual neural variability will be related to greater accuracy and faster response times on the letter n-back task. In addition, the IFJ may emerge as a region in which within-individual neural variability patterns may change depending on the trial type (vigilance: 0- and 1-back trials; working memory: 2- and 3-back trials).

A whole-brain cluster-wise analysis was performed using volumes acquired during the task blocks to create a within-individual neural variability map for the different trial types. When computing BOLD signal mean and variability scores across runs for each individual, we analyzed reaction time for correct trials only. We calculated mean RTs for each participant. Regression was used to minimize the effects of run, trial, and their interactions from RT trials separately for each task. Standardized RT residuals were then computed. We also analyzed accuracy with respect to BOLD signal mean and variability scores.

Group level analysis was conducted with AFNI *3dLME* (Chen et al., 2013), a program that performs traditional ANOVA- and ANCOVA-style computations, as it allowed for the inclusion of separate RTs for each trial type. For this analysis, mean RT and mean accuracy were separate within-subjects independent variables and within-individual neural variability was the between-subjects dependent variable. We looked at step-wise contrasts (neural variability in 1-back *versus* 0-back trials and mean RT and mean accuracy, 2-back *versus* 0-back trials and mean RT and mean accuracy, and 3-back *versus* 0-back trials and mean RT and mean accuracy) to

determine if increased cognitive load/effort in the n-back task resulted in different relationships between within-individual neural variability and mean RT and mean accuracy on the n-back task.

2.2.3 Analyses for Specific Aim 3

The hypotheses for Specific Aim 3 pertain to the relationship between within-individual neural variability on the n-back task and performance on standardized neuropsychological measures of working memory, vigilance, reading, and language.

We performed PLS regression analysis (McIntosh et al., 1996) in SPM12, using the identified ROIs from Aim 1 to examine the relationship between within-individual neural variability and performance on neuropsychological assessment measures. Forty-seven participants were included in these analyses because one participant did not have neuropsychological performance data for the WJ-III Passage Comprehension subtest, and PLS cannot be run when there is missing data. We did two PLS regressions, the first including performance on working memory measures (ACT and Digit Span Backwards z-scores) and the reading (WJ-III LW-ID and Passage Comprehension subtest z-scores) and language (D-KEFS Verbal Fluency and Color-Word Inhibition/Switching subtest z-scores) measures along with combined neural variability maps for 2- and 3-back trials, and the second including the vigilance measure (Digit Span Forward scores) and the reading and language measures along with the combined neural variability maps for 0- and 1-back trials. These PLS analyses included a correlation matrix for each domain between the variables of interest and the signal from the relevant ROIs identified in the letter n-back task, to calculate correlations across subjects. For this PLS regression, in addition to identifying the prominent brain factor and behavior factor, we looked deeper at subsequent prominent brain and behavior factors that also may explain interrelationships between working memory, vigilance, reading, and language.

2.2.4 Supplementary Planned Analyses

To identify activation, rather than deactivation, in regions involved in working memory, we subtracted each relevant n-back type *versus* crosshair: 2-back *versus* 0-back minus 2-back *versus* crosshair and 3-back *versus* 0-back minus 3-back *versus* crosshair. This analysis is important because levels of activation may be related to performance on more effortful working memory tasks (King et al., 2015). This supplementary analysis allowed us to probe further questions concerning within-individual neural variability in the context of activation versus deactivation in the working memory domain. For example, we were able to qualify if variability in the BOLD signal reflects changes in activation versus deactivation during specific tasks, compared to differences in the degree of activation or deactivation during specific tasks, and so on. Additionally, activation differences have been observed between healthy and clinical populations, specifically survivors of pediatric brain tumors (King et al., 2015). Any potential findings from this study pertaining to within-individual neural variability in the context of activation versus deactivation in a healthy population can help to inform future research examining this notion in clinical populations.

Also, we tested whether relationships in the specific ROIs pertaining to working memory and vigilance are specific to within-individual neural variability or also hold for the mean BOLD signal. In this way, mean BOLD signal acted as a planned control to aid in our interpretation of observed differences in neural variability.

2.2.5 Additional Planned Analyses

Pearson product-moment correlations between performance on the ACT and Digit Span Backwards were run to ensure concurrent validity such that ACT and Digit Span Backwards both measure working memory abilities.

3 RESULTS

3.1 Specific Aim 1

3.1.1 Hypothesis 1a

Paired samples t-tests were run to determine if there were differences in within-individual neural variability during different trial types on the n-back task. The Benjamini-Hochberg correction for multiple comparisons in neuroimaging analysis was used to decrease the possibility of committing a Type I error. In the seven stated ROIs associated with working memory (left dlPFC regions, vlPFC, ACC, dorsal inferior parietal cortex regions, cerebellum) for 2-back *versus* 0-back trials, variability was significantly greater with medium effect sizes (Cohen's *d*) in the second left dlPFC ROI ($t(47) = 4.434$, $p < .001$, $d = .64$), in the vlPFC ($t(47) = 3.968$, $p < .001$, $d = .57$), in the ACC ($t(47) = 4.021$, $p < .001$, $d = .58$), and in both stated dorsal inferior parietal cortex ROIs ($t(47) = 5.371$, $p < .001$, $d = .77$; $t(47) = 4.858$, $p < .001$, $d = .70$). For 3-back *versus* 0-back trials, also assessing working memory, variability was significantly greater, with small effect sizes in the second left dlPFC ROI ($t(47) = 2.810$, $p < .05$, $d = .41$), in the vlPFC ($t(47) = 2.737$, $p < .05$, $d = .40$), and with medium effect sizes in the ACC ($t(47) = 5.093$, $p < .001$, $d = .74$), and in both dorsal inferior parietal cortex ROIs ($t(47) = 5.292$, $p < .001$, $d = .76$; $t(47) = 4.402$, $p < .001$, $d = .64$). As far as the conjunction contrast [2-back *versus* 0-back AND 3-back *versus* 0-back contrast], the second left dlPFC ROI, the vlPFC, the ACC, and both dorsal inferior parietal cortices showed significance for both contrasts. These results are consistent with the hypothesis that working memory contrasts would reveal increased variability in these regions.

For the 0-back *versus* crosshair contrast to assess vigilance, there was significantly less within-individual neural variability in the lateral posterior parietal cortex ($t(47) = -3.616$, $p < .05$,

d = .52) with a medium effect size, contrary to the stated hypothesis. For the 1-back *versus* crosshair contrast, after correction for multiple comparisons, there were no significant differences in within-individual neural variability for any identified ROIs, again inconsistent with the stated hypothesis. For the [0-back *versus* crosshair AND 1-back *versus* crosshair] conjunction contrast, the lateral posterior parietal cortex was only significant in the 0-back *versus* crosshair contrast.

3.1.2 Hypothesis 1b

No significant differences in within-individual variability emerged for working memory contrasts (2-back *versus* 0-back, 3-back *versus* 0-back, [2-back *versus* 0-back AND 3-back *versus* 0-back]) or for vigilance contrasts (0-back *versus* crosshair, 1-back *versus* crosshair, [0-back *versus* crosshair AND 1-back *versus* crosshair]) for the cerebellar ROI (all corrected $p > .05$), contrary to the hypothesis which postulated increased variability in this region for working memory and vigilance.

Table 4. Results for Aim 1, hypotheses a and b

Contrast	ROI	t-value	Uncorrected p-value	Corrected p-value	Effect size
Working memory 2-back *versus* 0-back	Left dlPFC1	1.948	.057000	.115000	.28
	Left dlPFC2	4.434	.000055	.000276*	.64
	vlPFC	3.968	.000246	.000738*	.57
	ACC	4.021	.000209	.000738*	.58
	DIPC1	5.371	.000002	.000017*	.77
	DIPC2	4.858	.000014	.000081*	.70
	RCB	1.500	.140000	.140000	.22
Working memory	Left dlPFC1	1.391	.171000	.341400	.20

3-back *versus* 0-back	Left dlPFC2	2.810	.007192	.026166†	.41
	vlPFC	2.737	.008722	.026166†	.40
	ACC	5.093	.000006	.000037*	.74
	DIPC1	5.292	.000003	.000022*	.76
	DIPC2	4.402	.000061	.000307*	.64
	RCB	0.889	.376800	.378600	.13
Vigilance	Left dlPFC1	0.942	.351100	.872800	.03
0-back *versus* crosshair	Left dlPFC2	-0.190	.850400	.872800	.14
	ACC	-0.161	.872800	.872800	.02
	medialPPC	-1.566	.124000	.620000	.23
	lateralPPC	-3.616	.000729	.004371**	.52
	RCB	0.679	.500200	.872800	.10
Vigilance	Left dlPFC1	2.249	.029230	.140960	.14
1-back *versus* crosshair	Left dlPFC2	2.328	.024270	.140960	.03
	ACC	1.367	.178000	.178000	.02
	medialPPC	1.967	.055090	.140960	.23
	lateralPPC	-1.851	.070480	.140960	.52
	RCB	1.945	.057790	.140960	.10

* $p < .001$, ** $p < .01$, † $p < .05$

3.1.3 Hypothesis 1c

PLS regression analysis (McIntosh et al., 1996) was used to examine the relationship between within-individual neural variability in the identified working memory and vigilance ROIs and performance on neurocognitive measures of vigilance and working memory. To

increase power of the results when conducting the whole-brain PLS regression, we combined the SD variability maps for 0-back and 1-back trials, representative of vigilance, and the SD maps for 2-back and 3-back trials, representative of working memory. The working memory measures (ACT 9s, 18s, and 36s trials and Digit Span Backwards) and the vigilance measure (Digit Span Forward) were used in separate PLS regressions. We identified the prominent latent brain and behavior variables that explain working memory and vigilance performance.

A mask was created to be inclusive of all of the working memory ROIs, and this mask was applied to the 2- and 3-back combined variability z-scored brain map to examine important regions of interest that accounted for the most variance in performance on the working memory neuropsychological tasks. PLS extracted the brain component, which accounted for 21% of the working memory variability variance, and paired it with the behavioral factor with the greatest beta weight, obtained for Digit Span Backward z-scores (beta, $\beta = 2.7534$), followed by ACT 18s ($\beta = 2.5442$), ACT 36s ($\beta = 2.4138$), and ACT 9s ($\beta = 2.0761$), which accounted for 11% of the behavioral variation. The brain regions that predominantly accounted for the significant positive correlation between the brain variable and neuropsychological measure variables ($r(46) = .41$, $p = .0035$) were both of the left dlPFC ROIs, as hypothesized. However, the ACC and medial and lateral parietal cortex ROIs did not emerge as significant contributors to this first brain factor. Other ROIs that contributed to this factor included the vlPFC, IFJ, the left IFG, and the left occipito-temporal cortex (see Table 5). The positive beta weights and positive correlation suggests that increased neural variability in 2- and 3-back working memory trials of the n-back task is associated with increased performance on out-of-scanner neuropsychological tasks, consistent with the hypothesis.

A similar process was performed to obtain the brain factor regions that explained performance on the Digit Span Forward measure of vigilance. A mask was created to be inclusive of the identified vigilance ROIs, and this mask was applied to the 0- and 1-back combined variability z-scored brain map. The first brain component extracted by PLS accounted for 23% of the variance in vigilance variability, and paired it with the behavioral factor with the greatest beta weight, Digit Span Forward z-score β = 2.9510, which accounted for 18% of behavioral variance. The positive correlation ($r(46) = .43$, $p = .0023$) between neural variability in vigilance trials and performance on the Digit Span Forward task was accounted for by the following brain regions: the lateral posterior parietal cortex as hypothesized, as well as the IFJ, the left IFG, and the left occipito-temporal cortex (see Table 5). The positive beta weight and the positive correlation that was observed is in opposition to our hypothesis; the results indicate that increased variability in vigilance trials of the n-back task is associated with increased performance on the Digit Span Forward task.

Table 5. Results for Aim 1, hypothesis c

	Component pair # (variance %)	**Brain regions**	**Behavioral measures**	**r**	**p**
0-back and 1-back combined (ROI masked)	1 (23%, 18%)	Lateral PPC IFJ Left IFG Left OTC	Digit Span Forward	.43	.0023**
2-back and 3-back combined	1 (21%, 11%)	Left dlPFC1 vlPFC IFJ	Digit Span Backward ACT 9s	.41	.0035**

(ROI masked)		IFG Left OTC	ACT 18s ACT 36s		
** $p < .01$					

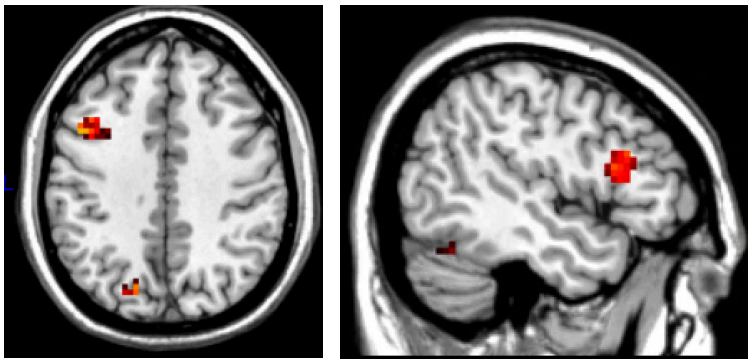

Figure 3. Regions involved in first component for vigilance variability map (0-back and 1-back combined) and vigilance neuropsychological measure (Digit Span Forward)
Left = lateral PPC and IFJ; right = IFG and left OTC; visualized in Mricron

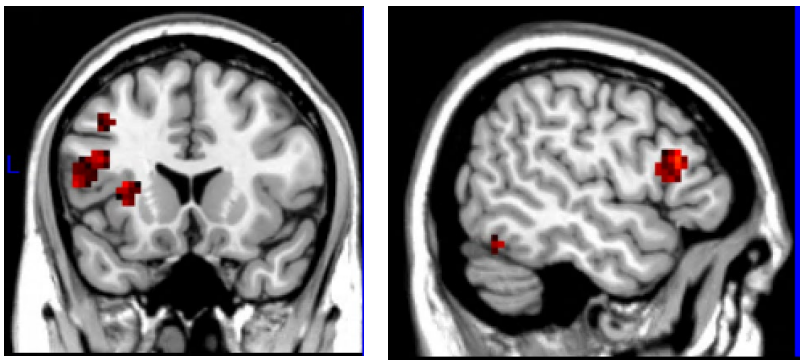

Figure 4. Regions involved in first component for working memory variability map (2-back and 3-back combined) and working memory neuropsychological measures (Digit Span Backward, ACT 9s, 18s, 36s trials)
Left = left dlPFC, vlPFC, IFJ; right = left IFG and left OTC; visualized in Mricron

3.2 Specific Aim 2

3.2.1 Hypothesis 2

Pearson product-moment correlation coefficients were run to determine if the difference in within-individual neural variability in the IFJ ROIs between trial types (i.e., 1-back *versus* 0-

back, 2-back *versus* 0-back, 3-back *versus* 0-back) was correlated with differences in accuracy between different trial types (i.e., 1-back *versus* 0-back accuracy) or with differences in reaction time between different trial types (i.e., 1-back *versus* 0-back reaction time) on the n-back task. Overall, for each of the contrasts, no significant correlations were observed between the difference in within-individual neural variability in the IFJ across trial types and the difference in accuracy or reaction time across trial types (all $p > .05$; see Table 6). Accuracy and reaction time data was not collected for crosshair trials, thus the correlation between the difference in within-individual neural variability compared to crosshair (0-back *versus* crosshair) and the difference in accuracy and reaction time for 0-back trial types was not able to be examined.

Table 6. Results for Aim 2, hypothesis 2, region of interest analyses

Contrast	Region of interest	r (Accuracy)	p (Accuracy)	r (Reaction Time)	p (Reaction Time)
1-back *versus* 0-back	IFJ1	.10	.49	-.03	.85
	IFJ2	.07	.63	-.16	.29
2-back *versus* 0-back	IFJ1	.12	.40	-.20	.18
	IFJ 2	.13	.39	.02	.92
3-back *versus* 0-back	IFJ 1	.15	.30	-.16	.27
	IFJ 2	.11	.47	-.02	.88

In addition to looking at this at the ROI-level, we looked at whole-brain data to evaluate whether a significant cluster would emerge in the IFJ, as this region has been shown to exhibit a double dissociation in tasks requiring cognitive flexibility or cognitive stability (Armbruster-Genc et al., 2016). After performing cluster correction (*3dClustSim*), the minimum cluster size was set to 15 voxels, with $p < .001$. For accuracy, in 0-back trials, increased variability was

observed in the right inferior parietal lobule (xyz: -31.5, 40.5, 22.5; $p < .01$), suggestive of a positive correlation between neural variability and accuracy for 0-back trials in this area, and decreased variability was found in the right superior frontal gyrus (xyz: -19.5, -10.5, 43.5; $p < .03$), suggestive of a negative correlation between neural variability and accuracy for 0-back trials in this area. For accuracy, no clusters passed the cluster correction threshold for 1-, 2-, and 3-back trials. In terms of contrasts for accuracy, no additional clusters were significant for 3-back *versus* 0-back. For the 2-back *versus* 0-back contrast, there were significant negative variability clusters in the right inferior parietal lobule (xyz: -31.5, 40.5, 22.5; $p < .01$), in the left superior temporal gyrus (xyz: 43.5, -13.5, -31.5; $p < .02$), and in the left parahippocampal gyrus (xyz: 16.5, 22.5, -25.5; $p < .02$) suggesting that decreased variability in these clusters was correlated with increased accuracy. Finally, for the 1-back *versus* 0-back contrasts, there was also a significant negative correlation between variability in the left parahippocampal gyrus (xyz: 10.5, 7.5, -22.5, $p < .01$) and accuracy. For reaction time, no clusters were significant for any of the n-back trial types, or for 3-back *versus* 0-back, 2-back *versus* 0-back, or 1-back *versus* 0-back contrasts after cluster correction was completed, indicating no correlations between neural variability and reaction time.

3.3 Specific Aim 3

3.3.1 Hypothesis 3a

PLS regression was used to determine the relationship between within-individual neural variability in the IFJ and performance on vigilance (Digit Span Forward) and working memory (Auditory Consonant Trigrams and Digit Span Backwards) measures when combined with measures of reading and language. Again, to increase power of the results, we used the combined

SD variability maps for 0-back and 1-back trials and for 2-back and 3-back trials in order to conduct the whole-brain PLS regression.

For the combined 0- and 1-back variability maps at the whole-brain level, the first component, which explained 21% of the variance in neuropsychological measure scores, revealed the highest beta weights for the D-KEFS Verbal Fluency measures (Letter Fluency (β = 5.4859) and Category Fluency (β = 2.9219)), suggesting that variability in neural activity during vigilance trials best explained verbal fluency performance compared to the other measures included in the analysis (see Table 7). We then correlated the brain variability component and the neuropsychological scores component and found that variability for vigilance was positively correlated with the neuropsychological scores ($r(45) = .74$, $p < .001$). When extracting the brain regions for this dominant component, we found that after z-scoring the combined 0- and 1-back variability maps, neural variability in the cerebellum, brainstem, and inferior frontal lobes were correlated with the D-KEFS Verbal Fluency measures (see Figure 5). After probing the second and third components, which accounted for 13% and 12% of the variance in the behavioral variables, respectively, verbal fluency continued to emerge as the neuropsychological domain most related to neural variability for vigilance, but the associated brain region reflected the whole cortex. The correlations with this brain "component" were high (see Table 7), but covariance was low, which means that the correlation was significant but small in magnitude.

For the combined 2- and 3-back variability maps at the whole-brain level, the first component, explaining 21% of the variance in the behavioral measures, revealed the highest beta weight for Digit Span Backward (β = -.9983), representative of working memory, with a correlation of $r(45) = .77$, $p < .001$ (see Table 7). Notably this was a mainly negative component, suggesting that decreased variability was associated with increased Digit Span Backward scores.

The whole cortex emerged when looking at the brain regions that explained this correlation. The second component, which explained 18% of the variance in the neuropsychological measures, revealed the highest beta weights for the D-KEFS Verbal Fluency measures (Letter Fluency (β = 1.1490) and Category Fluency (β = 0.6440), but also a third highest beta weight for D-KEFS Color-Word Inhibition/Switching (β = 0.4967). Variability for working memory was positively correlated with scores on these neuropsychological performance measures ($r(45) = .81$, $p < .001$; see Table 7). Similarly to the results from the whole-brain combined 0- and 1-back neural variability maps that identified the highest beta weights for the Verbal Fluency measures in the first component, we found that the brain regions that explained this correlation were the cerebellum, brainstem, and inferior frontal lobes (see Figure 6). The third probed component explained only 10% of the variance in the behavioral measures, but revealed the highest beta weights for the ACT trials (9s: β = .5720; 18s: β = 1.6740; 36s: β = 1.6271) with a significant positive correlation of r(45) = .84, p < .001 (see Table 7). This third component also revealed that the correlation was explained throughout the whole cortex.

Variability in voxels throughout the brain unrelated to the n-back task may have influenced these component results. To look more specifically at potential impacts of neural variability in voxels more likely related to the n-back task, we created single masks for vigilance and working memory inclusive of the ROIs proposed to be involved in vigilance and working memory, respectively.

For the combined 0- and 1-back ROI variability maps, the first brain component that accounted for 24% of variance in vigilance neural variability, which explained 6% of the variance in the behavioral measures, revealed the lowest beta weight for Digit Span Forward z-scores (β = -2.2138), with a positive correlation of $r(45) = 0.47$, $p < .001$ (see Table 7),

suggesting that decreased variability for 0- and 1-back trials, requiring vigilance, is associated with higher Digit Span Forward scores. The IFJ ROI did not emerge as an ROI that contributed to this variance. Though hypothesized that greater within-individual neural variability in the IFJ would be related to lower vigilance scores, the correlation between this first brain component and first behavioral component did not include the IFJ, suggesting that variability in this region may not be important to performance on the vigilance measure. The fourth component, which explained only 8% of the variance in behavioral measure scores revealed the highest beta weight for the Digit Span Forward measure ($\beta = 3.4022$). There was a significant positive correlation for this component ($r(45) = .62$, $p < .001$; see Table 7), and again, the IFJ did not emerge as a region to explain the correlation, indicating that contrary to the hypothesis, greater variability in the IFJ was not related to lower vigilance scores.

For the combined 2- and 3-back ROI variability maps, the first brain component, which explained 26% of the working memory variability variance and 4% of the behavioral measure variance, the highest beta weights were demonstrated for Digit Span Backward z-scores ($\beta = 2.2159$), and for the 9s ($\beta = 1.1670$), 18s ($\beta = 1.3366$), and 36s ($\beta = 1.2013$) trials of the ACT. This finding is logical because these measures are the neuropsychological measures used to represent working memory. The significant positive correlation ($r(45) = .41$, $p = 0.0042$; see Table 7) indicates that increased variability in the brain regions that make up this component is related to increased scores on these measures. Among the brain regions that made up this first component was the IFJ. Consistent with the hypothesis, the IFJ did emerge as a region that described the correlation between working memory neural variability and performance on measures of working memory.

3.3.2 Hypothesis 3b

According to our PLS regression analyses, for the 0- and 1-back combined ROI variability map, the second brain component identified the highest beta weights for the language measures. This second component accounted for 11% of the variance in both vigilance neural variability and behavioral measure scores and revealed the highest beta weights for the D-KEFS Verbal Fluency measures (Letter Fluency β = 2.7159; Category Fluency β = 3.4223) and the D-KEFS Color-Word Inhibition/Switching measure (β = 1.7859). This component, and its positive correlation with these measures ($r(45) = .53$, $p < .001$; see Table 7), was mostly accounted for in the brain by increased variability in the medial and lateral posterior parietal cortices and the IFJ as hypothesized, but also by the right cerebellum, which was not included in the original hypothesis. Additionally, variability within the left IFG did not emerge as a significant contributor to this "language" brain component.

For the 2- and 3-back combined ROI variability map, the second component, which explained 13% of the variance in working memory neural variability, could be used to explain language abilities. This component produced a beta value of .2970 for D-KEFS Category Fluency, and a beta of 1.9268 for D-KEFS Color-Word Inhibition/Switching. The significant correlation for this component ($r(45) = .47$, $p < .005$; see Table 7) was based on diffuse regions: the left dlPFC, vlPFC, dorsal inferior parietal cortex, lateral occipito-temporal cortex, and right cerebellum, in addition to the hypothesized regions of the left IFG and the IFJ, but not the posterior parietal cortex.

3.3.3 Hypothesis 3c

For the 0- and 1-back combined ROI variability map, after assessing the first 10 components, no component emerged that identifiably produced high beta weights for the reading

measures. This demonstrates that within the ROIs included in the combined vigilance variability mask, there is not much neural variability associated with performance on reading measures. The variance in reading measure z-scores was low (SD for Letter-Word ID z-scores = .52, SD for Passage Comprehension z-scores = .55). This may have also contributed to the lack of emergence of a strong behavioral component for reading measures.

For the 2- and 3-back combined ROI variability map, the third component of the PLS regression which accounted for only 4% of the variance in working memory neural variability but 13% of the variance in behavioral measures, illustrated the highest beta weights for the reading measures (WJ-III Letter-Word Identification, $\beta = -.7055$; WJ-III Passage Comprehension, $\beta = -.4899$), in addition to the D-KEFS Color-Word Inhibition/Switching measure ($\beta = -.5380$). The negative beta weights indicate that increased variability was associated with decreased scores on the reading measures. The brain regions that explain the significant positive correlation ($r(45) = .65$, $p < .001$; see Table 7) between working memory variability and performance on these reading measures were the left dlPFC, dorsal inferior parietal cortex, left IFG, and the hypothesized left occipito-temporal cortex. The posterior parietal cortex did not emerge as a region that explained this component.

Table 7. Results for Aim 3, hypotheses a-c

	Component pair # (brain variance%, behavioral variance %)	**Brain regions**	**Behavioral measures**	**r**	**p**	**Corrected p**
0-back and 1-back combined (whole-brain)	1 (8%, 21%)	Bilateral CB Brainstem Inferior Frontal Lobe	Letter-Word ID Passage Comprehension Digit Span Forward D-KEFS Letter Fluency	.74	3.8779e-09	7.7558e-09

			D-KEFS Category Fluency D-KEFS CWI Inhibition/Switching			
	2 (8%, 13%)	Whole cortex	Same as above	.70	5.9466e-08	5.9466e-08
	3 (6%, 12%)	Whole cortex	Same as above	.84	2.1961e-13	6.5883e-13
0-back and 1-back combined (ROI masked)	1 (24%, 6%)	Left OTC Right CB	Same as above	.47	8.9106e-04	8.9106e-04
	2 (11%, 11%)	Medial PPC Lateral PPC IFJ Right CB	Same as above	.53	0.0001	2.0000e-04
	4 (8%, 8%)	Left OTC Right CB	Same as above	.62	2.9039e-06	8.7117e-06
2-back and 3-back combined (whole-brain)	1 (6%, 21%)	Whole cortex	Letter-Word ID Passage Comprehension Digit Span Backward ACT (9s, 18s, 36s) D-KEFS Letter Fluency D-KEFS Category Fluency D-KEFS CWI Inhibition/Switching	.77	3.8291e-10	3.8291e-10
	2 (6%, 18%)	Bilateral CB Brainstem Inferior Frontal Lobe	Same as above	.81	.6166e-12	1.2332e-12
	3 (5%, 10%)	Whole cortex	Same as above	.84	1.3239e-13	3.9717e-13
2-back and 3-back combined (ROI masked)	1 (26%, 4%)	Left dlPFC vlPFC ACC DIPC IFJ Left IFG Left OTC	Same as above	.41	0.0042	.0042
	2 (13%, 7%)	Left dlPFC vlPFC DIPC IFJ	Same as above	.47	0.0008	.0016

		Left IFG Left OTC Right CB				
	3 (4%, 13%)	Left dlPFC DIPC Left IFG Left OTC	Same as above	.65	5.9967e-07	1.79901e-06

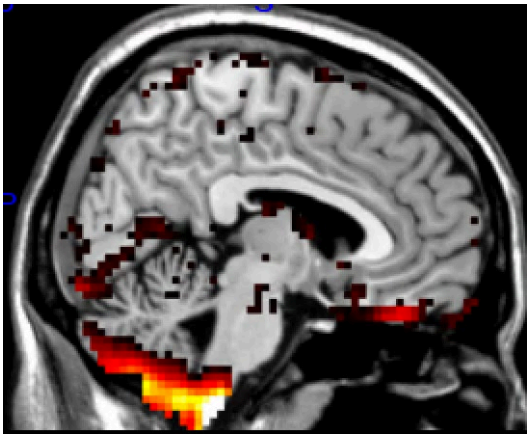

Figure 5. Regions in combined neural variability map for 0- and 1-back trials correlated with PLS component 1, explained by D-KEFS Verbal Fluency measures (Letter and Category Fluency)
Visualized in Mricron

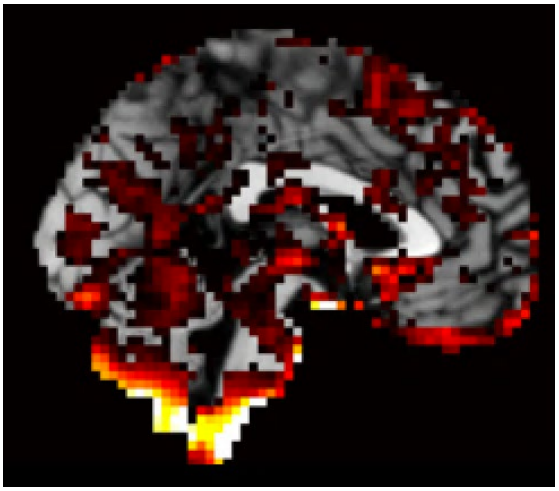

Figure 6. Regions in combined neural variability map for 2- and 3-back trials correlated with PLS component 2, explained by D-KEFS Verbal Fluency measures (Letter and Category Fluency) and D-KEFS Color-Word Inhibition/Switching measure
Visualized in Mricron

3.4 Supplementary Planned Analyses

In order to identify whether differences in variability stemmed from fluctuations in activation versus deactivation in ROIs associated with working memory (left dlPFC ROIs, vlPFC, ACC, dorsal inferior parietal cortex ROIs, cerebellum), we subtracted each relevant n-back type (2- and 3-back) *versus* crosshair. After using the Benjamini-Hochberg correction, this analysis determined that in the vlPFC, ACC, and dorsal inferior parietal regions, there was significantly greater activation than crosshair, indicating that these ROIs were activated rather than deactivated during working memory trials (see Table 8).

Table 8. Results for supplementary planned analyses

ROI	Contrast	t value	p value	Corrected p value
LdlPFC1	3-back vs. crosshair	1.194	.235500	.6253
	2-back vs. crosshair	1.4077	.162500	.6253
LdlPFC2	3-back vs. crosshair	1.5472	.125200	.6253
	2-back vs. crosshair	2.4029	.018230	.1276
vlPFC	3-back vs. crosshair	2.2662	.025740	.1544
	2-back vs. crosshair	2.9671	.003817	.0344†
ACC	3-back vs. crosshair	3.0517	.002962	.0296†
	2-back vs. crosshair	2.6332	.009911	.0793
DlPC1	3-back vs. crosshair	4.4069	.000029	.0004*
	2-back vs. crosshair	4.6521	.000011	.0002*
DlPC2	3-back vs. crosshair	3.3312	.001237	.0148†
	2-back vs. crosshair	3.1196	.002405	.0265†
RCB	3-back vs. crosshair	0.4899	.625300	.6253

	2-back vs. crosshair	0.5810	.562600	.6253
* $p < .001$, † $p < .05$				

Pearson correlations were also run to assess if the relationship between within-individual neural variability in the n-back task in the nine identified working memory and vigilance ROIs (left dlPFC regions, vlPFC, ACC, dorsal inferior parietal cortex regions, medial and lateral posterior parietal cortex regions, and right cerebellum) and reaction time and accuracy on the n-back task was unique to variability, or if the same relationships would hold true for mean signal. At the individual ROI level, variability only within the medial posterior parietal cortex ROI demonstrated a significant positive correlation with mean accuracy in the n-back task in 2-back ($r(46) = .313$, $p = .030$) and 3-back ($r(46) = .341$, $p = .018$) trials; for all eight other ROIs, all $p > .05$. These significant correlations between neural variability and accuracy in 2- and 3-back trials did not hold up when mean signal was correlated with accuracy in the medial posterior parietal cortex ROI ($p > .05$).

3.5 Additional Planned Analyses

To ensure that the tasks that were collapsed together as measures of working memory were concurrently valid, we ran Pearson product-moment correlations. Performance on the ACT (9 second z-score, 18 second z-score, and 36 second z-score) and Digit Span Backwards z-score was significantly correlated. See Table 9 for correlations and p-values. These results indicate that both of these measures are associated with each other and likely assess the same cognitive process.

Table 9. Results for additional planned analyses for working memory

		ACT z-score (9s)	ACT z-score (18s)	ACT z-score (36s)	WMS Digits Backward z-score
ACT z-score (9s)	Correlation	1	.645**	.656**	.454**
	Sig. (2-tailed)		.000	.000	.001
ACT z-score (18s)	Correlation	.645**	1	.737**	.345†
	Sig. (2-tailed)	.000		.000	.016
ACT z-score (36s)	Correlation	.656**	.737**	1	.490**
	Sig. (2-tailed)	.000	.000		.000
WMS Digits Backward z-score	Correlation	.454**	.345†	.490**	1
	Sig. (2-tailed)	.001	.016	.000	

** p < .01, † p < .05

4 DISCUSSION

4.1 Discussion of Aim 1 Results

In Aim 1 of this study, we set out to explore the relationship between within-individual neural variability and performance on working memory and vigilance trials of a letter n-back task. A priori ROIs for both working memory and vigilance constructs were used based on prior literature. After correcting for multiple comparisons, our results indicate increased variability in the 2-back trials *versus* 0-back trials for five of the seven ROIs. Significant results with medium effect sizes were found in one of the left dlPFC ROIs, the vlPFC, the ACC, and the dorsal inferior parietal cortex. Additionally, after correcting for multiple comparisons, significantly greater variability was observed in 3-back *versus* 0-back trials in the same five ROIs, though the

effect size was small in the same left dlPFC ROI and vlPFC, and was medium in the ACC and dorsal inferior parietal cortex ROIs. The increased variability in both 2-back *versus* 0-back trials and 3-back *versus* 0-back trials in the same five ROIs is encouraging, suggesting a consistent pattern of increased variability in working memory trials in regions of a frontoparietal network. The significant increased variability in these regions supports hypothesis 1a, and complements a recent study related to mean-squared-successive-differences (MSSD) based variability in the context of healthy aging, which reported increased variability compared to mean variability during working memory (more complex) trials compared to less complex trials in related, but not identical ROIs (Boylan et al., 2020). The notions that working memory requires some cognitive flexibility, that working memory and cognitive flexibility share component processes like planning (Clark et al., 2021), and that cognitive flexibility is associated with greater variability (Armbruster-Genc et al., 2016), also support our current findings in healthy young adults.

It is interesting that we did not find significant ROIs in the 1-back *versus* crosshair contrast. It is possible that the Benjamini-Hochberg correction method was too stringent, and if a different method was used, variability in the hypothesized ROIs may have emerged as significantly different than crosshair. Additionally, it is interesting that we found significantly less variability in 0-back trials *versus* crosshair for the lateral posterior parietal cortex ROI. These findings combined suggest that increased variability may not be associated with vigilance processes, and in fact, more stable activity in some regions, such as the lateral posterior parietal cortex, may occur when individuals use sustained attention. As stated by Armbruster-Genc et al. (2016), increased variability during sustained attention tasks may decrease performance. Thus, this may explain the decreased variability or lack of significant change in variability during the vigilance trials of the n-back task observed in this study. The lack of significance in the right

cerebellar ROI is inconsistent with our hypothesis 1b. It is possible that cerebellar involvement in the specific coordinates identified for this region of interest was not strong enough to detect changes in variability during the letter n-back task. In addition, it may be that stability of activity in the cerebellum, specifically in the posterior cerebellum, may be more important during working memory and vigilance trials as the cerebellum plays an important role in attending to information and relaying this information to the cortex, while refining and modulating cortical functions (Schmahmann et al., 2019).

When PLS regression was used to identify the brain regions that explained performance on the working memory neuropsychological measures, the left dlPFC ROI was implicated. This supports the widely held view that the dlPFC is involved in working memory processes (Dove et al., 2001; Owen et al., 2005; Owen, 1997). The results indicate that increased variability may predict better working memory scores. This is consistent with research by Armbruster-Genc et al. (2016), which found that working memory, a process that relies on cognitive flexibility, actually benefits from neural variability. The other regions of the hypothesized working memory network, including vigilance ROIs, as vigilance is important to working memory (the ACC, and medial and lateral parietal cortex ROIs), did not emerge as regions that explained the correlation between neural variability in the 2- and 3-back trials of the n-back task and performance on the Digit Span Backwards and ACT measures. The ACC ROI identified may be part of the subgenual portion of the ACC, which is more likely involved in limbic and autonomic processes, as opposed to the middle cingulate cortex, which has been shown to have higher connectivity with cognitive (dorsal PFC) related areas (Stevens et al., 2011). This may be why the ACC was not a region that contributed to performance on the working memory measures. The lack of involvement of the medial and lateral parietal cortex ROIs suggests that it may be neural

variability within the dlPFC only, not in other parts of the frontoparietal working memory network, that explains working memory task performance. Involvement of the vlPFC is well supported, as this region is also important to working memory (Dove et al., 2001; Owen et al., 2005; Owen, 1997). The importance of the IFJ, left IFG, and left occipito-temporal cortex in explaining the correlation between neural variability in working memory trials and performance on the working memory tasks is interesting because these regions, according to the zeitgeist in the literature, are involved in task switching, or reading respectively. It is possible that because task switching involves heightened cognitive flexibility, and because cognitive flexibility is related to working memory, the IFJ was involved. The working memory neuropsychological measures did not require reading; all items for these tasks are presented orally. Outside of reading, the IFG has been found to play a role in verbal working memory and subvocal rehearsal for verbal information (Chein & Fiez, 2001; Emch et al., 2019; Logie et al., 2003), explaining why the IFG was involved. Additionally, the IFG plays a role in behavioral response inhibition (Swick et al., 2008), which is important in n-back tasks. The left occipito-temporal cortex may have been involved to an extent because the n-back task required decoding of letters in the scanner (i.e., B and b as the same, B and d as different). The left occipito-temporal cortex plays a role in recognition of letter case (Sebastian et al., 2014), highlighting its relevance in the n-back paradigm used; however, its role in the neuropsychological working memory tasks is worthy of further investigation.

PLS regression revealed that the lateral posterior parietal cortex was involved in explaining the correlation between neural variability during the vigilance trials of the n-back task and performance on a neuropsychological measure of vigilance (Digit Span Forward). This was consistent with the hypothesis, and also with research suggesting that the parietal lobes play a

role in sustained attention (Behrmann et al., 2004). Compared to its involvement in working memory and due to its role in task switching based on its importance in cognitive flexibility, the involvement of the IFJ makes less sense here; however, task switching may not be the only function of this region. In a functional connectivity study, the IFJ was significantly co-activated with areas in the posterior parietal cortex, suggesting its role in cognitive control (working memory, task switching, inhibitory control) may be linked to attention processes (Sundermann & Pfleiderer, 2012). Again, the Digit Span Forward task is an orally presented task. Involvement of the IFG may again be due to its involvement in subvocal rehearsal of verbal information (Logie et al., 2003). The occipito-temporal cortex involvement is perplexing, though it may just be that the n-back letter task required reading.

4.2 Discussion of Aim 2 Results

Contrary to the stated hypothesis presuming a double dissociation in the IFJ for working memory (requiring cognitive flexibility) and vigilance (requiring cognitive stability), we did not find any significant correlations in variability between n-back trial types (i.e., 2-back *versus* 0-back, 3-back *versus* 0-back) and differences in accuracy between different trial types (i.e., 2-back *versus* 0-back accuracy) or differences in reaction time between different trial types (i.e., 2-back *versus* 0-back reaction time). Variability in the IFJ was not significantly correlated with faster reaction times and fewer errors for the 2- and 3-back trials. It is possible that our ROIs (IFJ1 and IFJ2) were too narrow subregions within the IFJ to detect a significant effect for this double dissociation.

As a result, we also used a whole-brain cluster-wise analysis to evaluate whether broader effects of variability may emerge in the IFJ related to accuracy and reaction time on the n-back task; however, IFJ clusters did not emerge. First, for accuracy, the 2-back *versus* 0-back contrast

demonstrated significant negative variability clusters in the right inferior parietal lobule, in the left superior temporal gyrus, and in the left parahippocampal gyrus, and the 1-back *versus* 0-back contrast also revealed a significant negative variability cluster in the left parahippocampal gyrus. In general, the parietal lobe is involved in the advanced perception of visual information, specifically maintaining attentive control on a task, as well as responding to important new task information (Singh-Curry & Husain, 2009). Because the n-back task was a visual task, it is possible that decreased variability in this region, even in a working memory trial (2-back), is reflective of increased sustained attention; this increased attention to visual information could account for greater accuracy on the n-back task. The superior temporal gyrus is typically involved in auditory processing. Because the n-back task was not an auditory task, decreased variability in this region is perplexing. It may be that decreased variability in this region suppresses a response to any auditory distractors (i.e., scanner noise). The parahippocampal gyrus is known for its role in memory formation due to its proximity to the hippocampus, and for its ability to perform complex visual processing, as a result of its location near the fusiform cortex (Aminoff et al., 2013). The decreased variability in the 2-back *versus* 0-back contrast in the parahippocampal gyrus is harder to explain, because in theory, increased variability should enhance working memory, and thus, increase accuracy on the task; however, the decreased variability in this region for the 1-back *versus* 0-back contrast is consistent with the idea that less variability is beneficial for sustained attention (Armbruster-Genc et al., 2016), and the finding that hippocampal volume is associated with auditory attention (Jayakar et al., 2015). It is possible that the parahippocampal gyrus is involved in other, broader attention processes, like visual attention, explaining the lesser variability in this region in the 1-back *versus* 0-back contrast. These whole-brain clusters suggest that there is a complex relationship between

variability and performance on the n-back task, such that increased variability is present in some regions, while decreased variability is present in others to obtain optimal performance.

For reaction time, we did not find significant clusters for any of the n-back trial types, nor for 3-back *versus* 0-back, 2-back *versus* 0-back, or 1-back *versus* 0-back contrasts. These findings are likely due to the overall weak main effect of reaction time, as well as the overall weak interaction between stimulus type and mean reaction time across runs.

4.3 Discussion of Aim 3 Results

For Aim 3, we sought to examine how within-individual neural variability would be linked to performance on neuropsychological measures outside of the scanner. Traditional measures of working memory, sustained attention, reading, and language were used to look at how within-individual neural variability could be related to these cognitive processes, a topic of interest in the recent literature.

We found that at the whole-brain level, neural variability for vigilance (in 0- and 1-back combined variability maps) was most associated with neuropsychological performance on verbal fluency measures, represented by the highest beta weights, potentially suggesting that sustained attention is important for letter-based and category-based word retrieval. Neural variability in the whole-brain in 0- and 1-back trials of the n-back task was not associated with a neuropsychological measure of vigilance, Digit Span Forward, as each probed component yielded a low beta weight for this measure. This is consistent with results found recently by Boylan et al. (2020), who reported that BOLD variability measured with mean-squared-successive-differences (MSSD) did not show a significant association with Digit Span Forward. Neural variability in the whole-brain in 2- and 3-back trials of the n-back task was associated with performance on common neuropsychological measures of working memory (Digit Span

Backward, ACT), demonstrated by the highest beta weights for these behavioral variables, consistent with the idea that increased variability may help explain increased working memory performance (Armbruster-Genc et al., 2016); however, this pattern may only exist for young healthy individuals (Garrett et al., 2011), as recent research has suggested that increased neural variability may cause poorer working memory performance with age (Boylan et al., 2020). At the whole-brain level, for both 0- and 1-back, and 2- and 3-back combined variability maps, the brain regions associated with the primary components identified by PLS were in the bilateral cerebellum, brainstem, and bilateral inferior frontal lobes. Previous research (Garrett et al., 2011; Garrett et al., 2010) identified patterns of subcortical variability in older adults, which is different from the population of interest in this study; however, these subcortical regions play a role in arousal and automated attention, both needed for the n-back task and for neuropsychological tasks, which may explain their strong influence. It is also possible that the variability detected in these subcortical regions is due to physiological or scanning artifact, which warrants further investigation.

When masked with the appropriate ROIs, neural variability in working memory and in vigilance processes could be better visualized with regard to performance on neuropsychological measures of working memory, vigilance, reading and language. First, we set out to determine the association between variability within the IFJ ROI and performance on measures of vigilance and working memory when combined with measures of reading and language. The IFJ did not emerge as a region during 0- and 1-back trials of the n-back task to explain Digit Span Forward performance, though variability in 2- and 3-back trials of the n-back task in the IFJ did help explain Digit Span Backward and ACT performance, consistent with hypothesis 3a. This pattern of results for the neuropsychological measures replicates findings that suggest a double

dissociation in the IFJ such that increased variability in the IFJ is related to facilitation of cognitive flexibility, which is needed for working memory and task-switching tasks, whereas less variability (or not a meaningful amount of variability) in the IFJ is related to cognitive stability, necessary for vigilance (Armbruster-Genc et al., 2016).

For hypothesis 3b, we examined 0- and 1-back variability maps to examine how neural variability for vigilance was associated with language measures (D-KEFS Verbal Fluency, Category Fluency, and Inhibition/Switching). Increased variability in the medial and lateral posterior parietal cortices and the IFJ as hypothesized, but also by the right cerebellum accounted for performance on these measures, indicating that performance on language measures is associated with brain regions typically involved in attention (the parietal cortices) and task switching (the IFJ). The cerebellum has been implicated in attention as well as in language processes (Marien et al., 2001). Though hypothesized that the left IFG would play a role in language, due to the substantial overlap in processes involved in reading and language, such as phonological awareness, the IFG did not explain language measure performance. For the combined 2- and 3-back variability maps, more diffuse regions of the brain were involved in explaining language measure performance – the left dlPFC, vlPFC, dorsal inferior parietal cortex, IFJ, and right cerebellum as well. The increased variability in the cerebellum in these analyses, compared to the lack of significant variability findings in the cerebellar regions in hypothesis 1b, may be indicative of a distinct relationship between variability in the cerebellum and language processes, such that increased variability allows for greater facility with word retrieval processes, whereas stable activation patterns are more important for more basic cognitive processes like vigilance and working memory. Variability in the left IFG and in the lateral occipito-temporal cortex was also important to language performance. Variability in these

multiple regions could be interpreted as representative of language as a distributed process throughout the brain; the selected language tasks also may involve different cognitive processes (i.e., retrieving words for Verbal and Category Fluency may rely on working memory – dlPFC/vlPFC). The Inhibition/Switching subtest is a prime measure for cognitive flexibility, which again explains the involvement of the IFJ in this brain component. The dorsal inferior parietal cortex is involved when task effort increases (Ravizza et al., 2004), so it is possible that these language tasks required increased effort to either retrieve words or to inhibit prepotent language responses.

Finally, for hypothesis 3c, we examined neural variability in the combined vigilance brain maps and working memory brain maps to evaluate whether variability in specific regions influenced reading performance. For the 0- and 1-back combined neural variability map, no major component emerged to account for variability in either the brain or the reading measures (WJ-III Letter-Word Identification, WJ-III Passage Comprehension). This may be due to low levels of variability in the ROIs for reading tasks, or a low amount of variance in performance on the reading measures. For the 2- and 3-back combined neural variability map, the brain regions that contributed to reading measure performance were the hypothesized left IFG and the left occipito-temporal cortex, supporting research that implicates these regions in a "reading" brain network (Aboud et al., 2016; Malins et al., 2018; Martin et al., 2015), in addition to the left dlPFC, and dorsal inferior parietal cortex. Working memory is important to reading as well (Biotteau et al., 2019; Walcott et al., 2009), explaining the role of the dlPFC in this brain component. The dorsal inferior parietal cortex may have been involved because the 2- and 3-back trials of the n-back task required greater cognitive effort. Increased variability in these regions across vigilance and working memory brain maps, but negative beta weights for the

reading measures suggests that increased variability may hinder reading performance, supporting the neural noise hypothesis of dyslexia (Hancock et al., 2017), consistent with hypothesis 3c, which states that more "neural noise" would decrease reading performance abilities. However, what is meant by neural "noise" is currently debated in the field (Uddin, 2020). Though the current finding supports the present hypotheses, recent research identified a positive correlation between within-individual neural variability and reading skill (Malins et al., 2018). Malins et al. (2018) used only the Letter-Word Identification subtest measure as an index of reading, whereas this study also included the Passage Comprehension subtest. It is possible that there is an intricate relationship between neural variability and sight word reading or reading comprehension that may explain the discrepancy in results in the current study with those of Malins et al. (2018). For example, the higher beta weight obtained for the Passage Comprehension subtest demonstrates that variability for that subtest is driving the negative correlation between neural variability and reading performance scores in this study. Future research should continue to examine the relationship between neural variability and elements of reading abilities.

4.4 Discussion of Planned Supplementary and Additional Analyses

When we subtracted each stimulus type of the n-back task (0-back, 1-back, 2-back, and 3-back) *versus* crosshair, we found that in each of the identified working memory ROIs besides those in the dlPFC and cerebellum, there was significantly greater variability than crosshair, indicating that these ROIs were activated rather than deactivated during working memory trials. These results support the idea that these regions are involved in working memory (Botvinick et al., 2004; Dove et al., 2001; Jonides et al., 1998; Kolling et al., 2016; Owen et al., 2005; Owen, 1997; Ravizza et al., 2004; Wager & Smith, 2003), and also that increased variability in more

complex trials may be beneficial for working memory n-back task performance (Boylan et al., 2020).

The significant positive correlation between within-individual neural variability in the medial posterior parietal cortex ROI and mean accuracy on the n-back task suggests that variability within specific ROIs may be important to accurate performance on this type of letter n-back task for specific trial types. Because this relationship did not hold with mean signal, our finding suggests that within-individual neural variability may provide meaningful information not provided by using a mean signal measure, consistent with prior research (Garrett et al., 2011; Garrett et al., 2010).

Significant Pearson product-moment correlations between the ACT and Digit Span Backwards provide evidence that the ACT and Digit Span Backwards assess the same construct.

4.5 Limitations and Strengths

This study has weaknesses and strengths that should be discussed. First, because this study used data from a block design experiment, a typical general linear model regression framework was not used, as it would result in only one beta value per block of each task condition. A general linear model is typically done as a precursor to mean activation analyses. In this study, we performed mean and SD computations on the corrected time series itself. Based on the sample size and the fact that there were many important regions to consider in these various cognitive domains, standard corrections for multiple comparisons (i.e., Bonferroni correction method; dividing the proposed alpha value by the number of regions tested) may have produced underpowered results. To avoid underpowered results, we used less conservative correction methods such as the Benjamini-Hochberg correction method to decrease Type I error. The potential problem of multiple comparisons can be resolved in future studies by including a larger

sample size. Additionally, as a result of using ROI and cluster-based analyses, our findings are limited to specialized regions, and may not capture within-individual variability patterns in other regions not selected.

The sample that was recruited for this study was screened for any history of, or current psychopathology. Individuals with ADHD were not included in the final sample. Thus, the sample reflects healthy young adults without learning difficulties, neurological disorders, or emotional challenges. In addition, the sample is comprised predominantly of undergraduate students (77.1%). However, the fact that this study was conducted at a large urban southeastern university with a large proportion of first generation college students, makes the sample more representative of a young adult community sample in the United States (e.g., in terms of participants' mothers' education level, which ranged from a high school degree or less ($N = 19$) to a college degree or graduate degree ($N = 27$)). The sample also reflects important diversity in terms of race (25% African-American, 16.7% Asian, and 8.3% Hispanic/Latinx).

This study used a novel approach to examine and investigate within-individual neural variability and its relation to various cognitive domains. To our knowledge, this is the first study that investigates these specific relationships between within-individual neural variability, working memory, vigilance, reading skills and language fluency, which can inform the larger burgeoning field of brain variability research, as well as the broader research community about potentially important brain-behavior relationships in a healthy population. We believe that findings in this population can inform future research pertaining to various clinical populations. The AFNI processing pipeline outlined in this proposal used typically acquired MRI scans in clinical practice, and if programmed, this pipeline can be used to perform analyses without substantial researcher involvement, thus reducing time and potential interpretation bias. Since the

MRI sequences used are common in clinical practice, and the methods we have used reveal important brain-behavior relationships, this method could be utilized more frequently to examine within-individual neural variability, rather than relying on analyses using mean activation levels.

4.6 Conclusions and Future Directions

This study contributes to the relatively new literature examining the importance of within-individual neural variability in cognitive processes: working memory, vigilance, reading, and language.

Specific to the letter n-back task, we found that there was a significant main effect of stimulus type, such that more complex trials (3-back and 2-back) representative of working memory had increased variability compared to less complex trials (1-back and 0-back) representative of vigilance. Importantly, for common contrasts used in n-back paradigms, we were able to show that there was increased variability in regions of the working memory network – left dlPFC ROIs, the vlPFC, the ACC, and the dorsal inferior parietal cortex – during working memory trials, and decreased variability, or a lack of a significant change in variability, during vigilance trials, suggesting that the amount of variability in specific regions of the brain may change depending on the task, which was also noted by Misic and colleagues (2010).

Though previous research identified a double-dissociation within the IFJ for variability in cognitive flexibility versus cognitive stability (Armbruster-Genc et al., 2016), our results did not replicate this finding in the context of the n-back task for working memory and vigilance. It is possible that our task, the n-back task, did not adequately parse out these disparate cognitive processes in order to examine this relationship. It is plausible that using a more intricately designed task in the scanner to probe cognitive flexibility and stability, similar to the task used by Armbruster-Genc and colleagues (2016), which involved determining if a number was odd or

even while also distinguishing the brightness of stimuli and then responding appropriately with a button box, could yield a double dissociation within the IFJ for flexibility and stability processes.

This study predominantly focuses on examining WINV in specific ROIs that were determined a priori. Whole-brain analyses were intended as exploratory, in complement to ROI findings. Based on the whole-brain cluster-wise analyses, decreased variability in some areas (right inferior parietal lobule, left superior temporal gyrus, and left parahippocampal gyrus) was associated with greater accuracy on the n-back task. This suggests that there may be a complex relationship with variability across the brain (Misic et al., 2010), such that increased variability in some regions, like those identified with ROI analyses, but decreased variability in other regions, like those identified with whole-brain analyses, may occur in order to achieve maximum accuracy performance on a letter n-back task. Further research probing WINV at the whole-brain level would be helpful to elucidate these different patterns.

Finally, we were able to examine how within-individual neural variability across the brain during working memory and vigilance trials of the n-back task explained performance on neuropsychological measures of working memory, vigilance, reading, and language. At the whole-brain level, subcortical regions for both working memory and vigilance trials predominantly contributed to performance on language and working memory tasks. This finding highlights the importance of subcortical-cortical relationships in cognition. When filtered to examine the relevant ROIs for each of the identified cognitive processes, the lateral posterior parietal cortex helped to explain the correlation between neural variability during vigilance trials and performance on Digit Span Forward, and the left dlPFC ROI was implicated in explaining the relationship between neural variability in working memory trials and Digit Span Backward and ACT performance. In terms of variability and language, variability during vigilance trials in

the IFG and the left occipito-temporal cortex accounted for performance on D-KEFS Verbal Fluency, Category Fluency, and Color-Word Inhibition/Switching tasks, indicating that performance on language measures relies on vigilance variability in brain regions typically involved in the reading network, whereas variability in working memory trials explained language performance across different areas of the brain. For reading, neural variability in vigilance trials in the medial posterior parietal cortex and left occipito-temporal cortex emerged as regions that explained performance, whereas in working memory trials, neural variability in the dlPFC, vlPFC, and left occipito-temporal cortex explained reading performance. Taken together, these results indicate that different patterns of neural variability exist in vigilance trials and working memory trials, and this variation results in different brain areas associated with performance on different neuropsychological measures. Future research is needed to confirm or replicate the current findings.

The current study uses innovative WINV methodology to contribute to advancing the understanding of neural variability in healthy individuals using innovative WINV methodology. Knowledge of WINV and its role in various cognitive functions in a healthy sample is crucial before investigating likely differences that may exist in WINV patterns in clinical populations, across the lifespan, especially those recovering from diffuse brain injury (Raja Beharelle et al., 2012). Future research can continue to examine how WINV relates to building block executive functions such as sustained attention and working memory, and how variability in these domains in turn affects other skills such as reading and language, which are essential to function in our world. As more research emerges pertaining to WINV, variability may become an important biomarker helpful in precision medicine, as well as may inform potential neurochemical

(Alavash et al., 2018) or other neuromodulatory interventions to increase or decrease neural variability appropriately to maximize cognitive functioning.

REFERENCES

Aboitiz, F., Garcia, R.R., Bosman, C., & Brunetti, E. (2006). Cortical memory mechanisms and language origins. *Brain and Language, 98,* 40–56. doi: 10.1016/j.bandl.2006.01.006

Aboud, K.S., Bailey, S.K., Petrill, S.A., & Cutting, L.E. (2016). Comprehending text versus reading words in young readers with varying reading ability: distinct patterns of functional connectivity from common processing hubs. *Developmental Science, 19,* 632-656. doi: 10.1111/desc.12422

Aguirre, G.K., Zarahn, E., & D'Esposito, M. (1998). The variability of human, BOLD hemodynamic responses. *Neuroimage, 8*, 360–369. doi: 10.1006/nimg.1998.0369

Ailion, A.S., King, T.Z., Roberts, S.R., Tang, B., Turner, J.A., Conway, C.M., & Crosson, B. (2020). Double dissociation of auditory attention span and visual attention in long-term survivors of childhood cerebellar tumor: a deterministic tractography study of the cerebellar-frontal and superior longitudinal fasciculus pathways. *JINS,* 1-15. doi: 10.1017/S1355617720000417

Alavash, M., Lim, S.-J., Thiel, C., Sehm, B., Deserno, L., & Obleser, J. (2018). Dopaminergic modulation of hemodynamic signal variability and the functional connectome during cognitive performance. *Neuroimage, 172,* 341-356. doi: 10.1016/j.neuroimage.2018.01.048

Alvarez, J.A. & Emory, E. (2006). Executive function and the frontal lobes: a meta-analytic review. *Neuropsychology Review, 16,* 17-42. doi: 10.1007/s11065-006-9002-x

Aminoff, E.M., Kveraga, K., & Bar, M. (2013). The role of the parahippocampal cortex in cognition. *Trends in Cognitive Sciences, 17,* 379-390. doi: 10.1016/j.tics.2013.06.009

Arazi, A., Yeshurun, Y., & Dinstein, I. (2019). Neural variability is quenched by attention. *The Journal of Neuroscience, 39,* 5975-5985. doi: 10.1523/JNEUROSCI.0355-19.2019

Argyropoulos, G.P. (2016). The cerebellum, internal models and prediction in 'non-motor' aspects of language: A critical review. *Brain and Language, 161*, 4-17. doi: 10.1016/j.bandl.2015.08.003

Arieli, A., Sterkin, A., Grinvald, A., & Aertsen, A. (1996). Dynamics of ongoing activity: explanation of the large variability in evoked cortical responses. *Science, 273,* 1868-1871. doi: 10.1126/science.273.5283.1868

Armbruster-Genc, D.J.N., Ueltzhoffer, K., & Fiebach, C.J. (2016). Brain signal variability differentially affects cognitive flexibility and cognitive stability. *The Journal of Neuroscience, 36,* 3978-3987. doi: 10.1523/JNEUROSCI.2517-14.2016

Armbruster-Genc, D.J.N., Ueltzhoffer, K., Basten, U., & Fiebach, C.J. (2012). Prefrontal cortical mechanisms underlying individual differences in cognitive flexibility and stability. *Journal of Cognitive Neuroscience, 24,* 2385-2399. doi: 10.1162/jocn_a_00286

Baddeley, A. (2012). Working memory: Theories, models, and controversies. *Annual Review of Psychology, 63*, 1–29. doi: 10.1146/annurev-psych-120710-100422

Baddeley, A., Gathercole, S., & Papagno, C. (1998). The phonological loop as a language learning device. *Psychological Review, 105,* 158-173. doi: 10.1037/0033-295X.105.1.158

Baddeley, A. (1992). Working memory. *Science*, *255*, 556-559. doi: 10.1126/science.1736359

Baddeley, A.D. & Hitch, G. (1974). Working Memory. In G.H. Bower (Ed.), *The psychology of learning and motivation: Advances in research and theory* (Vol 8, 47-89). New York: Academic Press.

Balsters, J.H., Laird, A.R., Fox, P.T., & Eickhoff, S.B. (2014). Bridging the gap between functional and anatomical features of cortico-cerebellar circuits using meta-analytic connectivity modeling. *Human Brain Mapping, 35,* 3152-3169. doi: 10.1002/hbm.22392

Behrmann, M., Geng, J.J., & Shomstein, S. (2004). Parietal cortex and attention. *Current Opinion in Neurobiology, 14,* 212-217. doi: 10.1016/j.conb.2004.03.012

Biotteau, M., Tournay, E., Baudou, E., Lelong, S., Iannuzzi, S., Faure-Marie, N., Castelnau, P., Schweitzer, E., Rodriguez, D., Kemlin, I., Dorison, N., Rivier, F., Carneiro, M., Preclaire, E., Barbarot, S., Lauwers-Cances, V., & Chaix, Y. (2019). What can attention abilities teach us about reading comprehension in NF1? *Journal of Neurophysiology and Neurological Disorders, 5,* 1-16.

Booth, J.R., Wood, L., Lu, D., Houk, J.C., & Bitan, T. (2007). The role of the basal ganglia and cerebellum in language processing. *Brain Research, 1133,* 136-144. doi: 10.1016/j.brainres.2006.11.074

Bopp, K.L. & Verhaeghen, P. (2018). Aging and n-back performance: a meta-analysis. *The Journals of Gerontology, 75,* 229-240. doi: 10.1093/geronb/gby024

Botvinick, M.M., Cohen, J.D., & Carter, C.S. (2004). Conflict monitoring and anterior cingulate cortex: an update. *Trends in Cognitive Sciences*, *8*, 539–546. doi: 10.1016/j.tics.2004.10.003

Boylan, M.A., Foster, C.M., Pongpipat, E.E., Webb, C.E., Rodrigue, K.M., & Kennedy, K.M. (2020). Greater BOLD variability is associated with poorer cognitive function in an adult lifespan sample. *Cerebral Cortex,* 1-13. doi: 10.1093/cercor/bhaa243

Brown, J. (1958). Some tests of the decay theory of immediate memory. *Quarterly Journal of Experimental Psychology, 10*, 12–21. doi: 10.1080/17470215808416249

Buckner, R.L. (2013). The cerebellum and cognitive function: 25 years of insight from anatomy and neuroimaging. *Neuron, 80,* 807-815. doi: 10.1016/j.neuron.2013.10.044

Carpenter, P., Just, M., & Reichle, E.D. (2000). Working memory and executive function:

evidence from neuroimaging. *Current Opinion in Neurobiology*, *10*, 195–199. doi: 10.1016/s0959-4388(00)00074-x

Chein, J.M. & Fiez, J.A. (2001). Dissociation of verbal working memory system components using a delayed serial recall task. *Cerebral Cortex, 11,* 1003–1014. doi: 10.1093/cercor/11.11.1003

Chen, G., Adleman, N.E., Saad, Z.S., Leibenluft, E., & Cox, R.W. (2014). Applications of multivariate modeling to neuroimaging group analysis: acomprehensive alternative to univariate general linear model. *NeuroImage, 99,* 571-588. doi: 10.1016/j.neuroimage.2014.06.027

Chen, G., Saad, Z.S., Britton, J.C., Pine, D.S., & Cox, R.W. (2013). Linear mixed-effects modeling approach to fMRI group analysis. *NeuroImage, 73*, 176-190. doi: 10.1016/j.neuroimage.2013.01.047

Chen, S.H. & Desmond, J.E. (2005). Temporal dynamics of cerebro-cerebellar network recruitment during a cognitive task. *Neuropsychologia*, *43,* 1227–1237. doi: 10.1016/j.neuropsychologia.2004.12.015

Clark, S.V., Semmel, E.S., Aleksonis, H.A., Steinberg, S.N., & King, T.Z. (2021). Cerebellar-subcortical-cortical systems as modulators of cognitive functions. *Neuropsychology Review*. doi: 10.1007/s11065-020-09465-1

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

Dally, K. (2006). The influence of phonological processing and inattentive behavior on reading acquisition. *Journal of Educational Psychology, 98*, 420–437. doi: 10.1037/0022-

0663.98.2.420

Daneman, M. (1991). Working memory as a predictor of verbal fluency. *Journal of Psycholinguistic Research, 20,* 445-464. doi: 10.1007/BF01067637

Daneman, M. & Carpenter, P. A. (1980). Individual differences in working memory and reading. *Journal of Verbal Learning and Verbal Behavior, 19*, 450–466. doi: 10.1016/S0022-5371(80)90312-6

Daniel, T.A., Katz, J.S., & Robinson, J.L. (2016). Delayed match-to-sample in working memory: a BrainMap meta-analysis. *Biological Psychology, 120*, 10-20. doi: 10.1016/j.biopsycho.2016.07.015

Deak, G. (2003). The development of cognitive flexibility and language abilities. *Advances in Child Development and Behavior, 31,* 271-327. doi: 10.1016/S0065-2407(03)31007-9

Deco, G., Rolls, E.T., & Romo, R. (2009). Stochastic dynamics as a principle of brain function. *Progress in Neurobiology, 88,* 1-16. doi:10.1016/j.pneurobio.2009.01.006

Delis, D.C., Kaplan, E., & Kramer, J.H. (2001). *Delis-Kaplan Executive Function System: Technical Manual*. San Antonio, TX: Harcourt Assessment Company.

de Paula, J.J., de Castro Paiva, G.C., & de Souza Costa, D. (2015). Use of a modified version of the switching verbal fluency test for the assessment of cognitive flexibility. *Dementia & Neuropsychologia, 9,* 258-264. doi: 10.1590/1980-57642015DN93000008

Derrfuss, J., Brass, M., Neumann, J., & von Cramon, D.Y. (2005). Involvement of the inferior frontal junction in cognitive control: meta-analyses of switching and Stroop studies. *Human Brain Mapping, 25*, 22–34. doi: 10.1002/hbm.20127

Diamond, A. (2012). Executive functions. *Annual Review of Psycholo*gy, *64*, 135-168. doi: 10.1146/annurev-psych-113011-143750

Dinstein, I., Heeger, D.J., & Behrmann, M. (2015). Neural variability: friend or foe? *Trends in Cognitive Sciences, 19,* 322-328. doi: 10.1016/j.tics.2015.04.005

Dove, A., Rowe, J.B., & Owen, A.M. (2001). Neural correlates of passive and active encoding and retrieval : A 3T fMRI study. *Neuroimage*, *13*, 660. doi: 10.1016/S1053-8119(01)92003-8

Eckert, M., Leonard, C., Richards, T., Aylward, E., Thomson, J., & Berninger, V. (2003). Anatomical correlates of dyslexia: frontal and cerebellar findings. *Brain, 126,* 482-494. doi: 10.1093/brain/awg026

Edelstein, K., Spiegler, B.J., Fung, S., Panzarella, T., Mabbott, D.J., Jewitt, N., D'Agostino, N., Mason, W.P., Bouffet, E., Tabori, U., Laperriere, N., & Hodgson, D.C. (2011). Early aging in adult survivors of childhood medulloblastoma: long-term neurocognitive, functional, and physical outcomes. *Neuro-Oncology*, *13*, 536–545. http://doi.org/10.1093/neuonc/nor015

Emch, M., von Bastian, C.C., & Koch, K. (2019). Neural correlates of verbal working memory: an fMRI meta-analysis. *Frontiers in Human Neuroscience, 13,* 1-17. doi: 10.3389/fnhum.2019.00180

Faisal, A.A., Selen, L.P., & Wolpert, D.M. (2008). Noise in the nervous system. *Nature Reviews Neuroscience, 9*, 292–303. doi: 10.1038/nrn2258

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*, 1149-1160. doi: 10.3758/BRM.41.4.1149

First, M.B. & Gibbon, M. (2004). The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) and the Structured Clinical Interview for DSM-IV Axis II Disorders

(SCID-II) In M. Hersen (Ed.), *Comprehensive Handbook of Psychological Assessment* (pp. 134-143).

First, M.B., Spitzer, R.L., Gibbon, M., & Williams, J.B. (2002). *Structured clinical interview for DSM-IV-TR axis I disorders, research version, patient edition (SCID-I/P).* New York: Biometrics Research, New York State Psychiatric Institute.

First, M.B., Spitzer, R.L., Gibbon, M., & Williams, J.B.W. (1997). *Structured clinical interview for DSM-IV axis 1 disorders (SCID-I) - clinical version.* Arlington, VA: American Psychiatric Publishing.

Fulbright, R.K., Jenner, A.R., Mencl, W.E., Pugh, K.R., Shaywitz, B.A., Shaywitz, S.E., Frost, S.J., Skudlarski, P., Constable, R.T., Lacadie, C.M., Marchione, K.E., & Gore, J.C. (1999). The cerebellum's role in reading: a functional MR imaging study. *American Journal of Radiology, 20,* 1925-1930.

Gajewski, P.D., Hanisch, E., Falkenstein, M., Thones, S., & Wascher, E. (2018). What does the n-back task measure as we get older? Relations between working-memory measures and other cognitive functions across the lifespan. *Frontiers in Psychology, 9,* 1-17. doi: 10.3389/fpsyg.2018.02208

Garrett, D.D., Samanez-Larkin, G.R., MacDonald, S.W., Lindenberger, U., McIntosh, A.R., & Grady, C.L. (2013). Moment-to-moment brain signal variability: a next frontier in human brain mapping? *Neuroscience and Biobehavioral Reviews, 37,* 610 – 624. doi: 10.1016/j.neubiorev.2013.02.015

Garrett, D.D., Kovacevic, N., McIntosh, A.R., & Grady, C.L. (2011). The importance of being variable. *The Journal of Neuroscience, 31*, 4496-4503. doi: 10.1523/JNEUROSCI.5641-10.2011

Garrett, D.D., Kovacevic, N., McIntosh, A.R., & Grady, C.L. (2010). Blood oxygen level-dependent signal variability is more than just noise. *The Journal of Neuroscience, 30,* 4914-4921. doi: 10.1523/JNEUROSCI.5166-09.2010

Gevins, A. & Cutillo, B. (1993). Spatiotemporal dynamics of component processes in human working memory. *Electroencephalography and Clinical Neurophysiology, 87,* 128-143. doi: /10.1016/0013-4694(93)90119-G

Glover, G. (2011). Overview of functional magnetic resonance imaging. *Neurosurgery Clinics of North America, 22,* 133-139. doi:10.1016/j.nec.2010.11.001

Gottwald, B., Mihajlovic, Z., Wilde, B., & Mehdorn, H.M. (2003). Does the cerebellum contribute to specific aspects of attention? *Neuropsychologia, 41,* 1452-1460. doi: 10.1016/S0028-3932(03)00090-3

Grady, C.L. & Garrett, D.D. (2014). Understanding variability in the BOLD signal and why it matters for aging. *Brain Imaging & Behavior, 8,* 274-283. doi: 10.1007/s11682-013-9253-0

Guell, X., Gabrieli, J.D.E., & Schmahmann, J.D. (2018). Triple representation of language, working memory, social and emotion processing in the cerebellum: convergent evidence from task and seed-based resting-state fMRI analyses in a single large cohort. *Neuroimage, 172,* 437-449. doi: 10.1016/j.neuroimage.2018.01.082

Gurd, J.M., Amunts, K., Weiss, P.H., Zafiris, O., Zilles, K., Marshall, J.C., & Fink, G.R. (2002). Posterior parietal cortex is implicated in continuous switching between verbal fluency tasks: an fMRI study with clinical implications. *Brain, 125*, 1024-1038. doi: 10.1093/brain/awf093

Hall, J., O'Carroll, R.E., & Frith, C.D. (2010). Neuropsychology. In E.C. Johnstone et al. (Eds.), *Companion to Psychiatric Studies* (pp. 121-140).

Hancock, R., Pugh, K.R., & Hoeft, F. (2017). Neural noise hypothesis of developmental dyslexia. *Trends in Cognitive Sciences, 21,* 434-448. doi: 10.1016/j.tics.2017.03.008

Hansen, J. & Bowey, J.A. (1994). Phonological analysis skills, verbal working memory, and reading ability in second-grade children. *Child Development, 65,* 938-950. doi: 10.2307/1131429

Hillman, E.M.C. (2014). Coupling mechanism and significance of the BOLD signal: a status report. *Annual Reviews Neuroscience, 37*, 161-181. doi: 10.1146/annurev-neuro-071013-014111

Huettel, S.A., Singerman, J.D., & McCarthy, G. (2001). The effects of aging upon the hemodynamic response measured by functional MRI. *Neuroimage, 13*, 161–175. doi: 10.1006/nimg.2000.0675

Hultsch, D.F., Strauss, E., Hunter, M.A., & MacDonald, S.W.S. (2008). Intraindividual variability, cognition, and aging. In F.I.M. Craik & T.A. Salthouse (Eds.), *The handbook of aging and cognition*, *Ed 3* (pp. 2491–2556). New York: Psychology.

Irby, S.M. & Floyd, R.G. (2013). Review of Wechsler Abbreviated Scale of Intelligence, Second Edition [Review of the test Wechsler abbreviated scale of intelligence, second edition, by D. Wechsler]. *Canadian Journal of School Psychology, 28*, 295–299. doi: 10.1177/0829573513493982

Jayakar, R., King, T.Z., Morris, R., & Na, S. (2015). Hippocampal volume and auditory attention on a verbal working memory task with adult survivors of pediatric brain tumor. *Neuropsychology, 29,* 303-319. doi: 10.1037/neu0000183

Jonides, J., Schumacher, E.H., Smith, E.E., Koeppe, R.A., Awh, E., Reuter-Lorenz, P.A., Marshuetz, C., & Willis, C.R. (1998). The role of parietal cortex in verbal working memory. *The Journal of Neuroscience*, *18*, 5026–5034. doi: 10.1523/JNEUROSCI.18-13-05026.1998

Jones, T.B., Bandettini, P.A., & Birn, R.M. (2008) Integration of motion correction and physiological noise regression in fMRI. *Neuroimage, 42,* 582–590. doi: 10.1016/j.neuroimage.2008.05.019

King, T.Z., Ailion, A.S., Fox, M.E., & Hufstetler, S.M. (2017). Neurodevelopmental model of long-term outcomes of adult survivors of childhood brain tumors. *Child Neuropsychology,* 1-21. doi: 10.1080/09297049.2017.1380178

King, T.Z., Na, S., & Mao, H. (2015). Neural underpinnings of working memory in adult survivors of childhood brain tumors. *Journal of the International Neuropsychological Society, 21,* 1-12. doi: 10.1017/S135561771500051X

Kolling, N., Behrens, T.E.J., Wittmann, M.K., & Rushworth, M.F.S. (2016). Multiple signals in anterior cingulate cortex. *Current Opinion in Neurobiology, 37,* 36-43. doi: 10.1016/j.conb.2015.12.007

Koziol, L.F., Budding, D., Andreasen, N., D'Arrigo, S., Bulgheroni, S., Imamizu, H., Ito, M., Manto, M., Marvel, C., Parker, K., Pezzulo, G., Ramnani, N., Riva, D., Schmahmann, J., Vandervert, L., & Yamazaki, T. (2015). Consensus paper: the cerebellum's role in movement and cognition. *Cerebellum, 13,* 151-177. doi: 10.1007/s12311-013-0511-x

Kuper, M., Kaschani, P., Thurling, M., Stefanescu, M.R., Burciu, R.G., Goricke, S., Maderwald, S., Ladd, M.E., Hautzel, H., & Timmann, D. (2016). Cerebellar fMRI activation increases with increasing working memory demands. *Cerebellum, 15,* 322-335. doi: 10.1007/s12311-015-0703-7

Lakens, D. (2013). Calculating and reporting effect sizes to facilitate cumulative science: a practical primer for t-tests and ANOVAs. *Frontiers in Psychology, 4,* 1-12. doi: 10.3389/fpsyg.2013.00863

Lawlor-Savage, L. & Goghari, V.M. (2016). Dual n-back working memory training in healthy adults: a randomized comparison to processing speed training. *PLoS One, 11*, e0151817. doi: 10.1371/journal.pone.0151817

Levy, F. & Hobbes, C. (1989). Reading, spelling, and vigilance in attention deficit and conduct disorder. *Journal of Abnormal Child Psychology, 17,* 291-298. doi: 10.1007/BF00917400

Lobbestael, J., Leurgans, M., & Arntz, A. (2011). Inter-rater reliability of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID I) and Axis II Disorders (SCID II). *Clinical Psychology & Psychotherapy, 18,* 75-79. doi: 10.1002/cpp.693

Logie, R.H., Venneri, A., Della Sala, S., Redpath, T.W., & Marshall, I. (2003). Brain activation and the phonological loop: the impact of rehearsal. *Brain and Cognition, 53,* 293-296. doi: 10.1016/S0278-2626(03)00129-5

MacDonald, S.W.S., Li, S.C., & Backman, L. (2009). Neural underpinnings of within-person variability in cognitive functioning. *Psychology and Aging, 24,* 792– 808. doi: 10.1037/a0017798

MacDonald, S.W.S., Nyberg, L., & Backman, L. (2006). Intra-individual variability in behavior: links to brain structure, neurotransmission and neuronal activity. *Trends in Neurosciences, 29*, 474-480. doi: 10.1016/j.tins.2006.06.011

MacDonald, S.W.S., Hultsch, D.F., & Bunce, D. (2006). Intraindividual variability in vigilance performance: does degrading visual stimuli mimic age-related “neural noise”? *Journal of Clinical and Experimental Neuropsychology, 28,* 655-675. doi:

10.1080/13803390590954245

Malins, J.G., Pugh, K.R., Buis, B., Frost, S.J., Hoeft, F., Landi, N., Mencl, W.E., Kurian, A., Staples, R., Molfese, P.J., Sevcik, R., & Morris, R. (2018). Individual differences in reading skill are related to trial-by-trial neural activation variability in the reading network. *The Journal of Neuroscience, 12,* 2981-2989. doi: 10.1523/JNEUROSCI.0907-17.2018

Marien, P. & Beaton, A. (2014). The enigmatic linguistic cerebellum: clinical relevance and unanswered questions on nonmotor speech and language deficits in cerebellar disorders. *Cerebellum Ataxias*, *1,* 12. doi: 10.1186/2053-8871-1-12

Marien, P., Engelborghs, S., Fabbro, F., & De Deyn, P.P. (2001). The lateralized linguistic cerebellum: a review and a new hypothesis. *Brain and Language, 79*, 580-600. doi: 10.1006/brln.2001.2569

Martin, A., Schurz, M., Kronbichler, M., & Richlan, F. (2015). Reading in the brain of children and adults: a meta-analysis of 40 functional magnetic resonance imaging studies. *Human Brain Mapping, 36,* 1963-1981. doi: 10.1002/hbm.22749

McIntosh, A.R., Kovacevic, N., & Itier, R.J. (2008). Increased brain signal variability accompanies lower behavioral variability in development. PLoS Computational Biology, 4, e1000106. doi: 10.1371/journal.pcbi.1000106

McIntosh, A.R., Bookstein, F.L., Haxby, J.V., & Grady, C.L. (1996) Spatial pattern analysis of functional brain images using partial least squares. *Neuroimage, 3*, 143–157. doi: 10.1006/nimg.1996.0016

Meule, A. (2017). Reporting and interpreting working memory performance in n-back tasks. *Frontiers in Psychology, 8,* 352-353. doi: 10.3389/fpsyg.2017.00352

Middleton, F.A. & Strick, P.L. (1998). Cerebellar output: motor and cognitive channels. *Trends*

in Cognitive Sciences, 2, 348-354. doi: 10.1016/S1364-6613(98)01220-0

Miller, M.B., Van Horn, J.D., Wolford, G.L., Handy, T.C., Valsangkar-Smyth, M., Inati, S., Grafton, S., & Gazzaniga, M.S. (2002). Extensive individual differences in brain activations associated with episodic retrieval are reliable over time. *Journal of Cognitive Neuroscience, 14,* 1200 –1214. doi: 10.1162/089892902760807203

Misic, B., Mills, T., Taylor, M.J., & McIntosh, A.R. (2010). Brain noise is task dependent and region specific. *Journal of Neurophysiology, 104,* 2667-2676. doi: 10.1152/jn.00648.2010

Miyake, A., Friedman, N.P., Emerson, M.J., Witzki, A.H., Howerter, A., & Wager, T.D. (2000). The unity and diversity of executive functions and their contributions to complex "frontal lobe" tasks: a latent variable analysis. *Cognitive Psychology, 41*, 49-100. doi: 10.1006/cogp.1999.0734

Na, S., Li, L., Crosson, B., Dotson, V., MacDonald, T.J., Mao, H., & King, T.Z. (2018). White matter network topology relates to cognitive flexibility and cumulative neurological risk in adult survivors of pediatric brain tumors. *Neuroimage: Clinical, 20,* 485-497. doi: 10.1016/j.nicl.2018.08.015

Nagel, B.J., Delis, D.C., Palmer, S.L., Reeves, C., Gajjar, A., & Mulhern, R.K. (2006). Early patterns of verbal memory impairment in children treated for medulloblastoma. *Neuropsychology*, *20*, 105–112. http://doi.org/10.1037/0894-4105.20.1.105

Neumann, J., Lohmann, G., Zysset, S., & von Cramon, D.Y. (2003). Within-subject variability of BOLD response dynamics. *Neuroimage, 19,* 784-796. doi: 10.1016/S1053-8119(03)00177-0

Nomi, J.S., Bolt, T.S., Chiemeka Ezie, C.E., Uddin, L.Q., & Heller, A.S. (2017). Moment-to-moment BOLD signal variability reflects regional changes in neural flexibility across the

lifespan. *The Journal of Neuroscience, 37,* 5539-5548. doi: 10.1523/JNEUROSCI.3408-16.2017

Oken, B.S., Salinsky, M.C., & Elsas, S.M. (2010). Vigilance, alertness, or sustained attention: physiological basis and measurement. *Clinical Neurophysiology, 117*, 1885-1901. doi: 10.1016/j.clinph.2006.01.017

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*, 46-59. doi: 10.1002/hbm.20131

Owen, A.M. (1997). The functional organization of working memory processes within human lateral frontal cortex: The contribution of functional neuroimaging. *European Journal of Neuroscience*, *9*, 1329-1339. doi: 10.1111/j.1460-9568.1997.tb01487.

Peterson, L. R. & Peterson, M. J. (1959). Short-term retention of individual verbal items. *Journal of Experimental Psychology, 58*, 193–198. doi: 10.1037/h0049234

Raghubar, K.P., Mahone, E.M., Yeates, K.O., Cecil, K.M., Makola, M., & Ris, M.D. (2017). Working memory and attention in pediatric brain tumor patients treated with and without radiation therapy. *Child Neuropsychology, 23,* 642-654. doi: 10.1080/09297049.2016.1183608

Raja Beharelle, A., Kovacevic , N., McIntosh, A.R., & Levine, B. (2012). Brain signal variability relates to stability of behavior after recovery from diffuse brain injury. *Neuroimage, 60*, 1528–1537. doi: 10.1016/j.neuroimage.2012.01.037

Ravizza, S.M., Delgado, M.R., Chein, J.M., Becker, J.T., & Fiez, J.A. (2004). Functional dissociations within the inferior prefrontal cortex in verbal working memory. *Neuroimage 22*, 562–573. doi: 10.1016/j.neuroimage.2004.01.039

Roalf, D.R., Gur, R.E., Ruparel, K., Calkins, M.E., Satterthwaite, T.D., Bilker, W.B., Hakonarson, H., Harris, L.J., & Gur, R.C. (2014). Within-individual variability in neurocognitive performance: age and sex related differences in children and youths from ages 8 to 21. *Neuropsychology, 28,* 506-518. doi: 10.1037/neu0000067

Roberts, R.P., Grady, C.L., & Addis, D.R. (2020). Creative, internally-directed cognition is associated with reduced BOLD variability. *NeuroImage,* 116758. doi: 10.1016/j.neuroimage.2020.116758

Rosenthal, E.N., Riccio, C.A., Gsanger, K.M., & Jarratt, K.P. (2006). Digit Span components as predictors of attention problems and executive functioning in children. *Archives of Clinical Neuropsychology, 21*, 131-139. doi: 10.1016/j.acn.2005.08.004

Runnqvist, E., Bonnard, M., Gauvin, H.S., Attarian, S., Trebuchon, A., Hartsuiker, R.J., & Alario, F.X. (2016). Internal modeling of upcoming speech: A causal role of the right posterior cerebellum in non-motor aspects of language production. *Cortex, 81,* 203-214. doi: 10.1016/j.cortex.2016.05.008

Schmahmann, J.D., Guell, X., Stoodley, C.J., & Halko, M.A. (2019). The theory and neuroscience of cerebellar cognition. *Annual Review of Neuroscience, 42*, 337–364. doi: 10.1146/ annurev-neuro-070918-050258

Schmahmann, J.D. & Pandya, D.N. (1997). The cerebrocerebellar system. *International Review of Neurobiology, 41,* 31-60. doi: 10.1016/s0074-7742(08)60346-3

Schmiedek, F., Lovden, M., & Lindenberger, U. (2009). On the relation of mean reaction time and intraindividual reaction time variability. *Psychology and Aging, 24,* 841-857. doi: 10.1037/a0017799

Schrank, F.A., McGrew, K.S., & Woodcock, R.W. (2001). *Technical Abstract* (Woodcock-

Johnson III Assessment Service Bulletin No. 2). Itasca, IL: Riverside Publishing.

Sebastian, R., Gomez, Y., Leigh, R., Davis, C., Newhart, M., & Hillis, A.E. (2014). The roles of occipitotemporal cortex in reading, spelling, and naming. *Cognitive Neuropsychology, 31,* 511-528. doi: 10.1080/02643294.2014.884060

Seghier, M.L. & Price, C.J. (2018). Interpreting and utilising intersubject variability in brain function. *Trends in Cognitive Sciences, 22,* 517-530. doi: 10.1016/j.tics.2018.03.003

Sesma, H.W., Mahone, E.M., Levine, T., Eason, S.H., & Cutting, L.E. (2009). The contribution of executive skills to reading comprehension. *Child Neuropsychology, 15,* 232-246. doi: 10.1080/09297040802220029

Shao, Z., Janse, E., Visser, K., & Meyer, A.S. (2014). What do verbal fluency tasks measure? Predictors of verbal fluency performance in older adults. *Frontiers in Psychology, 5,* 1-10. doi: 10.3389/fpsyg.2014.00772

Sheremata, S.L., Somers, D.C., & Shomstein, S. (2018). Visual short-term memory activity in parietal lobe reflects cognitive processes beyond attentional selection. *The Journal of Neuroscience, 38,* 1511-1519. doi: 10.1523/JNEUROSCI.1716-17.2017

Shura, R.D., Rowland, J.A., & Miskey, H.M. (2016). Auditory consonant trigrams: a psychometric update. *Archives of Clinical Neuropsychology, 31*, 47-57. doi: 10.1093/arclin/acv083

Singh-Curry, V. & Husain, M. (2009). The functional role of the inferior parietal lobe in the dorsal and ventral stream dichotomy. *Neuropsychologia, 47,* 1434-1448. doi: 10.1016/j.neuropsychologia.2008.11.033

Smith, S.M., Beckmann, C.F., Ramnani, N., Woolrich, M.W., Bannister, P.R., Jenkinson, M., Matthews, P.M., & McGonigle, D.J. (2005). Variability in fMRI: a re-examination of inter-

session differences. *Human Brain Mapping, 24,* 248-257. doi: 10.1002/hbm.20080

Smith, E.E. & Jonides, J. (1998). Neuroimaging analyses of human working memory. *PNAS USA*, *95*, 12061-12068. doi: 10.1073/pnas.95.20.12061

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

Stein, R.B., Gossen, E.R., & Jones, K.E. (2005). Neuronal variability: noise or part of the signal? *Nature Reviews Neuroscience, 6*, 389-397. doi: 10.1038/nrn1668

Steinberg, S.N., Greenfield, J.P., & Perrine, K. (2020). Neuroanatomic correlates for the neuropsychological manifestations of Chiari Malformation Type I. *World Neurosurgery, 136C,* 462-469. doi: 10.1016/j.wneu.2020.01.149

Stevens, F.L., Hurley, R.A., & Taber, K.H. (2011). Anterior cingulate cortex: unique role in cognition and emotion. *T he Journal of Neuropsychiatry and Clinical Neurosciences, 23,* 121-125.

Stoodley, C.J. & Schmahmann, J.D. (2010). Evidence for topographic organization in the cerebellum of motor control versus cognitive and affective processing. *Cortex, 46,* 831-844. doi: 10.1016/j.cortex.2009.11.008

Stoodley, C.J. & Schmahmann, J.D. (2009). The cerebellum and language: evidence from patients with cerebellar degeneration. *Brain and Language, 110,* 149-153. doi: 10.1016/j.bandl.2009.07.006

Stuss, D.T., Stethem, L.L., & Pelchat, G. (1988). Three tests of attention and rapid information processing: An extension. *The Clinical Neuropsychologist, 2,* 246–250. doi: 10.1080/13854048808520107

Sundermann, B. & Pfleiderer, B. (2012). Functional connectivity profile of the human inferior

frontal junction: involvement in a cognitive control network. *BMC Neuroscience, 13,* 1-13.

Swick, D., Ashley, V., & Turken, U. (2008). Left inferior frontal gyrus is critical for response inhibition. *BMC Neuroscience, 9.* doi: 10.1186/1471-2202-9-102

Uddin, L. (2020). Bring the noise: reconceptualizing spontaneous neural activity. *Trends in Cognitive Sciences, 24,* 734-746. doi: 10.1016/j.tics.2020.06.003

Van Horn, J.D., Grafton, S.T., & Miller, M.B. (2008). Individual variability in brain activity: a nuisance or an opportunity? *Brain Imaging and Behavior, 2,* 327-334. doi: 10.1007/s11682-008-9049-9

Vlachos, F., Papathanasiou, I., & Andreou, G. (2007). Cerebellum and reading. *Folia Phoniatrica et Logopaedica, 59,* 177-183. doi: 10.1159/000102929

Wager, T. D. & Smith, E. E. (2003). Neuroimaging studies of working memory: a meta-analysis. *Cognitive, Affective, & Behavioral Neuroscience*, *3*, 255-274. doi: 10.3758/CABN.3.4.255

Walcott, C.M., Scheemaker, A., & Bielski, K. (2009). A longitudinal investigation of inattention and preliteracy development. *Journal of Attention Disorders, 14*, 79–85. doi: 10.1177/1087054709333330

Waschke, L., Kloosterman, N.A., Obleser, J., & Garrett, D.D. (2021). Behavior needs neural variability. *Neuron, 109,* 751-766. doi: 10.1016/j.neuron.2021.01.023

Waters, G.S. & Caplan, D. (2003). The reliability and stability of verbal working memory measures. *Behavior Research Methods, Instruments, & Computers, 35,* 550-564. doi: 10.3758/bf03195534

Wechsler, D. (2011). *Wechsler Abbreviated Scale of Intelligence - Second Edition Manual.* Bloomington, MN: Pearson.

Wechsler, D. (1997). *Wechsler Memory Scale - Third edition. Administration and scoring manual.* San Antonio, TX: The Psychological Corporation.

Woodcock, R.W., McGrew, K.S., & Mather, N. (2001). *Woodcock-Johnson III Tests of Achievement.* Itasca, IL: Riverside Publishing.

Yaple, Z.A., Stevens, W.D., & Arsalidou, M. (2019). Meta-analyses of the n-back working memory task: fMRI evidence of age-related changes in prefrontal cortex involvement across the adult lifespan. *NeuroImage, 196,* 16-31. doi: 10.1016/j.neuroimage.2019.03.074