PARAMETRIC MODULATION OF PRACTICE-RELATED CHANGES OVER TIME IN NEURAL ACTIVITY DURING A SPATIAL WORKING MEMORY TASK

by

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(Under the Direction of L. Stephen Miller)

ABSTRACT

Working Memory (WM) has been studied extensively due to its predictive validity and impairment in mental disorders. Neuroimaging studies of the WM network generally have found involvement of the prefrontal cortex, parietal cortex, cerebellum, and occasionally the striatum. Neuroimaging studies have also demonstrated practice-related changes in neural activity during WM tasks. Practice effects have demonstrated between-group differences, as well as within-subject variability in neural activation between scans taken in different times (Sadek, 2001; Weissman, Woldorff, Hazlett, & Mangun, 2002.) These differences appear to correspond with both reductions and increases in neural activity, which are interpreted as a decrease in cognitive effort. Several studies have demonstrated effects of task domain on practice effects (Kelly & Garavan, 2005), with more basic sensorimotor tasks associated with increased activation over time, and higher-order tasks associated with decreased activation over time. Few experiments have specifically tested practice effects across runs of a single scanning session (Landau, 2005). This experiment aimed to demonstrate the effects of practice and task domain on neural activity over time. A series of experiments investigated intra-run changes in neural activity during a spatial 3-back, a working memory task, and 0-back, a visual attention task. We hypothesized

increased activation in strategy-specific brain regions (i.e., posterior parietal cortex) and decreased activation in task non-specific regions (i.e., dorsolateral prefrontal cortex), with more pronounced decreases during the more demanding WM task, compared with the 0-back task. Results from the WM task revealed a general decrease in neural activity in both the dorsolateral prefrontal cortex and the posterior parietal cortex. Results from the visual attention task revealed an increase in dorsolateral prefrontal cortex. Behavioral results failed to demonstrate significant practice effects on performance measures. These results appear to reflect a practice-related decrease in cognitive effort during the higher-order task (i.e., WM), and an increased need for attentional control, possibly due to fatigue, during the less demanding task (i.e., visual attention.) Results of this study demonstrate the importance of understanding the temporal pattern of the WM network in describing WM abilities. More generally, they demonstrate the effects of uncontrolled variables on replicability in fMRI studies.

INDEX WORDS: Working Memory, FMRI, Practice effects, Changes over time, Dynamic changes

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CHAPTER 1

INTRODUCTION AND LITERATURE REVIEW

Working Memory

The term 'working memory' (WM) is often accredited to Miller, Galantar, and Pribram (1960), but is most widely identified with the tripartite model suggested by Baddeley and Hitch (1974). According to their early definition, WM is the ability to temporarily maintain information for use in ongoing mental operations. A 2007 search on PsycINFO reveals that 9774 studies were conducted on, or used measures of working memory. In 2007, 989 articles on working memory were published, 95 of which were brain-imaging studies. This wealth of research concerning working memory reflects its predictive value, as well as its crucial role in several psychological and neurological disorders.

Correlation to Intelligence

Working memory accounts for a significant amount of variance in general intellectual abilities (Conway, Kane, Bunting, Hambrick, Wilhelm, & Engle, 2005). Its association with intelligence is viewed by some as an indication that the two constructs are "isomorphic," or identical (Engle, 2002; Van Rooy, Stough, Pipingas, Hocking, & Silberstein, 2001). Ackerman, Beier, and Boyle (2005) conducted a meta-analysis of 86 studies of working memory and intelligence to examine the relationship between the two constructs. Their results suggest that while the two concepts are related, working memory only explains 22.9% to 42.6% of the variance in tests of general intelligence. The authors

concluded that while WM is related to executive control and attention capacity, it does not account for all individual differences in these capabilities.

Within the intelligence literature, WM is frequently associated with general fluid intelligence (Gf), an aspect of intelligence identified mostly with attention and executive control (Ackerman, Beier, & Boyle, 2005). Gray, Chabris, and Braver (2003) examined the correlation of Gf, as measured with a standard novel problem-solving test, and WM, as measured by an object n-back task. In this functional magnetic resonance imaging (fMRI) study, the high-Gf participants performed better than the lower-Gf participants. In addition, they displayed greater recruitment of dorsal anterior cingulate, lateral prefrontal cortex, and inferior parietal lobule, areas often associated with working memory.

Predictive Validity

Given the significant association between WM and Gf, WM tasks could serve as predictors of some aspects of intelligence. The more recent and complex working memory measures (i.e., span tasks) appear to be sensitive to individual differences, and correlated with fluid intelligence (Engle, Tuholski, Laughlin, & Conway, 1999). Borella, Carretti, and Mammarella (2006) explored the relationship between working memory and fluid intelligence. Specifically, the authors hypothesized that, as stronger fluid intelligence and working memory abilities are associated with resistance to interference, the latter could be the executive component in working memory tasks that predicts individual differences. Ninety participants, divided into three age groups (ages 18-86), were administered two working memory tasks (i.e., a categorization span task and a proactive interference task) with varying requirements for interference resistance, as well as a measure of fluid intelligence (Raven's Progressive Matrices). Results of regression analysis indicated that the span working memory measure with minimal proactive

interference was the most potent predictor of the participants' performance on the fluid intelligence measure.

In addition to intelligence, working memory performance has been successfully used as an assessment tool to predict cognitive abilities across domains, including reading comprehension, inhibition, and learning a new language (Unsworth, Heitz, Schrock, & Engle, 2005; Atkins & Baddeley, 1998; Conway, Kane, Bunting, Hambrick, Wilhelm, & Engle, 2005). In children, performance on working memory tasks was found to be associated with academic and attentional/behavioral difficulties in school (Aronen, Vuontela, Steenari, Salmi, & Carlson, 2005), achievements in school (St Clair-Thompson & Gathercole, 2006), and performance on national curriculum tests (Jarvis & Gathercole, 2003).

WM could potentially be used as a clinical assessment tool with patients. For example, performance on measures of working memory was found to predict subjective cognitive complaints in HIV positive patients. In the absence of neuropsychological tests, subjective cognitive complaints are frequently used as an indicator for brain impairment, and affect treatment planning. Bassel, Rouke, Halman, and Smith (2002) studied cognitive performance in 36 adult individuals with HIV infection. The administered battery included measures of depression and cognitive complaints, as well as tests of verbal learning, psychomotor abilities, working memory, and delayed recall. While complaints about cognitive performance was correlated with increased depression, complex psychomotor abilities, and working memory, a regression analysis revealed that the latter was its strongest predictor. The authors stressed the importance of intact working memory in daily activities, regardless of the actual integrity of specific learning and memory systems.

Effects of Illness on Working Memory

Working memory deficits are found in several psychological and neurological disorders (Deveney & Deldin, 2004; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005; Conway, Kane, Bunting, Hambrick, Wilhelm, & Engle, 2005). In children with Attention-deficit/Hyperactive Disorder (ADHD), symptoms are commonly attributed to executive dysfunction, including WM deficits. In a meta-analysis of 83 studies comparing children with ADHD and without, working memory, planning, inhibition, and vigilance were found to display the strongest and most consistent effects. The observed group differences were not explained by intelligence, academic achievement, or symptoms of comorbid disorders (Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005).

Schizophrenia is associated with working memory deficits across tasks (Johnson et al., 2006; Goldberg, Patterson, Taqqu, & Wilder, 1998; Park & Holzman, 1992; Perlstein, Carter, Noll, & Cohen, 2001; Lee & Park, 2005; Sacco et al., 2006). Pantelis et al. (2004) administered a battery of cognitive tests to a group of 54 long-stay inpatients and 43 community patients with enduring schizophrenia. The goal of their study was to identify associations of cognitive abilities with behavioral manifestations of the disease. The authors found a correlation between spatial working memory deficits and negative symptoms of the disorder, specifically psychomotor poverty. This finding was not explained by premorbid intelligence, geographical location, duration of illness, or use of antipsychotic medications. The authors explained this correlation as indicating a general difficulty to represent large amounts of information internally that involves the prefrontal cortex.

In neuroimaging studies, individuals with schizophrenia display aberrant dorsolateral prefrontal cortex (DLPFC) activation. Imaging studies have shown that

individuals with schizophrenia display under- as well as over-activation in the DLPFC. Johnson et al. (2006) examined activation in the DLPFC as a function of working-memory task load. They obtained functional magnetic resonance images from 18 individuals with Schizophrenia or Schizoaffective Disorder performing a modified Sternberg Item recognition task with five loads. Their results suggest weaker increases in neural activation in the schizophrenia group in response to increased WM load. In contrast, participants in the schizophrenia group displayed greater cortical recruitment than participants in the control group during successful retrieval. The authors concluded that WM deficits in schizophrenia may be manifested differently during the different phases of memory due to the effects of several factors that contribute to the observed dysfunction.

Individuals diagnosed with Alzheimer's disease are another group that demonstrates working memory deficits (Baddeley, Logie, Bressi, Della Sala, & Spinnler, 1986; Greene, Hodges, & Baddeley, 1995). Logie, Cocchini, Della Sala and Baddeley (2004) compared groups of Alzheimer's disease patients and healthy older adults on a dual span task of visuospatial tracking and digit sequence recall. The study included three separate experiments, during which participants were first asked to perform each task separately and then perform the concurrent tasks with varying degrees of demand. All participants displayed reduced performance during high versus low demand tasks. Participants who were diagnosed with Alzheimer's disease displayed a clear dual task deficit, which according to the authors, reflected impaired dual task coordination abilities. The authors suggested that dual task coordination is one of the cognitive resources included in the multi-component executive control of working memory.

Natural aging is also associated with reduced WM abilities (Smith, Geva, Jonides, Miller, Reuter-Lorenz, & Koeppe, 2000). Colcombe, Kramer, Erickson, and Scalf (2005) conducted an fMRI study, in which they compared performance and brain morphology of younger and older adults. They found among the group of older adults, participants who preformed better on the Backward Digit Span (a working memory task) showed greater anterior white matter concentrations. Those results suggest that hemispheric connectivity is important for both neural recruitment and task performance.

Changes in the Definition of Working Memory

The concept of WM has undergone significant developments in recent years that are reflected in the various definitions of the construct and their different emphases. Goldman-Rakic (1996) defined WM as remembered information that is maintained on-line to guide behavior in the absence of external cues or prompts. According to Bunge, Klingberg, Jacobsen and Gabrieli (2000), working memory is the process whereby information is temporarily maintained in memory for use in ongoing mental operations. It includes verbal and spatial short-term stores, as well as executive processes that operate on the contents of these stores. Executive processes are thought to be executed in the prefrontal cortex, and include multiple task coordination, set-shifting, interference resolution, and memory updating. Jonides, Lacey, and Nee (2005) described WM as consisting of the storage buffers that retain information briefly, rehearsal processes that refresh the buffers, and executive processes that manipulate the stored information. Finally, Conway, Kane, Bunting, Hambrick, Wilhelm, and Engle (2005) defined WM as a multi-component system responsible for active maintenance of information in the face of ongoing processing and/or distraction.

The different conceptualizations of WM reflect the researchers' orientations, with human cognitive researchers focusing on the higher order aspects of WM, whereas researchers who work with non-human primates emphasize short-term storage and active maintenance abilities. Owen, McMillan, Laird, and Bullmore (2005). It also reflects more recent developments in this concept, specifically, the inclusion of more executive functions (e.g., interference tolerance). The refinement in the concept of WM has been accompanied by development of more sophisticated tasks that are able to isolate the variety of cognitive processes required to actively maintain and manipulate information.

Baddeley's model of working memory.

One of the most extensive works on WM that demonstrates the evolution in this concept was done by Baddeley. In 1974, Baddeley and Hitch used the term of Working Memory to separate their tripartite model from other models of short-term memory. According to their model, a control system (i.e., the central executive) with limited attentional capacity facilitates cognitive processes (e.g., reasoning and learning) using two subsidiary systems. The two systems were the phonological loop and the visual sketchpad. The phonological loop was described as comprising a phonological store for brief memory traces of sound and language, as well as an articulatory rehearsal process that reactivates the stored information. The main function of the phonological loop was later described as learning new words during childhood (Baddeley, Gathercole, & Papagno, 1998). Similarly to the phonological loop, the visual sketchpad is comprised of both storing and rehearsal processes. This system has not been studied extensively as the phonological loop. It currently includes all non-verbal information, that is spatial, visual, and object. Its hypothesized functions are related to creative mental synthesis (Baddeley, 2003).

In 1986, Baddeley modified the early WM model by distinguishing within the executive system between automatic processes that relied on schemas or habits; and processes that required a supervisory activating system for activities that required attention and flexibility. WM was newly defined as a cognitive system for the temporary storage and manipulation of remembered information. This model has been generally supported by research, but had several theoretical difficulties, including simplified and over-inclusive definitions of the three components. The majority of the criticism focused on the executive system, specifically for not accounting for 'chunking effects,' and for not including a mechanism through which the two subsidiary systems could interact (Baddeley, 2003).

In 2000, Baddeley introduced a fourth component to his model, the episodic buffer, which "binds" information to form representations of integrated episodes. This process is hypothesized to be controlled attentionally by the executive system, possibly its storage component, and accessible to awareness. This model stresses ability of WM to manipulate and create new representations, rather than simply retrieve old memories from long-term memory.

Long-term working memory.

The theory of Long-Term Working memory (LTWM; Ericsson & Kintsch, 1995) addresses the duration of WM maintenance, and relates to the inclusion of interruption tolerance to the concept of working memory. Specifically, it explains the ability to construct and keep updated large representations despite significant interference. Interference tolerance is viewed as an evolutionary adaptive requirement to perform in a reality of constant interferences. For example, the ability to "safeguard" processed

information is more developed in skilled workers, who are able to store large representations of task-specific information more quickly.

Oulasvirta and Saariluoma (2006) studied the mental skills and resources needed to encode and safeguard task representations in long-term working memory. In an intricate series of studies, they manipulated the encoding process of an expository text in skilled readers. The reading material was presented and paced by a computer, after which a multiplication verification task was used for interference, followed by 30 more seconds of presentation of the reading material. The four experiments differed on their pre-interference period, difficulty level of the interfering task, difficulty rehearsing the information, and reading rate. Results of this study revealed that memory was safeguarded and resistant to interference until significant time pressure was imposed to the encoding process in the pre-interference phase. The authors concluded that their results suggest the two competing theories of interference tolerance, auditory rehearsal and time-based retrieval cues, were not used to safeguard the presented information.

Current Theoretical Understanding of Working Memory

To summarize, current theories of WM are derivatives or responses to Baddeley and Hitch's (1974) multi-component model. The attention to WM's functional importance (Conway, Kane, Bunting, Hambrick, Wilhelm, & Engle, 2005) as a distinction from short-term memory has emphasized the role of its executive component. Specifically, recent definitions in cognitive psychology include the evolutionary advantage and ecological validity of WM's ability to resist interference over time (Engle, Tuholski, Laughlin, & Conway, 1999; Conway, Kane, Bunting, Hambrick, Wilhelm, & Engle, 2005).

Research on Working Memory

The development of the concept of WM has been accompanied by extensive behavioral, physiological, and imaging research. The various methods and levels of investigation of this concept have helped shape our current understanding of working memory. In the next few sections, we will review studies that examined the physiological correlates of WM, its common measures, and its associated brain regions.

Physiological Research

Various studies have used animal models to reveal the underlying neural mechanisms of WM. Castner, Goldman-Rakic, and Williams (2004), reviewed the key rodent and non-human primate models of WM studies. Their review suggested that sensitization by injected phencyclidine (PCP) or amphetamines, as well as neurodevelopmental insults, impair WM. The reviewed studies demonstrated the significance of aberrant dopaminergic and glutamatergic signaling in medial prefrontal cortex for working memory deficits.

While the crucial role of the dopaminergic system of the prefrontal cortex in working memory is known in non-humans, studies with human subjects have yielded conflicting results. The complexity of the human working memory system was demonstrated in a study that controlled the levels of tyrosine, precursor to the neurotransmitters dopamine and noradrenaline, in 18 healthy male participants (Ellis, Mehta, Wesnes, Armstrong, & Nathan, 2005). Participants were tested on three occasions, performing a spatial working memory delayed-recognition task, non-spatial working memory task, and spatial n-back task. On each testing day, participants were treated with placebo, amino acids to induce acute tyrosine depletion, or both amino acids and pergolide, a D1/D2 agonist. In contrast with previous data from primate studies,

acute tyrosine depletion (used as means to decrease dopaminergic signaling) did not impair working memory. However, participants who received the combined condition of acute tyrosine depletion and a dopamine agonist displayed slight impairments in WM. The authors emphasized that their results question the reliability of acute tyrosine depletion as a modulator of dopaminergic function and WM performance in humans.

In addition to studying the underlying mechanisms of WM, attention has also been given to its susceptibility to various chemicals. Levin, McCleronon, and Rezvani (2006) reviewed the effects of nicotine on working memory. According to the authors, nicotinic agonists that attach to α4β2 and α7 nicotinic receptors have been shown to improve working memory performance in normal rats. Furthermore, chronic nicotine infusion was found to reverse working memory deficits in rats with lesions of the fibria medial basalocortical projection. Fewer human studies of nicotine with non-smokers were reported, and their results were mixed. However, according to the authors, initial studies on Alzheimer's disease, schizophrenia, Attention Deficit Hyperactivity Disorder, and Parkinson's disease have shown positive therapeutic effects with nicotinic agonists.

In contrast, antipsychotic medications are known to impair working memory abilities. Karl, Duffy, O'brien, Matsumoto, and Dedova (2006) administered high doses of either haloperidol or risperidone to Sprague-Dawley rats. The administered drugs are known to block dopamine D2 receptors and, at high doses, to induce extrapyramidal symptoms. After 28 days of drug administration via osmotic minipumps, both groups of rats displayed working memory deficits, as well as diminished motor activity, and increased anxiety levels.

The change in working memory abilities in response to drugs has created interest in developing psychopharmacological treatments for memory deficits. One possible

treatment involves increasing the cortical levels of extracellular superoxide dismutase (EC-SOD), an enzyme that destroys superdioxide ions. EC-SOD limits oxidative stress-induced neural degeneration that occurs in normal aging, as well as in acute episodes (e.g., following cerebral ischemia) by quenching free radicals (Levin, 2005). At the present, most EC-SOD studies use animal models.

Behavioral Research

According to Owen, McMillan, Laird, and Bullmore (2005), the n-back is one of the most popular paradigms for functional imaging. Conway, Kane, Bunting, Hambrick, Wilhelm, and Engle (2005) stated that span tasks are among the most widely used tasks in cognitive psychology due to their methodological merits and theoretical base. In the following pages, I will define and review the literature of each task, as well as explain our rationale for deciding on using a spatial n-back task for this study.

N-back.

The n-back task includes several cognitive processes, including on-line monitoring, updating, and manipulation of remembered information. Across modalities of this task (e.g., verbal, spatial, or object), it requires participants to attend to a series of items, and judge whether a given item is identical to a different item that was presented n-trials back. Increasing the numbers of trials back the participants need to remember (i.e., N= 1, 2, 3, or 4) in order to successfully perform this task manipulates its working memory demand.

Hockey and Geffen (2004) conducted a study of the concurrent validity and test-retest reliability of the spatial n-back (n range 0 to 3). Seventy participants performed the task twice, with one week between sessions. On the second session they were administered a computerized version of the Multidimensional Aptitude Battery (MAB), a

measure of intelligence. Test-retest reliability was generally moderate for percentage accuracy, except for the 3-back condition (r = 0.732), and high for reaction time, across n-back levels (r ranged from 0.715 to 0.806). Concurrent validity of the spatial n-back was supported, as faster reaction times were correlated with higher general mental abilities. In addition, performance at the easier levels of the n-back was negatively correlated with participants' scores on the MAB, while performance at the more difficult levels of the n-back was positively associated with MAB scores. The authors concluded that their results support the view that intelligence is a product of faster speed of information processing and greater working memory capacity.

Owen, McMillan, Laird, and Bullmore (2005) conducted a meta-analysis using the Activation Likelihood Estimation (ALE) technique of 24 functional imaging studies of the n-back task from 1994 through 2003. Robust activation across n-back modalities was found in the following areas: bilateral and medial posterior parietal cortex (e.g., precuneus, inferior parietal lobules, BA7, 40), an area involved in the rehearsal and storage of working memory; bilateral premotor cortex (BA6, 8), an area activated during working memory tasks that require maintenance of visuospatial attention; dorsal cingulated / medial premotor cortex (BA32, 6); bilateral frontal pole (BA10), a region known to be involved in integration of several cognitive operations; bilateral mid-ventrolateral prefrontal cortex or frontal operculum (BA45, 47), a region involved in explicit retrieval of information that was intended to be remembered; and bilateral DLPFC (BA9, 46), an area thought to contribute to the strategic organization and control of working memory contents. Specifically, DLPFC activation is associated with the selection of appropriate high-order organizational chunks that facilitate memory by reducing overall cognitive load. Additional activation was found in the medial

cerebellum, and nonverbal location-monitoring n-back tasks demonstrated stronger right hemisphere activation.

Span tasks.

Span tasks were developed to study the capacity of the executive functioning component of working memory through concurrent processing of two tasks. Span tasks were found to be powerful predictors of the Scholastic Aptitude Test, and sensitive to developmental or disease-related cognitive changes (Bunge, Klingberg, Jacobsen & Gabrieli, 2000). Current span tasks recreate Daneman and Carpenter's (1980) reading span task requirements of inserting distracting activities between the to-be-remembered items, and recalling the items in the order in which they were presented (Unsworth, Heitz, Schrock & Engle, 2005).

Conway, Kane, Bunting, Hambrick, Wilhelm, and Engle (2005) reviewed previous assessments of the reliability and validity of reading span, operation span, and counting span tasks. The review that included over a hundred independent studies with thousands of subjects revealed strong reliability across tasks, with coefficient alphas ranging from 0.70 to 0.90. Test-retest correlations of 0.70 to 0.80 suggested scores were stable over time. In terms of the tasks' validity, convergent and construct validity were supported, as scores on span tasks correlate with higher order cognitive tasks (e.g., reading comprehension, reasoning, suppressing intrusive thoughts, and social cognition). In addition, discriminant validity was supported in their review, as performance on span tasks did not predict performance on tasks that rely on automatic processing (e.g., prosaccade eye movement).

Span tasks vary in their distracting activity (e.g., level of difficulty, similarity to the items to-be-remembered), as well as in the nature and difficulty of the target items.

Regardless of the domain-specific abilities that are required by the different span tasks (e.g., reading or counting), they are designed to access domain-general executive attention of WM. A 1.5T fMRI study conducted by Bunge, Klingberg, Jacobsen and Gabrieli (2000) examined whether performing a dual task would result in enhanced recruitment of task-specific brain regions or in new areas specialized for dual task-specific processes, such as task coordination. Eight healthy, young participants were scanned performing four tasks: the WM span test (i.e., sentence evaluation and word memory task), its two components tasks, and a baseline condition (i.e., pressing buttons in response to viewing meaningless consonant strings). Behaviorally, dual tasking affected the speed, but not the accuracy of performance. All brain regions that were active in the working memory span task were active during the component tasks, with no exclusive or novel activity during the dual task. The authors modified their study by scanning eight new participants using a 3T scanner. Participants performed an easier word memory task, but had an inter-trial interval to allow approximately 12 seconds for the recall-related hemodynamic response to subside. Behavioral results of this study indicated that performance was slower and less accurate in the dual task. Consistent with the first experiment, dual task was associated with enhanced brain activity in regions activated in the component tasks in prefrontal and parietal regions. The results of this study suggest that dual task processing might not involve a separate brain region that integrates and manages the component tasks. It appears that dual task performance is possible through simply increased involvement of brain regions necessary for the individual component tasks.

Recent developments in span tasks include automatization of the task, which provides greater accuracy in item presentation and data collection. Unsworth, Heitz,

Schrock and Engle (2005) presented an automated version of the operation span (O-span) that allows an easy and accurate manipulation of item exposure time based on past performance of the participant, and provides accurate behavioral measures including response time, and error types. The duration of the computerized task is approximately 20 minutes, during which participants are asked to read aloud and evaluate a solution to simple math problems (e.g., is (8/2) -1 = 1?), and at the end of the task to recall, in order, the words that were presented following each math problem. The performance of 252 young adults on the automated O-span was compared with their scores on a traditional operation span task (r = 0.448), and with the Raven Progressive Matrices, a measure of abstract reasoning (r = 0.423). The test-retest reliability of the automated O-span was estimated on 78 participants that were randomly selected from the original 252 participant pool. Test-retest was 0.83, and alpha of internal consistency was 0.78.

The theory-based methodology of the span tasks offers precise manipulation of the type, timing, and level of distracter and item difficulty. As a result, it allows isolation of specific executive functions related to working memory. When used in imaging studies, this methodology poses several obstacles in interpretation of observed neural activation. First, span tasks are “not perfect or process pure” (Conway, Kane, Bunting, Hambrick, Wilhelm, & Engle 2005), as they require concurrent processing of several cognitive abilities (e.g., memory, reading, calculation). This results in regions of activations that are not unique to working memory. Additionally, while interference resistance serves as a good measure of WM capabilities, it also presents as another confounding variable on the statistical parametric maps of neural activation. Nelson (2006) located processing of interference resolution during a verbal working memory task in the left inferior gyrus, a common area of activation in WM studies. Therefore, it

may be difficult to determine whether observed activation in the left inferior gyrus is related to working memory or interference resistance. In contrast, the uninterrupted n-back task requires continuous maintenance and updating of the presented WM information. While it allows more limited isolation of working memory functions, it presents significant advantages in imaging studies. First, due to the relatively simple n-back paradigm, the observed activation will not include irrelevant cognitive functions (e.g., reading comprehension, calculation). Second, neural activation derived from a spatial n-back task is expected to include only activity unique to spatial WM, with no overlapping activity from additional higher-order cognitive functions (e.g., interference tolerance). For those reasons, this study will use the spatial n-back, a working memory task that has been used in previous studies from our laboratory.

Brain Imaging Studies

Functional magnetic resonance imaging.

Functional brain imaging techniques have revolutionized brain-imaging research. Unlike earlier brain imaging techniques that only provide structural data, the functional techniques, such as Positron Emission Tomography (PET) and Functional Magnetic Resonance Imaging (fMRI), possess the ability to identify generally the magnitude and location of brain activity. They offer new insights into the brain, specifically the localization of processing of sensory, motor, and cognitive tasks.

Functional Magnetic Resonance Imaging (fMRI), enables the detection of changes in the flow rate of blood, either directly using perfusion imaging techniques (e.g., Wong, Buxton, & Frank, 1997) or, more commonly, indirectly using oxygenation level that is assumed to be associated with local changes in neural activity. During a typical fMRI scanning procedure, functional and three-dimensional anatomical images of

the brain are constructed. Images are created using an MRI scanner, taking advantage of the phenomenon of nuclear magnetic resonance (NMR) to image the nucleus in the abundant protium isotope of hydrogen (^1H), which is comprised of only one proton and which resides in non-deuterated water primarily within tissue, through interactions between their nuclear magnetic moments and external magnetic fields. In the presence of a homogeneous magnetic field (e.g., in the bore of an MRI scanner, where participants are inserted during a study), all ^1H nuclei will have a characteristic resonant frequency that is proportional to the strength of the magnetic field (Cohen, 1999). The magnetic moments of the nuclei will line up parallel or anti-parallel with this magnetic field; in the presence of a strong field, a small excess of moments will line up in parallel, resulting in a slight nuclear magnetization in all localities of the tissue. These local magnetizations will precess in an orbit at the resonant frequency if perturbed (Cohen, 1999). During an MRI procedure, the patient is inserted into the bore of the scanner, followed by the emission of electromagnetic energy in the radio frequency (RF) band in the form of a second oscillating magnetic field. The frequency range of this emission is tuned to overlap with the resonant frequency of the hydrogen nuclei, exciting them and causing the tissue magnetizations to precess coherently (Noll, 1999). Finally, the MRI scanner detects the coherent precessing magnetizations as a small voltage change in a coil. Properties of the tissue, such as the local magnetic characteristics of nearby molecules, will cause small spatial variations in the resonant frequencies and corresponding precession rates of the magnetizations. At the time of signal measurement, regions or tissues containing large variations in precession rate within individual “units” of spatial resolution (i.e., pixel or voxel) will contribute little signal, because the different rates contribute to a large dispersion in the precessional “phase” of the local magnetizations

within that region. The phase dispersion represents incoherence of precession between neighboring local regions, allowing the signal from one region to negate the signal from another. In a similar manner, regions with a fairly consistent precession rate will contribute more signal. Repeated measurements of this signal, in conjunction with different spatial preparations of the tissue magnetization using so-called "gradient" magnetic fields, allows the MRI scanner to reconstruct an image showing the spatial distribution of different tissue types.

To create functional images, researchers utilize the hemodynamic response, which is the net effect of physiological changes in blood flow, blood volume, and blood oxygenation in response to local neural activity (Savoy, 1997). In many studies (including this one), Blood Oxygen Level Dependent (BOLD) effects are measured, resulting from changes in the oxygen-to-deoxygenated blood ratio. Increases in deoxygenated blood cause increased phase dispersion in neighboring protons as compared to oxygenated blood, resulting in weaker signals than those detected from oxygenated blood (Ogawa, 1993). During task performance, areas in the brain that are associated with the task performance have a higher blood flow that is rich in oxygenated blood. Conventional BOLD-contrast fMRI studies use a subtractive methodology, subtracting the filtered temporal changes in intensity observed in fMRI images, or "activity", during task performance and a "rest" condition. Statistical computer software, such as Statistical Parametric Mapping (SPM; Wellcome Department of Cognitive Neurology, London, UK), constructs a map of statistical parameters, allowing for F- or t-tests between the measured rest and activation in each pixel and the predicted response function, for example. The detected changes between rest and activation are presented as a functional map showing the loci of vascular beds feeding the increased metabolism

associated with local neural activity during the task performance. Finally, the functional images are co-registered to a three-dimensional anatomical picture of the brain, allowing identification of the brain structures in which the activation occurred during the scan.

FMRI is a non-invasive technique that images ^{1}H that resides primarily in water. It can be safely used repeatedly, and therefore possesses some advantages to other brain imaging techniques such as positron emission tomography (PET), which uses ionizing radiation. FMRI also has high spatial resolution at reasonable temporal resolutions, with a spatial resolution of a few millimeters and a temporal resolution of less than a second. However, in fMRI, smaller voxel volumes decrease the available signal to-noise (SNR) ratio. In order to improve the SNR, activity across multiple trials is averaged, at the cost of compromising temporal resolution within an individual trial.

These qualities make fMRI a potentially useful clinical tool. It may be a more precise assessor than classical neuropsychological assessment tests, for it may detect changes in patterns of activity, even when behaviorally there is no apparent change of function (Price & Friston, 1999). According to Gordon (1999), its functional abilities are being used to subdivide patients suffering from a particular disease to different treatment groups, based on specific patterns of neural activation. Functional imaging can also supply an objective measure of treatment outcomes.

Functional imaging of working memory.

Jonides, Lacey, and Nee (2005), reviewed animal and neuroimaging studies of brain mechanisms involved in the storage and rehearsal processes of spatial working memory. Their hypothesis was based on the storage and rehearsal stages in Baddeley's model of working memory (2000). Based on the reviewed studies, they suggested that during the storage stage, information is processed in parietal and temporal regions that

specialize in perceptual processing. The representation of the stimuli slowly fades following the removal of the stimuli. Information remains accessible during the rehearsal stage, by activation of attention shifting mechanisms in the brain, mostly superior parietal and frontal brain regions.

The relationship between attention and WM has been studied in humans as well. Postle, Awh, Jonides, Smith, and D'Esposito (2004) constructed an event-related fMRI study to investigate the link between spatial attention and spatial WM by studying the topography and the mechanism of attention-based rehearsal. The encoding and updating of spatial information in working memory is reportedly achieved by increased attention to the memorized locations. The resulted increase in neural signals in areas representing the attended locations is known to improve visual processing, and therefore task-performance. Nine healthy, young participants were asked to judge whether a probe stimulus of two aligned bars, was "nearer" or "farther" from the fixation cross, compared to the target bar that was presented and followed by a delay period of 7.5 seconds. This study included two delayed conditions, a "filled" screen with flickering checkerboard and an "unfilled" screen with a fixation cross. Contrasting the two delay conditions revealed greater lateralized activation in extrastriate (BA 18 and 19) and superior parietal lobule in the unfilled condition, suggesting attention-based rehearsal process during a spatial working memory task.

Working memory has been studied by additional neuro-functional techniques. Brumback, Low, Gratton, and Fabiani (2005) conducted an event-related potential (ERP) experiment using the operation span task to study the effects of working memory function on integration of information. Event-related brain potentials and reaction time of 69 participants were recorded, as they performed an auditory operation span task. Tones

presented to participants were preceded by either a similar or a different tone. The authors hypothesized that working memory capacity would affect response to changing contexts between current and previous stimuli. Results demonstrated that participants with low WM span displayed larger brain responses to changing context between stimuli than participants with high WM span. The authors interpreted the group differences as suggesting that participants with low WM span are more easily distracted by changes in the environment, which hinders their ability to maintain their attention on the overall sequence.

In general, WM tasks have been found to involve the prefrontal cortex, parietal cortex, cerebellum, and occasionally the striatum. DLPFC may be recruited in WM tasks involving only maintenance when the WM load exceeds the processing limits of ventrolateral PFC (Bunge, Klingberg, Jacobsen & Gabrieli, 2000). Wager and Smith (2003) reviewed 60 functional neuroimaging studies (from 1993 to 2002) of spatial, verbal, and object working memory in order to study the neural basis of working memory in the brain. Their meta-analysis included studies on the three leading theories of the organization of working memory storage by material type. The first theory postulates that spatial information involves a dorsal processing stream, including the inferior parietal lobule, the intraparietal sulcus, superior dorsolateral cortex, and the superior frontal sulcus. In contrast, object information processing involves a ventral stream, which includes the inferior frontal pole, as well as mid and inferior frontal regions. Consistent with this theory, storage in the posterior cortex involved parietal cortex when spatial information was used, and the inferior temporal cortex was involved when object information was studied. However, this dissociation was not found in the prefrontal cortex, as was suggested by previous studies.

The second theory postulates that working memory of verbal information is processed in the left frontal lobe. Results for this theory were mixed, with most studies revealing left lateralization of verbal working memory in the inferior frontal cortex. This effect was weaker than expected based on past individual studies.

The third theory postulates that working memory of spatial information involves the right hemisphere, whereas processing of object working memory is left lateralized. Findings of this meta-analysis generally did not support this theory. Specifically, object storage demonstrated right lateralization in the frontal cortex, and on demanding tasks, spatial storage involved right lateralization limited to the frontal cortex.

In addition to the three storage theories, Wager and Smith reviewed support for a theory of the specialized organization of the executive component of working memory. According to this theory (D'Esposito et al., 1998; Owen, 1997, 2000), generalized executive processing involves the superior frontal cortex, whereas the ventral frontal lobe is involved in rehearsal during simple storage tasks. For the purpose of Wager and Smith's meta-analysis of PET and fMRI studies, three executive functions were studied: continuous updating, memory for temporal order, and information manipulation. Results of their study suggested specialization of bilateral DLPFC and superior frontal sulcus (specifically BA 6, 8, and 9) in continuous updating and memory for temporal order. BA 7 was involved across executive functioning tasks. Based on the results of the meta-analysis, a fourth executive function of selective attention was proposed. This function was associated with increased activation in the medial prefrontal cortex (BA 32).

Practice Effects in Imaging Studies

Practice is a task-related variable that affects neural activity. Several fMRI studies have demonstrated between-group practice effects (Weissman, Woldorff, Hazlett, &

Mangun, 2002; Sadek, 2001). Kassubek, Schmidtke, Kimmig, Luecking, and Greenlee (2001) designed an fMRI experiment that examined changes in cortical activity associated with procedural learning (PL). The authors defined PL as the acquisition and improvement of skills through practice. Earlier studies with sensorimotor tasks demonstrated decrease in cerebral activation that occurred after PL (e.g., Karni, Meyer, Jezzard, Adams, Turner, & Ungerleider, 1995).

The authors tested the hypothesis that such decrease in activation would occur with a non-motor task of mirror reading. The authors hypothesized that intensive practice would increase neural efficiency to the extent that less effortful processing would be needed. In the fMRI environment, less effortful processing would be demonstrated by decreased functional activity in task-related regions. The authors scanned ten young subjects on two separate days. On the first day, the subjects performed the novel task without prior practice. Scanning on the second day was done after intensive training of the task. To be qualified for scanning, each subject had to demonstrate the ability to read forty eight-letter mirror script words in sixty seconds. Significant activation decrease in task related brain regions in the striate, parietal, visual, and premotor cortexes was found. The authors concluded that through practice, PL of a non-motor task leads to a decrease in cortical activation. According to the authors, several mechanisms contributed to the decrease in activation, including decreased demand and increased efficiency.

Jessen et al. (2001) designed an event-related fMRI experiment of a verbal recognition task that compared neural activity during recognition at first repetition with recognition at second repetition. Seventeen young participants performed a continuous recognition task, during which they were asked to identify repeated target items (German

nouns) from novel ones. Neural activity was found to be greater at first repetition versus the second in the frontal cortex, which suggested a retrieval effort-dependent activity.

Spatial working memory has been studied extensively, and brain regions that are associated with processing of spatial working memory tasks have been identified. In addition, practice effects have demonstrated between-group differences, as well as within-subject variability in neural activation between scans taken in different times (Weissman, Woldorff, Hazlett, and Mangun, 2002; Sadek, 2001; Kassubek, Schmidtke, Kimmig, Luecking, and Greenlee 2001).

The exact nature of practice effects is still debated. Several other imaging studies found practice-dependent increases in neural activity (Awh et al., 1999; Smith, McEvoy, & Gevins, 1999; Kirschen, Chen, Schraedley-Desmond, & Desmond, 2005). This increase in neural activity has also been conceptualized as an increase in efficiency. Jansma, Ramsey, Slagter, and Kahn (2001) discuss the possibility that as automatization of task performance occurs, the initial load on working memory and executive functioning regions (e.g., DLPFC) is shifted to strategy-specific areas (e.g., in the parietal lobule). Weissman, Woldorff, Hazlett, and Mangun (2002) investigated practice-related changes in neural activity during a task of executive control. Fifteen young adults performing a cued global/local attention task were scanned during this event-related fMRI study. Participants practiced the stroop-like interference task during the 50-minute scanning. Practice was correlated with a reduction in neural activity in the left inferior parietal lobe, a region generally involved in attention orientation. In addition, practice was associated with increased activity in midline frontal regions that are specific to processing stroop-like interference. Results of this study support practice-related

decreases in neural activity in task non-specific areas, along with increases in task-relevant brain regions.

Practice and repeated exposure to a task are known to demonstrate both behavioral and neural effects. Behaviorally, people who receive practice display more accurate and faster reactions to a task than people who do not receive practice. These differences appear to correspond with a reduction in neural activity, which is interpreted as a decrease in cognitive effort. Jansma, Ramsey, Slagter, and Kahn (2001) examined practice effects on shifting the processing of a working memory task from controlled to automatic. Practice effects were associated with a more accurate, faster performance. They were also associated with a reduction in activation of regions related to working memory, such as DLPFC.

Kelly and Garavan (2005) reviewed 27 functional neuroimaging studies of practice effects. Their literature review identified three main patterns in response to practice: increased activation, decreased activation, and functional reorganization. They suggested that functional reorganization can be further distinguished into two processes: Redistribution of functional activation, and 'true' reorganization of activation. Redistribution includes observed increases and decreases in the same brain regions across task performance. In redistribution, increased activation reflects increased reliance on strategies, while decreased activation reflects decreased reliance on control and attentional processes. In contrast, 'true' reorganization of functional activities reflects a shift between cognitive processes and strategies. They concluded that in addition to the type of reorganization (i.e., redistribution versus reorganization) practice effects are affected by the task domain, individual differences, and past exposure to the task. Finally, the authors stressed the effect of the time-window of imaging on the observed practice

effects. They suggested imaging studies should allow adequate scanning time to capture the entire impact of practice on neural activity.

Remaining Questions

Practice-related changes in neural activity have been observed in paradigms that administer a practice session between scanning sessions. As participants in most fMRI studies perform a novel task repeatedly, the duration of scanning could be viewed as a practice session. Therefore, it is reasonable to assume that practice-related changes in neural activation could be detected across runs in a single scanning of a subject. To our knowledge, only a single experiment has specifically tested practice effects across runs of a single scanning. Landau (2005) conducted a series of event-related fMRI studies that investigated intra-run changes in neural activity during working memory tasks (object and spatial). Results of her studies suggested a decrease in neural activity, specifically during the encoding stage, without significant improvement in behavioral measures of performance. In addition, she compared changes in neural activity in domain-specific areas ("fast changes" indicative of immediate practice effects) with changes in domain general neural networks ("slow" changes indicative of functional reorganization). Specifically, performance and neural activity during a complex motor sequence was compared between two groups of professional pianists and non-pianists. Both groups displayed "fast" changes in terms of decreased neural activity in bilateral motor and parietal regions. However, the group of professional pianists also showed a general increase in the right hemisphere. Results of this study suggest that analysis of intra-run changes in neural activity could be used in studying the underlying mechanisms of WM.

An additional reason it is important to recognize and understand the influence of these variables on neural activation is practical. Knowing which task or subject-related

variables (other than the independent variable) may undesirably influence the subject's performance could help eliminate their influence by changing the design of the experiment or accounting for them statistically. Reducing error and increasing the accountability for systematic variance will help increase power and reliability in functional brain imaging studies.

Practice-related changes in neural activity over time.

Previous studies from our laboratory investigated intra-run practice and fatigue effects on neural activity during a short spatial working memory task, as measured by a 1.5 Tesla fMRI scanner (Kessel, Miller, Yanasak, & Maher, 2006, February, 2007, February.) Practice and fatigue effects were tested on a practice group that received a 10-minute practice session prior to scanning, and on a Control group that received a two-minute practice. Practicing the task during scanning was hypothesized to produce a decrease in neural activity, only in the Control group, due to increased efficiency; fatigue was predicted to be associated with an increase in neural activation in both groups. Behaviorally, we expected the Practice group to be faster and more accurate than the Control group. Fatigue measures, including a Fatigue State, 1-7 Likert Scale, were predicted to be correlated with changes in neural activity. For purpose of analyzing the behavioral data, neural activity was operationalized as the average of the highest z score in each of the activated clusters. Results demonstrated an initial practice-dependent decrease in neural activity in both groups, with greater decrease in the Control group. An increase in posterior parietal neural activity, only in the Control group, was observed towards the end of scanning. This pattern of change in neural activity appears to reflect continuing practice effects rather than fatigue effects. Similarly to Landau's study (2005), most behavioral measures failed to reflect group differences or did not correlate with

neural activity. Results of this study demonstrate the importance of controlling the effects of variables such as practice, to improve reliability in functional brain imaging.

Limitations of the previous study.

The Kessel et al. study (2006, February, 2007, February) demonstrated significant and predictable changes in neural activity over the course of a single scanning session. This experiment generally failed to demonstrate behavioral changes usually found in participants who received practice, that is improved accuracy and shorter response time (Schulze, Luders, & Jancke, 2002; Zeng, Miao, & Huangfu, 2003; Basso, Carona, Lowery, & Axelrod, 2002). These results could suggest that the observed group differences in neural activity may not reflect practice-dependent effects, but effects of an uncontrolled variable. However, it is more likely that statistical significance on behavioral measures was not reached due to the small sample size and relatively high standard deviations. The groups' means did differ in the direction of our hypothesis, with faster and more accurate performance in the Practice group, but were also accompanied by substantial within-group variance. It is also possible that the manipulation of practice was not powerful enough to demonstrate significant between-group behavioral practice effects in a small sample, several days after the practice session. In addition to a small sample size and relatively short scanning duration, other limitations of this study that could explain our results are the chosen analysis of the behavioral data and the operationalization of neural activity. The pilot study used correlations and t-tests to study the association between neural activity and task performance. Given the dynamic nature of this study, regression analysis would have been better suited to study changes over time in task performance and neural activity. A later regression analysis of practice and Percent Accuracy suggested that practice across 20-minutes of scanning predicted

increased accuracy in the Control group on the 3-back task ($r = 0.29$, $p < 0.001$). Findings also suggested that practice remained on a trajectory of continued increased accuracy in 3-back performance at the end of the scanning sessions (20 minutes). Furthermore, using an average of z-scores to operationalize neural activity, and a 1-7 Likert scale to operationalize fatigue resulted in a limited range of values that could have contributed to our failure to detect a correlation between the behavioral and neural variables.

Statement of Purpose

This experiment is aimed at demonstrating and plotting practice effects across time on observed neural activity of participants performing the spatial n-back, a working memory task. Two, 20-minute runs of the working memory task will enable intra-run comparisons that are sensitive to the systematic and dynamic effects of practice during a single scanning session. This experiment presents several improvements upon the pilot study. Technically, participants will be scanned in a 3 Tesla fMRI scanner, with higher temporal and spatial resolutions than the 1.5 Tesla scanner used in the pilot study. The high-performance magnetic gradient system within a 3 Tesla scanner also provides whole-brain functional imaging versus a 15-slice coverage that was used in the pilot study. Methodologically, a longer scanning time will be used to provide a more comprehensive understanding of changes in neural activity over time; a larger sample size will increase this study's power to detect real effects of practice. In terms of data analysis, regression analysis of time and percent accuracy and response time will provide a more time-sensitive measure of practice effects. Our goal is to provide useful information for future studies, primarily on the nature of changes due to practice effects. Knowing the function of changes in neural activity during a spatial working memory task could improve reliability in fMRI studies. For example, providing sufficient practice

prior to scanning in order to ensure relatively stable neural response could increase the probability of replicating results, thus increasing test-retest reliability. In addition, it will add a dimension of understanding neural processing of spatial working memory in healthy adults, which could be compared in the future with similar studies of individuals with disorders that are known to affect WM (e.g., schizophrenia, ADHD.)

Hypotheses

1. Over the course of scanning, participants will show decreasing activation in the prefrontal cortex. The decreased activity will be evident by a negative linear relationship between time and neural activation observed in this area.

2. In contrast, over the course of scanning, participants will show increasing activation in the posterior parietal cortex. The change in neural activity will be evident by a positive linear relationship between time and neural activation observed in this area.

3. Practice effects (i.e., changes in neural activity over time) in the prefrontal cortex will be more pronounced in the demanding and controlled task of the 3-back than in the 0-back.

CHAPTER 2

METHOD

Participants

This experiment included 20 young adult male participants, ages 18-22. The number of participants was based on an extension of a previous study from our laboratory, which failed to statistically demonstrate behavioral changes due to practice. Therefore, to increase our power to detect the effects of practice on Percent Accuracy and Response Time, this study more than doubled the number of participants and increased total scanning duration from 20 to 40 minutes.

Participants were recruited from the undergraduate population of the University of Georgia. Participants were screened using the Folstein Mental Status Exam (Folstein, Folstein, & McHugh, 1975) to indicate broadly intact general cognitive ability (MMSE score ≥ 29). Additional exclusion criteria to ensure intact cognitive ability consisted of self-reported history of neurological or psychological condition, a past head injury resulting in loss of consciousness, and active psychoactive medication use. To increase the homogeneity of the sample, the experiment only consisted of male participants with strong right-handedness, based on a screening interview. All subjects gave written informed consent to participate in this study, which had Institutional Review Board approval.

Measurements

Mini Mental State Examination (MMSE).

The MMSE was developed by Folstein, Folstein, and McHugh (1975) as a measure of cognitive impairment. The eleven-item test was designed to assess impairment in five cognitive domains: orientation, registration, attention, calculation, and language. The test correlates with the Wechsler Adult Intelligence Scale (0.78 for verbal IQ), and its inter-rater and test-retest reliabilities are usually well above 0.80 (Rogers, 1995). Scores on the MMSE vary within the population by age and years of education. According to Crum, Anthony, Bassett, and Folstein (1993), the median score for people under the age of 65, with at least nine years of education, is 29. The goal of this study was to study practice effects in cognitively intact individuals, and therefore participants whose scores suggested cognitive impairment (i.e., MMSE score < 29) were excluded.

State/Trait Anxiety Inventory (STAI).

The STAI Form Y is a measure of stable disposition to experiencing anxiety (i.e., Anxiety Trait), as well as transitory emotional and physiological state of apprehension and tension (i.e., Anxiety State). It was first developed by Spielberger in1964, and has been modified to its current revision, Form Y. The test consists of forty statements (20 Trait statements and 20 State statements), and scoring is based on the frequency with which individuals endorse them on a four-point Likert scale. On a test-retest reliability study with Undergraduate students, test-retest correlations ranged from 0.73 to 0.86 for the Trait scale, and from 0.16 to 0.54 for the State scale, as expected from a measure of a transient state (Spielberger, Gorsuch, & Lushene, 1970). Similarly, internal consistency, using a Cronbach alpha coefficient, ranged from 0.83 to 0.92. Validity testing, obtained by comparing STAI scores of 206 college students and 66 patients with scores on

alternative anxiety measures (e.g., IPAT Anxiety Scale) yielded correlation coefficients ranging from 0.75 to 0.83.

Handedness questionnaire.

Participants' handedness was assessed during the screening process. All participants were asked to complete a five-item handedness questionnaire. The questionnaire assessed participants' preference level in using their dominant hand for over-learned motor activities (e.g., brushing teeth, throwing a ball) on a five-point range. Only participants who will endorse strong right hand preference (i.e., total score of 5) were included in this study.

Spatial n-back.

This experiment used spatial 0-back and 3-back tasks, adapted for the MRI environment. Participants were asked to fixate their eyes on a digit (3 or 0, depending on the condition) in the middle of the screen they viewed through goggles, inside the scanner. A white square appeared on the screen for 500 ms, followed by 2500 ms of inter-stimulus interval, during which only a cross was seen on the screen. As shown in Figure 1.1, the squares appeared in a fixed-random pattern in one of eight different places on the edges of the black screen (along the screen's frame). In the 3-back condition, participants were asked to respond "yes" every time the square appeared in the same location it appeared three trials back. A "no" response was given when the square appeared in a different location. In the 0-back condition, participants were asked to respond "yes" every time the square appeared in the top left location. A "no" response was given when the square appeared in a different location. The stimulus presented in the 0-back condition is identical to the stimulus on the 3-back. However, since the 0-back does not require working memory abilities, this condition was used as a control task for

later contrasts. An additional "resting" control task in this study was a fixation cross. In this condition, participants were asked to fixate their eyes on the cross in the middle of the screen for six seconds before each n-back condition. The responses to the stimuli were registered through a hand activation unit the participants wore on their dominant hand. Participants were trained to press a button placed under their index finger to answer "yes," and on the button under their middle finger to answer "no."

Visual stimuli were presented on goggles made by Resonance Technology Inc., and behavioral data were acquired and processed using BrainWave Hardware Lite (GE Applications), suitable for research use within the MRI environment. The presentation package in this system includes goggles, headphones, and a two-button response unit for user input and reaction timing. Collected behavioral data included percentage of correct answers (percent accuracy) and response time for all participants for each response.

Practice measurements.

Practice effects were evaluated by two behavioral measures of the participants' performance- Percent Accuracy and Response Time. In this experiment, an increase in Percent Accuracy and a decrease in Response Time indicated increased processing efficiency due to practice. In addition, measures of dispersion and intensity of neural activation were derived from the functional data for the purpose of testing the effect of practice on neural activity. Dispersion of neural activity was defined as the number of activated voxels within a region of interest (ROI) divided by the total number of voxels in the ROI. Activation intensity was defined as the average percent signal intensity change (PIC) of the highest two percent activated voxels within the ROIs.

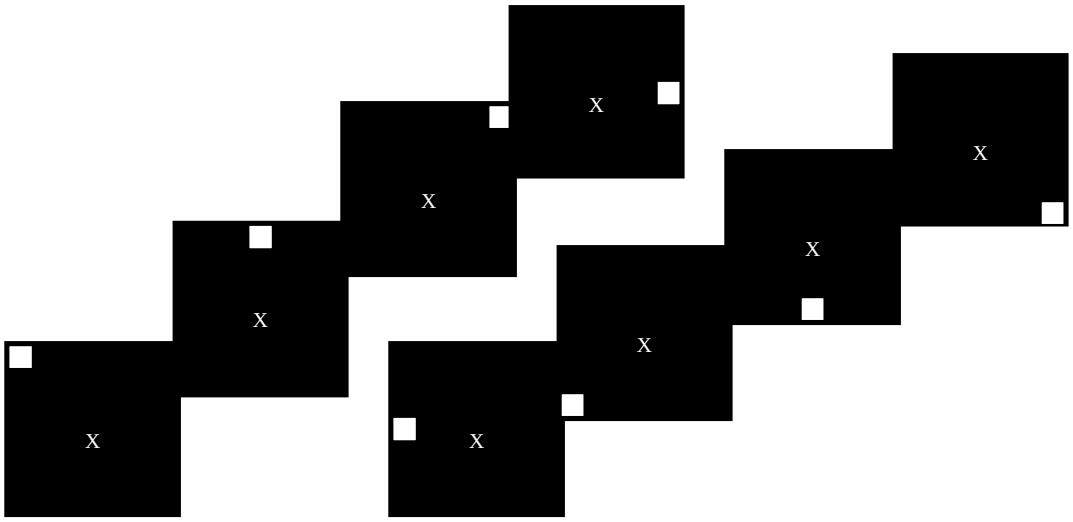


Figure 2.1. The Spatial 3-Back Task Requires Participants to Remember the Location of a Flashing Square From 3 Trials Back, From 8 Possible Locations.

Procedure

Participants were recruited from the undergraduate population of the University of Georgia through the Psychology Department. All participants signed informed written consent, after which they were screened for exclusion criteria. At this stage, the participants were interviewed to determine handedness and given the MMSE. Participants also completed an MR Procedure Screening Form. Participants who reported claustrophobia, metal implants (e.g., intracranial and intracochlear implants, metal fragments in the eye, pace makers), problematic past MRI examinations, allergies, recent use of drugs, or diseases affecting their respiratory system or blood were also excluded from the experiment at this stage.

Next, in order to decrease possible anxiety during scanning, all participants were simulated in an fMRI simulator located at the BIRC. The simulation session included an explanation of the fMRI environment, as well as the specific n-back task. All participants

received a short, 30- trial practice session to ensure sufficient understanding of the task. Then, in order to assess their pre-scanning anxiety to be used as a potential covariate in later analyses, all participants completed an Anxiety State Inventory (Spielberger, Gorsuch, & Luchene, 1970).

Following simulation, participants proceeded to the scanning. Each scanning session began with a structural MRI scan of higher-resolution (detailed below). As shown in figure 1.2, during the 40-minute scanning session, all participants were presented with twenty, 54-second blocks of the 3-back condition, consisting of 360 trials of the 3-back task; twenty, 54-second blocks of the 0-back condition, consisting of 360 trials of the 0-back task; and thirty-six, 6-second blocks of a fixation cross condition, presented at the beginning of each n-back block. The 3-back and 0-back blocks, preceded by six seconds of the fixation cross condition, switched every 60 seconds (i.e., after 18 trials).

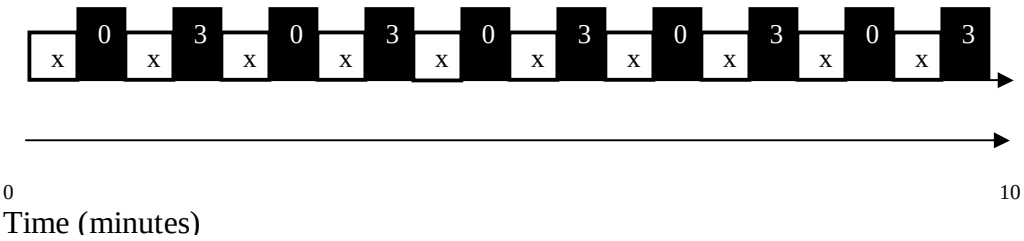


Figure 2.2. Block Presentation of the 3-Back, 0-Back, and Fixation Cross Conditions.

Magnetic Resonance Imaging Parameters

During the working memory task, 800 sets of brain volume images were acquired, using a 3.0T GE Signa HDx fMRI scanner (GE Medical Systems, Milwaukee, WI). This scanner allowed for functional whole brain coverage, using 32 adjacent, oblique, axial planes of fMRI. These T2*-weighted fMRI images were obtained using an EPI pulse sequence. Thirty-two, 4-mm slices (one mm slice gap with interleave), were collected

every 3.0 seconds using a TR of 3000 milliseconds. Functional imaging parameters were as follows: axial, TE 30 ms, Flip angle 90 deg, Equivalent Acquisition Matrix (64 x 64), 24 cm field of view. Five additional three-second RF excitations were executed before each run to reduce T1 saturation effects. In addition, each scanning session included one three-dimensional T1-weighted structural MRI scan of higher-resolution (Matrix 256 x 256 x 146, 25.6 cm field of view, slice thickness 1.3 mm) for definition of anatomical structures within each brain. This anatomical image of the entire brain was acquired using the following 3D FSPGR protocol: axial, 146 slices, TE 3 ms, TR 7.4 ms, Flip angle 20 deg.

Signal drift.

In this experiment, data processing used high pass filtering to reduce signal drift effects. Signal drift was further reduced using [n-back minus fixation cross] or [3-back minus 0-back] contrasts, depending on the tested hypothesis, that subtracted neural activity of two temporally adjacent blocks that are assumed to have similar drift. Subtracting neural activity of the 0-back condition from the 3-back condition left changes in activation that were working memory-related. Subtracting neural activity of the fixation cross condition from either of the n-back conditions left changes in activation that were associated with that task.

Data Analysis

FMRI data analysis.

Prior to analysis, all fMRI and structural image files were reconstructed into Analyze-format images. Each temporal fMRI scan was reconstituted as a single 3D image. Data was analyzed using Statistical Parametric Mapping software (SPM2; Wellcome Department of Cognitive Neurology, London, UK). This software compares

variations in image intensity within each voxel with the expected functional time dependence of blood oxygen level dependent (BOLD) response for a particular experiment. Scanning voxel size was set at 3.75mm x 3.75mm x 4mm. SPM2 resliced voxels into a different size during the normalization stage to [2mm x 2mm x 2mm], and displayed all cluster and voxel results using this value. In order to capture and represent the resolution of the original scanning voxel size more accurately, this experiment defined a cluster as eight or more contiguous voxels produced during the normalization stage. Using the general linear model (Friston, Holmes, & Worsley, 1995), SPM2 created a statistical map characterizing the correlation between this intensity variation and BOLD response.

Application of this software to fMRI data requires that the regional variation of intensities conform to characteristics of a Gaussian field (Siegmond & Worsley, 1995). With this assumption, statistical inferences can be made about activity within a particular region (Friston, Worsley, & Frackowiak, 1994). Head motion of the participant during a scanning run, which can lead to significant changes in brain region represented by each voxel during a scan, was corrected using the six-parameter rigid-body realignment algorithm within SPM2 (Friston, Ashburner, & Poline, 1995). Functional and structural data was then normalized into a standard stereotaxic space using a 12-parameter affine transformation algorithm within the SPM2 environment (Friston, Ashburner, & Poline, 1995). Coordinates within this MNI space (from the Montreal Neurological Institute; Collins, Neelin, Peters, & Evans, 1994), were translated to the coordinate system of the Talairach atlas (Talairach & Tournoux, 1988) for reporting the localization of functional activations using the mni2tal routine of Brett (2002). The data were smoothed spatially using a Gaussian kernel having a full-width at half of maximum value (FWHM) of twice

the voxel size (7.5 mm x 7.5 mm x 8 mm), to improve the signal to noise and to de-emphasize non-Gaussian intensity correlations between adjacent voxels.

Within SPM2, signal variations were fitted to a BOLD response function using linear regression, yielding fitting weights and residuals. The response function was modeled as a box-car waveform to simulate continual stimulation during particular conditions during an epoch convolved with a reference hemodynamic response function (HRF; Figure 2.3). The significance of the fit of our data to the response function was quantified using an F-test. Before regression, the effects of variable activity global to the whole brain (e.g., cardio-vascular changes) were minimized via high-pass filtering of the data and temporal smoothing of the data using the reference HRF as a kernel. The reduction in functional variability improves the signal to noise ratio, and thus increases results' sensitivity, power, and ability to compare activation across individuals. Within SPM2, the map of F-statistics was transformed to the unit normal distribution to give a Z map. Resultant images of these Z maps were generated for a subset of the data based on significance and probability values. P-values uncorrected for the number of voxels included in the map were calculated within SPM2. This experiment used an uncorrected p-value of 0.001 as a significance threshold for the results retained in this analysis. In addition to the Z maps, uncorrected p values for these Z values and Z statistics for clusters of activation (i.e., contiguous regions of significant voxels) and their respective uncorrected p values are also reported.

In addition, the level of neural activity was operationalized for statistical analyses over time using two measures of dispersion and the intensity of neural activation. Degrees of dispersion and intensity were represented in each individual by defining two regions of interest (ROI), the DLPFC and posterior parietal cortex (PPC), using PickAtlas

(PickAtlas; Wake Forest University School of Medicine, Wake Forest, NC), a toolbox within SPM2. In this study, dispersion was operationalized as the number of significantly activated voxels within the ROI divided by the ROI's total number of voxels. Activation intensity was represented as an average of percent signal intensity change (PIC) of the highest two percent of activated voxels within the ROI between the 3- and 0-back cognitive states. Dispersion and activation intensity data were extracted and averaged every 200 sets of brain volume images. The individual measures of dispersion and intensity were then averaged across participants to create group means of dispersion and intensity for each run and ROI.

Finally, SPM's within-subject ANOVA and t-tests were utilized to parametrically modulate time as the specified regressor representing practice. Parametric modulation is a statistical approach designed to explore changes over time in neural activity that result from neural adaptation to a specific task over the course of scanning. In this study, parametric modulation was used to identify the magnitude and location of neural activity that demonstrates either a decrease or an increase in neural activity during the 40-minute imaging session.

Functional data were analyzed by creating two levels of contrasts. Contrasts in the first level were designed to isolate specific neural activity for hypothesis testing and to help monitor signal drift. To test changes over time in the DLPFC and PPC related to processing of WM, neural activity during the 0-back condition was subtracted from neural activity during the 3-back condition ([3-back] – [0-back].) When comparing differential changes over time in the 0-back and 3-back conditions, activation during the fixation cross condition was subtracted from each of the n-back conditions separately. Neural activity identified from these contrasts was later used in all second-level contrasts,

and will be referred in the next sections simply as ‘neural activity’. Second-level contrasts were performed using SPM’s within-subject F-test (i.e., repeated measures ANOVA), which contrasted neural activity found in the four runs. Statistically significant F-tests were followed by t-contrasts that modeled positive and negative linear and quadratic functions.

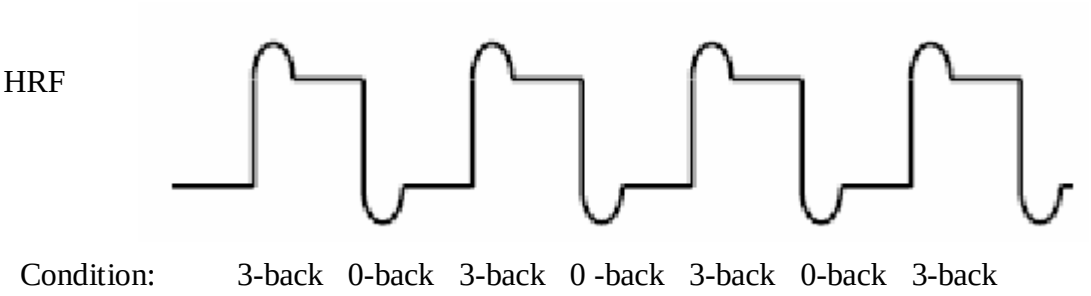


Figure 2.3. Predicted HRF Modeled as a Box-Car WaveForm.

Behavioral data analysis - practice effects.

Analysis of behavioral data was done with the Statistical Package for the Social Sciences (SPSS), version 16.0. One-way repeated measure analysis of variance (ANOVA) was used to test the hypothesis of practice effects on the behavioral variables over time. Analyses were done by comparing percent accuracy and response time across runs separately for the 3-back and 0-back conditions. Two-way repeated measure ANOVA was later used to test task domain effects by comparing the 0-back and 3-back tasks on measures of performance and neural activity.

In addition, one-way repeated measure ANOVA was used in the analysis of the dispersion and activation intensity measures of neural activity to explore the effects of practice on neural activity. Those dispersion and intensity measures of neural activity were also used in regressions conducted on each run to determine their association with

percent accuracy and response time. As described above, for the purpose of those analyses, dispersion of neural activity was defined as the average percent of activated voxels within each of the two ROI. Activation intensity was defined as the average percent intensity change of the highest two percent of activated voxels within each of the ROIs.

CHAPTER 3

NEURAL ACTIVITY CHANGES OVER TIME DURING REPEATED PERFORMANCE OF A SPATIAL WORKING MEMORY TASK[1]

[1] Yfat Kessel, L. Stephen Miller, Nathan E. Yanasak, Carlos Faraco, J. Evan Mackey, and Collin Cannon. To be submitted to *NeuroImage***.**

Abstract

Neuroimaging studies have demonstrated practice-related changes in neural activity during working memory (WM) tasks. Practice effects have demonstrated between-group differences, as well as within-subject variability in neural activation between scans taken in different times. These differences appear to correspond with both reductions and increases in neural activity, which are interpreted as a decrease in cognitive effort. While practice-related changes in neural activity have been observed in paradigms that administer a practice session between scanning sessions, few experiments have specifically tested practice effects across runs of a single scanning session (Landau, 2005). This experiment demonstrates effects of repeated performance across time, examining neural activity of participants performing the spatial n-back for 40 minutes. Specifically, we hypothesized that over the course of scanning, participants would show decreasing activation in strategy non-specific regions (i.e. dorsolateral prefrontal cortex; DLPFC) and increasing activation in strategy-specific regions (i.e. posterior parietal cortex; PPC.) Consistent with our hypothesis, neural activity decreased in the DLPFC across runs; however, activation also decreased in the PPC. The involvement of PPC in WM was demonstrated in within-run analyses indicating an association between greater PPC activation and increased performance. Behavioral results failed to demonstrate significant improvement on performance measures, possibly due to inattention during the long scanning session. Results of this study demonstrate the importance of understanding the temporal pattern of the WM network in describing WM abilities.

Introduction

The term 'working memory' (WM) is often accredited to Miller, Galantar, and Pribram (1960), but is most widely identified with the tripartite model suggested by Baddeley and Hitch (1974). According to their early definition, WM is the ability to temporarily maintain information for use in ongoing mental operations. A 2008 search on PsycINFO reveals that in 2007, 989 articles on WM were published, 95 of which were brain-imaging studies. This wealth of research concerning WM reflects its predictive value (Aronen, Vuontela, Steenari, Salmi, & Carlson, 2005; Conway, Kane, Bunting, Hambrick, Wilhelm, & Engle, 2005; St Clair-Thompson & Gathercole, 2006; Unsworth, Heitz, Schrock, & Engle, 2005), as well as its crucial role in several psychological and neurological disorders (Conway et al., 2005; Deveney & Deldin, 2004; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005.)

The n-back task is frequently used to study WM. Across modalities of this task (e.g., verbal, spatial, or object), participants are required to attend to a series of items, and judge whether a given item is identical to a different item that was presented n-trials back. Increasing the numbers of trials back the participants need to remember (i.e., N= 1, 2, or 3) in order to successfully perform this task increases its WM demand.

The n-back is one of the most popular WM paradigms for functional imaging. Meta-analysis of 24 functional imaging studies of the n-back task from 1994 through 2003 (Owen, McMillan, Laird, and Bullmore 2005), indicates that robust activation across n-back modalities is found in the following areas: Bilateral and medial posterior parietal cortex (e.g., precuneus, inferior parietal lobules, BA7, 40), an area involved in the rehearsal and storage of WM; bilateral premotor cortex (BA6, 8), an area activated during WM tasks that require maintenance of visuospatial attention; dorsal cingulated /

medial premotor cortex (BA32, 6), areas activated during identity monitoring of non-verbal stimuli; bilateral frontal pole (BA10), a region known to be involved in integration of several cognitive operations; bilateral mid-ventrolateral prefrontal cortex or frontal operculum (BA45, 47), a region involved in explicit retrieval of information that was intended to be remembered; and bilateral DLPFC (BA9, 46), an area thought to contribute to the selection of appropriate high-order organizational chunks that reduce overall cognitive load. Additional activation is found in the medial cerebellum.

While the WM circuitry has been replicated across studies, the temporal pattern of activation in these areas (i.e., decrease or increase over time) varies. This variation may be partially explained by practice effects due to repeated performance that occur during the course of scanning. Practice is known to demonstrate both behavioral and neural effects (Jessen et al., 2001; Karni, Meyer Jezzard, Adams, Turner, & Ungerleider, 1995; Kassubek, Schmidtke, Kimmig, Luecking, & Greenlee, 2001; Sadek, 2001; Weissman, Woldorff, Hazlett, & Mangun, 2002.) Jansma, Ramsey, Slagter, and Kahn (2001) examined practice effects on shifting the processing of a WM task from controlled to automatic. Practice effects were associated with a reduction in activation of regions related to WM, such as DLPFC. Behaviorally, practice was associated with a more accurate, faster performance. The improved performance appeared to correspond with a reduction in neural activity, which was interpreted as a decrease in cognitive effort.

The exact nature of practice effects is still debated. Several imaging studies found practice-dependent increases in neural activity (Awh et al., 1999; Kirschen, Chen, Schraedley-Desmond, & Desmond, 2005; Smith, McEvoy, & Gevins, 1999), conceptualized as an increase in efficiency. Jansma et al. (2001) discuss the possibility that as automatization of task performance occurs, initial load on WM and executive

functioning regions (e.g., DLPFC) is shifted to strategy-specific areas (e.g., in the parietal lobule). Weissman et al. (2002) investigated practice-related changes in neural activity during a task of executive control. Fifteen adult subjects practiced a stroop-like task during a 50-minute fMRI scanning. Practice was correlated with a reduction in neural activity in the left inferior parietal lobe, a region involved in attention orientation, as well as with an increase in midline frontal regions that are specific to processing stroop-like interference. Results of this study support practice-related decreases in neural activity in task non-specific areas, along with increases in task-relevant brain regions.

Kelly and Garavan (2005) reviewed 27 functional neuroimaging studies of practice effects. They identified three main patterns in response to practice: increased activation, decreased activation, and functional reorganization. Reorganization was divided into redistribution of functional activation, and 'true' reorganization of activation. Redistribution includes observed increases and decreases in the same brain regions across task performance stemming from increased reliance on strategies and decreased reliance on control and attentional processes, respectively. In contrast, 'true' reorganization reflects a shift between cognitive processes and strategies. In addition, the authors discussed the effects of the time-window of imaging, and suggested imaging studies should allow adequate scanning time to capture the entire impact of practice on neural activity.

Changes in neural activity following repeated performance have been observed in paradigms that administer a practice session between scanning sessions. As participants in most fMRI studies perform a novel task repeatedly, the duration of scanning could be viewed as a practice session. Therefore, it is reasonable to assume that changes in neural activation following repeated performance could be detected across runs in a single

scanning. To our knowledge, few experiments have specifically tested effects of repeated performance across runs of a single scanning (Ganis, Thompson, & Kosslyn, 2005). Landau (2005) conducted a series of event-related fMRI studies that investigated intra-run changes in neural activity during WM tasks. Results of her studies suggested a decrease in neural activity, without significant improvement in behavioral measures of performance. In addition, neural activity during a complex motor sequence preformed by professional and non-pianists displayed immediate practice effects, as neural activity decreased in bilateral motor and parietal regions. The professional pianists also showed a general increase in the right hemisphere, indicating reorganization. Results of this study suggest that analysis of intra-run changes in neural activity could be used in studying the underlying mechanisms of WM.

In summary, spatial WM has been studied extensively, and brain regions that are associated with processing of spatial WM tasks have been identified. In addition, effects associated with repeated performance have demonstrated both between-group differences, as well as within-subject variability in neural activation between scans taken in different times. Finally, the mixed temporal pattern of decreases in neural activity in task non-specific areas (e.g., DLPFC) and increases in task-relevant brain regions (e.g. posterior parietal cortex) during WM tasks may be partially attributable to redistribution due to practice effects.

This experiment was aimed at demonstrating effects of repeated performance across time on observed neural activity of participants performing the spatial n-back, a WM task, for 40 minutes. We hypothesized that over the course of scanning, participants would show linear decrease in activation in the DLPFC, a strategy non-specific region involved in processing of spatial WM tasks. In contrast, participants were hypothesized to

show increasing activation in the posterior parietal cortex (PPC), a strategy specific region involved in processing of WM tasks.

Materials and methods

Subjects

Subjects were twenty right handed males (mean age 19.1 years; range 18-22), recruited from the undergraduate population of the University of Georgia for research credit hours. All subjects met criteria for intact general cognitive ability (Folstein Mental Status Exam Score > 28; Folstein, Folstein, & McHugh, 1975), no history of neurological or psychological condition, no past head injury resulting in loss of consciousness, nor active psychoactive medication use. All participants gave their written informed consent to participate in this study.

Behavioral task

This experiment used a spatial n-back task of 0-back and 3-back exposures, adapted for fMRI. Subjects were asked to fixate their eyes on the digit zero or three (for the 0-back and 3-back conditions, respectively) located in the center of a black screen that was placed in front of them, inside the scanner. A white square appeared on the screen for 500 ms, followed by 2500 ms of inter-stimulus interval, during which only the digit was seen on the screen. As shown in Figure 2.1, the squares appeared in one of eight different places on the edges of the black screen (along the screen's frame). Depending on the condition, subjects were asked to respond "yes" every time the square appeared in the top left location (for the 0-back condition) or in the same location it appeared three trials back (for the 3-back condition). A "no" response was given when the square

appeared in a different location. The responses to the stimuli were registered through a two-button hand activation unit the participants wore on their dominant hand (Resonance Technology Inc.) For six seconds before and after each n-back condition, participants were asked to fixate their eyes on a cross in the middle of the screen.

The experiment was performed on one day. First, subjects were interviewed and screened for exclusion criteria. Then, they received a simulation session in an fMRI simulator, in order to decrease possible anxiety and to ensure adequate understanding of the task. All subjects received a short, 2-minute practice session. Next, subjects completed an Anxiety State Inventory (Spielberger, Gorsuch, & Luchene, 1970) to assess their pre-scanning anxiety. During scanning, subjects completed four, 10-minute runs of the spatial n-back task. Each run included both the 0-back and the 3-back conditions, switching every 18 trials (54 seconds), to a total of 360 trials for each condition. Visual stimuli were presented on goggles made by Resonance Technology Inc., and behavioral data were initially acquired and processed using BrainWave Hardware Lite (GE Applications), suitable for research use within the MRI environment. Upon completion of scanning, subjects completed an Anxiety State Inventory again to assess their post-scanning anxiety.

FMRI data acquisition

Imaging was performed on a 3.0T GE Signa HDx fMRI scanner (GE Medical Systems, Milwaukee, WI) using an EPI pulse sequence. For anatomical imaging, 146, 3D T1-weighted axial images were obtained using a 3D FSPGR protocol (TE = 3 ms, TR = 7.4 ms, FA = 20°, Matrix = 256 x 256 x 146, FOV=25.6 cm, 146 slice locations per slab, slice thickness 1.3 mm). For functional imaging, 800 T2*-weighted oblique, axial images were obtained (TE = 30 ms, TR = 3 sec, FA = 90°, Matrix = 64 x 64, FOV=24 cm). Each

fMRI scan, spanning 32, 4-mm slices (one mm slice gap with interleave), was collected every 3 seconds. These 32 adjacent, oblique, axial planes of fMRI provided full coverage of the brain. Five additional 3-second RF excitations were executed before each run to reduce T1 saturation effects.

Analysis of fMRI data

Data were analyzed using Statistical Parametric Mapping software (SPM2; Wellcome Department of Cognitive Neurology, London, UK). Prior to analysis, head motion of the participant during a scanning run was corrected using the six-parameter rigid-body realignment algorithm within SPM2 (Friston, Ashburner, & Poline, 1995). Functional and structural data were normalized into a standard stereotaxic space using a 12-parameter affine transformation algorithm within the SPM2 environment. Coordinates within this MNI space (from the Montreal Neurological Institute; Collins, Neelin, Peters, & Evans, 1994), were later translated to the coordinate system of the Talairach atlas (Talairach & Tournoux, 1988) for reporting the localization of functional activations using the mni2tal routine of Brett (2002). Data were smoothed spatially using a Gaussian kernel having a full-width at half of maximum (FWHM) value of twice the voxel size (7.5 mm x 7.5 mm x 8 mm), to improve the signal to noise and to de-emphasize non-Gaussian intensity correlations between adjacent voxels. Effects of variable activity global to the whole brain (e.g., cardio-vascular changes) were minimized via high-pass filtering of the data and temporal smoothing of the data using the reference HRF as a kernel. Signal drift was reduced using high-pass filtering and a ([3-back]-[0-back]) contrast that subtracted neural activity of two temporally adjacent blocks of the 0-back and the 3-back that are assumed to have similar drift.

Within SPM2, signal variations were fit to a BOLD response function using linear regression, yielding fitting weights and residuals. The response function was modeled as a box-car waveform to simulate continual stimulation during particular conditions during an epoch convolved with a reference hemodynamic response function (HRF; see Figure2.3.) Within SPM2, the map of F- and t-statistics was transformed to the unit normal distribution to give a Z map. Resultant images of these Z maps were generated for a subset of the data based on significance and probability values of uncorrected $p< 0.001$ for both the voxel and cluster levels. Voxel size was set at 3.75mm x 3.75mm x 4mm, and a cluster was defined as eight or more contiguous voxels.

FMRI data were used to test this experiment's hypotheses by creating two levels of contrasts. The contrast in the first level subtracted neural activity during the 0-back from neural activity during the 3-back ([3-back] – [0-back]) to present only WM-related activity. Neural activity identified from this contrast was later used in all second-level contrasts, and is referred in the next sections simply as 'neural activity'. Second-level contrasts were performed using SPM's within-subject ANOVA models (i.e., repeated measure ANOVA.) Specific t-contrasts were defined to test linear and quadratic functions across the four runs. Neural activity in the regions of interest (ROI) was defined by identifying specific Brodmann Areas in the DLPFC (BA 9 and 46) and PPC (BA 5,7,39, and 40) using the PickAtlas toolbox in SPM2 (PickAtlas; Wake Forest University School of Medicine, Wake Forest, NC.)

Analysis of behavioral data

Analysis of behavioral data was performed using the Statistical Package for the Social Sciences (SPSS), version 16.0. Repeated measure ANOVA was used to test the hypotheses of repeated performance effects on percent accuracy and response time across

the four runs. Regression was then used to study changes over time in these behavioral variables within each run. Analyses were done by regressing percent accuracy and response time separately for the 3-back and 0-back conditions.

Repeated measure ANOVA was also used to test the effects of repeated performance on the dispersion and intensity of neural activation across the four runs. As described above, for the purpose of those analyses, dispersion of neural activity was defined as the number of activated voxels within the ROI, divided by the total number of voxels within the ROI. Activation intensity was defined as the average percent signal intensity change (PIC) of the highest two percent of activated voxels within the ROI. In addition, regression coefficients were calculated for the dispersion and activation intensity measures of neural activity with response time and percent accuracy. Those coefficients determined the relationships between behavioral measures of repeated performance and neural activity during the duration of a single scanning session.

Results

Imaging results

Twenty-two participants were scanned, and two participants were excluded post-scanning for not meeting the cutoff performance (60% accuracy) requirement during scanning. SPM results of the WM contrast (3back-0back) suggest that the 3-back task was more cognitively demanding than the 0-back task. As shown in Figure 3.1, participants showed greater activation during the 3-back than in the 0-back task. In run1, activation was greater during the 3-back condition, compared with the 0-back condition, in the left angular gyrus, (BA 39), bilateral middle frontal gyrus (BA9, BA10), left

thalamus, and in the bilateral cerebellum. In run2, activation was greater during the 3-back condition in the left DLPFC (BA9), right precuneus (BA7), right superior frontal gyrus (BA10), left thalamus, bilateral cerebellum, left fusiform gyrus (BA37), and the right putamen. In run3, activation was greater during the 3-back condition in left inferior parietal lobule (BA 40), left middle frontal gyrus (BA9), right middle frontal gyrus (BA10), bilateral cerebellum, and bilateral thalamus. In run4, activation was greater during the 3-back condition in bilateral middle frontal gyrus (BA9), left inferior parietal lobule (BA 40), left insula (BA13), right inferior frontal gyrus (BA47), left inferior frontal gyrus (BA44), right superior frontal gyrus (BA10), right precentral gyrus (BA6), and right cerebellum.

SPM results from an omnibus F-test of the ([3-back]-[0-back]) contrast across the four runs revealed changes in activation mainly in the left middle frontal gyrus (BA 9 and BA 46,) as well as in bilateral medial frontal gyrus and cingulate gyrus (BA 8 and BA32.) In the DLPFC, a strategy non-specific region for analysis of spatial WM, we hypothesized a decrease in neural activity across runs. In line with our hypothesis, t-contrasts that modeled linear functions across the four runs in the DLPFC revealed only decreased activation, bilateral, but mainly in the left middle frontal gyrus (BA 9 and BA46; see Figure 3.2, Table 3.1.) Additional t-contrasts designed to model positive and negative quadratic functions failed to yield any statistically significant set, cluster, or voxel of activation.

In the PPC, a strategy specific region for analysis of spatial WM, we hypothesized an increase in neural activity across runs. Contrary to our hypothesis, t-contrasts that modeled linear functions across the four runs in the PPC revealed only decreased activation in right postcentral gyrus (BA 5 and BA7), left supramarginal gyrus (BA40),

right precuneus (BA7), and left inferior parietal lobule (BA40 see Figure 3.3., Table 3.1.) Additional t-contrasts designed to model positive and negative quadratic functions failed to yield any statistically significant set, cluster, or voxel of activation.

Behavioral results

Subjects' pre- and post-scanning self-report on the State Anxiety Inventory was not significantly different ($t(17) = -0.697$, $p>0.05$), and indicated low anxiety levels. Following post-scanning reports of increased fatigue from several subjects, participants were asked to rate their alertness on a 1 to 10 Likert Scale, where 1 is "completely alert" and 10 is "exhausted". Responses collected from nine of the twenty participants suggested a significant increase in fatigue by the end of the 40-minute scanning ($t(8) = 4.61$, $p<0.01$.)

Changes over time in the DLPFC.

A one-way repeated measure analysis of variance (ANOVA) was conducted to explore the impact of repeated performance, as measured by runs, on the dispersion of neural activation in the DLPFC, as measured by percent of activated voxels within this ROI. Consistent with our hypothesis, the main effect of repeated performance was statistically significant [$F(3, 57) = 4.896$, $p = 0.004$; partial Eta squared = 0.205] with a significant linear component [$F(1,19) = 8.339$, $p = 0.009$; see Figure 3.4.] A post-hoc comparison with a Bonferroni adjustment for multiple comparisons revealed a trend toward a decrease in dispersion of activation from run1 to run4 (mean difference = 0.105, p 0.058.) An additional one-way repeated measure ANOVA was conducted to explore the impact of repeated performance, as measured by runs, on the intensity of neural activation in the DLPFC, as measured by percent of signal intensity change (PIC.) The sphericity assumption was not met so the Huynh-Feldt correction was applied. Contrary

to our hypothesis, the main effect of repeated performance did not meet statistical significance [F(2.64, 50.1) = 1.274, p > .05.]

Changes over time in the PPC.

A one-way repeated measure analysis of variance (ANOVA) was conducted to explore the impact of repeated performance, as measured by runs, on the dispersion of neural activation in the PPC, as measured by percent of activated voxels within this ROI. The sphericity assumption was not met so the Huynh-Feldt correction was applied. Consistent with SPM results, the main effect of repeated performance demonstrated a strong trend toward statistical significance [F(2.128, 40.428) = 3.15, p = 0.051; partial Eta squared = 0.142] with a trend toward a linear component [F(1,19) = 4.277, p = 0.053.], as the dispersion of neural activity demonstrated a slight decrease across runs (see Figure 3.4.) An additional one-way repeated measure ANOVA was conducted to explore the impact of repeated performance, as measured by runs, on the intensity of neural activation in the PPC, as measured by percent of signal intensity change (PIC.) The sphericity assumption was not met so the Huynh-Feldt correction was applied. Contrary to our hypothesis, the main effect of repeated performance did not meet statistical significance [F(1.929, 36.645) = 0.948, p >.05.]

Changes in performance over time.

A series of one-way repeated measure ANOVAs were conducted to explore changes in behavioral performance parameters over time for each of the n-back tasks. The sphericity assumption was not met for any of the ANOVAS, and the Huynh-Feldt correction was applied. Contrary to our hypothesis, response time did not reach statistical significance in the 0-back condition [F(1.369, 26.009) = 1.262, p > .05] or in the 3-back condition [F(2.153, 40.914) = 0.682, p > .05;] Similarly, percent accuracy did not reach

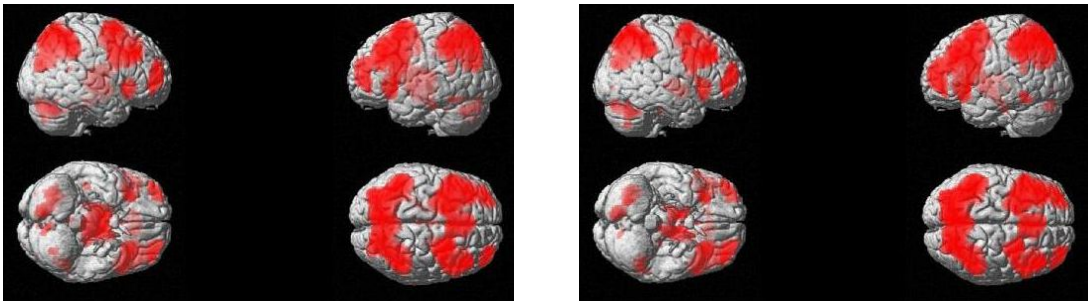
statistical significance as well in the 0-back condition [$F(1.163, 22.089) = 2.252$, $p > .05$] or in the 3-back condition [$F(2.186, 41.535) = 0.392$, $p > .05$.]

Follow-up multiple regression analyses were performed to test whether dispersion and intensity of neural activity predicted performance within separate runs. For run1 and run2, only PIC values were associated with response time. In run1, only models predicting response time during the 0-back and 3-back from PIC values in the DLPFC and PPC were statistically significant [Adjusted $R^2 = 0.279$; $F(2,17) = 4.684$, $p < .05$, and Adjusted $R^2 = 0.247$; $F(2,17) = 4.114$, $p < .05$, respectively.] Stronger activation intensity (i.e., higher PIC values) in the PPC was associated with shorter response time in the 0-back condition (Beta = -0.678, $p < .01$.) Similarly, in run2, only models predicting response time during the 0-back and 3-back from PIC values in the DLPFC and PPC were statistically significant [Adjusted $R^2 = 0.314$; $F(2,17) = 5.344$, $p < .02$, and Adjusted $R^2 = 0.226$; $F(2,17) = 3.77$, $p < .05$, respectively.] In the 0-back condition, higher PIC values in the DLPFC were associated with slower response time (Beta = 0.58, $p < .05$); in contrast, higher PIC values in the PPC were associated with faster response time (Beta = -0.734, $p < .01$.) In the 3-back condition, only higher PIC values in the PPC were associated with faster response time (Beta = -0.674, $p < .02$.)

In run3 and run4, dispersion values were associated with percent accuracy. In run3, only models predicting percent accuracy during the 0-back and 3-back from dispersion values in the DLPFC and PPC were statistically significant [Adjusted $R^2 = 0.224F(2,17) = 3.737$, $p < .05$, and Adjusted $R^2 = 0.47$; $F(2,17) = 9.409$, $p < .01$, respectively.] In the 3-back condition, more limited dispersion in the DLPFC was associated with more accurate performance (Beta = -0.87, $p < .02$) while greater dispersion in the PPC was associated with greater accuracy. (Beta = 1.29, $p < .001$.)

Similarly, in run4, models predicting percent accuracy during the 0-back and 3-back from dispersion values in the DLPFC and PPC were statistically significant [Adjusted R^2 = 0.224; $F(2,17) = 3.748$, $p < .05$, and Adjusted R^2 = 0.263; $F(2,17) = 4.38$, $p = < .05$, respectively.] In addition, for run4, the model predicting response time in the 0-back condition and the model predicting percent accuracy in the 3-back from PIC values in the DLPFC and PPC were statistically significant [Adjusted R^2 = 0.266; $F(2,17) = 4.451$, $p < .05$, and Adjusted R^2 = 0.303; $F(2,17) = 5.134$, $p < .02$, respectively.] During the 3-back task, stronger activation intensity in the PPC was associated with more accurate performance (Beta = 0.627, $p < .02$.)

Run1 **Run2**



Run3 **Run4**

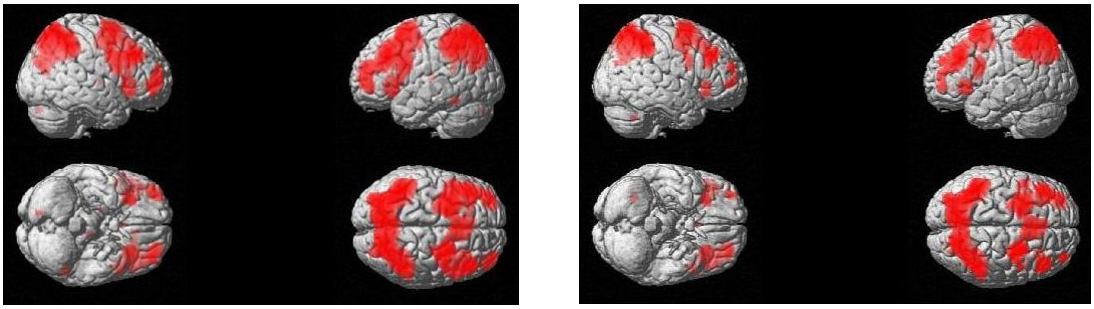


Figure 3.1. Statistical Parametric Maps of the [(3-Back)-(0-Back)] Contrast Across the Four Runs.

Table 3.1. Areas of Activation at p< 0.001 and Cluster Size of 8 Voxels Demonstrating a Linear Decrease Over Time in DLPFC and PPC.

Hemisphere	X	Y	Z	SPM(Z)	Brain Structure	BA*
DLPFC:						
Left	-44	23	25	5.51	Middle Frontal Gyrus	46
Left	-48	27	30	4.62	Middle Frontal Gyrus	9
Left	-44	33	37	4.27	Middle Frontal Gyrus	9
Right	14	31	28	4.49	Cingulate Gyrus	32
Right	8	25	32	4.44	Cingulate Gyrus	32
Left	-4	29	35	4.31	Middle Frontal Gyrus	6
Right	53	15	32	3.20	Middle Frontal Gyrus	9
PPC:						
Right	36	-45	61	3.92	Postcentral Gyrus	5
Left	-42	-45	34	3.78	Supramarginal Gyrus	40
Right	8	-50	69	3.70	Postcentral Gyrus	7
Right	4	-54	49	3.60	Preconeus Gyrus	7
Left	-50	-58	40	3.58	Inferior Parietal Lobule	40
Left	-55	-52	41	3.26	Inferior Parietal Lobule	40
Right	16	-48	49	3.50	Preconeus Gyrus	7
Left	-34	-38	53	3.47	Inferior Parietal Lobule	40
Left	-36	-44	59	3.36	Postcentral Gyrus	5

*Brodmann's Area

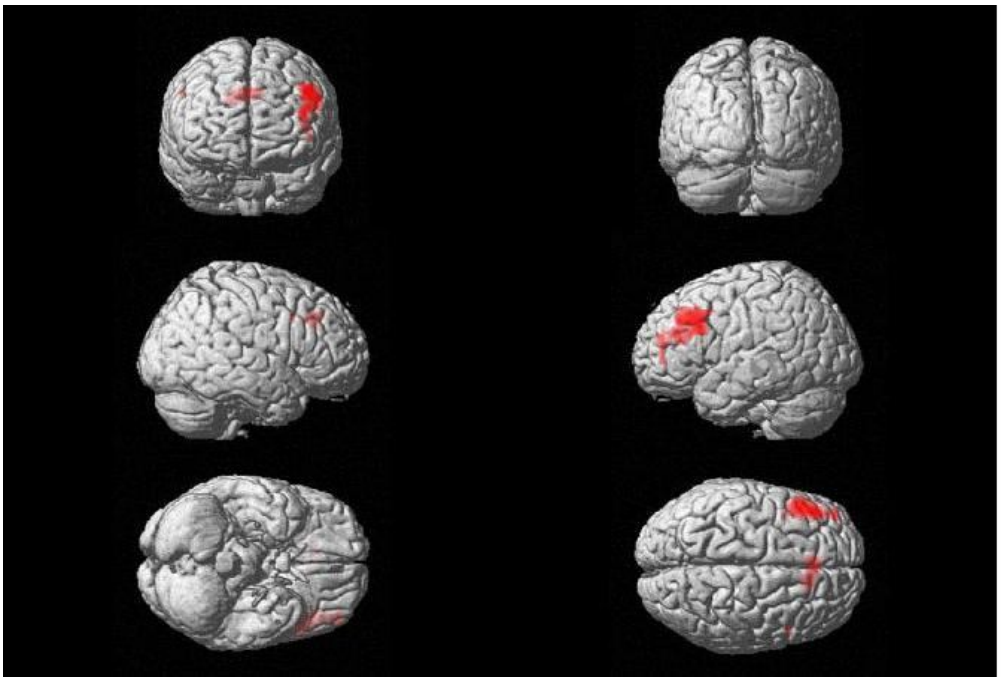


Figure 3.2. Statistical Parametric Map [(3-back)–(0-back)] of a Negative Linear Function in the DLFPC.

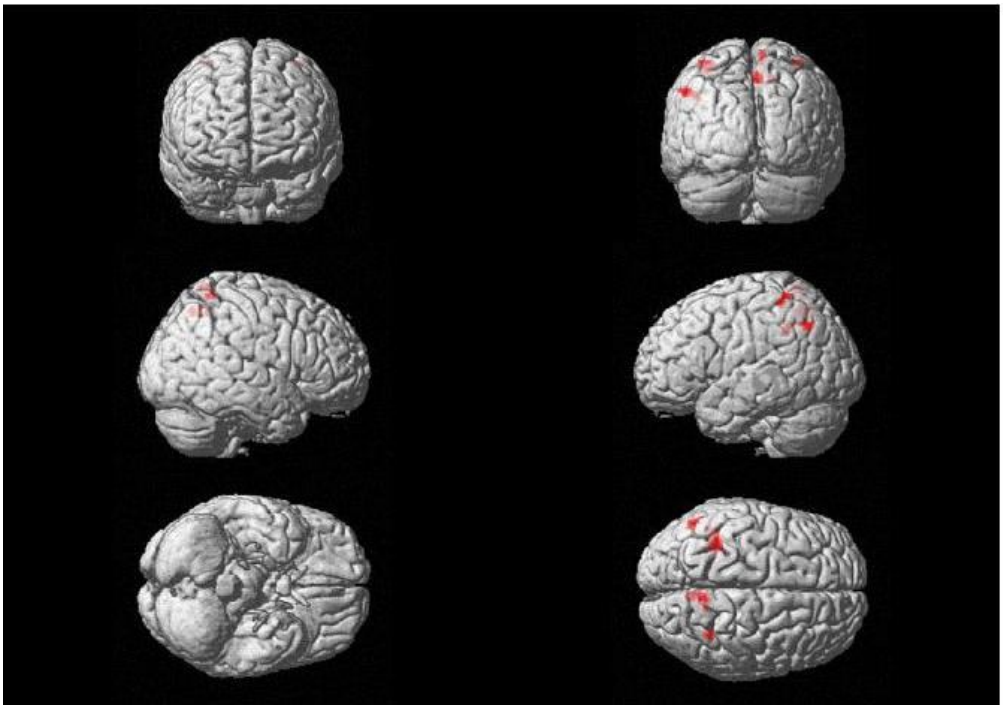


Figure 3.3. Statistical Parametric Map [(3-back)–(0-back)] of a Negative Linear Function in the PPC.

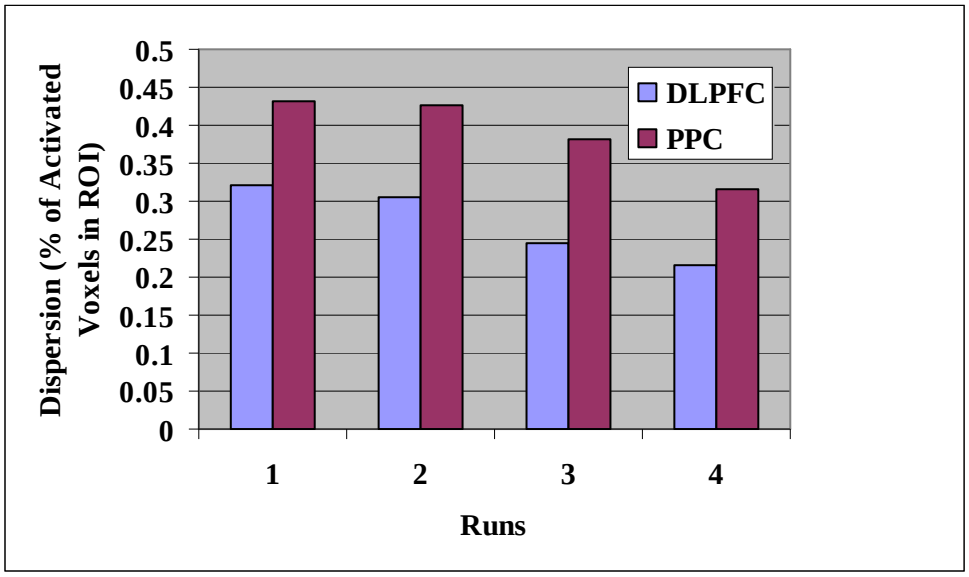


Figure 3.4. Mean Dispersion in the DLPFC and PPC Across the Four Runs.

Discussion

This study tested changes over time in neural activity during a spatial WM task. Specifically, neural activity was hypothesized to decrease over time in strategy non-specific regions (i.e., DLPFC) and increase over time in strategy-specific regions (PPC.) In line with our hypothesis, fMRI results from the DLPFC (BA 9 and BA46) show a significant decrease in activation over time. Contrary to our hypothesis, fMRI results from the PPC also show a decrease in activation over time. Consistent with SPM results, analysis of the activation dispersion demonstrated decreased dispersion in both ROIs across the four runs.

Based on the hypothesis of decreases over time in strategy-specific regions and increases in strategy non-specific regions, the general decrease in activation in both ROI may indicate that the PPC is not a strategy-specific region. However, follow-up analyses within each run revealed an association between behavioral practice effects and

differential neural activity in the two ROIs that are consistent with our hypotheses. In the first half of scanning (i.e., run1 and run2) there was an association between the intensity of activation and response time. By the second run, during the 0-back, stronger activation in the DLPFC was associated with slower performance, while stronger activation in the PPC was associated with faster performance. During the 3-back, stronger activation in the PPC was associated with faster response time. In the second half of the scanning session (i.e., run3 and run4), performance accuracy was predicted by the measures of dispersion and intensity of activation. In run3 during the 3-back task, higher accuracy was associated with more limited dispersion in the DLPFC and with greater dispersion in the PPC. During run4, greater activation intensity in the PPC was associated with better accuracy.

While activation in the PPC did not demonstrate the hypothesized increase in activation over time, the association of activity in this ROI with more accurate and faster performance suggests its involvement in successful processing of spatial WM.
The observed general decrease in activation across runs in both strategy-specific and strategy non-specific ROIs may reflect an overall decrease in cognitive effort associated with repeated exposure and increased familiarity with the n-back task. Results of this study demonstrate the importance of understanding the effects of the “time-window of imaging” mentioned in Kelly and Garavan’s (2005) meta-analysis of practice effects. While our study allowed for a significant time-window of imaging, the long duration of the current study could have resulted in loss of sensitivity to intra-run changes in activation.

Results from behavioral measures failed to demonstrate practice effects across the four runs on response time and percent accuracy in either of the n-back levels. This

pattern of significant changes in neural activity along with difficulty demonstrating behavioral practice effects was evident in previous experiments in our laboratory (Kessel, Miller, Yanasak, & Maher, 2006, February, 2007, February), as well as in independent studies of practice effects over time (Landau, 2005.) This failure to demonstrate behavioral practice effects suggests that the observed neural changes over time represent familiarity effects due to repeated exposure, rather than practice effects. Finally, this pattern could also be an indirect result of the time window of imaging used in this study. A significant increase in reported fatigue that was collected from a subset of participants suggests that the long duration of scanning could have introduced fatigue effects that counteracted practice effects.

In summary, results of this study replicated the well-established neural network of WM by demonstrating involvement of the DLPFC, parietal cortex, striatum, and cerebellum. In addition, time-sensitive analysis of the functional data characterized the temporal changes in this neural network in healthy individuals. Results of this study suggest an additional dimension of understanding WM abilities in healthy adults by attending not only to regions that are known to be related to processing of WM, but also to their changed role in processing over time. The presented pattern of decreased activation during a spatial WM task in healthy adults could be different in individuals with disorders that are known to affect WM (e.g., schizophrenia, ADHD.) Future studies should compare the temporal patterns of practice effects between these populations. Therefore, recognizing and understanding the influence of repeated exposure and familiarity on neural activation in healthy adults could be the first step in improving our understanding of those psychological and neurological disorders.

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CHAPTER 4

INTER-RUN CHANGES IN NEURAL ACTIVITY DURING REPEATED PERFORMANCE OF SPATIAL 0- AND 3-BACK WORKING MEMORY TASKS[1]

[1] Yfat Kessel, L. Stephen Miller, Nathan E. Yanasak, Carlos Faraco, J. Evan Mackey, and Collin Cannon. To be submitted to *NeuroImage***.**

Abstract

Neuroimaging studies have demonstrated practice-related between-group differences, as well as within-subject variability in neural activation between scans taken at different times. Few experiments have tested the effects of repeated performance within a single scanning session (Landau, 2005). Practice effects due to repeated performance appear to correspond with both reductions and increases in neural activity, which are interpreted as an increase in neural efficiency. Several studies have demonstrated effects of task domain on practice effects (Kelly & Garavan, 2005), with more basic sensorimotor tasks associated with increased activation over time, and higher-order tasks (e.g., working memory) associated with decreased activation over time. This experiment demonstrates the effects of task domain on repeated performance effects across time by examining changes in neural activity of subjects performing a spatial working memory task and a visual attention task. We hypothesized that over the course of scanning, subjects performing the more demanding task will show stronger effects of repeated performance, compared with the 0-back task. Effects of repeated performance included decreased neural activity in prefrontal cortex, increased accuracy, and decreased response time. Consistent with our hypothesis, a linear decrease in prefrontal activation was found during the 3-back. Contrary to our hypothesis, activity during the 0-back increased linearly. Behaviorally, compared with the 0-back, performance on the 3-back was significantly slower, less accurate, and more intense and extensive neurally. However, repeated performance failed to improve performance. These results appear to reflect increased need for attentional control, possibly due to fatigue, demonstrating the importance of understanding the effects of uncontrolled variables on neural activation.

Improving our understanding of such intra-run changes could improve replicability in fMRI studies.

Introduction

Practice to a task and repeated performance are known to demonstrate behavioral and neural effects (Weissman, Woldorff, Hazlett, & Mangun, 2002; Sadek, 2001; Kassubek, Schmidtke, Kimmig, Luecking, & Greenlee, 2001; Karni, Meyer Jezzard, Adams, Turner, & Ungerleider, 1995; Jessen et al., 2001). Jansma, Ramsey, Slagter, and Kahn (2001) examined practice effects on shifting the processing of a WM task from controlled to automatic. Practice effects were associated with a reduction in activation of regions related to WM, such as DLPFC. Behaviorally, repeated performance was associated with a more accurate, faster performance. The improved performance appeared to correspond with a reduction in neural activity, which was interpreted as a decrease in cognitive effort.

Kelly and Garavan (2005) reviewed 27 functional neuroimaging studies of practice effects. They identified three main patterns in response to practice: increased activation, decreased activation, and functional reorganization. Reorganization was divided into redistribution of functional activation, and 'true' reorganization of activation. Redistribution includes observed increases and decreases in the same brain regions across task performance stemming from increased reliance on strategies and decreased reliance on control and attentional processes, respectively. In contrast, 'true' reorganization reflects a shift between cognitive processes and strategies.

Kelly and Garavan (2005) suggested several additional variables that affect effects of repeated performance, including task domain. Results of their study suggested that while studies that used more basic sensorimotor tasks were associated with increased activation over time, higher-order tasks (e.g., WM) were associated with decreased activation over time. The 0-back and 3-back tasks used in the present study are assumed to represent different task domains (i.e., visual attention and working memory, respectively) and therefore demonstrate different effects to repeated performance. While continuous performance of the spatial 0-back, a visual attention task, is known to show no practice effects in adults or children (Karatekin, Marcus, & Couperus, 2007), practice is known to increase accuracy and decrease response time in n-back tasks that require working memory (i.e., $n > 0$; Oberauer, 2006; Verhaeghen, Cerella, & Basak, 2004).

Kelly's and Garavan's study (2005) found that practice effects following repeated performance were also dependent on the time-window of imaging. They suggested imaging studies should allow adequate scanning time to capture the entire impact of practice on neural activity. The authors' discussion on the effects of the window time of imaging is particularly interesting when considering that most studies of practice-related changes in neural activity use a between scanning sessions comparison. As subjects in most fMRI studies perform a novel task repeatedly, the duration of scanning could be viewed as a practice session. Therefore, it is reasonable to assume that changes in neural activation associated with repeated performance could be detected across runs in a single scanning of a subject.

To our knowledge, very few experiments have specifically tested repeated performance effects across runs of a single scanning (Ganis, Thompson, & Kosslyn, 2005). Landau (2005) conducted a series of event-related fMRI studies that investigated

intra-run changes in neural activity during working memory tasks (object and spatial). Results of her studies suggested a decrease in neural activity, without significant improvement in behavioral measures of performance. In addition, neural activity during a complex motor sequence preformed by professional pianists and non-pianists displayed "fast" (i.e., immediate effects following repeated performance) changes in terms of decreased neural activity in bilateral motor and parietal regions. However, the group of professional pianists also showed a general increase in the right hemisphere (i.e., reorganization.) Results of this study suggest that analysis of intra-run changes in neural activity could be used in studying the underlying mechanisms of WM.

This experiment is aimed at demonstrating effects of repeated performance across time on observed neural activity of subjects performing the spatial 3-back, a working memory task, and the spatial 0-back, an attention task. Four, 10-minute runs of the working memory task were completed, allowing intra-run comparisons sensitive to the systematic and dynamic effects of repeated performance during a single scanning session. We hypothesized that over the course of scanning subjects would generally show decreasing activation in the dorsolateral prefrontal cortex (DLPFC). As aforementioned, the DLPFC is known to be a strategy non-specific region associated with reducing overall cognitive load. Therefore, the decrease in DLPFC activation was expected to be more pronounced in the complex 3-back task than in the simple 0-back task. This would be evident by a significant difference between the negative linear relationships between time and neural activation observed in this area for each task.

Materials and methods

Subjects

Subjects were twenty right handed males (mean age 19.1 years; range 18-22), recruited from an undergraduate population for research credit hours. All subjects met criteria for intact general cognitive ability (Folstein Mental Status Exam Score > 28; Folstein, Folstein, & McHugh, 1975), no history of neurological or psychological condition, no past head injury resulting in loss of consciousness, nor active psychoactive medication use. All subjects gave written informed consent to participate in this study, which had Institutional Review Board approval.

Behavioral task

This experiment used a spatial n-back task of 0-back and 3-back exposures, adapted for fMRI. Subjects were asked to fixate their eyes on the digit zero or three (for the 0-back and 3-back conditions, respectively) located in the center of a black screen that was placed in front of them, inside the scanner. A white square appeared on the screen for 500 ms, followed by 2500 ms of inter-stimulus interval, during which only the digit was seen on the screen. As shown in Figure 2.1, the squares appeared in one of eight different places on the edges of the black screen (along the screen's frame). Depending on the condition, subjects were asked to respond "yes" every time the square appeared in the top left location (for the 0-back condition) or in the same location it appeared three trials back (for the 3-back condition). A "no" response was given when the square appeared in a different location. The responses to the stimuli were registered through a two-button hand activation unit the subjects wore on their dominant hand. For six seconds before and after each n-back condition, subjects were asked to fixate their eyes on a cross in the middle of the screen.

The experiment was performed on a single day. First, subjects were interviewed and screened for exclusion criteria. Then, they received a simulation session in an fMRI simulator, in order to decrease possible anxiety and to ensure adequate understanding of the task. All subjects received a short, 2-minute practice session. Next, subjects completed an Anxiety State Inventory to assess their pre-scanning anxiety (Spielberger, Gorsuch, & Luchene, 1970). During scanning, subjects completed four, 10-minute runs of the spatial n-back task. Each run included both the 0-back and the 3-back conditions, switching every 18 trials (54 seconds), to a total of 360 trials for each condition. Visual stimuli were presented on goggles (Resonance Technology Inc.,) and behavioral data were initially acquired and processed using BrainWave Hardware Lite (GE Applications), suitable for research use within the MRI environment. Upon completion of scanning, subjects completed an Anxiety State Inventory again to assess their post-scanning anxiety.

FMRI data acquisition

Imaging was performed on a 3.0T GE Signa HDx fMRI scanner (GE Medical Systems, Milwaukee, WI) using an EPI pulse sequence. For anatomical imaging, 146, 3D T1-weighted axial images were obtained using a 3D FSPGR protocol (TE = 3 ms, TR = 7.4 ms, FA = 20°, Matrix = 256 x 256 x 146, FOV=25.6 cm, 146 slice locations per slab, slice thickness 1.3 mm). For functional imaging, 800 T2*-weighted oblique, axial images were obtained (TE = 30 ms, TR = 3 sec, FA = 90°, Matrix = (64 x 64), FOV=24 cm). Each fMRI scan, spanning 32, 4-mm slices (one mm slice gap with interleave), was collected every 3 seconds and provided full coverage of the brain. Five additional 3-second RF excitations were executed before each run to reduce T1 saturation effects.

Analysis of fMRI data

Data were analyzed using Statistical Parametric Mapping software (SPM2; Wellcome Department of Cognitive Neurology, London, UK). Prior to analysis, head motion of the subject during a scanning run was corrected using the six-parameter rigid-body realignment algorithm within SPM2 (Friston, Ashburner, & Poline, 1995). Functional and structural data were normalized into a standard stereotaxic space using a 12-parameter affine transformation algorithm within the SPM2 environment. Coordinates within this MNI space (from the Montreal Neurological Institute; Collins, Neelin, Peters, & Evans, 1994), were later translated to the coordinate system of the Talairach atlas (Talairach & Tournoux, 1988) for reporting the localization of functional activations using the mni2tal routine of Brett (2002). Data were smoothed spatially using a Gaussian kernel having a full-width at half of maximum (FWHM) value of twice the voxel size (7.5 mm x 7.5 mm x 8 mm), to improve the signal to noise and to de-emphasize non-Gaussian intensity correlations between adjacent voxels. Effects of variable activity global to the whole brain (e.g., cardio-vascular changes) were minimized via high-pass filtering of the data and temporal smoothing of the data using the reference HRF as a kernel. Signal drift was reduced using high-pass filtering and [3-back-fixation cross] or [0-back-fixation cross] contrasts that subtracted neural activity of two temporally adjacent blocks that are assumed to have similar drift.

Within SPM2, signal variations were fit to a BOLD response function using linear regression, yielding fitting weights and residuals. The response function was modeled as a box-car waveform to simulate continual stimulation during particular conditions during an epoch convolved with a reference hemodynamic response function (HRF). Within SPM2, the maps of F- and t-statistics were transformed to the unit normal distribution to

give a Z map. Resultant images of these Z maps were generated for a subset of the data based on significance and probability values of uncorrected $p< 0.001$ for both the voxel and cluster levels. Voxel size was set at 3.75mm x 3.75mm x 4mm, and a cluster was defined as eight or more contiguous voxels.

FMRI data were used to test this experiment's hypotheses by creating two levels of contrasts. The contrasts in the first level subtracted neural activity during one of the n-back conditions from neural activity during the fixation cross condition (i.e., [3-back-fixation cross] for the 3-back task and [0-back-fixation cross] for the 0-back task) to present only task-specific activity. Neural activity identified from these contrasts was later used in all second-level contrasts, and is referred in the next sections simply as 'neural activity'. Second-level contrasts were performed using SPM's within-subject ANOVA models (i.e., repeated measure ANOVA). To test for changes over time in neural activity across the four runs in the DLPFC during the 3-back and 0-back tasks, specific t-contrasts of linear and quadratic functions were defined. Neural activity in the region of interest (ROI) was defined by identifying specific Brodmann Areas in the DLPFC (BA 9 and 46) using the PickAtlas toolbox in SPM2 (PickAtlas; Wake Forest University School of Medicine, Wake Forest, NC.)

Analysis of behavioral data

Analysis of behavioral data was done with the Statistical Package for the Social Sciences (SPSS), version 16.0. Two-way repeated measure analyses of variance (ANOVA) were used to support differential changes in neural activity across the four runs in the 0-back and 3-back conditions. As described above, for the purpose of those analyses, neural activity was operationalized by deriving measures of dispersion and intensity of neural activation from the functional data. Dispersion of neural activity was

defined as the number of activated voxels in the DLPFC (i.e., BA 9 and 46) divided by the total number of voxels within the DLPFC. Activation intensity was defined as the average percent signal intensity change of the highest two percent (80 voxels) of activated voxels within the ROI. A two-way repeated measure ANOVA was also used to support differential changes in Percent Accuracy and Response Time across the four runs in the 0-back and 3-back conditions.

Results

Imaging results

Twenty-two subjects were scanned, and two subjects were excluded post-scanning for failing to meet the cutoff performance (60% accuracy) requirement during scanning. As shown in Figure 3.1, SPM results of the working memory contrast (3back-0back) suggest that the 3back task was more cognitively demanding than the 0-back task. Subjects showed greater activation during the 3-back than in the 0-back task. In run1, activation was greater during the 3-back condition, compared with the 0-back condition, in the left angular gyrus,(BA 39), bilateral middle frontal gyrus (BA9, BA10), left thalamus, and in the bilateral cerebellum. In run2, activation was greater during the 3-back condition in the left DLPFC (BA9), right precuneus (BA7), right superior frontal gyrus (BA10), left thalamus, bilateral cerebellum, left fusiform gyrus (BA37), and the right putamen. In run3, activation was greater during the 3-back condition in left inferior parietal lobule (BA 40), left middle frontal gyrus (BA9), right middle frontal gyrus (BA10), bilateral cerebellum, and bilateral thalamus. In run4, activation was greater during the 3-back condition in bilateral middle frontal gyrus (BA9), left inferior parietal

lobule (BA 40), left insula (BA13), right inferior frontal gyrus (BA47), left inferior frontal gyrus (BA44), right superior frontal gyrus (BA10), right precentral gyrus (BA6), and right cerebellum. T-contrasts that modeled linear functions across the four runs in the region of interest (DLPFC) revealed only decreased activation, mainly in the left middle frontal gyrus (BA 9 and BA46.)

SPM results from an omnibus F-test of the 3-back condition ([3-back]-fixation cross) across the four runs revealed a small change in activation in the cingulated gyrus (BA 32.) In support of our hypothesis, follow-up SPM results of a t-contrast modeling a negative linear function demonstrated decreased activation in that region across runs (see Figure 4.1.) Additional t-contrasts designed to model a positive linear function, as well as positive and negative quadratic functions failed to yield any statistically significant set, cluster, or voxel of activation.

SPM results from an omnibus F-test of the 0-back condition ([0-back]-fixation cross) across the four runs revealed a bilateral change in activation in the middle frontal gyrus (BA 9 and BA46). In support of our hypothesis, follow-up SPM results of a t-contrast modeling a negative linear function in the DLFPC failed to yield any statistically significant set, cluster, or voxel of activation. In addition, no significantly activated clusters (i.e., cluster size greater than eight voxels) were found in either of the t-contrasts designed to model positive and negative quadratic functions. SPM results of a t-contrast modeling a positive linear function in the DLFPC demonstrated increased activation particularly in the right DLPFC (BA 9 and BA46) across runs (see Figure 4.2.)

Table 4.1. Areas of Activation in the DLPFC at p< 0.001 and Cluster Size of 8 Voxels That Demonstrated a Linear Decrease During the 3-Back Condition and a Linear Increase During the 0-Back Condition.

Hemisphere	X	Y	Z	SPM(Z)	Brain Structure	BA*
Linear Decrease During the 3-Back:						
Left	-2	29	28	3.11	Cingulate Gyrus	32
Linear Increase During the 0-Back:						
Right	46	15	34	4.29	Middle Frontal Gyrus	9
Right	53	25	24	3.59	Middle Frontal Gyrus	46
Left	-55	25	22	3.44	Middle Frontal Gyrus	46

*Brodmann's Area

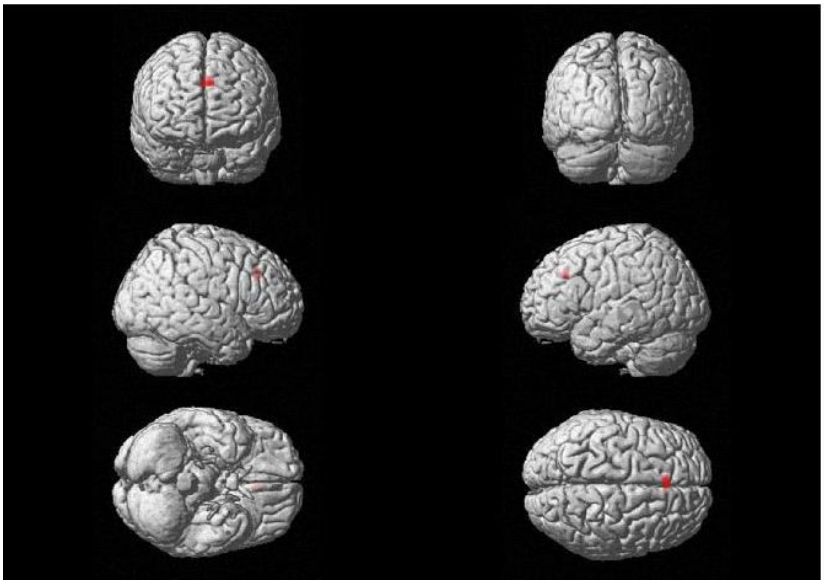

Figure 4.1. Statistical Parametric Map of a Negative Linear Function in the Frontal Lobe Across Four Runs [(3-back)-Fixation Cross] at the Coordinates of the Highest Activated Voxel.

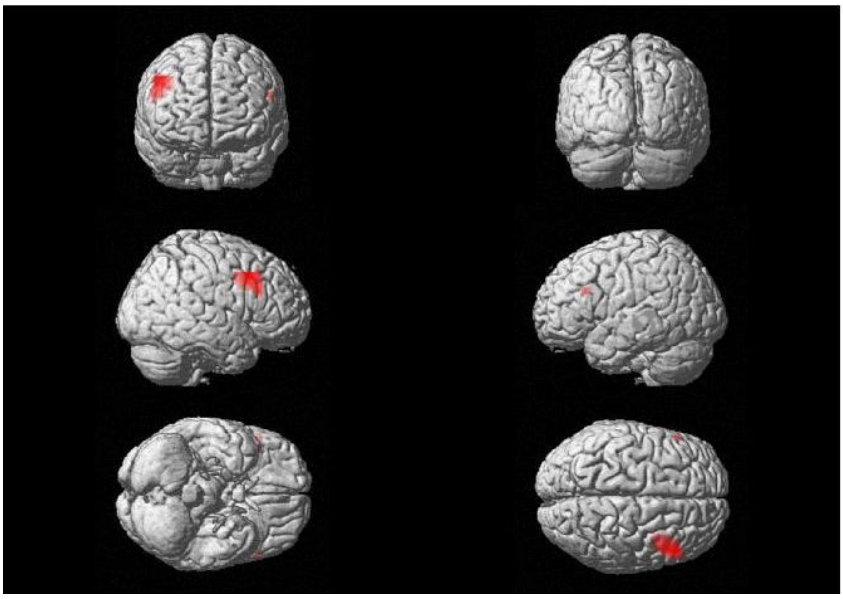

Figure 4.2. Statistical Parametric Map of a Positive Linear Function in the Frontal Lobe Across Four Runs [(0-back)-Fixation Cross] at the Coordinates of the Highest Activated Voxel.

Behavioral results

Subjects' pre- and post-scanning self-report on the State Anxiety Inventory was not significantly different ($t(17) = -0.697$, $p>0.05$), and indicated low anxiety levels. Following post-scanning reports of increased fatigue from several subjects, participants were asked to rate their alertness on a 1 to 10 Likert Scale, where 1 is "completely alert" and 10 is "exhausted". Responses collected from nine of the twenty participants suggested a significant increase in fatigue by the end of the 40-minute scanning ($t(8) = 4.61$, $p<0.01$.) A two-way repeated measure analysis of variance was conducted to explore the impact of repeated performance and task domain on levels of neural activation in the DLPFC, as measured by percent of signal intensity change (PIC.) Consistent with our hypothesis, there was a statistically significant large main effect of task domain [$F(1,19) = 28.768$, $p < 0.05$; partial Eta squared = 0.602], as subjects demonstrated stronger neural activity in the 3-back than in the 0-back condition. Contrary

to our hypothesis, the main effect of repeated performance, as measured by runs, [$F(3,17) = 1.599$, $p > 0.05$] and the interaction effect [$F(3,17) = 2.987$, $p > 0.05$] did not reach statistical significance. However, there was a trend toward statistical significance for the interaction effect from Run3 to Run4, as the PIC values in the 3-back condition decreased while the PIC values in the 0-back condition increased [$F(1,19) = 4.064$, $p = 0.058$; see Figure 4.2a.] Similar results were found in the two-way analysis of variance of the impact of repeated performance and task domain on the dispersion of neural activation in the DLPFC. While the main effect of repeated performance did not reach statistical significance [$F(3,17) = 0.270$, $p > 0.05$], there was a statistically significant large main effect for task domain [$F(1,19) = 23.105$, $p < 0.01$; partial Eta squared = 0.549], as well as a statistically significant interaction effect [$F(3,17) = 3.865$, $p < 0.03$; partial Eta squared = 0.405]. Similarly to the trend observed with the PIC values, dispersion in the 3-back condition decreased over time, while it increased over time in the 0-back condition, and became statistically significant between run 3 and run4 [$F(1,19) = 5.197$, $p < 0.04$; see Figure 4.2b.] A follow-up one-way repeated measure ANOVA that tested the impact of repeated performance on dispersion during the 3-back task revealed a statistically significant practice effect [$F(3,57) = 4.896$, $p < 0.01$; partial Eta squared = 0.205]. The change in dispersion in the DLPFC had a significant negative linear component [$F(1,19) = 8.399$, $p < 0.01$; partial Eta squared = 0.307], as dispersion in the DLPFC decreased over time.

To determine whether repeated performance and task domain were manifested in observable behavioral measures, two-way repeated measure analyses of variance were performed on response time and percent accuracy. With regards to response time, there was a statistically significant interaction effect [$F(3,17) = 3.280$, $p < 0.05$; partial Eta

squared = 0.367], as repeated performance affected response time differently in the 3-back and 0-back conditions. There was a large and statistically significant main effect for task domain [$F(1,19) = 29.175$, $p < 0.01$; partial Eta squared = 0.606], as subjects were significantly faster on the 0-back task than on the 3-back task (see figure 4.2c). The main effect of repeated performance [$F(3,17) = 1.523$, $p > 0.05$] did not reach statistical significance. With regards to percent accuracy, there was a large and statistically significant main effect for task domain [$F(1,19) = 45.875$, $p < 0.01$; partial Eta squared = 0.707], as subjects were significantly more accurate on the 0-back task than on the 3-back task (see figure 4.2d). The main effect of repeated performance [$F(3,17) = 0.39$, $p > 0.05$] and the interaction effect [$F(3,17) = 2.072$, $p > 0.05$] did not reach statistical significance.

Table 4.2. Summary of Two-Way Repeated Measure Analyses of Variance for Task, Practice, and Task*Interaction for PIC, Dispersion, Response Time, and Accuracy.

	F	Hypothesis df	Error df	Sig. (p)	Partial E^2
% Intensity Change					
Task	28.768	1	19	<0.01	0.602
Practice	1.599	3	17	0.227	0.220
Task*Practice	2.987	3	17	0.06	0.345
Dispersion					
Task	23.105	1	19	<0.01	0.549
Practice	0.270	3	17	0.846	0.045
Task*Practice	3.865	3	17	0.028	0.450
Response Time					
Task	29.175	1	19	<0.01	0.606
Practice	1.523	3	17	0.245	0.212
Task*Practice	3.280	3	17	0.046	0.367
Accuracy					
Task	45.875	1	19	<0.01	0.707
Practice	0.390	3	17	0.761	0.064
Task*Practice	2.072	3	17	0.142	0.268

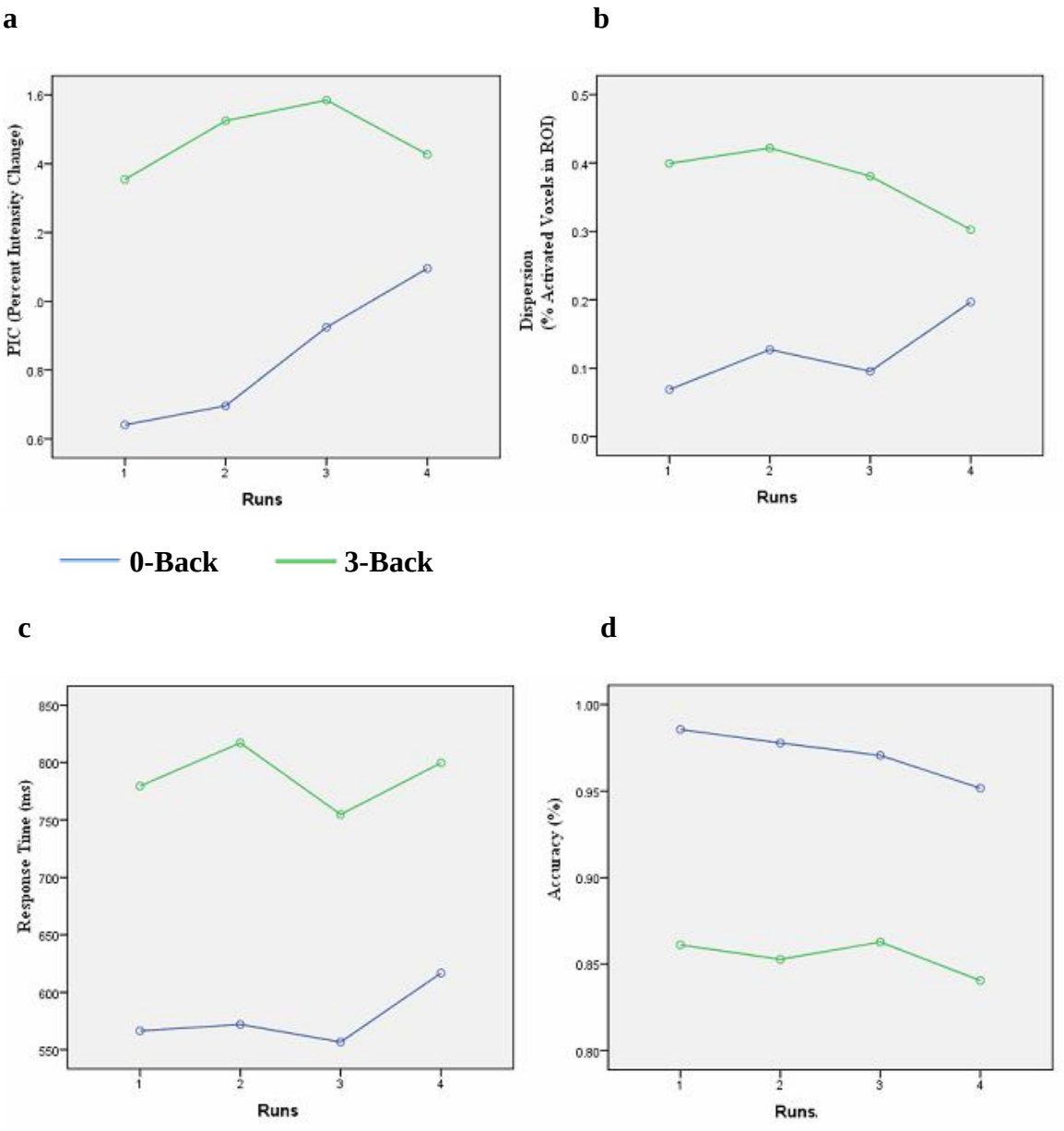

Figure 4.3. Estimated Marginal Means of PIC (a), Dispersion (b), Response Time (c), and Percent Accuracy (d) for the 0-back (green) and 3-Back (Blue) conditions.

Discussion

This study tested the effects of task-domain and practice on neural activity during a single scanning session. Specifically, neural activity was hypothesized to demonstrate a more pronounced decrease in activation in the DLPFC during the 3-back, compared with the 0-back task. In line with our hypothesis, SPM results of the 3-back condition [(3-back) - fixation cross] indicated only a linear decrease in activation in the DLPFC. SPM results of the 0-back condition [(0-back) - fixation cross] failed to yield any statistically significant set, cluster, or voxel of DLPFC activation that decreased in activation across runs; however, contrary to our hypothesis, there was a significant increase in activation across runs, mainly in the right DLPFC.

Results from behavioral measures indicated a strong main effect for task domain. Across runs, subjects demonstrated stronger and more extensive neural activity during the 3-back task, compared with the 0-back task. Behaviorally, subjects' performance on the 3-back, compared with the 0-back, was slower and less accurate. Intensity and dispersion of activation failed to demonstrate a main effect for practice when compared together on the 3- and 0-back conditions. Toward the end of scanning, both measures demonstrated a trend toward statistical significance of a decrease in intensity and dispersion in the 3-back condition and an increase in intensity and dispersion in the 0-back condition. When tested separately, results indicated a statistically significant decrease in dispersion across runs of the 3-back task.

With regard to the behavioral measures of response time and percent accuracy, performance remained stable across runs and there were no main effects for practice. Results from behavioral measures failed to demonstrate practice effects across the four runs on response time and percent accuracy in either of the n-back levels. Follow-up

regression analysis within each run revealed an association between behavioral practice effects and differential neural activity in the DLPFC. Specifically, in the first half of scanning (i.e., run1 and run2) there was an association between the intensity measure of neural activation and response time. By the second run, during the 0-back, stronger activation in the DLPFC was uniquely associated with slower performance. In the second half of the scanning session (i.e., run3 and run4), performance accuracy was predicted by the measures of dispersion and intensity of activation. In run3 during the 3-back task, higher accuracy was associated with more limited dispersion in the DLPFC.

This pattern of significant changes in neural activity along with difficulty demonstrating behavioral practice effects was evident in previous experiments in our laboratory (Kessel, Miller, Yanasak, & Maher, 2006, February, 2007, February), as well as in independent studies of practice effects over time (Landau, 2005.) This failure to demonstrate behavioral practice effects could be interpreted in several ways. First, it is possible the observed change in DLPFC represents a cognitive process independent of practice. Second, the overall changes in DLPFC could be the result of more than one cognitive process, in addition to increased efficiency. Third, changes in neural activation of the DLPFC could reflect practice effects of neural redistribution that are yet to be manifested in improved performance.

The association between performance and DLPFC activation indicates that this area is involved in successful processing of the task. It is possible that while neural activation changed in response to redistribution and strategy shift, the changes were either unsuccessful in improving task performance, or not yet manifested behaviorally. It is more likely that the observed pattern of neural changes over time without behavioral improvements in performance suggests familiarity effects due to repeated exposure,

rather than practice effects. Furthermore, the opposite directions of change over time in the 3- and 0-back levels strongly suggest that there could be an additional competing process that affected performance and neural activity, with a stronger effect on the 0-back condition. Given the long duration of scanning and the less engaging and challenging nature of the 0-back, fatigue or inattention could be partially responsible for the increased DLPFC activation over time in the 0-back level.

Fatigue is a subject-related variable that can influence neural activity (Liu et al., 2003). Starbuck, Kay, Platenberg, Lin, and Zielinski (2000) examined the effects of sleepiness on neural activity during the Paced Auditory Serial Addition Test (PASAT), a mental arithmetic task. For three days, 14 subjects received placebo or sleepiness-inducing medications before receiving fMRI scans. Starbuck et al. demonstrated how the decreased activation that is associated with task familiarity could be reversed when subjects are fatigued. Results indicated a positive correlation between self-rated or drug induced sleepiness and frontal brain activation. The authors concluded that sedation masks and reverses familiarity effects. Similar increased frontal activation was found in other functional imaging studies (Drummond et al., 1999.)

Results of the current study demonstrate a pattern consistent with fatigue effects that is increased frontal activation in the less cognitively demanding task, along with a statistically significant increase in fatigue reports found in a subset of the subjects. It is possible that familiarity effects were partially masked in the 3-back condition and even fully masked in the 0-back condition. The differential effects of repeated exposure, and possibly fatigue, on current functional and behavioral data highlight the importance of understanding the effects of uncontrolled variables on neural activity. Identifying the neural network of WM alone could be insufficient if not taken in the context of additional

variables that affect neural activity directly (e.g., increased familiarity and fatigue) or interact with the effects of other variables (e.g., task domain.)

The goal of this study was to provide useful information for future studies, primarily on the nature of changes due to effects of repeated exposure and task domain. Knowing the function of changes in neural activity during a spatial working memory task could improve reliability in fMRI studies. For example, providing sufficient practice prior to scanning in order to ensure relatively stable neural response could increase the probability of replicating results, thus increasing test-retest reliability. Results of this study demonstrated how uncontrolled variables (e.g., fatigue) can possibly reverse activation patterns if not attended to or minimized. Knowing in advance which task or subject-related variables (other than the independent variable) may undesirably influence the subject's performance could also help eliminate their influence by changing the design of the experiment or accounting for them statistically. Given the prevalence of WM deficits in psychological and neurological disorders, future studies should explore how these variables affect and interact with the study's population in order to increase power and reliability in functional brain imaging studies.

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CHAPTER 5

DISCUSSION

Results of this experiment demonstrate the changes in the level of involvement of regions in the WM neural circuitry and how they are affected by controlled and uncontrolled variables. In line with our first hypothesis, fMRI results from the DLPFC, a strategy non-specific region, show a significant decrease in activation over time. Contrary to our second hypothesis, fMRI results from the PPC, a strategy-specific region, also show a decrease in activation over time. Consistent with SPM results, analysis of the activation dispersion demonstrated decreased dispersion in both ROIs across the four runs.

Based on the hypothesis of decreases over time in strategy-specific regions and increases in strategy non-specific regions, the general decrease in activation in both ROI may indicate that the PPC is not a strategy-specific region. However, follow-up analyses within each run revealed an association between behavioral practice effects and differential neural activity in the two ROIs that are consistent with our hypotheses. In the first half of scanning (i.e., run1 and run2) there was an association between the intensity of activation and response time. By the second run, during the 0-back, stronger activation in the DLPFC was associated with slower performance, while stronger activation in the PPC was associated with faster performance. During the 3-back, stronger activation in the PPC was associated with faster response time. In the second half of the scanning session (i.e., run3 and run4), performance accuracy was predicted by the measures of dispersion

and intensity of activation. In run3 during the 3-back task, higher accuracy was associated with more limited dispersion in the DLPFC and with greater dispersion in the PPC. During run4, greater activation intensity in the PPC was associated with better accuracy.

While activation in the PPC did not demonstrate the hypothesized increase in activation over time, the association of activity in this ROI with more accurate and faster performance indicates its role in successful processing of spatial WM. The observed general decrease in activation across runs in both strategy-specific and strategy non-specific ROIs most likely reflects an overall decrease in cognitive effort during the 40-minute performance of the n-back task. Results of this study demonstrate the importance of understanding the effects of the "time-window of imaging" mentioned in Kelly and Garavan's (2005) meta-analysis of practice effects. While our study allowed for a significant time-window of imaging of practice effects, the long duration of the current study could have resulted in loss of sensitivity to intra-run changes in activation.

Results from behavioral measures failed to demonstrate practice effects across the four runs on response time and percent accuracy in either of the n-back levels. This pattern of significant changes in neural activity along with difficulty demonstrating behavioral practice effects was evident in previous experiments from our laboratory (Kessel, Miller, Yanasak, & Maher, 2006, February, 2007, February,) as well as in independent studies of practice effects over time (Landau, 2005.) This failure to demonstrate behavioral practice effects could also be an indirect result of the time window of imaging used in this study. The long duration of scanning could have introduced effects of uncontrolled variables such as fatigue and inattention to the task that counteracted practice effects.

Results from our comparison of the two task domains (i.e., WM in the 3-back condition and visual attention in the 0-back condition) offer further support for the hypothesis of competing fatigue effects. In line with our third hypothesis, SPM results of the 3-back condition [(3-back) - fixation cross] indicated only a linear decrease in activation in the DLPFC. SPM results of the 0-back condition [(0-back) - fixation cross] failed to yield any statistically significant set, cluster, or voxel of DLPFC activation that decreased in activation across runs; however, contrary to our hypothesis, there was a significant increase in activation across runs, mainly in the right DLPFC.

Results from behavioral measures indicated a strong main effect for task domain. Across runs, subjects demonstrated stronger and more extensive neural activity during the 3-back task, compared with the 0-back task. Behaviorally, subjects' performance on the 3-back, compared with the 0-back, was slower and less accurate. Intensity and dispersion of activation failed to demonstrate a main effect for practice when compared together on the 3- and 0-back conditions. Toward the end of scanning, both measures demonstrated a trend toward statistical significance of a decrease in intensity and dispersion in the 3-back condition and an increase in intensity and dispersion in the 0-back condition. When tested separately, results indicated a statistically significant decrease in dispersion across runs of the 3-back task.

As aforementioned, there was no main effect for practice on performance, as response time and percent accuracy remained stable across runs in both tasks. This pattern of significant changes in neural activity along with difficulty demonstrating behavioral practice effects could be interpreted in several ways. First, it is possible the observed changes in ROIs represent a cognitive process independent of practice. Second, the overall changes in both ROIs could be the result of more than one cognitive process,

in addition to increased efficiency. Third, changes in neural activation of the ROIs could reflect practice effects of neural redistribution that are yet to be manifested in improved performance.

The association between performance and activation in both ROIs indicates that these areas are involved in successful processing of the task. In addition, the 3-back task is known to respond to practice, and the 40-minute exposure to the task appears to be an adequate time for task familiarity. It is also very likely that while neural activation changed in response to redistribution and strategy shift, the changes were either unsuccessful in improving task performance, or not yet manifested behaviorally. Nevertheless, the opposite directions of change over time in neural activity measures in the 3- and 0-back levels strongly suggest that there could be an additional competing process that affected performance and neural activity, with a stronger effect on the 0-back condition. Given the long duration of scanning and the less engaging and challenging nature of the 0-back, fatigue or inattention could be partially responsible for the increased DLPFC activation over time in the 0-back level.

Fatigue is a subject-related variable that can influence neural activity (Liu et al., 2003). Starbuck, Kay, Platenberg, Lin, and Zielinski (2000) examined the effects of sleepiness on neural activity during the Paced Auditory Serial Addition Test (PASAT), a mental arithmetic task. For three days, 14 subjects received placebo or sleepiness-inducing medications before receiving fMRI scans. Starbuck et al. demonstrated how the decreased activation that is associated with task familiarity could be reversed when subjects are fatigued. Results indicated a positive correlation between self-rated or drug induced sleepiness and frontal brain activation. The authors concluded that sedation

masks and reverses familiarity effects. Similar increased frontal activation was found in other functional imaging studies (Drummond et al., 1999.)

Results of the current study demonstrate a pattern consistent with fatigue effects that is increased frontal activation in the less cognitively demanding task, along with a statistically significant increase in fatigue reports found in a subset of the subjects. It is possible that practice effects were partially masked in the 3-back condition and even reversed in the 0-back condition. The differential effects of practice, and possibly fatigue, on current functional and behavioral data highlight the importance of understanding the effects of uncontrolled variables on neural activity. Identifying the neural network of WM alone could be insufficient if not taken in the context of additional variables that affect neural activity directly (e.g., practice and fatigue) or interact with the effects of other variables (e.g., task domain.)

The goal of this study was to provide useful information for future studies, primarily on the nature of changes due to practice effects and task domain. Knowing the function of changes in neural activity during a spatial working memory task could improve reliability in fMRI studies. For example, providing sufficient practice prior to scanning in order to ensure relatively stable neural response could increase the probability of replicating results, thus increasing test-retest reliability. Results of this study demonstrated how uncontrolled variables (e.g., fatigue) can possibly reverse activation patterns if not attended to or minimized. Knowing in advance which task or subject-related variables (other than the independent variable) may undesirably influence the subject's performance could also help eliminate their influence by changing the design of the experiment or accounting for them statistically.

Understanding the effects of practice and possibly fatigue on the processing of WM over time offers a theoretical advantage as well. Results of this study suggest an additional dimension of understanding WM abilities in healthy adults by attending to the changed role of regions in the WM circuitry over time and their response to practice and fatigue. The presented pattern of decreased activation during a spatial WM task and increased activation during a visual attention task could be different in individuals with disorders that are known to affect WM (e.g., schizophrenia, ADHD.) Future studies could compare the temporal patterns of practice effects of populations with intact and affected WM abilities. Therefore, recognizing and understanding the influence of practice on neural activation in healthy adults could be the first step in improving our understanding of those psychological and neurological disorders.

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APPENDICES

APPENDIX A

DEMOGRAPHIC/MEDICAL HISTORY QUESTIONNAIRE

Demographic/Medical History Questionnaire

Code: _____ SCID: _____ Date: _____
Group Placement: _____ Mo / Day / Yr

****

FOR PARTICIPANT TO FILL OUT

Date of Birth: ____/____/____
Mo / Day / Yr

Born in USA (Circle one)?: Yes / No If Yes, which state? _____

Race (Check one)

_____White, not of Hispanic Origin
_____Black, not of Hispanic origin
_____American Indian or Alaskan native
_____Asian or Pacific Islander
_____Hispanic
_____Mixed Race
_____Other

Marital Status (Check one):

_____Single
_____Married
_____Divorced

Gender (Check one) :

_____ Male
_____ Female

Approximate weight in lbs: _____

Working? Yes / No

Occupation Type (Check one):
_____Student _____ Blue Collar
_____ White Collar _____ Retired
_____ Unemployed

Current Living Status (Check one):
_____Live with spouse
_____Live alone independently
_____Live with other family members
_____Live in Personal Care or Assisted Living Facility
_____Live in Nursing Home

Highest Grade in School Finished (Check one) _____<9 _____ 9-12
_____ H.S. Grad _____ Some College
_____College Degree _____ Post Graduate

Native Language if other than English: _____

List any medications you are taking or have taken within the past month:

1. _____
2. _____
3. _____
4. _____
5. _____

How much do you drink? (Check one):____None ____ 1-3 /wk ____ 4-8/wk ____>8/wk

Dominant Hand (Check one): _____Right _____Left

(Circle one)

Have you ever had a concussion or other head injury?	Yes / No
Have you ever had a stroke?	Yes / No
Have you ever been diagnosed with a neurologic condition?	Yes / No
Have you ever been diagnosed with Diabetes?	Yes / No
Have you ever been treated for depression?	Yes / No
Have you ever been hospitalized for psychiatric care?	Yes / No
Do you have a Learning Disability, Dyslexia, or Attention Deficit Disorder?	Yes / No
Do you smoke?	Yes / No
Do you have a parent, brother or sister who has been diagnosed with Alzheimer's disease?	Yes / No
Women Only: Are you taking Estrogen Replacement Therapy?	Yes / No

In the recent past, have you had trouble...(Circle one):

Remembering Lists?	No / A little / A lot
Remembering Conversations?	No / A little / A lot
Remembering Recent Events?	No / A little / A lot
Handling Money/Making Change?	No / A little / A lot
Balancing your Checkbook?	No / A little / A lot
Getting Lost in Familiar Areas?	No / A little / A lot
Feeling Down for no Reason?	No / A little / A lot
Losing your Temper over Little Things?	No / A little / A lot

In the recent past, have you had difficulty with any of the following, not due to such things as arthritis, weakness, or other physical limitations (Circle one)

Doing Chores?	No / A little / A lot
Eating?	No / A little / A lot
Dressing?	No / A little / A lot
Bathing/Grooming?	No / A little / A lot
Walking?	No / A little / A lot

APPENDIX B

HANDEDNESS SCREENING QUESTIONNAIRE

Code # _____

Handedness

With which hand do you prefer to WRITE?

STRONGLY prefer RIGHT	(1) _____
MILDLY prefer RIGHT	(2) _____
NO preference	(3) _____
MILDLY prefer LEFT	(4) _____
STRONGLY prefer LEFT	(5) _____

With which hand do you prefer to THROW A BALL?

STRONGLY prefer RIGHT	(1) _____
MILDLY prefer RIGHT	(2) _____
NO preference	(3) _____
MILDLY prefer LEFT	(4) _____
STRONGLY prefer LEFT	(5) _____

With which hand do you prefer to BRUSH YOUR TEETH?

STRONGLY prefer RIGHT	(1) _____
MILDLY prefer RIGHT	(2) _____
NO preference	(3) _____
MILDLY prefer LEFT	(4) _____
STRONGLY prefer LEFT	(5) _____

With which hand do you prefer to DRAW?

STRONGLY prefer RIGHT	(1) _____
MILDLY prefer RIGHT	(2) _____
NO preference	(3) _____
MILDLY prefer LEFT	(4) _____
STRONGLY prefer LEFT	(5) _____

With which hand do you prefer to USE SCISSORS?

STRONGLY prefer RIGHT	(1) _____
MILDLY prefer RIGHT	(2) _____
NO preference	(3) _____
MILDLY prefer LEFT	(4) _____
STRONGLY prefer LEFT	(5) _____

APPENDIX C

STATE ANXIETY INVENTORY

State Anxiety Inventory

A number of statements which people have used to describe themselves are given below. Read each statement and then select the appropriate one to indicate how you feel **right now**, that is, at this moment. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

	Not at all	Somewhat	Moderately So	Very Much So
I feel calm	x	x	x	x
I feel secure	x	x	x	x
I am tense	x	x	x	x
I am regretful	x	x	x	x
I feel at ease	x	x	x	x
I feel upset	x	x	x	x
I am presently worrying over possible misfortunes	x	x	x	x
I feel rested	x	x	x	x
I feel anxious	x	x	x	x
I feel comfortable	x	x	x	x
I feel self-confident	x	x	x	x
I feel nervous	x	x	x	x
I am jittery	x	x	x	x
I feel "high strung"	x	x	x	x
I am relaxed	x	x	x	x
I feel content	x	x	x	x
I am worried	x	x	x	x
I feel overexcited and rattled	x	x	x	x
I feel joyful	x	x	x	x
I feel pleasant	x	x	x	x

APPENDIX D

MINI MENTAL STATE EXAMINATION

MMSE™

Date of Examination ___/___/___ Examiner _____

Name _____ Age _____ Years of School Completed _____

Instructions: Words in boldface type should be read aloud clearly and slowly to the examinee. Item substitutions appear in parentheses. Administration should be conducted privately and in the examinee's primary language. Circle 0 if the response is incorrect, or 1 if the response is correct. Begin by asking the following two questions:

Do you have any trouble with your memory? **May I ask you some questions about your memory?**

ORIENTATION TO TIME		RESPONSE	SCORE (circle one)
What is the...	**year?**	_____	0 1
	season?	_____	0 1
	month of the year?	_____	0 1
	day of the week?	_____	0 1
	date?	_____	0 1

ORIENTATION TO PLACE*

Where are we now? What is the...

state (province)**?**	_____	0 1
county (or city/town)**?**	_____	0 1
city/town (or part of city/neighborhood)**?**	_____	0 1
building (name or type)**?**	_____	0 1
floor of the building (room number or address)**?**	_____	0 1

*Alternative place words that are appropriate for the setting and increasingly precise may be substituted and noted.

REGISTRATION*

Listen carefully. I am going to say three words. You say them back after I stop. Ready? Here they are... APPLE [*pause*], **PENNY** [*pause*], **TABLE** [*pause*]. **Now repeat those words back to me.**
[*Repeat up to 5 times, but score only the first trial.*]

APPLE	_____	0 1
PENNY	_____	0 1
TABLE	_____	0 1

Now keep those words in mind. I am going to ask you to say them again in a few minutes.

*Alternative word sets (e.g., PONY, QUARTER, ORANGE) may be substituted and noted when retesting an examinee.

ATTENTION AND CALCULATION [Serial 7s]*

Now I'd like you to subtract 7 from 100. Then keep subtracting 7 from each answer until I tell you to stop.

What is 100 take away 7?	[93]	_____	0 1
If needed, say: **Keep going.**	[86]	_____	0 1
If needed, say: **Keep going.**	[79]	_____	0 1
If needed, say: **Keep going.**	[72]	_____	0 1
If needed, say: **Keep going.**	[65]	_____	0 1

*Alternative item (WORLD backward) should only be administered if the examinee refuses to perform the Serial 7s task. →

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Substitute and score this item only if the examinee refuses to perform the Serial 7s task.

Spell WORLD forward, then backward.
Correct forward spelling if misspelled,
but score only the backward spelling.

(D = 1) (L = 1) (R = 1) (O = 1) (W = 1) (0 to 5)

RECALL	RESPONSE	SCORE (circle one)
What were those three words I asked you to remember? [*Do not offer any hints.*]		
APPLE		0 1
PENNY		0 1
TABLE		0 1

NAMING*

What is this? [*Point to a pencil or pen.*]		0 1
What is this? [*Point to a watch.*]		0 1

*Alternative common objects (e.g., eyeglasses, chair, keys) may be substituted and noted.

REPETITION

Now I am going to ask you to repeat what I say. Ready? "NO IFS, ANDS, OR BUTS." Now you say that.
[*Repeat up to 5 times, but score only the first trial.*]

NO IFS, ANDS, OR BUTS.		0 1

Detach the next page along the lengthwise perforation, and then tear it in half along the horizontal perforation. Use the upper half of the page (blank) for the Comprehension, Writing, and Drawing items that follow. Use the lower half of the page as a stimulus form for the Reading ("CLOSE YOUR EYES") and Drawing (intersecting pentagons) items.

COMPREHENSION

Listen carefully because I am going to ask you to do something.
Take this paper in your right hand [*pause*], **fold it in half** [*pause*], **and put it on the floor** (*or* **table**).

TAKE IN RIGHT HAND		0 1
FOLD IN HALF		0 1
PUT ON FLOOR (*or* TABLE)		0 1

READING

Please read this and do what it says. [*Show examinee the words on the stimulus form.*]

CLOSE YOUR EYES		0 1

WRITING

Please write a sentence. [*If examinee does not respond, say:* **Write about the weather.**] 0 1
Place the blank piece of paper (unfolded) in front of the examinee and provide a pen or pencil. Score 1 point if the sentence is comprehensible and contains a subject and a verb. Ignore errors in grammar or spelling.

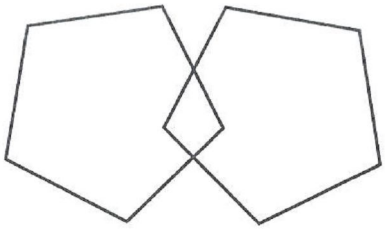
DRAWING

Please copy this design. [*Display the intersecting pentagons on the stimulus form.*] 0 1
Score 1 point if the drawing consists of two 5-sided figures that intersect to form a 4-sided figure.

Total Score = _____
(*Sum all item scores.*) (30 points max.)

Assessment of level of consciousness.

Alert/ Responsive	Drowsy	Stuporous	Comatose/ Unresponsive



CLOSE YOUR EYES

APPENDIX E

MRI SCREENING FORM

University of Georgia BioImaging Research Center

MAGNETIC RESONANCE (MR) PROCEDURE SCREENING FORM FOR RESEARCH PARTICIPANTS

Date _____/_____/_____ Study ID_____

Name _____ Age _____ Height _____ Weight _____
Last name First name Middle Initial

Date of Birth _____/_____/_____ Male ❒ Female ❒ Body Part to be Scanned_____
month day year

Reason for MRI (e.g., Research Participation) _____

1. Have you had prior surgery or an operation (e.g., arthroscopy, endoscopy, etc.) of any kind? ❒ No ❒ Yes
   If yes, please indicate approximate date and type of surgery:
   Date _____ Type of surgery _____
   Date _____ Type of surgery _____
2. Have you had a prior diagnostic imaging study or examination (MRI, CT, X-ray, etc.)? ❒No ❒ Yes
   If yes, please list: Body part Approx Date
   MRI _____ _____
   CT/CAT Scan _____ _____
   X-Ray _____ _____
   Other_____ _____ _____
3. Have you experienced any problem related to a previous MRI examination or MR procedure? ❒ No ❒ Yes
   If yes, please describe: _____
4. Have you had an injury to the eye involving a metallic object or fragment (e.g., metallic slivers, shavings, foreign body, etc.)? ❒ No ❒ Yes
   If yes, please describe: _____
5. Have you ever been injured by a metallic object or foreign body (e.g., BB, bullet, shrapnel, etc.)? ❒ No ❒ Yes
   If yes, please describe: _____
6. Are you currently taking or have you recently taken any medication or drug? ❒ No ❒ Yes
   If yes, please list:_____
7. Are you allergic to any medication? ❒ No ❒ Yes
   If yes, please list:_____
8. Do you have anemia or any disease(s) that affects your blood, a history of renal (kidney) disease, or seizures ❒ No ❒ Yes
   If yes, please describe: _____

For female patients:

9. Date of last menstrual period:_____ Post menopausal? ❒ No ❒ Yes
10. Are you pregnant or experiencing a late menstrual period? ❒ No ❒ Yes
11. Are you taking oral contraceptives or receiving hormonal treatment? ❒ No ❒ Yes
12. Are you taking any type of fertility medication or having fertility treatments? ❒ No ❒ Yes
    If yes, please describe: _____
13. Are you currently breastfeeding? ❒ No ❒ Yes

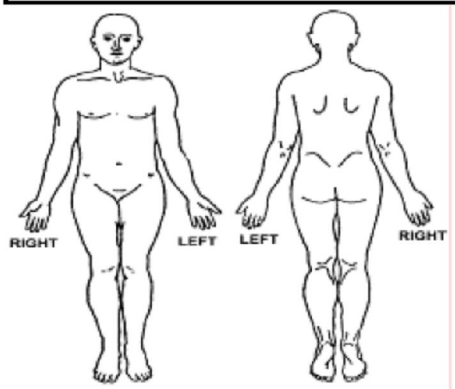
University of Georgia BioImaging Research Center

WARNING: Certain implants, devices, or objects may be hazardous to you and/or may interfere with the MR procedure (i.e., MRI, MR angiography, functional MRI, MR spectroscopy). **Do not enter** the MR system room or MR environment if you have any question or concern regarding an implant, device, or object. Consult the MRI Technologist BEFORE entering the MR system room. **The MR system magnet is ALWAYS on.**

Please indicate if you have any of the following:

❒ Yes	❒ No	Aneurysm clip(s)
❒ Yes	❒ No	Cardiac pacemaker
❒ Yes	❒ No	Implanted cardioverter defibrillator (ICD)
❒ Yes	❒ No	Electronic implant or device
❒ Yes	❒ No	Magnetically-activated implant or device
❒ Yes	❒ No	Neurostimulation system
❒ Yes	❒ No	Spinal cord stimulator
❒ Yes	❒ No	Internal electrodes or wires
❒ Yes	❒ No	Bone growth/bone fusion stimulator
❒ Yes	❒ No	Cochlear, otologic, or other ear implant
❒ Yes	❒ No	Insulin or other infusion pump
❒ Yes	❒ No	Implanted drug infusion device
❒ Yes	❒ No	Any type of prosthesis (eye, penile, etc.)
❒ Yes	❒ No	Heart valve prosthesis
❒ Yes	❒ No	Eyelid spring or wire
❒ Yes	❒ No	Artificial or prosthetic limb
❒ Yes	❒ No	Metallic stent, filter, or coil
❒ Yes	❒ No	Shunt (spinal or intraventricular)
❒ Yes	❒ No	Vascular access port and/or catheter
❒ Yes	❒ No	Radiation seeds or implants
❒ Yes	❒ No	Swan-Ganz or thermodilution catheter
❒ Yes	❒ No	Medication patch (Nicotine, Nitroglycerine)
❒ Yes	❒ No	Any metallic fragment or foreign body
❒ Yes	❒ No	Wire mesh implant
❒ Yes	❒ No	Tissue expander (e.g., breast)
❒ Yes	❒ No	Surgical staples, clips, or metallic sutures
❒ Yes	❒ No	Joint replacement (hip, knee, etc.)
❒ Yes	❒ No	Bone/joint pin, screw, nail, wire, plate, etc.
❒ Yes	❒ No	IUD, diaphragm, or pessary
❒ Yes	❒ No	Dentures or partial plates
❒ Yes	❒ No	Tattoo or permanent makeup
❒ Yes	❒ No	Body piercing jewelry
❒ Yes	❒ No	Hearing aid *(Remove before entering MR system room)*
❒ Yes	❒ No	Other implant _____
❒ Yes	❒ No	Breathing problem or motion disorder
❒ Yes	❒ No	Claustrophobia

Please mark on the figure(s) below the location of any implant or metal inside of or on your body.



IMPORTANT INSTRUCTIONS

Before entering the MR environment or MR system room, you must remove all metallic objects including hearing aids, dentures, partial plates, keys, beeper, cell phone, eyeglasses, hair pins, barrettes, jewelry, body piercing jewelry, watch, safety pins, paperclips, money clip, credit cards, bank cards, magnetic strip cards, coins, pens, pocket knife, nail clipper, tools, clothing with metal fasteners, & clothing with metallic threads.

Please consult the MRI Technologist if you have any question or concern BEFORE you enter the MR system room.

NOTE: You may be advised or required to wear earplugs or other hearing protection during the MR procedure to prevent possible problems or hazards related to acoustic noise.

I attest that the above information is correct to the best of my knowledge. I read and understand the contents of this form and had the opportunity to ask questions regarding the information on this form and regarding the MR procedure that I am about to undergo.

Signature of Person Completing Form: _____ Date ____/____/____
Signature

Form Completed By: ❒ Participant ❒ Relative ❒ Nurse _____ _____
Print name Relationship to Participant

Form Information Reviewed By: _____ _____
Print name Signature

❒ MRI Technologist ❒ PI ❒ Other_____