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NEUROPSYCHOLOGICAL CORRELATES AND UNDERLYING CORTICAL MECHANISMS OF WORKING MEMORY IN MODERATE TO SEVERE TRAUMATIC BRAIN INJURY

Jessica Ann Clark
University of Kentucky, jessicaclarkms@gmail.com

ABSTRACT OF DISSERTATION

Jessica Ann Clark

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University of Kentucky
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ABSTRACT OF DISSERTATION

A dissertation submitted in partial fulfillment of the
requirements for the degree of Doctor of Philosophy in the
College of Arts and Sciences
at the University of Kentucky

By
Jessica Ann Clark
Lexington, Kentucky
Co-Directors: Dr. David T. R. Berry, Professor of Psychology
and Dr. Walter M. High, Jr., Professor of Physical Medicine
& Rehabilitation & Psychology
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Functional magnetic resonance imaging (fMRI) is a relatively new tool that has been used to examine patterns of neural activation within those with traumatic brain injuries (TBI). A review of relevant literature is presented, including alterations in activity within the frontal and parietal regions that are thought to be compensatory in nature. In addition, possible explanations for discrepancies within this research are discussed. The current study expands upon previous work by incorporating a delayed-match-to-sample (DMS) task within an event-related paradigm and neuropsychological testing to compare 12 individuals with a history of TBI to 12 control participants with orthopedic injuries (OI). Participants in the TBI group were high functioning and in the chronic stage of recovery. Neuropsychological testing revealed statistically significant group differences in measures of working memory, processing speed, memory, and executive functioning. However, groups were comparable in accuracy on the DMS task. Percent signal changes in fMRI data revealed statistically significantly increased activation within the right dorsolateral prefrontal cortex (BA 46) for the TBI group compared to controls. Additional alterations in activation were found between groups within the inferior temporal (BA 37) and parietal (BA 7) regions. Regression analyses showed no relationship between neuropsychological testing and percent signal change within BA 46, but predictive relationships between testing and BA 37 and BA 7. Logistic regression analyses suggest that fMRI data did not add any incremental predictive value beyond neuropsychological testing alone when attempting to predict group (TBI vs. OI) membership.

KEYWORDS*:* fMRI, brain injury, TBI, delayed-match-to-sample, DMS

____*Jessica Ann Clark*_____
Student's Signature

_____
Date

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By

Jessica Ann Clark

David T.R. Berry, Ph.D.
Co-Director of Dissertation

Walter M. High, Jr., Ph.D.
Co-Director of Dissertation

David T.R. Berry, Ph.D.
Director of Graduate Studies

(Date)

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In dedication to my wonderful family and friends, without whom this dissertation, doctorate, and graduate school in general, would not have been possible. Thank you for your love, support, and patience throughout this entire journey.

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CHAPTER ONE: INTRODUCTION

Traumatic brain injury (TBI) is a prevalent and devastating problem that can strike individuals of any age, many during the prime of life. According to the Center for Disease Control and Prevention (CDC, 2000), 1.4 million people in the United States sustain a traumatic brain injury per year, resulting in 50,000 deaths, 1.1 million emergency room visits, and 235,000 hospitalizations. TBI research has tended to focus on the assessment of neuropsychological deficits related to TBI, whereas research concerning the adaptation and rehabilitation of these cognitive deficits is comparatively limited and inconsistent. Although paper-and-pencil and computer testing have been the predominant tool of neuropsychologists for many years, new advances in neuroimaging suggest that functional magnetic resonance imaging (fMRI) may be useful for assessment and diagnostic purposes in patients with TBI. The following literature review will examine how fMRI has identified various regions of activation associated with working memory, as well as how these patterns of activation may differ for individuals with TBI. It will conclude by examining the potential for fMRI to be used with TBI patients in the future, including how it may be used in a rehabilitation setting.

First, however, the operation of various types of neuroimaging and how assumptions about brain functioning are made as a result of neuroimaging evidence will be described. The most common techniques used with TBI patients in a clinical setting include computed tomography (CT) and MRI. Although other types of neuroimaging such as positron emission tomography (PET), single proton emission tomography (SPECT), and magnetic resonance spectroscopy (MRS) are used within this population, the main topics to be discussed here will be CT (as most TBI patients receive this type of scan upon hospitalization) and MRI scans.

CT scans are routinely administered to TBI patients upon admission to the emergency room and are considered a standard of care in head injuries (Valadka & Narayan, 1996; Wilberger, 2000). CT scans are two-dimensional X-ray images taken around a single rotational axis. These images are then synthesized into a three-dimensional representation. Reasons contributing to the widespread prevalence of CT scans in this population include cost-effectiveness and ability to scan without restrictions common in other techniques (i.e. metal in the body, use of radioisotopes, etc.). Most important for emergency and acute treatment, however, is the ability of CT scans to detect swelling and bleeds in the brain (Young & Destian, 2002). In addition to identifying brain lesions and fractures in the skull, CT scans have been shown to be predictive of functional status after TBI (van der Naalt, Hew, Zomeren, Sluiter, & Minderhound, 1999; Englander, Cifu, Wright, & Black, 2003), although the associations between early CT scans and cognitive outcomes appear to be only moderate (Sherer, et al., 2006). Sherer, et al. (2006)

demonstrated that although quantitative CT analyses add a great deal of precision in locating lesions, this information did not improve over demographic factors and time to follow commands in predicting early cognitive outcomes for TBI patients. They suggest alternate neuroimaging techniques that are more sensitive to identifying the functional capability of white matter in order to predict cognitive outcome.

MRI is used to obtain a three dimensional representation of the brain without any ionizing radiation and may include both structural and functional images. In contrast to CT scans, MRI allows imaging of soft tissue, thereby making it useful in examining brain areas aside from lesion locations. MRI uses a powerful magnet (at typical strengths of 1.5 or 3 Teslas (T)) to align hydrogen atoms (protons) in the tissue with the magnetic field. Inherent physical properties of atoms within a magnetic field cause protons to spin and align in the same direction ("resonating" at the same frequency). After these protons are aligned, a specialized radiofrequency coil is used to transmit an electromagnetic pulse that perturbs the spin and direction of these protons, transitioning them into an excitatory state. Once excitement reaches optimal resonance, these protons recover and precess back into alignment, and radiofrequency coils "listen" to this recovery. Since different types of tissue (fat vs. muscle vs. water) effect the recovery rate of protons, variations in tissue can be identified based on known rates at which protons recover from excitement. MRI equipment (such as a radio frequency (Rf) head coil in the case of brain scanning) is able to then "listen" to specific frequencies of proton resonance in order to recreate an image. Various "slices" of tissue are accomplished by applying an additional magnetic gradient to the external magnetic field used during the scan. Only one plane within the tissue will have hydrogen atoms that are "on-resonance" (123 MHz) and therefore contribute to the signal being detected. These magnetic gradients are applied in the x, y and z directions of the scanner, thus allowing for axial, sagittal and coronal images, respectively. This procedure allows a structural image of the brain to be recreated.

A slight variation in the physics of the scan allows detection of cerebral blood flow (CBF) for functional imaging (fMRI). Since neurons themselves have no inherent energy reserves (such as glucose and oxygen), they have an immediate need for additional energy after firing. Blood therefore releases more oxygen to active neurons than it does to inactive neurons through hemodynamic processes. The difference between oxygenated and deoxygenated blood can be detected by MRI analyses, leading to blood-oxygen-level dependent (BOLD) fMRI. Through repetition of a task performed by an individual in the scanner, subsequent statistical analyses can be used to determine regions of the brain that demonstrate more of this difference in response to the task. Images obtained from functional images are later superimposed on top of

the structural image of the brain taken during the same scanning session in order to demarcate the location of functioning.

MRI contrasts are achieved in either a T1 or T2 weighted modality. T1 images are collected during a radio-frequency pulse and rapid gradient-echo (MPRAGE); indicating the moment when protons recover from excitement. In this anatomical scan (which serves as the structural scan on which functional images are superimposed), fatty tissue is expressed as variable bright shades of white while water is expressed in darker shades of gray and black. T2 images are collected in functional scans during the course of proton dephasing; a time when protons "fan out" before recovering from excitement. Conversely, in this scan fatty tissue is expressed as darker shades of gray and black while water is expressed as variable shades of white.

As previously mentioned, all fMRI studies rely on the repetition of a task in order to determine regions of the brain that demonstrate a difference in hemodynamic response in reaction to the task. There are two major types of experimental designs in the fMRI literature that deal with these repetitions in different ways. "Block design" is the most frequently used. This design condenses all responses regardless of correctness or stimulus type. While block design studies are shorter in duration, and are therefore less expensive and easier to perform, information regarding specific hemodynamic responses to specific stimuli is lost. Similarly, since activity in response to a task is averaged over time, a brain region that is active for only a short period of time in reaction to a stimulus may not seem active if activation is averaged over several minutes (D'Esposito, 2000; Hillary, et al., 2002). Furthermore, block-designs were initially developed for use with PET scans and do not utilize MRI's superior temporal resolution (Clare, et al., 1999). Conversely, "event-related designs" separately analyze correct and incorrect responses, as well as the specific type of stimulus (i.e. target, distracter, previously studied stimuli, etc.), and allow a single response to be extracted from the hemodynamic response (Hillary, et al., 2002). This design requires more repetitions of stimuli and longer periods of time in the scanner, therefore making it more expensive. However, it provides useful information about the cognitive task being utilized and is often preferred over block design.

MRI techniques have been used to assess various cognitive domains within an adult TBI population. Due to the physics involved in closed head injuries involving acceleration and deceleration, coupled with the boney protrusions within the skull, common areas of injury include the orbitofrontal lobe, inferior and anterior temporal lobe, as well as diffuse axonal injury (McAllister, 1992). It is well recognized that deficits in working memory, which consist of aspects of concentration/attention, memory, and executive functioning, are usually associated

with these injuries. While some fMRI studies examining these cognitive domains in a TBI population have included mild TBI patients, others include moderate to severe TBI.

Working memory is more than the ability to recall information. It can be conceptualized as a domain where attention, memory, and executive functioning overlap. Many times referred to as "cognitive control," this overlap consists of several processes that allow an individual to attend to and evaluate information while simultaneously blocking conflicting or previously used (but now irrelevant) information (Alexander, Stuss, Picton, Shallice, & Gillingham, 2007). Closely associated with the concept of cognitive control is Baddeley's model of a "central executive" (1974, 1981). This theoretical model places attention as a central hub of information processing and focuses on the brain as a central controller of memory. The central executive is therefore responsible for the allocation of resources to process and maintain information in the midst of incoming stimuli. In other words, the model suggests that this attentional control system mediates working memory processes, and that working memory in turn is a fundamental mechanism of executive functioning (Newsome, et al., 2007). Therefore, this model goes beyond signal or target detection and concentrates on the temporary storage of information in the brain, allowing not only for memory processes, but for sustained, divided, and alternating attention (Sohlberg & Mateer, 1987). Studies have also suggested that problems with the attentional central executive system of Baddeley's model account for functional deficits in working memory, and that these difficulties may manifest themselves as deficits in executive functioning on neuropsychological testing (McDowell, Whyte, & D'Esposito, 1997).

As such, the various cognitive domains associated with working memory (i.e. attention and executive functioning) are important to assess when evaluating individuals with moderate to severe TBI. Patterns of activation using fMRI in these domains will first be discussed in healthy normal participants, followed by a discussion of current evidence in adult studies of TBI.

Neuroimaging Literature Involving Healthy Subjects

Great advancements have been made in the past two decades in mapping the brain's attentional networks. Posner & Petersen (1990) explored attention in terms of three major functions: 1) orientation to sensory stimuli, 2) detection of stimuli for conscious processing, and 3) maintenance of sustained alertness. Conscious processing was later described more in terms of executive functioning and attentional control (Posner & Raichle, 1996). This attentional control network largely involves lateral frontoparietal activation, while orientation relies more on medial subregions of the frontal and parietal cortices (Woldorff, et al., 2004). Berger & Posner (2000) have suggested that all three of these networks may contribute in some way to brain pathologies such as Attention Deficit/Hyperactivity Disorder. Dysregulation of the executive function

network contributes to deficits in target and error detection, as well as deficits in more abstract abilities such as inhibition, conflict resolution, and goal-directed behaviors. Similarly, there may be a disactivation of the networks that keep individuals oriented and vigilant.

Since attention can be conceptualized as multidimensional, researchers have attempted to find the underlying neural pathways that correspond to various attentional networks. In examining selective attention, Kastner & Ungerleider (2000) have suggested that attention can simultaneously be a bottom-up function driven by sensory stimuli and a top-down mechanism biasing the signals to which the brain will attend. When multiple stimuli are presented at the same time, the brain does not process each separately. Rather, stimuli interact in a mutually suppressive way. Selective attention thereby functions by increasing stimulus salience (bottom-up) or increasing neural activity to filter unwanted information and attend to the desired stimulus (top-down). For visual stimuli, evidence suggests that posterior regions of the brain such as the extrastriate visual cortex are activated during the processing of visual attributes (i.e. color, angles, size, etc.), while more anterior regions process the selected information as faces or entire objects (Kastner & Ungerleider, 2000; Haxby, et al., 1994; Kanwisher et al., 1997; Grill-Spector, et al., 1998). Visual representations have also been shown to activate the fusiform gyrus (in the case of faces) and parahippocamus (for non-facial objects; Haxby, Gobbini, & Montgomery, 2004).

As selective attention has been shown to increase the neural representation of an object in the extrastriate cortex (which includes visual areas V2-V5), Yantis and colleagues (2002) examined brain activity when attention is shifted from one visual stimulus to another. Extrastriate increases in activation were seen during sustained contralateral attention. Additionally, posterior parietal regions were activated during a shift in spatial attention. This provides evidence that the parietal cortex is associated with a signal to shift spatial attention, and is not responsible for the maintenance of selective attention. Other studies have similarly described the intraparietal and superior frontal cortices as involved with top-down, goal-directed selection of attentional stimuli, while the temporoparietal and inferior frontal cortices act as a “circuit breaker” to shift attention to more salient or unexpected stimuli (Corbetta & Shulman,2002). In a more specific study, visual stimuli were partitioned into cues that were either closely related or disparate (Ng, Noblejas, Rodefer, Smith, & Poremba, 2007). The anterior and posterior cingulate cortices are essential to shifting attention to meaningful stimuli that are closely related, while the prefrontal cortex serves the same purpose for stimuli that are dissimilar. It is thought that the cingulate plays a special role in suppressing irrelevant background information, thereby freeing attentional resources to focus on pertinent cues. A summary of attentional maintenance, filtering, shifting and their respective associated brain areas can be found in Table 1.

The aforementioned studies of selective and alternating attention help to explain how one would be able to selectively maintain information, filter incoming stimuli, and shift attention to other meaningful stimuli as is suggested by Baddeley's model of working memory (1974, 1981). Accordingly, Collette & Van der Linden (2002) conducted a review of functional imaging studies specifically examining the central executive component of working memory. Their research revealed strong evidence for bilateral activation in the middle (BA 46, 9, and 10) and inferior (BA 45, 10, 44, 46, and 47) frontal regions (Cohen, Forman, Braver, Casey, Servan-Schreiber, & Noll, 1994; Mellers, et al., 1995; Petrides, Alivisatos, Evans, & Meyer, 1993). The authors of this review then parsed the concept of the central executive and looked more specifically at its components, namely 1) storage and processing, 2) updating of information for recall, 3) inhibition, 4) shifting, and 5) dual-task coordination. A number of studies taken together indicate the dorsolateral prefrontal cortex (DLPFC; BA 9/46) as the area associated with storage and processing, along with some areas in the ventrolateral prefrontal cortex (VLPFC; BA 44/45/47; D'Esposito, Postle, Ballard, & Lease, 1999; Postle, Berger, & D'Esposito, 1999). Similarly, both the dorsolateral prefrontal cortex (BA 9/46) and the left frontopolar cortex (BA 10) are implicated in updating memory load for recall procedures (Grasby, et al., 1994). Although it is difficult to differentiate between areas activated by the process of inhibition versus other aspects of the task being used such as memory or visual/auditory aspects of the stimuli, inhibition appears to be associated with the middle frontal region (BA 10; Garavan & Stein, 1999) and inferior prefrontal areas (BA 45/44; Konishi, et al., 1998). Shifting of set for stimuli that are not closely related in meaning appears to be linked to prefrontal regions such as the left anterior prefrontal cortex (BA 10 and 8) along with the right dorsolateral prefrontal cortex (BA 9/46; Rogers, Andrews, Grasby, Brooks, & Robbins, 2000). The dual-task coordination component of the central executive appeared to be the most difficult to define, as the studies attempting to examine this aspect all had different results. It is therefore suggested that dual-task coordination may not be dependent upon a specific area of the brain, as it involves the interplay of many specialized systems (Collette & Van der Linden, 2002).

Figure 1shows a visual representation of the Brodmann's Areas mentioned in the aforementioned findings across attention and various aspects of the central executive. Similarly, Table 2 outlines the Brodmann's Areas as approximated across the aforementioned studies. As noted earlier, both attention and other executive functions contribute to working memory. As can be seen in Figure 1, the areas implicated in working memory overlap with those found in selective attention, storage and processing of information, information updating, shifting and alternation of attention, and inhibition. fMRI studies of working memory using *n*-back tasks have

implicated bilateral frontal (BA 44, 6, & 8) and parietal activation (BA 9 & 46; Braver, et al., 1997; Cohen, et al., 1997). These *n*-back tasks involve the serial presentation of digits, and comparison of the currently presented digit to previous digits. For instance, in a 1-back condition, the current digit is compared to the very last digit presented (the digit that is "1-back"). A 2-back condition involves comparison to the digit presented 2 digits prior, etc. Therefore, this requires the maintenance and storage of information, selective attention to incoming information, and mental manipulation in comparing digits. In addition to the prefrontal cortex, both human and primate studies have indicated that the inferior and medial temporal cortex is key to maintaining object representations in visual working memory tasks (Ranganath & D'Esposito, 2005; Desimone, 1996; Chelazzi, Miller, Duncan, & Desimone, 1996; Miller, Erickson, Desimone, 1996). Studies utilizing a delayed-match-to-sample task on healthy adults have also suggested that hippocampal and parahippocampal regions may be important for matching familiar stimuli, as are prefrontal regions especially when there is a high risk of interference (Stern, Sherman, Kirchhoff, & Hasselmo, 2001). Stern, et al. (2001) also found that medial temporal regions are more important for matching novel stimuli.

In order to further clarify the various areas of the brain implicated in human memory, Fletcher and Henson (2001) reviewed studies of functional neuroimaging and identified three regions consistently activated by working memory in the lateral frontal cortex: the ventrolateral, dorsolateral, and anterior. These authors suggests that the ventrolateral cortex is responsible for the updating and maintenance of information, the dorsolateral cortex is responsible for selection, manipulation, and monitoring of that information, whereas the anterior frontal cortex is responsible for the selection of processes and goals. This evidence is consistent not only within studies of working memory, but also with studies of attention that require the same sorts of processes.

In addition to the patterns of activation seen in response to cognitive tasks, an understanding of a fundamental, resting baseline state is important. Raichle, et al. (2000) were among the first to examine this resting state by having participants lie awake in an fMRI scanner with eyes closed. They found that two areas showed greater activation in comparison to mean neural activation, the posterior cingulate/precuneus and the medial prefrontal cortex. Raichle and colleagues (2000) suggest that this "default network" remains active at rest in order to gather information about the environment (i.e. detecting predators), but this network "turns off" in order to allocate resources for successful task performance.

To summarize, although a broad range of cognitive tasks activate the frontal lobe, there seems to be a similar pattern of recruitment of dorsolateral prefrontal cortex, ventrolateral

prefrontal cortex, and the anterior cingulate (Duncan & Owen, 2000). Studies of working memory using both verbal and visual stimuli have indicated activation of the prefrontal and premotor regions of the frontal lobes (mid frontal or inferior frontal gyrus; Christodoulou, et al., 2001). In addition, parietal and temporal regions are important for switching attention and object representation during working memory tasks, respectively.

Literature Involving TBI and fMRI

In reviewing the literature utilizing fMRI in a TBI population, it is important to examine aspects such as how well defined the population is (in terms of demographics, severity, and injury type and location), the study design, task utilized, and strength of the MRI scanner (with higher Teslas able to differentiate finer differences in signal change). In addition to number of participants in each group, it is also important to examine the quality of the control group. While a healthy control group is a readily accessible population, it is widely held that studies should attempt to control for host factors such as personality and behaviors that may have led to the injury. As such, it is preferred that studies utilize control groups such as friends and/or relatives of TBI participants, or orthopedic patients who have not sustained a head injury (generally considered to be the gold standard). Tables 3 and 4 contain information regarding the TBI population involved in each of the following studies. Demographic characteristics of the control group are not statistically significantly different from the TBI group unless otherwise indicated. Table 5 provides details of each study design.

In discussing patterns of activation, changes in the magnitude of signal intensity are compared to a control via statistical analyses. Depending on the type of study, an actual baseline measure of functional activation may have been incorporated into the paradigm. For example, the participant may have been asked to press a button in response to a stimulus not related to the cognitive task. Care is often taken to ensure that key features such as luminosity (for visual tasks) are comparable to the cognitive task stimuli. In studies where a baseline is not incorporated into the paradigm, activation in response to one condition may be compared to another condition (i.e. 1-back vs. 0-back in the case of an *n*-back task) in order to assess the magnitude of change related to the condition of interest. Terms such as “increases” and “decreases” in activation, therefore, typically refer to relative statistically significant differences between TBI and control groups.

The first study to examine activation patterns of working memory in TBI patients was conducted in 1999 by McAllister and colleagues. Twelve patients with mild TBI were assessed one-month after injury and compared to 11 healthy control participants. The study utilized an *n*-back task with three conditions: 0-back, 1-back, and 2-back. Behavioral results indicated that mild TBI (mTBI) individuals performed generally as well as the control group both on the n-back

task and a neuropsychological battery, with some differences in speed and reaction time on the neuropsychological tests. Although behaviorally the two groups looked similar, a look at the underlying neural correlates showed a different pattern. Functional results obtained in a 1.5T scanner indicated that both groups showed significant bilateral frontal and bilateral parietal activation in response to increasing working memory load. Differences were seen, however, between the control and mTBI group across conditions. The controls showed increase in regions associated with working memory from the 0- to 1-back conditions, with minimal increases from 1- to 2-back. Conversely, mTBI patients showed less activation than controls in the 0- to 1-back conditions, but extensive activation as the memory load increased from 1- to 2-back. This difference was most pronounced in the right dorsolateral frontal and right parietal regions, as can be seen in Figure 2. It was also noted that the control subjects activated very focal regions of increased activation, while mTBI patients showed more extensive frontal and parietal increases. The authors postulate that differences in activation across conditions may relate to activation of a working memory network. Once this network is "turned on," normally functioning controls are able to handle moderate increases in working memory load. They suggest that mTBI patients may have difficulty "turning on" this system. McAllister, et al. (1999) also propose that this difference may illustrate a decrease in efficiency in the mTBI patients, and the subjective experience of increased effort may lead to more cognitive complaints in mTBI (compared to more severe injuries) even though neuropsychological testing might not show any deficits.

Christodoulou and colleagues (2001) looked at nine patients with moderate to severe TBI compared to seven healthy controls. A working memory task utilizing a modified version of the PASAT was used in conjunction with fMRI. Based on a previous PET study of severe TBI and an fMRI study of mild TBI, the authors hypothesized that the brains of TBI patients would recruit remote regions within contralateral hemispheres, thus altering the lateralization of cerebral activation. In addition, they hypothesized that adjacent areas to those areas activated in healthy persons would be locally expanded within TBI patients. Behavioral data indicated that TBI patients made significantly more errors on the modified PASAT (d = 0.79), although accuracy data indicated that these TBI patients were able to engage working memory processes during the task (accuracy: TBI = 72.21%; controls = 94.05%).

In order to test their hypotheses using a 1.5T MRI scanner, Christodoulou and colleagues (2001) found that healthy controls had significant activation mainly within the left frontal and left temporal lobes, with bilateral parietal activation. Frontal activation was found mainly within the mid frontal gyrus. The TBI group showed greater right lateralized activation in the frontal and temporal lobes, whereas the control group showed more left lateralization in the same regions.

Evidence of dispersion was also found, as the control group showed frontal activation primarily within the left mid frontal gyrus, whereas TBI patients recruited instead from the inferior frontal, superior frontal, and precentral gyri as seen in Figure 3. Although direct group comparisons did not reach significance, a dispersion index showed significantly more dispersed activation in the TBI group compared to the controls.

Research more closely resembling the current study was conducted by Perlstein and colleagues (2004). They looked at working memory performance in 26 healthy community volunteers, and 16 mild, 8 moderate, and 18 severe chronic TBI patients. A behavioral study examining accuracy and reaction times was conducted for the entire sample, whereas an fMRI study using the same task was later collected for a subset of the sample. The goal was to examine working memory functioning across both a range of severity and a range of working memory load difficulty using an auditory *n*-back task. Behaviorally, the study found that participants made more errors at higher load levels, and that TBI patients made more errors compared to controls at these higher load levels. It was also noted that increased error rates were associated with greater TBI severity, with moderate and severe groups differing statistically significantly from the control and mild TBI groups in the 2- and 3-back memory load conditions. Speed/accuracy tradeoffs and omissions (indicative of inattention to the task) were ruled out as possible explanations of group differences. Researchers also looked at performance of trial-type across participants. The stimuli presented consisted of targets, nontargets, and foils (which were nontargets that had been presented earlier within the response set). Statistically significant differences across all participants indicated more errors to foils than targets, and more errors to foils and targets compared to nontargets. Results also suggest that errors statistically significantly increased with injury severity and that there was an interaction between severity and trial-type, with more errors on foils and targets in the moderate to severe TBI group compared to mild and control groups. Differences in reaction time were also noted across all participants, with slowed reaction times for foils compared to target and nontarget trials. Given this pattern of behavioral data, Perlstein and colleagues suggest that TBI patients are able to maintain representations of the stimuli within working memory; however, TBI patients are unable to use more executive functions to sequence and accurately label stimuli.

Functional data from Perlstein, et al. (2004) was available for a subset of the participants described above (moderate to severe chronic TBI: n = 7; control: n = 7) who underwent scanning in a 3T MRI scanner. Behavioral results collected during the scanning generally paralleled those previously described. Evidence suggested that all participants activated superior and inferior regions of the prefrontal cortex, as is consistent with previous literature on working memory

tasks. Group differences were noted in the posterior parietal region, with TBI patients showing increased activation compared to controls, with no differences as a function of working memory load. However, a group by load interaction was noted in the right dorsolateral prefrontal cortex (BA 46/9), left Broca's area (BA 44), left parietal cortex (BA 40), and anterior cingulate gyrus (BA 32). In TBI patients, these areas showed a reduced increase in the magnitude of signal intensity with increased working memory load compared to controls. Combined with the behavioral data, this suggests that the control participants were able to respond to the increasingly challenging task with increased activation, whereas the TBI patients were unable to do so to the same extent, resulting in significant group differences in accuracy on the 2- and 3-back tasks. It is worth noting that these group differences were not observed within the 0- and 1-back trials, both of which did not require higher order functions such as active maintenance and sequencing of several stimuli. Within the frontal lobes, evidence also suggested increasing activity in the left dorsolateral prefrontal cortex for controls, while TBI showed increases in activity in the right dorsolateral prefrontal cortex. Additionally, the bilateral inferior frontal gyrus was activated for controls, whereas this area was activated on the right side only for TBI patients. A summary of these results can be seen in Table 6.

Using a similar *n*-back task, Newsome, et al. (2007) found a different pattern of activation between 10 severe TBI patients and 6 patients with orthopedic injuries (OI) and no evidence of head trauma. Groups were comparable on task performance. With regard to functional imaging, group differences were found in the 0- versus 1-back task, while no significant group differences were found in 0- versus 2-back. OI patients were found to activate bilateral frontal areas more extensively than TBI in the 0- versus 1-back, while TBI activated posterior regions more extensively than did OI patients. Newsome, et al. (2007) also examined changes in activation over time in the 1-back condition and found that while OI patients decreased bilateral anterior and posterior activation over time (likely corresponding to increased efficiency in response to the task), TBI patients actually increased activation (possibly indicating that they did not benefit from repeated exposure within that condition). These results can be seen in Figure 4. In the 2-back condition, analyses over time indicated that both groups decreased activation in the fusiform and parahippocampal gyri, while only the OI group showed increases in frontal, parietal, and temporal regions. In comparison to the Perlstein, et al. (2004) study, Newsome, et al. (2007) had similar performance on the fMRI task between the TBI and control group. Of note, the addition of the OI group as a control (instead of an uninjured healthy group) may have contributed to the difference in results.

Another study utilizing an *n*-back task was conducted by Sánchez-Carrión, et al., 2008 (a). Eighteen patients with severe TBI were compared to 18 healthy controls composed of family members or friends of the TBI patients. All TBI participants had evidence of diffuse axonal injury (DAI), and researchers excluded any participants with focal lesions. Neuropsychological testing was also conducted, in addition to the *n*-back task in a 1.5T scanner. The TBI group performed statistically significantly more poorly than healthy controls on measures of working memory, including WAIS-III Digits backward, Letter-Number Sequencing, and accuracy in the 2- and 3-back conditions. A direct comparison of TBI to control groups showed statistically significant decreases in activation in TBI participants compared to controls in the right superior and middle frontal cortex, and left sub-gyral regions for the 2-back condition. The 3-back condition showed hypoactivation in TBI participants again in the right superior and middle frontal cortex, as well as the left middle frontal cortex. Correlations between neuropsychological testing and activation of the prefrontal cortex were negative for the control group (higher performance on neuropsychological tests related to lower neural activation in the prefrontal cortex). A positive correlation in the right parietal and left parahippocampus was observed for the TBI group (higher performance on neuropsychological tests was related to greater activation of the prefrontal cortex). These results may indicate that high performers have hyperactivation while low performers have hypoactivation. A summary of these results can be found in Table 7.

In a follow-up study (Sánchez-Carrión, 2008b), 12 of the patients from the previous study were treated in a neurorehabilitation program that utilized physiotherapy, occupational therapy, and neuropsychological intervention. In order to account for practice effects, 10 of the same healthy family and friends of the TBI patients who participated in the first study served as a control group. The purpose of the study was not to examine the effectiveness of the treatment program, but rather to examine neural activation in the same individuals with TBI when performance on cognitive tasks has improved. The same *n*-back task was used as in the previous study, with a span of 6 months between scans. Again, neuropsychological testing was utilized; however, during the second testing, group differences were found for the Digits backward test only. The TBI group had improved on all neuropsychological tests, including 2- and 3-back conditions of the fMRI task. Although the previous study identified areas of hypoactivation within the frontal cortex, this study showed no statistically significant group differences. Paired t-tests between the first and second testing also revealed that the TBI patients showed increased activity in the left inferior frontal gyrus (BA 46 and 47) and the right middle frontal gyrus (BA 9), and that this corresponded to improved working memory scores on both neuropsychological

testing and the fMRI task. Results from the 3-back condition can be seen in Figure 5. Correlations between neuropsychological testing and brain activation were not conducted.

Turner & Levine (2008) designed a study to examine any differential impact of TBI on two different aspects of working memory: executive control versus storage and rehearsal. Eight individuals with moderate to severe TBI, with good functional recovery, were compared to 12 healthy control participants. All participants with TBI had DAI with no focal lesions, and were in the "chronic" stage of recovery, although actual time since injury was unspecified. Using an Alphaspan task in which consonant letter strings were presented (consisting of 3 or 5 letters), participants were asked to either maintain the set (storage and rehearsal) or alphabetize the letters (executive control) during an event-related fMRI scan within a 3T scanner. After a delay, a letter was presented, paired with an ordinal position. Participants responded by pressing one key if the pairing was correct, and another key if the pairing was incorrect. Results revealed that the TBI and OI groups had comparable performance on the task. However, even the best performers within the TBI group had a more extensive pattern of activation. TBI patients had increased activation within the left DLPFC and right VLPFC, as well as areas within the bilateral parietal cortices and the left temporo-occipital junction in comparison to controls. More specifically when the group by executive demand interaction was examined, the TBI group demonstrated increased activation within the bilateral, lateral PFC regions and the left parietal area with increasing demands on executive control. A summary of these findings can be found in Table 8.

As previously mentioned, working memory overlaps with areas of executive functioning. In order to fully address how the neural mechanisms of working memory may be compromised in TBI, it is therefore necessary to also examine evidence from executive functioning tasks. The first study of executive functioning included only one severely injured TBI patient (male, age 46, 1-year post-injury, no evidence of focal lesion) compared to a small control group of 3 women (ages 20-26) and one man (age 44; Scheibel, Pearson, Faria, et al., 2003). The purpose of the study was to examine whether or not severe diffuse TBI increases the extent of frontal tissue recruited for both an *n*-back task (utilizing black and white photos of faces) and an inhibition task focused on cognitive control (utilizing a combination of go-no-go and Stroop tasks). This second task utilized arrows as stimuli in both congruent (non-inhibition) and incongruent (inhibition) conditions. Performance on the *n*-back task was generally comparable between participants, while performance on the inhibition task was slightly worse for the participant with TBI. Using a 1.5T MRI, it was found that frontal activation increased during the 2-back condition relative to the 1-back condition in all participants. However, more extensive activation was found within the TBI patient when compared to the controls. Similarly, frontal activation increased with inhibition

on the arrows task, but was again greater in the participant with severe TBI as is shown in Figure 6. The authors posit that this difference in activation is evidence for the recruitment of additional neural resources for cognitive control.

In a larger follow-up study, Scheibel, Newsome, Steinberg, and colleagues (2007) used the same "arrows" inhibition task as Scheibel, et al.'s 2003 study to compare 14 moderate to severe TBI participants with 10 orthopedic control participants. The TBI group was composed of moderate to severe patients (postresuscitation GCS of 8 or less for severe injuries, and 9 – 12 with associated lesions on CT scans for moderate injuries) in the acute stage of recovery. All participants had cleared from post-traumatic amnesia by the time of the MRI study and had a score of 76 or greater on the Galveston Orientation and Amnesia Test. Previous studies of cognitive control had shown that activation in the anterior cingulate cortex (ACC) was related to conflict monitoring and error detection (MacDonald, Cohen, Stanger, & Carter, 2000; Botvinick, Cohen, & Carter, 2004). Additionally, studies have suggested that the ACC coactivates with the dorsolateral prefrontal cortex on tasks that increase demands on cognitive control (Gehring & Willoughby, 2002). Therefore, Scheibel, et al. (2007) hypothesized that TBI subjects would have a dysactivation of this system. Additionally, they sought to examine the relationship of activation patterns to number and location of focal lesions. Results indicated that the TBI participants showed an alteration in activation within the incompatible condition of the arrows/stroop task. They demonstrated increased activation in the left precentral gyrus and bilateral cingulate, medial frontal, mid frontal, and superior frontal gyri. Scheibel, et al. (2007) suggest that this more extensive activation may reflect increased utilization of neural resources to compensate for cognitive processes that are less efficient. Furthermore, they regressed anterior cingulate and medial prefrontal brain activation with performance accuracy in TBI and found no relationship. Although the TBI participants had greater activation than the orthopedic control group, this likely represents an inefficient utilization of neural processes. Regression of injury severity (GCS) and activation of deep brain structures (basal ganglia, thalamus, anterior cingulate gyrus, & corpus collosum) revealed a negative relationship. The participants with more severe TBI had greater activation, which is consistent with models of DAI in which deep structures are more likely to sustain damage. Scheibel, et al. (2007)found no relationship between number of lesions and patterns of activation. Results are summarized in Table 9.

In order to further examine the effect of TBI severity (as measured by GCS) on brain activity in response to a cognitive control task, Scheibel, et al. (2009) compared 30 individuals with TBI, at approximately three months post-injury, with an OI control group. Brain injury severity was classified as moderate (n=9), severe (n=8), or very severe (n=13). Groups did not

differ in performance on the "arrows" stimulus compatibility task previously described (Scheibel, et al. 2003). Multiple regression analyses revealed that lower GCS scores were associated with greater activation within a midline cluster consisting of the left anterior cingulate, bilateral thalami, basal ganglia, and areas within the frontal cortex (right precentral, inferior frontal, and middle frontal gyri) as seen in Figure 7. Of the GCS components (eye, motor, and verbal), the verbal score demonstrated the best predictive ability. Other variables, such as demographics, education, and premorbid IQ were examined with regard to their ability to predict neural activation as well, but these findings were less consistent. Scheibel, et al. (2009) concluded that over-activation was compensatory and was effective, at least in part, for improving performance.

Another study involving an inhibition task focused on the effect of TBI on the anterior cingulate cortex (ACC) (Soeda, Nakashima, Okumura, Kuwata, Shinoda, & Iwama, 2005). Using a modified Stroop task in a 1.5T scanner, Soeda, et al. (2005) compared 5 TBI patients with cognitive impairments to 11 healthy controls using a block design. All TBI participants were moderate to severe (initial GCS scores between 3 and 9), 1 year post-injury, with evidence of small focal and diffuse axonal damage. No participants showed evidence of massive contusions nor did any undergo neurosurgical procedures. Although there was a trend towards more errors for the TBI group, this difference did not reach significance ($p=0.051$). Results indicated that all participants activated areas typical in response to the Stroop task in healthy subjects, such as frontal (BA 6, 44, & 46), occipital (BA 19 & 37), and parietal (BA 7 & 40) regions. However, the TBI participants showed more regionally dispersed cerebral activation and diminished activity in the prefrontal and parietal regions when compared to the controls. As can be seen in Figure 8, the TBI participants also showed reduced activation in the ACC compared to the control group. Soeda, et al. (2005) postulate that these differences between TBI and controls may be reflective of a decrease in the connectivity of the parietal and prefrontal regions, as evidenced by a decrease in ACC activation. However, no formal connectivity analyses were conducted. Soeda, et al. (2005) suggest that the changes are likely a result of DAI within the TBI subjects and may reflect either cortical disinhibition attributable to disconnection

While the aforementioned studies of executive functioning used variants of the Stroop tasks, other fMRI researchers have focused on the Tower of London task. Rasmussen, et al. (2006) compared a group of 10 male chronic severe TBI patients (GCS 3-7, ages 17-36) to 10 healthy matched controls. Overall results using a 3T scanner indicated activation in the prefrontal cortices and occipital and parietal lobes (the latter two likely associated with perception, interpretation, and planning associated with spatial stimuli) for both control and TBI groups. The TBI group showed a more dispersed pattern of activation within the parietal and frontal lobes.

They also showed greater lateralization towards the right hemisphere, especially within the frontal lobes, when compared to the healthy control group. Rasmussen, et al. (2006) suggest that increased activation along the dorsal occipitoparietal stream in the TBI patients indicates compromised interpretation of spatial relationships that require additional recruitment of cortical resources to perform the task. Although the dorsolateral prefrontal cortex is typically implicated in tasks that require working memory, encoding visual space, and manipulation of spatial information, results here indicate similar areas of activation between the TBI and control groups and suggest that the groups may have used comparable strategies to perform the Tower of London task. However, the ventrolateral prefrontal cortex, an area recently found to be useful in sequencing and manipulating items in short term memory, showed more extensive activation within the TBI group as illustrated by Figure 9. Again, this may be indicative of additional recruitment of cognitive resources to sequence information in spatial working memory.

Cazalis, Feydy, Valabregue, Pelegrini-Issac, Pierot, & Azouvi (2006) also examined the Tower of London in a group of 10 patients with severe TBI compared to a group of 11 healthy controls. Members of the TBI group differed widely in time since injury with a range of 1.5 to 32.3 months (M = 11.3), and were free from focal lesions in the superior part of the brain. Given previous fMRI evidence that brain activation in healthy subjects differed according to performance (Cazalis, et al., 2003), this study sought to assess cortical activation relative to performance on the Tower of London. Therefore, participants were categorized as high performers (accuracy > 70%), standard performers (accuracy 55-70%), or poor performers (accuracy <55%). Similarly, the task was divided into a Control condition (0-1 move necessary to solve the problem), an Easy condition (2-3 moves), or a Difficult condition (4-6 moves). High performers included 4 TBI participants and 5 healthy controls. Poor performers included 6 TBI patients, while 6 healthy controls constituted the Standard performers. Cazalis, et al. (2006) examined various regions of interest to determine the effect of performance on brain activation. As shown in Figure 10, in the left dorsolateral prefrontal cortex the TBI high performers activated a statistically significantly larger area than the TBI poor performers and the healthy standard performers when looking at the Difficult vs. Control contrast. In the anterior cingulate, healthy standard performers activated a statistically significantly larger area than both TBI poor and TBI high performers. Cazalis, et al. suggest that both healthy and TBI high performers are able to use the same problem solving processes using the same cerebral network. It is apparent from the results that although this may be the case, TBI high performers needed to recruit additional areas of activation in order to have comparable accuracy. Poor TBI performers, conversely, were unable to activate the same networks and unable to recruit additional compensatory resources. It

is important to note that this study is greatly limited because of the wide range of participants' time post-injury, which included individuals within the sub-acute stage of recovery.

Synopsis of fMRI Studies on Patients with TBI

Given the heterogeneity of studies just reviewed, these findings will be summarized by breaking them into the following categories: 1) Increased dispersion of activation, 2) Right hemisphere lateralization, 3) Neural areas in which there is increased activation, and 4) Regions in which there is decreased activation. Obviously, the increases and decreases in activation represent opposite findings and possibilities for this contrast will be discussed.

Many of the studies discussed here suggest that TBI individuals show a more dispersed pattern of activation when compared to controls (Christodoulou, et al., 2001; Soeda, et al., 2005; Rasmussen, et al., 2006). TBI individuals appear to activate similar areas as controls, but often show larger cluster sizes on fMRI scans. This suggests that TBI participants likely activate the same neural networks as control participants, but may need the additional recruitment of cognitive resources to complete the same task. It is important to note, however, that this explanation is based on a pattern of results rather than actual connectivity analyses to look at the neural networks themselves.

As previously mentioned, three studies have suggested that TBI participants may have greater right hemisphere lateralization (Perlstein, et al., 2004; Christodoulou, et al., 2001; Rasmussen, et al., 2006). It should be noted that these three studies included moderate to severe (Perlstein, et al., 2004; Christodoulou, et al., 2001) or severe (Rasmussen, et al., 2006) TBI samples in the chronic phase of recovery. All studies included a healthy control group, and therefore may not account for any predisposing variations in brain activity such as personality factors and risk taking behaviors.

Across the aforementioned studies, many appear to indicate an increase in activation within the frontal lobes in TBI patients compared to controls (McAllister, et al., 1999; Christodoulou, et al., 2001; Perlstein, et al., 2004; Scheibel, et al., 2007; Rasmussen et al., 2006; Cazalis, et al., 2006; Turner & Levine, 2009; Scheibel, et al., 2009; and Sanchez-Carrion, 2008b), including what the authors describe as the medial, middle, superior frontal gyri and the dorsolateral and ventrolateral prefrontal cortex. Increases in activation in the parietal lobe have also been found in TBI compared to control groups in several studies (McAllister, et al., 1999; Perlstein, et al., 2004; Newsome, et al., 2007; Rasmussen, et al., 2006; Turner & Levine, 2009). Some evidence suggests that this activation in TBI patients appears to increase over time and is more prominent in TBI participants who are performing well. Taken together, this may suggest

that TBI individuals who are able to recruit additional neural resources to perform a task are able to compensate for any inefficiency in processing and perform well on a task.

In contrast, approximately half of the studies show a decrease in activation in the same frontal and parietal areas, as well as the anterior cingulate cortex (Perlstein, et al., 2004; Soeda, et al., 2005; Cazalis, et al., 2006; Newsome, et al., 2007; Sanchez-Carrion, et al., 2008). It has been noted across these studies that this decrease may correspond to an increase in task demands (such as an increase in memory load or the need for more executive functions in the course of a working memory task). It has also been suggested that TBI patients are often less able to respond to increasingly challenging tasks with increased activation (Perlstein, et al., 2004).

In support of this theory, performance on the aforementioned studies can be examined with regard to patterns of activation. For studies in which the TBI and control groups showed comparable performance on the fMRI task, patterns of activation generally suggested increased activation for the TBI group compared to controls (McAllister, et al., 1999; Newsome, et al., 2007; Sanchez-Carrion, et al., 2008b; Turner & Levine, 2008; Scheibel, et al., 2003; Scheibel, et al., 2007; Scheibel, et al., 2009; Rasmussen, et al., 2006). This is not completely consistent, however, as some studies show increased activation in *some regions* for the TBI group over controls even when TBI group performance on the fMRI task was statistically significantly worse than controls (Christodoulou, et al., 2001; Perlstein, et al., 2004). Nevertheless, studies in which the TBI group showed a general pattern of decreased activation in comparison to the control group all demonstrated statistically significantly worse performance for the TBI group on the fMRI task when compared to controls (Perlstein, et al., 2004; Sanchez-Carrion, 2008a; Soeda, et al., 2005).

Evidence from research involving fMRI, neurocognitive rehabilitation, and patients with TBI provides additional information that may be used to understand the relationship between patterns of activation and behavioral performance. This will be further discussed in the synopsis of the next section.

Neuroimaging, Rehabilitation, and TBI

In essence, trends from studies thus far involving TBI and fMRI have suggested that the typical patterns of activation seen in normal healthy samples in working memory tasks are disrupted in those who have TBI. There is some evidence to suggest that individuals with TBI who perform relatively well on cognitive tasks are able to recruit additional neural resources in order to complete cognitive tasks. There is also evidence to suggest that a decreased activation may correspond to an inability to perform well cognitively. Therefore, from a practical standpoint it is interesting to address whether or not individuals with TBI might be retrained to

perform well on cognitive tasks. The question then becomes: How might the brain respond when an individual with TBI undergoes cognitive rehabilitation?

Neuronal plasticity and reorganization is a concept initially examined in animal models. Kolb & Gibb (1991) examined the effect of frontal lesions in rodents on dendritic branching in the sensorimotor, visual, and temporal cortices four months after the injury. They found that there was significantly increased arborization in the parietal cortex as a result of exposure to an enriched environment. This correlated with improvement in forelimb reaching and spatial learning. Interestingly, the authors found that the sensorimotor cortex adapted to support functions usually seen within the prefrontal cortex, suggesting that the brain found ways to compensate for the initial loss of functioning. More recent studies of motor functioning have shown similar results, suggesting that recovery includes structural and functional changes in areas of the brain remote from the actual focal injury itself (Nudo, 2006). This suggests that the entire cortex plays a part in altering the networks involved in growth and repair.

Laatsch, Little, & Thulborn (2004) have specifically examined the effect of rehabilitation via fMRI, and have found results similar to those described above in which the brain showed reorganization in a compensatory manner. This case study involved a TBI individual who underwent a cognitive rehabilitation program, in which she attended 27 one-hour sessions over 8 months. A metacognitive approach to rehabilitation was used, in which cognitive abilities such as attention and concentration were targeted, and effort was made to increase the participant's awareness of her strengths and deficits. Improvement was noted on some neuropsychological tests of visual scanning, processing speed, as well as memory of reading material. Additionally the magnitude and distribution of brain activation changed between pre- and post-training fMRI scanning, using a functional task involving visual saccades and reading comprehension. New areas of activation with more intensity were seen near the areas of damage during the post-training fMRI on tasks of language and eye movement, which corresponded with improvement on neuropsychological testing.

In a slightly larger follow-up with 5 mild TBI (MTBI) participants, Laatsch, Thulborn, Krisky, Shobat, & Sweeney (2004) used a similar protocol to that just described. They found significant diversity within their subjects, with results presented in multiple baseline design. All subjects demonstrated improvement on at least one neuropsychological measure, and improvement of at least one standard deviation in half of the cognitive measures administered. Interestingly, the MRI results showed polar opposite, yet sensible, patterns of activation. One pattern was an increase in activation in the post-training scan compared to the pre-training scan. This makes sense because the brain would need to recruit additional resources in a compensatory

effort to increase ability. On the other hand, another pattern showed a decrease in activation, which also makes sense if the areas of activation seen initially were then working more efficiently as a result of rehabilitation efforts. It is important to point out that this sample of 5 individuals differed in time post-injury (2 to 24 months), and history of neurologic disorders. In addition, participants received differing hours of rehabilitation (varying from 12 to 24 hours).

Miotto, et al., (2006) examined 15 normal right-handed individuals to assess for the effect of strategic semantic cognitive training. Although these individuals had not sustained brain injury, the authors felt that an understanding of the underlying neural mechanisms associated with training would lead to a better understanding of recovery processes in brain injury. Using fMRI, they found that there was a significant increase in activation in the bilateral dorsolateral prefrontal cortex and orbitofrontal area after training, which correspond to areas known to be related to semantic processing and verbal encoding.

Westerberg & Klingberg (2007) took a similar approach involving three healthy adults undergoing computerized working memory training. Results indicated that performance on working memory tasks gradually improved after 5 weeks of training, with 4-6 days of training per week. Improvements lasted several months and generalized to non-trained working memory and reasoning tasks. Significantly increased activity related to working memory tasks was seen in the middle and inferior frontal gyrus. These changes in cortical activity were described as increases in the extent of the area of activated cortex and were not due to activations of additional areas of cortex. Group analysis also indicated increased activations of prefrontal and parietal cortices after training, suggesting neural plasticity as a result of working memory training (Olesen, Westerberg, & Klingberg, 2004).

In a study examining the plasticity of the attentional network after brain injury and cognitive retraining, Kim, et al. (2009) utilized a four-week cognitive rehabilitation paradigm. Computerized software was used consisting of 10 different tasks designed to train visual attention, auditory attention, vigilance, divided attention, and persistence. Each module had multiple subcomponents and multiple levels of task difficulty. Ten individuals with moderate TBI participated. All had evidence of DAI and focal injury, and time since injury ranged from 3-57 months. Fifteen healthy control participants were used as a comparison. A pre-training fMRI scan was conducted, followed by 4 weeks of training at 30 minutes per session three times per week, followed by a post-training fMRI. Only members of the TBI group participated in training. The fMRI scan utilized a visuospatial attention (vigilance) task, and baseline performance indicated statistically significantly lower results for TBI patients. Compared to controls at baseline, the TBI group showed greater activation in frontal and temporal parietal regions, and

less activation in the anterior cingulate, supplementary motor cortex, and temporooccipital region. Results suggested that, following training, TBI participants improved their performance on the visuospatial attention task and decreased activation in the bilateral middle and inferior frontal gyri and parietal regions, especially on the right. However, increased activation was found in the anterior cingulate, precuneus, and cerebellum. Unfortunately, group comparisons of the post-training scan were not presented, making interpretation of post-training activity difficult to interpret.

In the largest study on fMRI, TBI, and rehabilitation to date, Strangman and colleagues (2008) attempted to find fMRI predictors of memory rehabilitation outcomes. A group of 54 individuals who had sustained TBI of any severity (45% severe) and were at least 12 months post-injury was included in the study. Neuropsychological testing was conducted and fMRI scans utilizing a memory for word-list task were performed. Patients then went through 14 sessions of group memory interventions, including learning internal memory strategies as suggested by evidence-based practice standards. Patients then underwent neuropsychological testing immediately following the intervention, and one month post-intervention. No repeat fMRI was conducted. Regression analyses were conducted to examine the predictive value of fMRI within regions of interest established a priori, using HVLT-R and Rivermead Behavioural Memory Test-II scores as outcome variables. Results indicated that functional outcome was predicted by the magnitude of activation within the left VLPFC, even after accounting for variables such as demographics and injury severity. Interestingly, this relationship appeared to be quadratic, with subjects who underactivated the VLPFC performing poorly on neuropsychological measures, and patients who overactivated the VLPFC to a high extent performing poorly on neuropsychological measures. The authors posit that those who underactivated may have had damage to gray or white matter within the VLPFC and were unable to fully utilize this area, whereas those who overactivated may have unsuccessfully attempted to compensate for damage in other areas.

Synopsis of Neuroimaging, Rehabilitation, and TBI

The fMRI and cognitive rehabilitation results are clearly limited by the small number of studies, the small sample within most studies, and the lack of well-defined samples. Although most of the results from these studies indicate an increase in activation due to additional recruitment of neural resources, there is also some evidence to suggest that a rehabilitated brain works more efficiently and therefore activation decreases in response to more efficient processing. Therefore, the addition of the Strangman, et al. (2008) study provides insight into not only the effect of rehabilitation on patterns of neural activation, but also the discrepancy between patterns of activation within fMRI and TBI studies more generally. The inclusion of a large

number of subjects of differing severity and lesion location allows for an examination of the relation of fMRI and behavioral and/or neuropsychological test performance. The quadratic relationship described by Strangman, et al. (2008) may accurately describe this association, but it is often unseen in smaller studies because of understandable attempts to maintain homogeneity by including similar injuries and performance. However, the "inverted-U" relationship may help explain why some studies show deactivation of neural areas for TBI groups, while other studies show increased activation of similar areas for TBI groups. If behavioral or neuropsychological test performance is poor, brain regions may be underactivated due to an inability to recruit the appropriate neural resources (possibly because of damage to that region), or overactivated due to unsuccessful efforts to recruit compensatory resources. Alternatively, those who are able to recruit adequate neural resources to compensate for their deficits would show greater activation than control participants who do not need additional compensation. However, this pattern is not always apparent due to small samples and homogeneity of TBI participants.

Similarly, the field of cognitive rehabilitation itself is controversial due to a number of inconsistent findings. Numerous comprehensive reviews have been conducted in order to try to come to an understanding of the rehabilitation literature (i.e. Carney, et al., 1999; Cicerone, et al., 2000; Cicerone, et al., 2005; Riccio & French, 2004). These studies have attempted to organize the literature by looking at the cognitive domain being targeted, the number of studies, as well as the quality of the study. They have taken into account the number of participants, the presence and nature of a control group, as well as study design. However, despite attempts at elucidation improvements as a result of cognitive rehabilitation remain confusing.

After reviewing the literature on the remediation of attentional deficits, Cicerone and colleagues (2000, 2005) recommend attention strategy training as a professional "standard" in the treatment of individuals with attention problems in the post-acute phase of TBI recovery. Studies suggest an improvement on neuropsychological test scores, with greater benefit on more complex tasks requiring selective or divided attention (Sturm, Wilmes, & Orgrass, 1997), whereas basic reaction time and vigilance do not seem to improve as much (Ethier, Braun, & Baribeau, 1989; Sturm & Wilmes, 1991; Gray, Robertson, Pentland & Anderson, 1992; Sturm, Wilmes, & Orgrass, 1997). This same review specifically did not recommend remediation of attentional deficits during the acute phase of recovery (less than a year post-injury), due to insufficient evidence that the treatment, and not spontaneous recovery, was responsible for gains in attentional performance.

Rational for Current Study

Given this background, many avenues of scientific research aimed at helping those with TBI exist. First, although studies involving fMRI and TBI have been conducted, they are few in number since fMRI is a relatively new and expensive technology. These studies that have been conducted up until this point differ in the definition of their TBI samples and the nature of a control group (i.e. orthopedic patients, friends and family of TBI patients, healthy controls). Although possible theories to explain the inconsistencies in results across studies exist, further investigation is necessary to clarify the disruption seen in the cognitive processing of working memory tasks in TBI patients.

In terms of previous study designs, as indicated in Table 5, most studies define working memory as performance on an *n*-back task. Most of the MRI images are acquired using a 1.5T scanner; however, stronger magnets allowing for increased signal-to-noise ration and a finer resolution of images are becoming more readily available. Most of the previous studies rely on a block-design methodology. Although this design is faster and less expensive, it does not allow for the analysis of neural activation in reaction to different types of stimuli, nor does it allow for the analyses of correct vs. incorrect responses.

The ability to analyze the hemodynamic response to specific types of stimuli is important for several reasons. For example, how individuals with TBI respond to the repetition of information (e.g., previously studied material) has far reaching implications for rehabilitation and treatment of their cognitive deficits. Many cognitive rehabilitation programs rely on repeated presentation of information to retrain attentional and memory processes. In addition, compensatory strategies are often based on repeated exposure to material, schedules, and settings. Newsome, et al. (2007) suggested that an increase in activation within TBI patients (relative to a decrease in controls) within a relatively easy condition of their auditory *n*-back task was indicative of a diminished ability to benefit from repeated exposure to the stimuli. However, the block-design of the study and the *n*-back task itself allows only limited inferences to be drawn from the results. The block-design increases statistical power and is easy to implement, but the temporal resolution is limited to tens of seconds. Furthermore, the task and design do not allow for analyses of information across presentations (i.e. neural and behavioral activity during the initial presentation of the stimulus, 2nd presentation, and 3rd presentation), or for a comparison of activation between different stimulus types presented within the same paradigm (novel stimuli vs. previously studied stimuli). Therefore, an event-related study that allows researchers to look at activation patterns in relation to specific stimuli would be beneficial.

The present study aims to address the above noted issues by using event-related methodology, a 3T scanner, and a working memory task different from those used in previous studies. In includes neuropsychological test data to further examine the relationship between scores on these tests and the underlying cortical mechanisms associated with working memory.

DMS Task

The present study utilized a delayed-match-to-sample (DMS), event-related fMRI paradigm described below. The DMS task has been a classic paradigm used in studying neural mechanisms underlying working memory for decades, especially in monkey physiology studies (e.g. Goldman-Rakic 1997). A typical DMS task has a delay period, with blank visual stimulus, between target stimulus and test stimulus. Miller & Desimone (1994) applied a DMS paradigm with both matching targets and non-matching distracters during delay period. They reported "target enhancement" and "repetition suppression" cells in frontal and temporal cortices in monkeys' brain. Using fMRI, Jiang et al., (2000) found similar findings in the human frontal and temporal cortices when matching studied faces.

Recent literature on working memory has shown that the temporal cortex, along with the prefrontal cortex, plays important roles in suppressing distracters during working memory (see Ranganath, 2006 for review). The current version of the DMS task requires the participant to identify visual match targets among non-matching distracters. Adding a level of complexity to the task, both matching targets and non-matching distracters may be new or may have been studied prior to the task as part of the protocol, The DMS task is known to activate areas similar to those involved in working memory and cognitive control tasks. As with the aforementioned studies involving the processing of objects and faces in selective attention, the DMS task has indicated sustained frontal and temporal fMRI responses with regard to studied target detection (Jiang, Haxby, Martin, Ungerleider, & Parasuraman, 2000). Using both new and studied visual objects, Jiang and colleagues (2007) reported thatthe DMS task activated working memory areas BA 6, 9, 10, and 8 within the frontal cortex of normal healthy adults. Additionally, activation was seen in the fusiform, parahippocampus, hippocampus, middle and superior temporal sulcus, precuneus, cingulate, and occipital regions. Recall that the extrastriate cortex has been implicated in the processing of visual attributes (Kastner & Ungerleider, 2000). Similar evidence has shown a suppressed response in the superior frontal gyrus, midtemporal, and occipital areas that are thought to encode the prior presentation of a stimulus (Soto, Humphries, & Rotshtstein, 2007). This indicates that repetition of information translates into more efficient processing of stimuli. It also suggests that training processes that include repetition may result in a more efficient processing of stimuli.

Preliminary Studies

Recently conducted DMS studies first examined frontal interactions between repetition effects and working memory in young adults (Jiang, unpublished data). Results indicated that inferior and mid frontal regions are modulated by both working memory and the prior learning of objects. The study was then furthered by examining age related alterations in memory networks among normal-aging, older adults. Results indicated differential cortical changes in the frontal and posterior cortices of older adults during the DMS task, while behavioral testing showed age-equivalent memory performance. This suggests that older adults alter neural pathways in a compensatory manner. Pilot data have also indicated differences in older adults who are aging normally versus those with some form of pathological aging, such as mild cognitive impairment (MCI). Preliminary results suggest that those with MCI, as well as older adults with poor memory performance, are unable to make the same compensatory adaptations as healthy normal-aging adults.

Figure 11 shows the comparison of the brains of older and younger adults on the DMS task proposed in the current study. It can be seen that the activation patterns are typical for working memory tasks, and that patterns in the expected regions are different for older versus younger participants.

Although there is no literature as of this writing using a DMS task with a TBI sample, working memory studies in TBI show findings consistent with DMS aging studies. For example, the more dispersed activation patterns found in TBI are similar to compensatory patterns found in studies on aging. Research has shown that brain activation in normal aging participants looks quite different from that of young participants, suggesting that the brain finds new ways to compensate and maintain cognitive functioning when faced with gradual aging and decline. Similar to the McAllister, et al. (1999) study of mild TBI compared to uninjured controls, Jiang, et al., (2007), have suggested that while accuracy in a working memory task remains relatively consistent across ages, younger participants show more localized and intense activation, while activation in older individuals is more diffuse and less intense. This suggests that cortical alterations occur as individuals age, and that recruitment of more neural pathways by older individuals allow them to have behavioral responses similar to younger individuals (Jiang, et al., 2007; Davis, et al., 2007; Cabeza, 2002).

Similar results have been suggested by pilot data involving normal aging older participants and those older participants suffering from Mild Cognitive Impairment (MCI; Clark, et al., 2007). MCI individuals show a reduction in both cortical activation and behavioral performance (as measured by accuracy and reaction time), suggesting that these individuals are

unable to recruit the neural pathways needed to sustain performance equivalent to that of normal aging participants.

Purpose of Present Study

The present study is a cross-sectional investigation into the cortical activation of working memory in TBI individuals and the correlation of this activation to paper-and-pencil neuropsychological tests. It is intended to 1) examine performance on behavioral aspects of the DMS task (accuracy and reaction time) within individuals with TBI and an OI comparison group; 2) compare patterns of neural activation associated with the processing of visual information related to recognition and working memory; and 3) correlate this information with neuropsychological test data.

It was hypothesized that 1) TBI participants would activate similar areas shown to be involved in preliminary studies using the current DMS task, namely working memory areas within the frontal cortex as well as the fusiform, parahippocampus, hippocampus, middle and superior temporal sulcus, precuneus, cingulate, and occipital regions. However, it was also thought that TBI individuals would show increased activation compared to controls in the frontal and parietal areas. Although the literature is mixed with regard to activation versus deactivation due to the reasons already discussed, the current sample, by design, consists of individuals who are highly functioning enough to engage in a relatively demanding and fast-paced delayed-match-to-sample paradigm. Therefore, it was predicted that the current sample would include participants with relatively good outcomes, and would consequently show a pattern of greater activation. It was hypothesized that 2) TBI participants would show a positive correlation between neuropsychological test performance and brain activation, with better performance related to increases in activation in BA 7, 9/46, and 10. This is because it was anticipated that the better a TBI participant is able to perform on neuropsychological tests, the better he or she would be able to recruit the additional neural resources needed to compensate for deficits. The brain regions were chosen because of the literature implicating the involvement of the frontal and parietal areas in working memory tasks. It was hypothesized that 3) controls would show a negative correlation between neuropsychological testing and brain activation, with decreased activity in similar frontal and parietal areas, because they were not anticipated to need additional compensation. Therefore, the better the neuropsychological test performance, the more efficiently they would be able to perform the fMRI task.

Furthermore, as an exploratory component, aspects of the fMRI (delayed-match-to-sample) task were examined in relation to neural response. These included novelty of stimulus types (studied versus new) and match type (match versus non-match) as explained below.

Table 1.
Brain Regions Associated with Various Aspects of Attention

Aspects of Attention	Associated Brain Regions	Description
Maintenance	Extrastriate visual cortex	• Sustained attention • Bottom-up processing of visual attributes for selection
Filtering	Intraparietal regions Superior frontal cortices Cingulate	• Top-down, goal-directed selection of information • Suppressing irrelevant background information
Shifting	Temporoparietal region Inferior frontal cortices	• "Circuit breaker" to shift attention
	Anterior & posterior cingulate	• Shifting attention to meaningful stimuli (closely related)
	Prefrontal cortex	• Shifting attention to stimuli that are dissimilar

Table 2.
Summary of BA's for Various Cognitive Functions

Cognitive Function	BA 6	BA 7	BA 8	BA 9	BA 10	BA 17	BA 18	BA 19	BA 20	BA 21	BA 32	BA 37	BA 40	BA 44	BA 45	BA 46	BA 47
Selective Attention				X		X	X	X	X	X		X					
Storage & processing				X										X	X	X	X
Updating information				X	X											X	
Shifting	X	X	X	X	X				X				X			X	
Inhibition					X									X	X		
Working Memory	X	X	X	X				X		X	X	X		X		X	

Table 3.
TBI Group Demographics for Working Memory Studies

Study	**N (TBI)**	**Severity**	**Gender**	**Age** M(SD) Range	**Edu** M(SD) Range	**GCS** M(SD) Range	**Time Post-Injury** M(SD) Range
Sanchez-Carrion, et al., 2008 (a)	18	Sev	12 M 6 F	23.6(4.7) N/R	11.3(2.5) N/R	<9* N/R	224.9(125.1) days 6-18 mos.
Sanchez-Carrion, et al., 2008 (b)	12	Sev	8 M 4 F	24.4(4.8) N/R	11.6(2.8) N/R	4.9(1.6) N/R	263.9(123.2) days 12-24 mos.
Turner & Levine, 2008	8	Mod-Sev	6 M 2 F	32(6) N/R	15(1) N/R	9 (8.3-9.4)	"chronic"
Newsome, et al., 2007	10	Sev	N/R	21.7(2.0)	12.3(2.0) N/R	3.6(0.84) 3-5	12-18 wks. 4.2(2.0) mos.
Perlstein et al., 2004	7	Mod-Sev	5 M 2 F	42.0(4.68) 21-52	13.6(0.71) N/R	≤12* N/R	108(49) mos. 14-384 mos.
Christodoulou, et al., 2001	9	Mod-Sev	5 M 4 F	32.67(10.86) N/R	13.89(1.69) N/R	5.71(2.14) N/R	51.33(41.07) mos.
McAllister, et al., 1999	12	Mild	6 M 6 F	29.4(10.2) N/R	15.2(3.7) N/R	13-15 N/R	22.1(10.5) days

* Not an average – all subjects less than this value
Edu=Education (years)
Mod=Moderate
Sev=Severe
N/R=Not Reported

Table 3 (cont).
TBI Group Demographics for Working Memory Studies

Study	Control	Matched	Injury Type Location
Sanchez-Carrion, et al., 2008 (a)	18 Healthy Friends/Family	Yes	DAI - No focal lesions
Sanchez-Carrion, et al., 2008 (b)	10 Healthy Friends/Family	Yes	DAI - No focal lesions
Turner & Levine, 2008	12 Healthy	Yes	DAI - No focal lesions
Newsome, et al., 2007	6 OI	Yes	9 Pts. had lesions in various locations
Perlstein et al., 2004	7 Healthy	Yes	N/R
Christodoulou, et al., 2001	7 Healthy	Control Sig.Older 16.17(1.83)	3 Pts. had lesions in various locations
McAllister, et al., 1999	11 Healthy	Yes	No focal lesions

N/R=Not Reported
OI=Orthopedic Injury controls
DAI=Diffuse Axonal Injury

Table 4.
TBI Group Demographics for Executive Functioning Studies

Study	N (TBI)	Severity	Gender	Age M(SD) Range	Education M(SD) Range	GCS M(SD) Range	Time Post-Injury M(SD) Range
Scheibel, et al., 2009	30	Moderate, Severe, & Very Severe	N/R	46.3(7.3) 22.5(4.0) 24.1(7.0)	14.6(2.7) 13.5(2.5) 12.5(1.9)	12.7(1.2) 6.6(1.3) 3.15(0.3)	0.31(0.06) 0.30(0.04) 0.34(0.10)
Scheibel, et al., 2007	14	Moderate-Severe	11 M 3 F	31(14) N/R	13(2.2) N/R	≤8* 9-12	3.9(0.9) mos. N/R
Rasmussen, et al., 2006	10	Severe	10 M	25** 18-30	N/R	7** 3-7	4 yrs.** 1-6 yrs.
Cazalis, et al., 2006	10	Severe	5 M 5 F	27.7(N/R) 18-41	15.3(N/R) 12-20	≤8* N/R	11.3(N/R) mos. 1.5-32.3 mos.
Soeda, et al., 2005	5	Severe	3 M 2 F	29.8(6.4) 24-38	13.6(1.7)	N/R 3-8	45.6 (28.7) mos. 1-7 yrs.
Scheibel, et al., 2003	1	Severe	1 M	46	14	7	1 yr.

* Not an average – all subjects less than this value
**Median values
N/R=Not Reported

Table 4 (cont).
TBI Group Demographics for Executive Functioning Studies

Study	Control	Matched	Injury Type Location
Scheibel, et al., 2009	10 OI	N/A	DAI & lesions in various locations
Scheibel, et al., 2007	10 OI	Yes	Lesions in various locations
Rasmussen, et al., 2006	10 Healthy	Yes	DAI & lesions in various locations
Cazalis, et al., 2006	11 Healthy	Yes	DAI only – No focal lesions
Soeda, et al., 2005	11 Healthy	Yes	Small focal lesions; DAI; No massive contusions
Scheibel, et al., 2003	N/A	N/A	Intraventricular hemorrhage; No focal contusions

N/R=Not Reported
OI=Orthopedic Injury controls
DAI=Diffuse Axonal Injury

Table 5.
Study Details for All Studies Reviewed

Study	Task Utilized	Cognitive Domain Targeted	Design	Type of Magnet
Sanchez-Carrion, et al., 2008 (a)	*n*-back (numbers) 0, 1, 2, & 3 back conditions	Working Memory	Block-design	1.5T
Sanchez-Carrion, et al., 2008 (b)	*n*-back (numbers) 0, 1, 2, & 3 back conditions	Working Memory	Block-design	1.5T
Turner & Levine, 2008	Alphaspan task	Working Memory	Event-related	3T
Newsome, et al., 2007	*n*-back (faces) 0, 1, & 2 back conditions	Working Memory	Block-design	1.5T
Perlstein et al., 2004	*n*-back (letters) 0, 2, & 3 back conditions	Working Memory	Event-related	3T
Christodoulou, et al., 2001	Modified PASAT	Working Memory	Block-design	1.5T
McAllister, et al., 1999	*n*-back (letters) 0, 1, & 2 back conditions	Working Memory	Block-design	1.5T
Scheibel, et al., 2009	Arrows Task (Strook inhibition task)	Executive Functioning	Block-design	1.5T
Scheibel, et al., 2007	Arrows Task (Stroop inhibition task)	Executive Functioning	Block-design	1.5T
Rasmussen, et al., 2006	Tower of London	Executive Functioning	Block-design	3T
Cazalis, et al., 2006	Tower of London	Executive Functioning	Block-design	1.5T
Soeda, et al., 2005	Stroop	Executive Functioning	Block-design	1.5T
Scheibel, et al., 2003	Arrows Task (Stroop inhibition task)	Executive Functioning	Block-design	1.5T

Table 6.
Summary Perlstein, et al., 2004

TBI Group:	More errors than control group at higher memory loads.
	Increased activation within posterior parietal region and R DLPFC.
	Decreases in R DLPFC (BA 46,9), L Broca's area (BA 44), L Parietal (BA 40), and anterior cingulate (BA 32) only with increased memory load (Group x memory load interaction).
	Some R lateralization.

Table 7.
Summary Sánchez-Carrión, et al., 2008 (a)

TBI Group:	Poorer performance on working memory measures, including fMRI task. Decreased activation in R superior & mid frontal cortex for 2-back condition. Decreased activation in R superior & mid frontal cortex, & L mid frontal cortex for 3-back condition. Correlations between neuropsych testing and activation: negative for controls, positive for TBI.

Table 8
Summary of Turner and Levine, 2008

TBI Group:	Comparable group performance on fMRI Alphaspan task.
	Increased activation within L DLPFC, R VLPFC, bilateral parietal, and L temporo-occipital areas.
	Greater activation within bilateral, lateral PFC and L parietal cortex in response to greater demands on executive control.

Table 9.
Summary of Scheibel, et al., 2007

TBI Group:	Comparable performance on fMRI task.
	Increased activation in L precentral gyrus & bilateral cingulate.
	Increase in medial, middle, and superior frontal gyri.
	Negative correlation between GCS and increase in activation in deep brain structures.

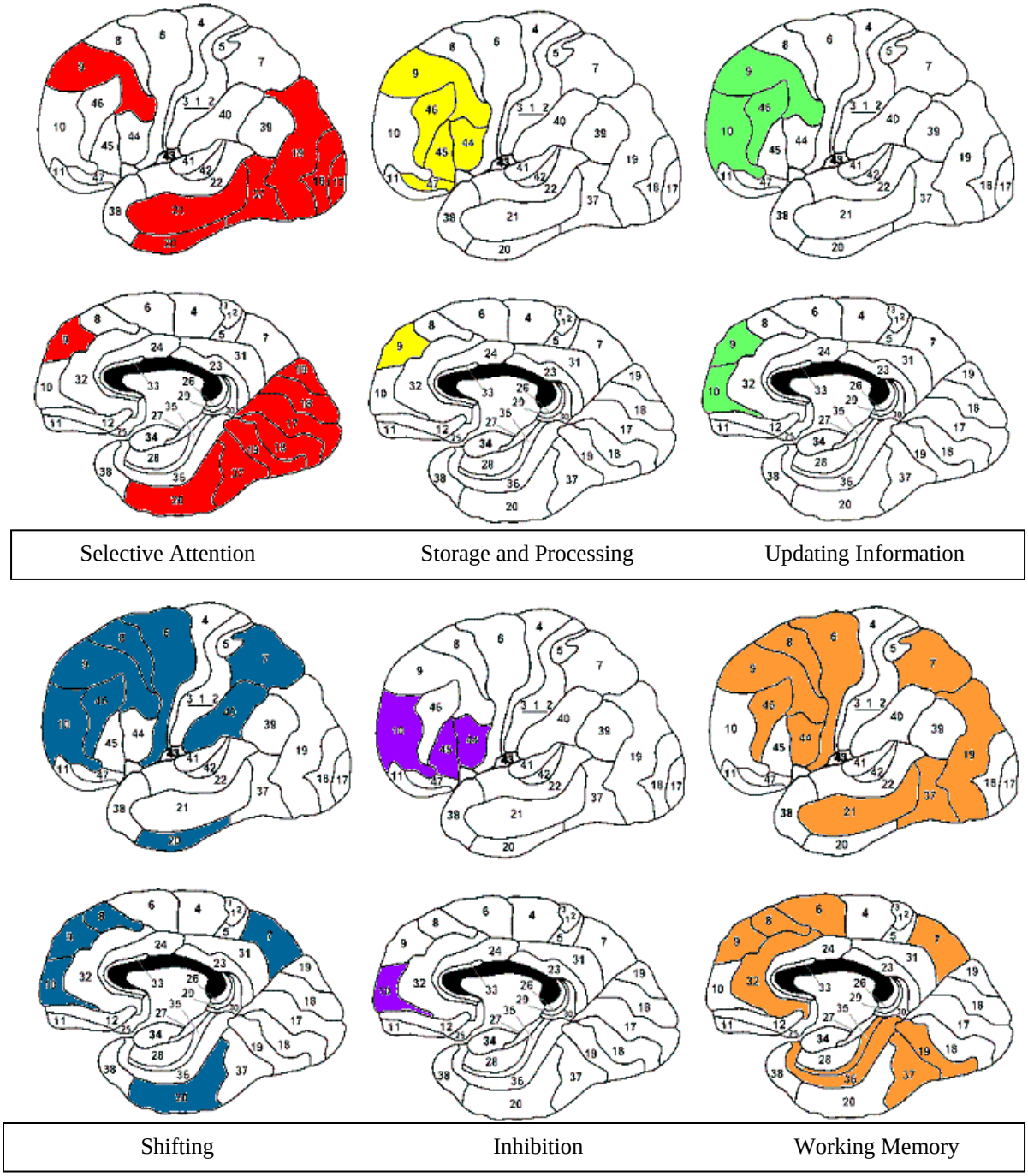
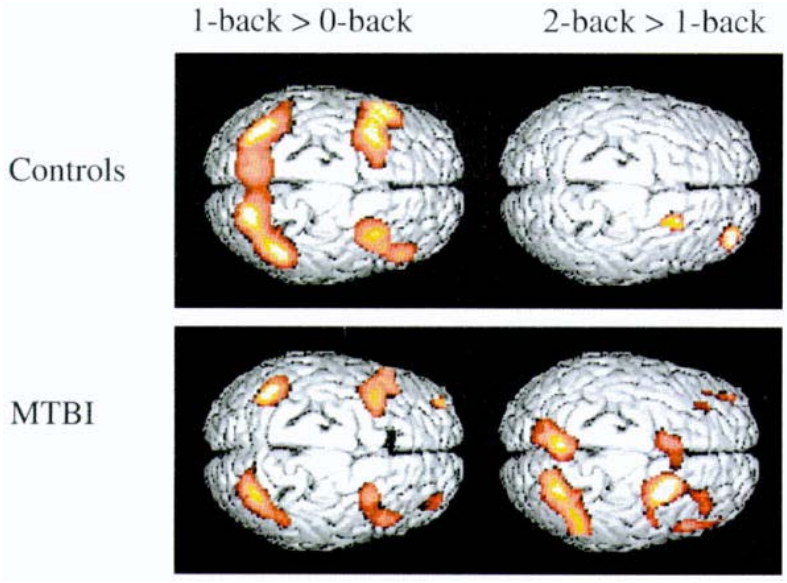
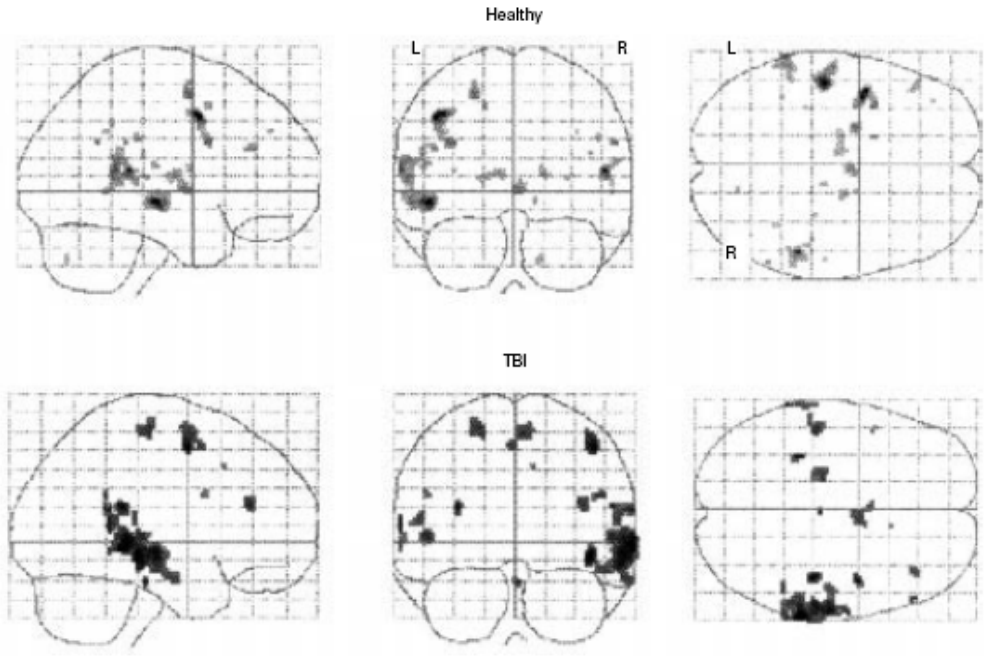


Figure 1. Brodmann's Areas (BA) representing various patterns of activation via fMRI within various cognitive domains in healthy adults.



TBI Group:	Comparable performance on fMRI task.
	Less activation than controls within 1-back> 0-back.
	Increased activation in R DLPFC & L Parietal regions within 2-back> 1-back.

Figure 2. Summary of McAllister, et al., 1999. Comparison of activations between TBI and controls within the 1-back> 0-back and 2-back> 1-back conditions. (McAllister, et al., 1999)

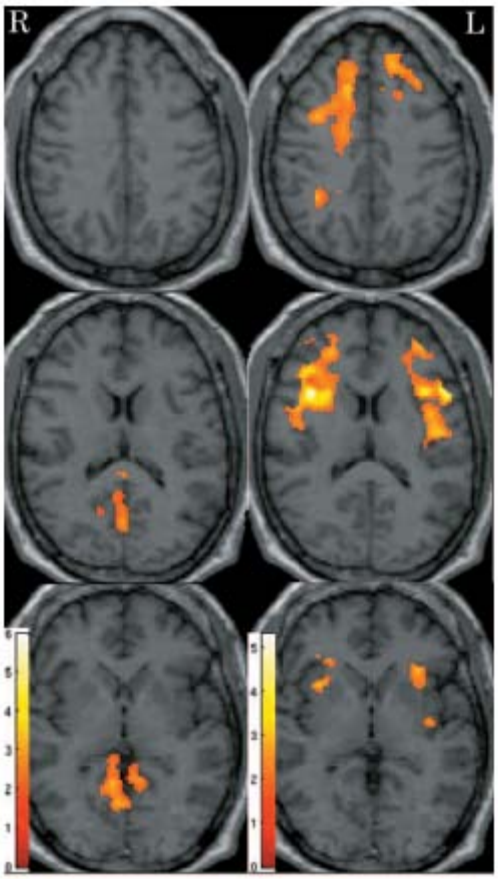


TBI Group: More errors than control group on fMRI task.

More R lateralization in the frontal and temporal lobes.

Increased dispersion in frontal lobes.

Figure 3. Summary of Christodoulou, et al., 2001. “Group activation patterns on the working memory task for the TBI (*n* = 9) and healthy control (*n* =7) groups. Maximum intensity projections in the three orthogonal views of the brain (sagittal, coronal, and axial) depict areas of significant activation.” (Christodoulou, et al., 2001, pp. 165).



TBI > OI OI > TBI

TBI Group: Comparable performance on fMRI task.

Significant fMRI differences only in 0-1 back comparison.

Decreased activation in bilateral frontal lobe.
Increased activation in posterior parietal lobe.
Increased activation over time.

Figure 4. Summary of Newsome, et al., 2007. "Activation in the 1-back condition for the TBI > OI (left side of figure) and OI > TBI comparisons. Left hemisphere is depicted on the right. Scales reflect t-values." (Newsome, et al., 2007, pp. 106)

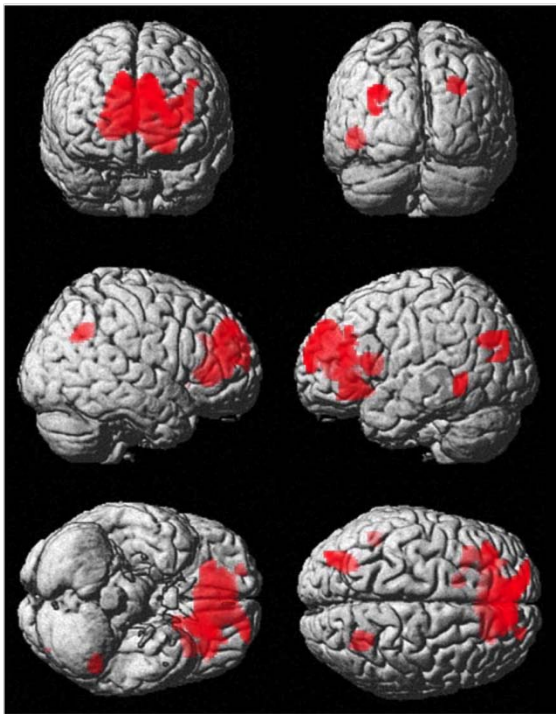


Figure 5. Summary of Sánchez-Carrión, et al., 2008 (b)

TBI Group:	Fewer group differences on neuropsychological testing and comparable performance on fMRI task. Increased activation in L inferior frontal gyrus (BA 46 & 47) & R mid frontal gyrus (BA 9) between scan 1 and scan 2 (after 6 months of unspecified neurorehabilitation). Although previous frontal hypoactivation was seen for the TBI compared to control groups, no group differences were found.

"Increased activation observed after 6-month evolution in TBI patients during the 3-back condition. The most striking changes were seen in the bilateral prefrontal cortex, with left hemisphere predominance. The second region that showed statistical significant changes was the biparietal posterior region. Both regions are involved in working memory processes. Statistical Parametric Maps with left as left." (Sanchez-Carrion, et al., 2008(b), pp.424)

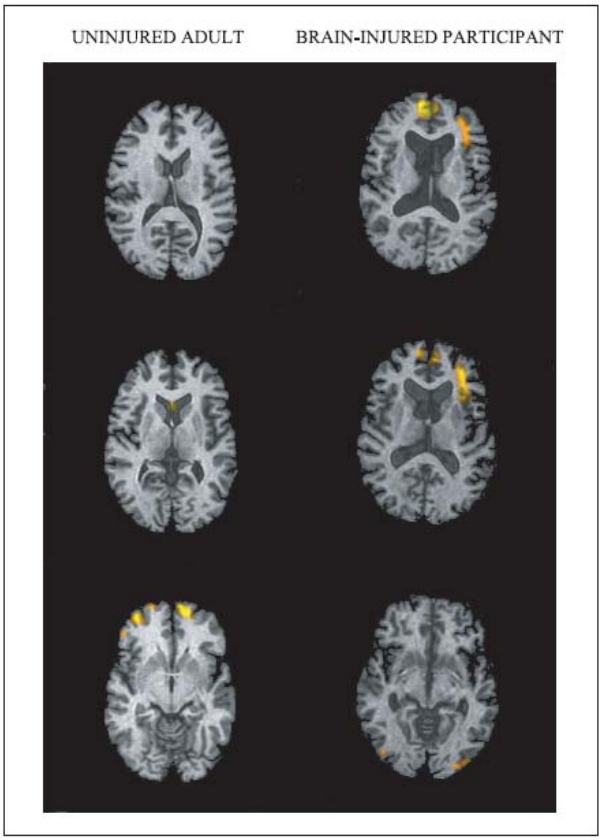


Figure 6. Summary of Scheibel, et al., 2003. Activation in response to "Arrows" task of cognitive control. Severe TBI patient shows more extensive frontal activation than controls (Scheibel, et al., 2003).

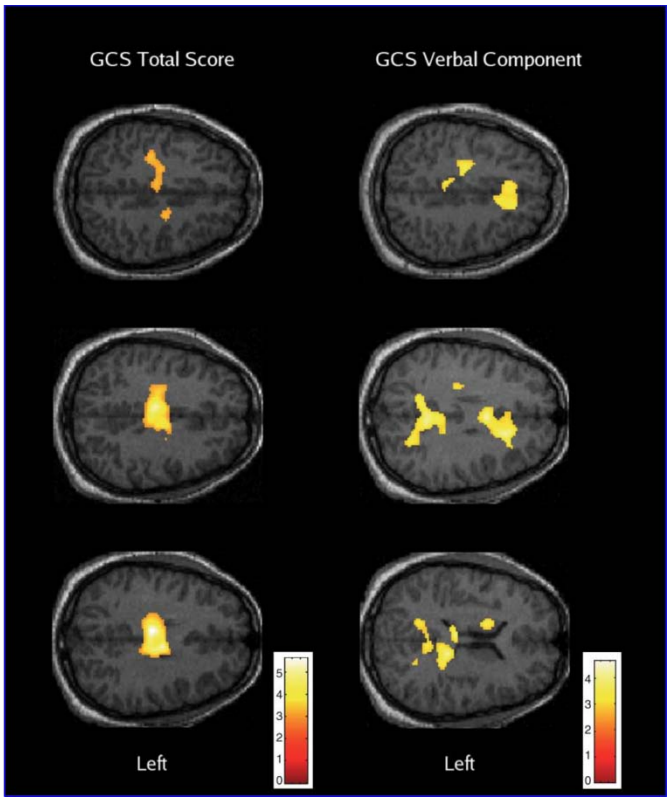
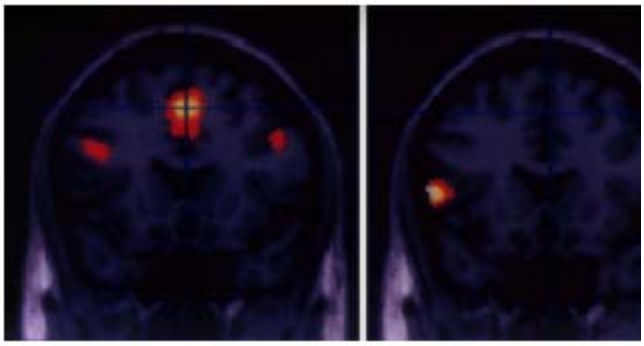


Figure 7. Summary of Scheibel, et al., 2009

TBI Group:	No group differences in fMRI task. Lower GCS scores associated with greater activation within a midline cluster (L ACC, bilateral thalami, basal ganglia, R precentral gyrus, inferior frontal, and mid-frontal gyri). Of GCS scores, association seen between verbal component and increased activation.

"Areas with a significant negative regression coefficient between brain activation and the GCS total score (left column, height threshold T=2.89, p=0.004) or verbal component score (right column, height threshold T=2.74, p=0.006) of TBI patients overlaid on axial anatomical images from a typical orthopedic injury patient." (Scheibel, et al., 2009, pp. 1451)



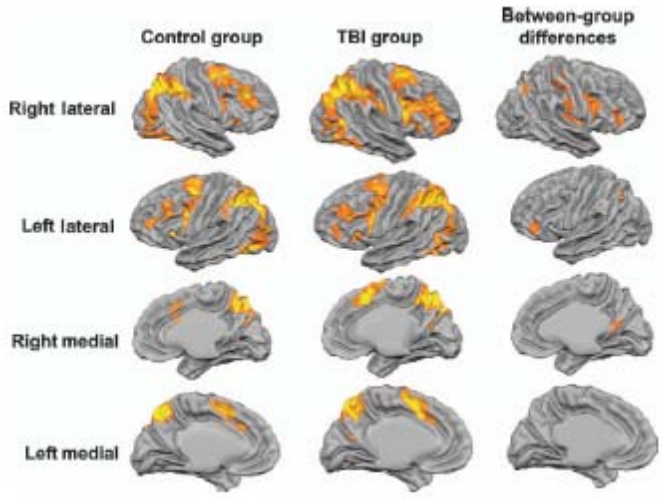
TBI Group:

Trend towards worse performance on fMRI task. More regionally dispersed.

Decreased activity in prefrontal & parietal areas.

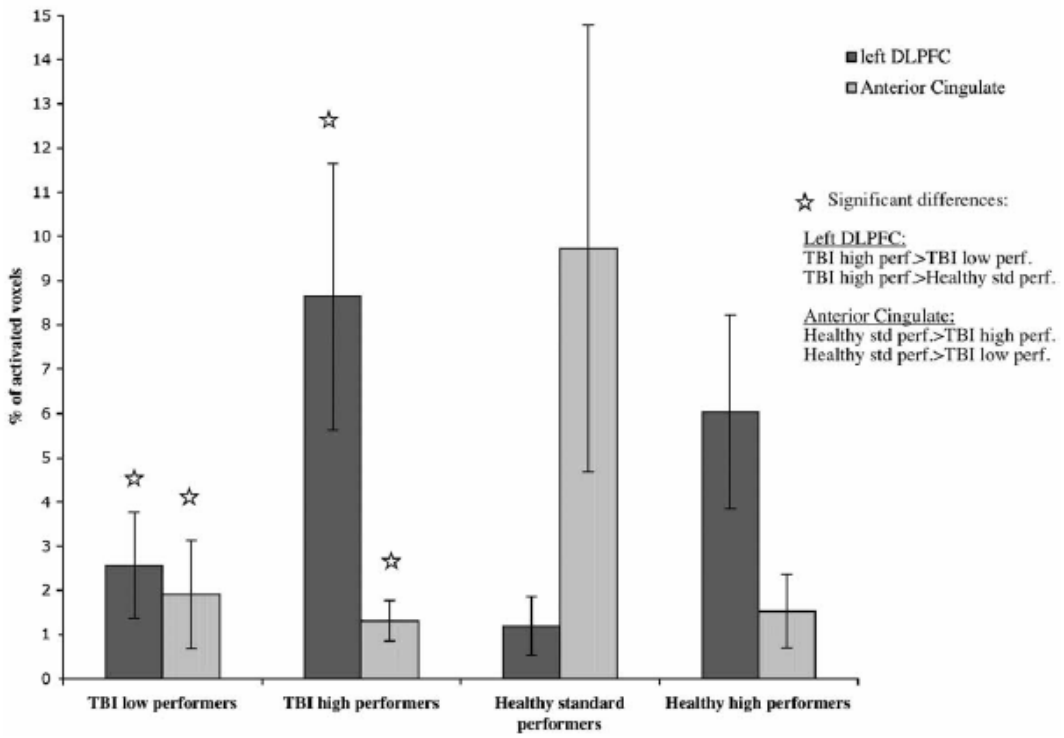
Decrease in ACC.

Figure 8. Summary of Soeda, et al., 2005. Significant activity was seen in the ACC for control participants (left) but not in TBI patients (right) (Soeda, et al., 2005)



TBI Group:	Comparable performance on fMRI task.
	Increased dispersion in parietal & frontal regions.
	Increased R lateralization most prominent in frontal lobes.
	Increased activation in ventrolateral prefrontal cortex.

Figure 9. Summary of Rasmussen, et al., 2006. Group differences in changes in BOLD activation for the control and TBI groups (Rasmussen, et al., 2006)



TBI Group:

High Performers: Larger areas of activation than Healthy Standard Performers or TBI Low Performers in the L DLPFC.

Both High and Low performers had smaller areas of activation than Healthy Standard Performers in the ACC.

Figure 10. Summary of Cazalis, et al., 2006. Comparison of activation during the Difficult condition between TBI and healthy subjects in the left dorsolateral prefrontal cortex (DLPFC) and anterior cingulate (Cazalis, et al., 2006)

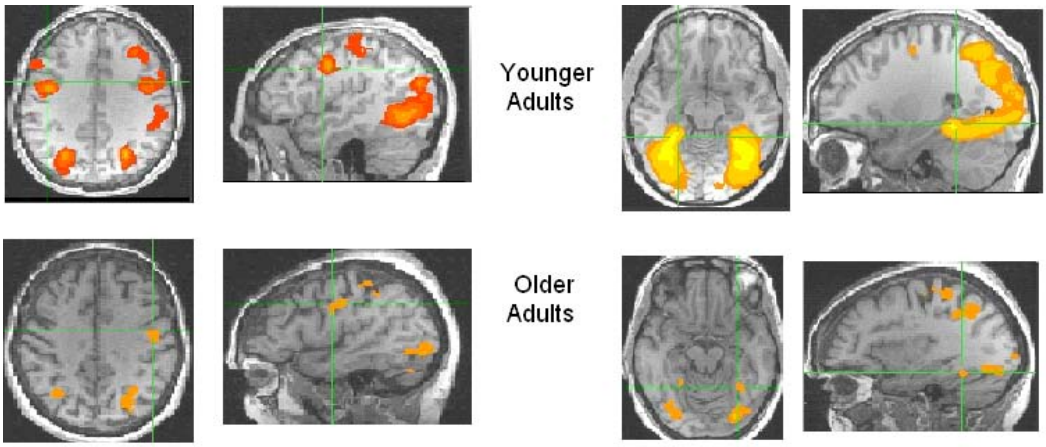


Figure 11. Activation patterns seen in the currently proposed DMS task comparing older versus younger adults. (Clark, Lawson, Guo, Kiser, & Jiang, 2007)

CHAPTER TWO: METHODS

Participants

The study was comprised of two clinical groups, the first included patients with a documented history of complicated mild (GCS of 13-15 with positive neuroimaging) to severe TBI (as evidenced by medical records, GCS, and/or neuroimaging) who were at least six months post injury. Although some participants in the TBI group required ventriculostomy for shunt placement to relieve intracranial pressure, none of the participants required additional neurosurgical intervention. This allowed for a comparison of whole brains without the removal of damaged tissue. The second group served as a control and included individuals with a history of orthopedic injury and no previous or current head injury. This control group was chosen in order to help account for preinjury host factors (i.e. impulsive behaviors, risk taking, poor decision making, etc.) and post-injury factors that could affect brain activation. Using orthopedic injured control participants has become the "gold-standard" in research in fMRI and TBI, and is preferable to using a healthy control group or using a family/friends control group to account for host factors. All research methodology, including recruitment, procedures, and analyses, was approved by the Institutional Review Board (IRB) at the University of Kentucky.

Recruitment: Participants in the TBI group were recruited through Cardinal Hill Rehabilitation Hospital, and had been treated by the University of Kentucky's Department of Physical Medicine and Rehabilitation while at Cardinal Hill. Patients who met criteria were sent a letter in the mail, informing them that a researcher would be contacting them and providing a number for recruits to call if they did not wish to be contacted. Patients were then contacted via telephone. Individuals in the orthopedic control group were recruited via flyers placed at clinics throughout the University of Kentucky, Cardinal Hill, as well as offices of physicians, chiropractors, and physical therapists throughout Lexington, KY. For all participants, a brief description of the study was given, and interested parties were screened to assess for inclusion and exclusion criteria. All participants were right-handed, native English speakers, and had normal or corrected-to-normal vision. Due to the nature of fMRI, participants could not have any metal in their heads (i.e. braces, plates, pins, screws), pacemakers, or large pieces of metal in their bodies (e.g. joint replacement). Smaller metal objects below the neck were allowed after checking for the material's MRI compatibility and obtaining permission from MRISC staff. Other exclusion criteria included use of medications that affect the central nervous system, severe psychopathology (i.e. psychotic or manic symptoms), language problems (i.e. aphasia), or claustrophobia. Those with preexisting neurologic conditions prior to TBI or seizure activity

were also excluded in order to rule out possible effects on brain activation. Informed consent was obtained and participants were paid for their time and the cost of transportation.

Current Sample: Seventeen participants were consented for the TBI group. Of these, five were not able to complete the study or were removed from analyses. One failed neurocognitive effort testing and was not scanned. Another was found to be too impaired to participate in the fMRI portion of the protocol. Another was removed from analyses due to motion artifact, while two others were removed from the study due to metal in the head (one was unaware of the metal at the time of screening, while the other underwent dental work between the time of the screening and the fMRI session). The 12 remaining participants included 6 men and 6 women aged 18 and older (M = 26.33, SD = 8.00). Fourteen participants were consented for the OI control group. Of these, one chose to discontinue the study early while another exceeded size constraints of the scanner. The remaining 12 individuals included 7 men and 5 women aged 18 and older (M = 27.33, SD = 6.69). Individuals in the orthopedic group included those who had sports-related injuries (66.7%), work-related injuries (25%), falls (16.7%), and a pedestrian versus car accident (8.3%). Some participants had multiple injuries and fell into multiple categories. Injuries included broken or fractured bones (e.g. wrist, ankle, ribs, foot), dislocated joints (e.g. shoulder), and torn ligaments (e.g. torn ACL).

All participants were paid $50 for the neuropsychological testing session and $50 for the fMRI session, while those who discontinued early were paid $5 for their time, as described in the consent form.

Power Analyses: Power analyses within the field of fMRI research are controversial and difficult to calculate. This is because social and behavioral research essentially relies on the predicted effect size (based on previous literature), the alpha value established for the study at hand, the number of desired groups, and the desired power to determine the number of total participants required to reach the established power. However, fMRI studies additionally rely not only on the number of subjects, but also on adequate repetitions of stimuli within each subject to reliably establish the activation in reaction to that stimulus. The signal-to-noise ratio of the scans also plays a factor in such calculations. Although fMRI researchers and statisticians continue to develop equations to appropriately address sample size and power a priori, empirical research investigating sample size during cognitive paradigms have suggested that 12 subjects represent an appropriate sample size (Ostrem, et al., 1994; Kapur, et al., 1995, Van Horn, et al., 1998). More recently, a study examining percent signal changes of approximately 0.5% and using an alpha level of 0.05, suggested that 12 subjects per group were necessary to insure 80% power (Desmond & Glover, 2002).

Given the inherent difficulties in the field when calculating sample size a priori, a post-hoc power analysis was conducted using the aforementioned sample size of 12 participants per group. The current parameters were entered into G Power 3.1 effect size calculator (Faul, Erdfelder, Buchner, & Lang, 2009). The correlation among repeated measures variables was calculated and entered into the calculator, along with a medium effect size, an alpha value of 0.05, total sample size of 24 participants in two groups, and total number of measures analyzed in a repeated measures, within and between subjects analysis of variance model. It was estimated that power for the current study was approximately 0.68-0.74. Power estimates using a multiple regression model suggested similar, yet slightly less power.

Procedure

The protocol included two sessions: a neuropsychological testing session and a separate fMRI session. These sessions were scheduled as close in proximity as possible for each individual participant, and varied from the same day to six weeks apart. The neuropsychological testing session lasted approximately 4 hours and included tests of executive functioning, language ability, attention, memory, visual spatial ability, motor functioning, and emotional state. The fMRI session was comprised of two parts, a training session in which participants were trained on a working memory task (which lasted approximately one hour), followed by the actual MRI scanning (for approximately one hour). The scanning included fMRI data acquisition, as well as structural MR imaging, diffusion tensor imaging and spectroscopy. Participants did not perform a task during these last three scans, and were asked only to lie still.

Neuropsychological Battery:

The neuropsychological battery assessed multiple domains of cognitive ability, but focused heavily on attention and executive processes needed for working memory. The neuropsychological battery follows below, according to cognitive domain. Brief descriptions of each test, including information regarding reliability and validity characteristics, can be found in Appendix A.

- *Orientation:* Galveston Orientation and Amnesia Test (GOAT; Levin, O'Donnell, & Grossman, 1979)
- *Attention:* Conners' Continuous Performance Test-II (CPT-II; Conners, 2004), Paced Auditory Serial Addition Task (PASAT; Gronwall, 1977)
- *Executive Function:* Delis-Kaplan Executive Function System (D-KEFS; Delis & Kaplan, 2001), Wisconsin Card Sorting Test – 64 Card Version (WCST-64; Heaton, 1981; Axelrod, Henry & Woodard, 1992), Iowa Gambling Task (IGT; Bechara, 2007)

- *Memory:* California Verbal Learning Test (CVLT-II; Delis, Kramer, Kaplan, & Ober, 2000), Continuous Recognition Memory Test (CRMT; Hannay, Levin, & Grossman, 1979)
- *Motor Functioning:* Finger Tapping (Halstead, 1947; Reitan & Wolfson, 1993; Spreen & Strauss, 1998)
- *Visual/Spatial:* Benton Form Discrimination (Benton, Sivan, Hamsher, Varney, & Spreen, 1994), Line Bisection (Schenkenberg, Bradford, & Ajax, 1980)
- *Language:* Multilingual Aphasia Examination (Visual Naming, Sentence Repetition, Tokens subtests; MAE; Benton & Hamsher, 1989; Benton, Hamsher, & Sivan, 1994)
- *Information Processing:* Processing Speed Index (WAIS-III subtests: Symbol Search, Digit Symbol – Coding; The Psychological Corporation, 1997)
- *Estimated Preinjury IQ:* Wechsler Test of Adult Reading (WTAR; The Psychological Corporation, 2001)
- *Effort:* Letter Memory Test (LMT; Inman, Vickery, Berry, Lamb, Edwards, and Smith, 1998)
- *Emotional/Behavioral:* Beck Depression Inventory – II (BDI-II; BDI-II; Beck, 1987; Beck, Steer, & Brown, 1996), Beck Anxiety Inventory (BAI; Beck et al., 1988), Personality Assessment Screen (PAS; Morey, 1999), UPPS-P Impulsive Behavior Scale (Whiteside & Lynam, 2003)
- *Functional Outcome:* Community Integration Questionnaire (CIQ; Dijkers, 1997)

DMS Task:

Stimuli: Stimuli consisted of 240 black and white line drawings of common objects developed by Snodgrass & Vanderwart (1980). Pictures were presented within a rectangular area of 8.3 cm by 5.8 cm, displayed in front of a black background using E-Prime presentation software. The computer screen was approximately 65cm from the participants, and the visual angle was about 7 degrees. As described below, some pictures were demarcated by a 6.5 mm green border where appropriate.

Of the 240 pictures, 80 were studied objects (half targets, half distracters). The other 160 were new objects that had not been studied (half new targets; half new distracters).

Delayed Match to Sample Task: The Delayed Match to Sample (DMS) task consisted of 40 trials separated into 4 blocks of 10 trials each. Each trial began with the presentation of two sample target objects for 2000 msec. Each target object was presented side by side on the same

screen and each was distinguished by a green border. The sample target objects were followed (ISI = 700 ± 100 msec) by 10 successive test objects with a stimulus duration of 2000 msec (ISI = 500 ± 200 msec). Each trial lasted 27.0 seconds.

Test objects were classified into one of four groups: (a) studied targets, (b) studied distracters, (c) new targets, or (d) new distracters. None of the objects, whether serving as a target or distracter, were used in any subsequent trials. The test portion of each trial contained a pseudo-random presentation of target and distracter objects where the target object, a studied distracter, and a new distracter are presented three times each, resulting in nine of the ten test items in a trial. One additional 'filler' object was included in each trial to reduce the potential for subject expectancy and serve either as a 4th studied target (16.7 % of trials), 4thnew target (16.7 % of trials), 4thstudied distracter (16.7 % of trials), or a new distracter never previously shown (50 % of trials). Across trials, stimuli from the three experimental conditions were equally distributed across all 10 serial positions. Figure 12 illustrates the distribution of objects in relation to repetition across the 10 serial test object positions.

fMRI Procedure:

Study Phase: Participants began the experiment with a study phase during which they observed 80 stimulus pictures for 5 seconds each. After a short break, the next portion of the study phase consisted of viewing the same 80 pictures at the participant's own pace, cycling through each by pressing the spacebar to move onto the next stimulus. After another short break, participants viewed the same 80 pictures again using the spacebar.

After these three study phases, each participant was asked to complete a recognition task during which they identified the pictures presented as "memorized" or "not memorized" by pressing the corresponding keyboard button (placement of the keys was counterbalanced). Participants were presented with 100 pictures, 60 of which were memorized in the study phases, and 40 of which were new. Accuracy scores were obtained for this task; if the participants did not achieve 90%, they were asked to go over the second study phase (at their own pace) once again. They were then tested for accuracy a second time, moving on to the next phase after attaining 90% accuracy. As previously described, one participant was unable to attain 90% accuracy, and study participation was discontinued.

Test Phase: Participants were told to hold the sample target objects in their mind and indicate whether the following 10 test objects were the same or different from the sample target picture by pressing one of two buttons using their right or left hand. Assignment of hands to indicate a target versus distracter object was counterbalanced across subjects. Of note, one participant in the TBI group used the index and middle fingers on the left hand due to limited

dexterity of the right hand. Participants were also instructed to forget the previous sample target objects only when two new sample target objects appeared. The task was broken into 4 blocks of 10 trials each, with short breaks between the blocks allowing the participant to rest. This task lasted approximately 25 minutes overall. Reaction time and accuracy of behavioral responses was recorded.

Functional MRI data acquisition and pre-processing analysis: Each participant completed the study phase on a computer in an adjacent room, followed by the test phase while they were scanned inside of a 3 Tesla Siemens Trio MRI scanner at the University of Kentucky's Magnetic Resonance Imaging and Spectroscopy Center (MRISC). High-resolution whole brain structural MRI were obtained for each subject. Twenty-two slices whole brain T2* weighted functional images were obtained every 2.0 seconds for each of the four series [T2*-weighted EPI: 64 x 64 matrix, 2.0 sec TR, whole brain, 3.6 mm cubic voxel size]. Images were realigned for head motion correction using AFNI software (Cox, 1996). The fMRI image volumes were reconstructed. Motion was corrected, the slice timing differences adjusted, and intensity normalized to allow for the calculation of activation as percentage signal change. General linear models were applied for the multiple regression analysis. The multiple regression models contain orthogonal contrasts of interest and additional regressors of no interest to obtain changes in mean fMRI signals.

Analyses:

Demographic and Neuropsychological Test Variables: T-tests and chi-square tests were conducted on demographic variables, as appropriate, to examine any group differences on potentially confounding variables. T-tests were also conducted on neuropsychological test scores to look for group differences. With regard to demographic and neuropsychological test variables, an alpha level of 0.01 was set in order to account for the large number of analyses.

Behavioral Data: Between- and within-group analyses of variance were conducted for behavioral data (accuracy and reaction time) on the DMS task. Corresponding to the types of stimuli presented, variables included new matches, studied matches, new non-matches, and studied non-matches. Therefore, 2 (Match Type: match vs. non-match) x 2 (Novelty: new vs. studied) x 2 (Group: TBI vs. OI) ANOVAs were conducted. Due to motor slowing associated with head injury, reaction time on the DMS task was covaried with performance on the Finger Tapping task, bilaterally, from neuropsychological testing.

fMRI Data: For fMRI analyses, twelve specific regions of interest (ROIs) were identified a priori based on prior research. In the frontal region, these included BA 9 and BA 46 (dorsolateral prefrontal cortex), BA 10, BA 45, and BA 47. In the temporal region, areas of

interest included BA 37, the hippocampus, and the parahippocampus. Parietal ROIs included BA 7 and BA 40. Finally, the anterior cingulate and posterior cingulate were examined. Each ROI was defined using a mask derived from AFNI software, and the percent signal change for each ROI was derived. Values for percent signal change were then transferred into PASW Stastistics 18 for further analyses.

Between- and within-group analyses of variance were then conducted for fMRI data to examine patterns of activation and look for group differences. This involved 2 (Match Type: match vs. non-match) x 2 (Novelty: new vs. studied) x 2 (Hemisphere: left vs. right) x 2 (Group: TBI vs. OI) ANOVAs within each ROI. Post-hoc analyses were conducted using ANOVA or t-tests as appropriate. Due to the large amount of data, post-hoc analyses were only probed if they involved group differences, as this directly applies to the research question. In addition, correlation analyses were performed to analyze the relationship between neuropsychological test data and patterns of activation. With regard to the fMRI data, an alpha level of 0.05 was set and conservative corrections were used. For ANOVAs, the Bonferroni correction was applied for multiple comparisons, and the Greenhouse-Geisser correction was used to correct *p* values when appropriate.

In addition to comparisons of percent signal changes described above, a "neural discrimination index" was calculated to examine each participant's ability to discriminate matches from non-matches. This involved the following calculation: match – mismatch, applied to new and studied items within each hemisphere. Analyses were then conducted to examine group differences, including 2 (Novelty: new vs. studied) x 2 (Hemisphere: left vs. right) x 2 (Group: TBI vs. OI) ANOVAs within each ROI. Post-hoc analyses were conducted as described above, and were again only probed if group differences were found.

Correlation and regression analyses were conducted to examine the relationship between neuropsychological test data and activation in key regions identified by the aforementioned analyses. As general correlational analyses alone yielded a large number of data points, simultaneous regression analyses were conducted to examine the change in activation in relation to changes in neuropsychological test performance. Further analyses of fMRI data included binary logistic regression analyses to examine the ability of neuropsychological tests and fMRI to predict group membership. The utility of fMRI to predict whether participants belonged to the TBI or OI group, over and above the utility of neuropsychological testing alone, may provide useful evidence in assessing deficits associated with TBI. Such a finding might contribute to assessing functional reorganization and rehabilitation outcome for rehabilitation in future studies.

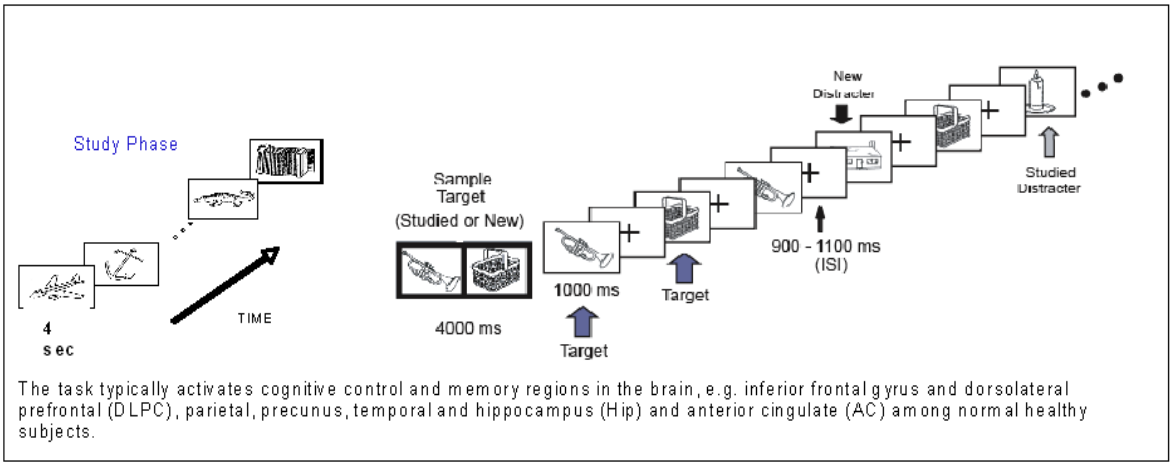


Figure 12. Example of the DMS task.

CHAPTER THREE: RESULTS

Background Information

Table 10 provides background information for age and education for each group. No statistically significant differences were found between groups. Table 11 provides background information for additional demographic information, including gender, race, marital status and socioeconomic status (SES), again with no statistically significant differences found between the groups. Thus, the two groups were comparable on these potentially confounding variables. Table 12 provides head injury severity data for the TBI group. Participants varied in severity from complicated-mild to severe injuries based on GCS and neuroimaging data. GCS scores collected while in the ER were used when available (participants 2, 3, and 4 did not have a GCS reported while in the ER, and the GCS recorded at the site of the injury was used). Table 13 provides information regarding time in acute care and sub-acute rehabilitation at Cardinal Hill Rehabilitation Hospital, as well as the time between the date of injury and the date of neuropsychological testing (in months), and the time between neuropsychological testing and the fMRI scan (in days).

Neuropsychological Test Scores

Neuropsychological test data appear in Table 14. No statistically significant group differences were found on a reading-based estimate of pre-injury IQ at $p < 0.01$. Measures of working memory, processing speed, and memory were statistically significantly lower in the TBI group as compared to the OI group. Executive functioning tests were variable. While measures of switching and inhibition were statistically significantly lower for the TBI group, other executive functioning measures of reasoning and concept formation showed no statistically significant group differences. Statistically significant group differences were also found bilaterally on a measure of gross motor speed. No statistically significant group differences were found on language, visual-spatial or attention measures. The deficits in working memory, recall, executive functioning, and processing speed are consistent with the deficits typically seen in patients with TBI. This is often due to the physics involved in closed head injuries involving acceleration and deceleration, coupled with the boney protrusions within the skull. Common areas of injury include the orbitofrontal lobe (associated with executive functioning and working memory), inferior and anterior temporal lobe (associated with learning, recall, and working memory), as well as diffuse axonal injury (associated with processing speed; McAllister, 1992). While other areas can also be affected in brain injuries, the current TBI group was highly functioning and other areas were generally intact.

Table 15 presents data regarding emotional functioning, impulsivity, and community integration. There were no statistically significant group differences on measures of depression or anxiety, nor were there differences on a screening measure of several types of emotional and behavioral problems. A measure of impulsivity was similar across groups, and showed no statistically significant group differences. No statistically significant group differences were found on a measure of community integration, including home integration, social integration, and productivity. In addition, nine of the participants in the TBI group scored 5/5 on the Glasgow Outcome Scale (GOS; 5=Able to return to work or school), whereas the other three scored a 4/5 on the GOS (4=able to live independently; unable to return to work or school), suggesting that these individuals had good outcomes.

DMS Task Behavioral Data

Two measures of behavioral performance, accuracy and reaction time, were obtained from the DMS task performed during the fMRI scan. Behavioral performance for both accuracy and reaction time is broken up into the match type (match versus non-match) and novelty (new versus studied) of the stimuli. Accuracy on the DMS task, presented in Table 16, indicates that there were no statistically significant group differences on any of the variables. Due to motor slowing associated with head injury, reaction time on the DMS task was covaried with performance on the Finger Tapping task, bilaterally, from neuropsychological testing. Table 17 indicates that the TBI group was statistically significant slower for studied matches, new non-matches, and studied non-matches, whereas new matches showed no statistically significant group differences.

MRI Images

In order to illustrate the structural differences between the TBI and OI participants, Figure 13 presents representative individuals from each group. No analyses were conducted regarding structural data, however, it can be seen that the participant from the TBI group has remarkably larger ventricles and sulci than does the participant from the OI group. It should be noted that the representative participants are similar in age (19 for TBI and 25 for OI) and gender, and any differences noted are not a result of acute injury, as the TBI participant was over a year post-injury. The enlarged ventricles and shrinkage of the cortices in the young TBI brain resembles typical structural MRI images seen in older adults in their 70s or 90s or patients with mild cognitive impairment (MCI).

fMRI Results - Testing of Hypothesis #1

Percent signal changes in response to the DMS task were calculated for 12 ROIs as described above. Table 18 presents data regarding the coordinates for the center of each ROI, as

reported by AFNI software. Two different sets of coordinates based on different brain atlases are presented for each: the Talairach-Tournoux Atlas and the Montreal Neurological Institute (MNI) Atlas.

Frontal Regions: Table 19 presents means squared, F-values, p-values, and η^2 from ANOVA analyses within the frontal regions.

Main Effects: A main effect of novelty was seen within all ROIs, in which new items resulted in increased activation and were statistically significantly different from studied items, which resulted in deceased activation. A main effect of match type was found in BA 10 and BA 47, in which matches resulted in increased signal and were statistically significantly different from non-matches, which resulted in decreased signal. BA 9 and BA 45 revealed a main effect of hemisphere, in which the right hemisphere was statistically significantly different from the left and resulted in an increase in activation. In BA 9, no change in activation was found within the left hemisphere. However, BA 45 showed a decrease in signal within the left hemisphere.

Interactions: The interactions of interest for this study are those that involve group, as the research question involves differences in patterns of neural activation between groups. Of the interactions found within the frontal ROIs, the hemisphere by group interaction found in BA 46 was further probed. Table 20 presents means, standard deviations, t-values, and d-scores for the probed interaction. Within the right hemisphere only, statistically significant group differences were found. TBI participants showed an increase in activation in BA 46, whereas the OI control group showed a decrease in activation in this area as seen in Figure 14. No group differences were found within the left hemisphere in BA 46. Figure 15 displays the pattern of neural activation for a representative OI participant (top) and TBI participant (bottom) within BA 46.

Temporal Regions: Table 21 presents means squared, F-values, p-values, and η^2 from ANOVA analyses within the temporal regions.

Main Effects: Within each ROI in the temporal region, a main effect of novelty was found in which signal increased in response to new items and decreased in response to studied stimuli, with statistically significant differences between novelty types. A main effect of match type was found in BA 37; signal decreased in response to matches and was statistically significantly different than the increased signal in response to non-matches.

Interactions: A statistically significant three way interaction was found between novelty, hemisphere, and group within BA 37. Table 22 presents means, standard deviations, F-values, and η^2 from post-hoc analyses within this ROI. As seen in Figure 16, there was an increase in percent signal change for new items, and a decrease in percent signal change for studied items. However, these differences reached statistical significance in the right hemisphere for the TBI

group only. Figure 17 presents images of the neural activation for individuals from the TBI and OI groups. Due to the inherent difficulty in interpreting four way interactions, the match type by novelty by hemisphere by group interaction was not probed further.

Parietal Regions: Table 23 presents means squared, F-values, p-values, and η^2 from ANOVA analyses within the parietal regions.

Main Effects: BA 7 demonstrated a main effect of novelty, in which new and studied items were statistically significantly different from one another, with new items resulting in an increase in signal and studied items resulting in a decrease in signal. In addition, hemispheric differences were found in which the right hemisphere demonstrated a statistically significantly greater decrease in activation than did the left hemisphere.

Interactions: BA 7 demonstrated two interactions involving group. Table 24 displays means, standard deviations, F-values, and η^2 values for the probed, three-way, novelty by hemisphere by group interaction within BA 7. For studied objects within the TBI group only, a statistically significantly greater decrease in activation was found in the right compared to the left hemisphere. No statistically significant differences were found within the OI group. Figure 18 illustrates the neural activation between the TBI and OI groups, while Figure 19 shows images for individuals from TBI and OI groups.

Table 25 presents means, standard deviations, F-values, and η^2 values for the probed, three-way, match type by novelty by group interaction within BA 7. After thorough analyses, statistically significant differences were found between new matches and studied matches within both the TBI and OI groups, although the difference was larger within the TBI group as seen in Figure 20. New matches resulted in increased activation within BA 7, whereas studied matches resulted in decreased activation. Images of the neural activation for individuals from the TBI and OI groups can be found in Figure 21.

Cingulate: Table 26 presents means squared, F-values, p-values, and η^2 from ANOVA analyses within the cingulate.

Main Effects: A main effect of novelty was observed in both the anterior cingulate and posterior cingulate. New items resulted in increased signal and were statistically significantly different from studied items, which resulted in decreased signal. A main effect of match type revealed statistically significant differences between matches and non-matches. The anterior cingulate increased signal in response to matches and decreased in signal in response to non-matches.

Interactions: There were no statistically significant group interactions within the cingulate region.

Neural Discrimination Index:

Again, the Neural Discrimination Index was calculated to examine each participant's ability to discriminate matches from non-matches, and involved the following calculation: match – nonmatch, applied to new and studied items within each hemisphere. Though an exploratory measure, it was thought that this index might be able to detect group differences better than the percent signal changes for matches and non-matches separately.

Neural Discrimination – Frontal Regions: Table 27 presents means squared, F-values, p-values, and η^2 from ANOVA analyses involving the neural discrimination index within the frontal regions.

A main effect of novelty was found across all regions (BA 9, BA 46, BA 10, BA 45, and BA 47), in which new items corresponded to increased activation within each area and were statistically significantly different from studied items that corresponded to decreased activation. No statistically significant group interactions were found; therefore, no interactions were further probed and reported.

Neural Discrimination – Temporal Regions: Means squared, F-values, p-values, and η^2 from ANOVA analyses involving the neural discrimination index within the temporal regions are presented in Table 28. A main effect of novelty was found across all regions (BA 37, hippocampus, and parahippocampus), in which new items corresponded in increased activation within each area and were statistically significantly different from studied items that corresponded to decreased activation. A three-way novelty by hemisphere by group interaction was found for BA 37. Table 29 presents means, standard deviations, F-values and η^2 for the probed interaction. Probing revealed that new items showed an increase in activation, and were statistically significantly different from studied items, which showed a decrease in activation, as presented in Figure 22. While this was observed in both right and left hemispheres within both TBI and OI groups, the differences varied in magnitude so that the TBI group demonstrated greater differences, more so within the right hemisphere.

Neural Discrimination – Parietal Regions: Table 30 presents means squared, F-values, p-values, and η^2 from ANOVA analyses involving the neural discrimination index within the parietal regions. A main effect of novelty was found within BA 7, in which new items, which corresponded to an increase in activation, were statistically significantly different from studied items, which corresponded to a decrease in activation. In addition, a novelty by group interaction was seen in BA 7, and the means, standard deviation, F-values, and η^2 are presented in Table 31. In the TBI group, the difference between new and studied objects was statistically significantly different, with new objects showing an increase in activation while studied objects showed a

decrease in activation. As seen in Figure 23, a similar pattern was seen within the OI group, with a smaller magnitude of change and statistically significant differences between new and studied objects.

Neural Discrimination – Cingulate Regions: Means squared, F-values, p-values, and η^2 for the cingulate region are presented in Table 32. A main effect was found for novelty in the anterior cingulate and posterior cingulate, in which new items corresponded to increased signal and were statistically significantly different from studied items, which corresponded to decreased signal. A main effect of hemisphere was also found, in which the right hemisphere showed a statistically significantly greater increase to the task than did the left hemisphere. No interactions involving group were found; therefore, no interactions were further probed and reported.

Simultaneous Regression Analyses - Testing of Hypotheses # 2 and # 3

As correlating neuropsychological test data with fMRI data yielded a large amount of data, simultaneous regression analyses were conducted to examine the ability of neuropsychological test data to predict percent signal change. Neuropsychological tests were chosen based on differences seen between groups (e.g., PASAT, WAIS-III Processing Speed Index, CVLT-II Short Delayed Free Recall, DKEFS Design Fluency, DKEFS Color Word Intereference, and DKEFS Color Word Interference/Switching). Similarly, due to the large amount of data available, specific ROIs were chosen for analyses because they had demonstrated group differences, namely, BA 46 (frontal), BA 37 (temporal), and BA 7 (parietal). Within each ROI, data were collapsed across stimulus type and novelty to produce one percent signal change score for each hemisphere.

Table 33 presents results from simultaneous multiple regression analyses within BA 46. Neuropsychological test data did not predict percent signal change within BA 46 for either the TBI or the OI control group.

Simultaneous multiple regression analyses for BA 37 are presented in Table 34. For the TBI group, the overall model did not explain a statistically significant amount of variance for percent signal change within either the left or right hemisphere; however, individual neuropsychological tests indicated statistically significant relationships with percent signal changes. For example, within the right hemisphere for the TBI group, the WAIS-III Processing Speed Index accounted for a statistically significant amount of variance in percent signal change within BA 37. For the OI group, the overall model did explain a statistically significant amount of variance for percent signal change in both the left ($F(5,6)=32.40$, $R^2=0.975$, $p < 0.01$) and right ($F(5,6)=5.878$, $R^2=0.876$, $p < 0.05$) hemispheres. Within the left hemisphere, the PASAT, WAIS-III Processing Speed Index, and DKEFS Color Word Interference were significant predictors. In

the right hemisphere, the PASAT, WAIS-III Processing Speed Index, and DKEFS Color Word Interference/Switching were significant predictors. Within both hemispheres, a positive relationship was seen for WAIS-III Processing Speed Index and percent signal change, indicating that signal increased with faster Processing Speed scores. A negative relationship was found for percent signal change and neuropsychological tests as follows: PASAT (bilaterally), Color Word Interference (left hemisphere), Color Word Interference/Switching (right hemisphere). This indicated that signal increased with poorer performance on these neuropsychological tests.

Table 35 presents simultaneous multiple regression analyses for BA 7. For the TBI group, the overall model did not explain a statistically significant amount of variance for percent signal change within either the left or right hemisphere; however, the WAIS-III Processing Speed Index indicated statistically significant relationships with percent signal changes within both the left and right hemispheres. This suggests that as processing speed increases, activation within BA 7 increases. Within the OI group, neither the overall model nor individual neuropsychological tests predicted percent signal changes in the left hemisphere. In the right hemisphere for the OI group, the overall model did not explain a statistically significant amount of variance for percent signal change; however, the WAIS-III Processing Speed Index again predicted percent signal change, with faster processing speed indicating greater activation within the right BA 7 for the OI group.

Binary Logistic Regression - Exploratory Analyses

The previous regression analyses suggest that neuropsychological test data may help predict percent signal changes in temporal and parietal ROIs. A next step in exploring these data was to examine whether or not a combination of neuropsychological test data and fMRI data can accurately predict group membership (i.e. TBI or OI). More specifically, to ascertain whether fMRI data added incremental evidence, compared to neuropsychological tests alone, in identifying a participant as a member of the TBI or OI groups. In order to determine which variables best predicted group membership, hierarchical (binary) logistic regression analyses were conducted. The neuropsychological test variables that were found to be statistically significantly different between groups were entered in the first step, whereas fMRI variables were entered in the second step. Only fMRI variables within the ROIs that demonstrated group differences, BA 46, BA 37, and BA 7, were entered in three separate sets of analyses. Stated another way, two sets of regressions were undertaken for each ROI (BA 46, BA 37, and BA 7). First, the following neuropsychological test variables were made available for conditional, stepwise entry: PASAT, WAIS-III PSI, CVLT-R – SDFR, DKEFS Design Fluency, DKEFS Color Word Interference, and DKEFS Color Word Interference Switching. Next, the fMRI

variables (new match, new non-match, studied match, studied non-match for each hemisphere) were made available for conditional, stepwise entry. After this was completed, the reverse order of entry was undertaken. Conditional, stepwise entry was deemed appropriate, as the following analyses were exploratory. It should be noted that the only difference between analyses within each ROI is the fMRI data; the neuropsychological test data used will clearly be the same data in each analysis.

Table 36 provides information regarding the incremental contribution of fMRI data within BA 46 (frontal region) relative to neuropsychological test data for predicting group membership in the TBI or OI group. Although several neuropsychological tests were available to enter stepwise and conditionally, only DKEFS Design Fluency (Total Scaled Score) and PASAT (T-score) were significant predictors. Next, the fMRI variables described above were made available for stepwise conditional entry; however, no fMRI data added to the model. When the reverse analysis was performed, with the fMRI data entered first, stepwise and conditionally, studied matches from both the right and left hemisphere in BA 46 were significant predictors. When the neuropsychological test data were entered second, stepwise and conditionally, the DKEFS Design Fluency score added statistically significant incremental predictive validity.

Table 37 provides information regarding the incremental predictive contribution of fMRI data within BA 37 (temporal region) relative to neuropsychological test data for predicting group membership in the TBI or OI group. After allowing the neuropsychological test data to enter stepwise and conditionally, both DKEFS Design Fluency and the PASAT added statistically significant incremental predictive validity. When fMRI data were made available for stepwise and conditional entry, the fMRI data did not add to the model. Upon running the reverse analysis, with the fMRI data entered first, stepwise and conditionally, fMRI data, again, did not add to the model. However, when the neuropsychological test data were made available for stepwise and conditional entry, the DKEFS Design Fluency and PASAT were statistically significant incremental contributors to predicting group membership.

Table 38 provides information regarding the incremental contribution of fMRI data within BA 7 (parietal region) and the neuropsychological test data in predicting group membership to the TBI or OI group. Similar to the last comparison, fMRI data did not add to the model when added either first or second.

Finally, it should be noted that the Neural Discrimination Indices for BA 7, BA 37, and BA 46 were also examined using similar analyses. In all cases, the neuropsychological test data predicted group membership, and the fMRI data did not add to the model when entered either first or second.

Table 10.
Group Comparisons of Continuous Background Variables

	TBI Group			OI Group					
	M	*SD*	Range	*M*	*SD*	Range	*t*	df	*d*
Age	26.33	8.00	18-39	27.33	6.69	20-40	-0.332	22	-0.14
Education	13.33	2.42	9-18	14.83	1.70	12-18	-1.760	22	-0.73
WTAR-FSIQ	100.5	8.57	81-110	108.6	8.99	88-117	-2.20	22	-0.93

$^{**}p<0.01$, $^{***}p<0.001$

Table 11.
Group Comparisons of Discrete Background Variables

		TBI Group		OI Group			
		N	%	N	%	c^2	df
Gender	Male	6	50.0%	7	58.3%	0.168	1
	Female	6	50.0%	5	41.7%		
Race	White	11	91.7%	8	66.7%	3.474	3
	African-American	0	0.0%	2	16.7%		
	Asian/PI	0	0.0%	1	8.3%		
	Other	1	8.3%	1	8.3%		
Marital Status	Single	7	58.3%	9	75.0%	1.390	2
	Married	4	33.3%	3	25.0%		
	Divorced	1	8.3%	0	0.0%		

**p<0.01, ***p<0.001

Table 12.
Head Injury Severity Data for the TBI Group

TBI Group	GCS at ER	Intubated	Evidence of DAI on Neuroimaging	Hemisphere	Surgical Intervention	Description of Injury
1	5	Yes	Yes	Bilateral	None	-BL frontal SAH -DAI R medial temporal lobe & L frontal lobe
2	3	Yes	Yes	Bilateral	Ventricu-lostomy	-BL frontal SDH -Diffuse DAI -L basal ganglia hemorrhage (1.8 x 0.8cm) -R parietal hemorrhage
3	3	Yes	No	Left	None	-L fronto-temporal SDH resulting in mass effect on L (5mm) -Non-displaced L temporal, skull base, and facial fractures
4	3	Yes	Yes	Left	Ventricu-lostomy	-Scattered posttraumatic hemorrhage -L frontal lobe edema
5	4	Yes	Yes	Bilateral	None	-R IVH causing herniation -BL temporal DAI -Basilar skull fracture

DAI=Diffuse Axonal Injury, N/A=Not available, R=Right, L=Left, BL=Bilateral, SAH=Subarachnoid hemorrhage, IVH-Intraventricular hemorrhage, SDH=subdural hematoma

Table 12. (cont.)

TBI Group	GCS at ER	Intubated	Evidence of DAI on Neuroimaging	Hemisphere	Surgical Intervention	Description of Injury
6	13	No	No	Left	None	-L frontal SDH (5mm) -Rightward midline shift (3mm)
7	11	No	No	Bilateral	None	-L frontal hemorrhage causing mass effect on L frontal lobe -Rightward midline shift -L temporal hemisphere contusion -R temporal fracture
8	5	Yes	Yes	Bilateral	Ventricu-lostomy	-DAI BL frontal lobes -L frontal SAH
9	6	Yes	Yes	Bilateral	Ventricu-lostomy	-L frontal hemorrhage -BL DAI -Punctate hemorrhages involving body of L caudate nucleus
10	N/A	Yes	Yes	Bilateral	Ventricu-lostomy	-L anterior temporal SDH -R lateral temporal SDH -Leftward midline shift (7mm) -BL frontal contusions -BL DAI

DAI=Diffuse Axonal Injury, N/A=Not available, R=Right, L=Left, BL=Bilateral, SAH=Subarachnoid hemorrhage, IVH-Intraventricular hemorrhage, SDH=subdural hematoma

Table 12. (cont.)

TBI Group	GCS at ER	Intubated	Evidence of DAI on Neuroimaging	Hemisphere	Surgical Intervention	Description of Injury
11	13	No	No	Bilateral	None	-R frontoparietal SAH -R temporal SDH -Hemorrhagic contusions in L cerebellum -Non-displaced L occipital fracture
12	8	Yes	Yes	Right	Ventricu-lostomy	-R posterior frontal hemorrhagic contusion -DAI

DAI=Diffuse Axonal Injury, N/A=Not available, R=Right, L=Left, BL=Bilateral, SAH=Subarachnoid hemorrhage, IVH-Intraventricular hemorrhage, SDH=subdural hematoma

Table 13.
Time of Hospitalization and Time to Evaluation for the TBI Group

TBI Group	Days in Acute Care	Days in Sub-Acute Care	Time Between Injury and Neuropsychological Testing (months)	Time Between Neuropsychological Testing and fMRI (days)
1	20	52	38	42
2	12	15	23	0
3	28	14	30	0
4	59	16	29	16
5	10	38	67	15
6	7	22	6	10
7	10	11	29	1
8	25	37	8	1
9	29	27	33	2
10	17	23	7	0
11	9	4	29	0
12	12	13	6	0
M	19.83	19.83	25.42	7.25
SD	14.52	13.74	17.60	12.51

Table 14.

Group Comparisons of Neuropsychological Test Scores

	TBI Group		OI Group				
	M	*SD*	*M*	*SD*	*t*	df	*d*
Neurocognitive Effort							
LMT – % correct	99.26	1.45	98.52	2.39	0.92	22	0.39
Language Functioning							
Visual Naming – adj. raw	52.67	5.48	56.83	4.04	-2.12	22	-0.87
Sentence Repetition – adj. raw	11.08	3.50	12.67	0.65	-1.54	11.76	-0.77
Token Test – raw	41.92	3.68	41.17	5.91	0.37	22	0.16
Visual-Spatial Abilities							
Line Bisection – raw	19.25	1.29	19.92	0.29	-1.75	12.10	-0.85
Visual Form Discrim. – raw	30.17	1.75	31.25	0.75	-1.97	14.95	-0.86
Attention							
CPT Omissions – T score	46.11	5.58	45.65	5.31	0.21	22	0.08
CPT Commissions – T score	46.68	10.45	53.72	12.10	-1.53	22	-0.62
CPT Hit RT – T score	52.59	8.88	45.62	12.28	1.59	22	0.66
CPT Hit RT SE – T score	52.30	11.41	45.66	9.01	1.58	22	0.65
Working Memory							
PASAT – T score	44.33	12.26	62.50	8.70	-4.19***	22	-1.73
Processing Speed							
WAIS-III PSI	96.25	21.31	118.5	10.48	-3.25**	22	-1.40
Memory Functioning							
CVLT-2: Trials 1-5 – T score	43.00	12.89	54.83	8.47	-2.66	22	-1.11
CVLT-2: SDFR – z score	-1.00	1.64	0.46	0.66	-2.86**	14.44	-1.27
CVLT-2: LDFR – z score	-0.96	1.66	0.33	0.49	-2.59	12.93	-1.20
CVLT-2: Rec. Discrim. (d')	-0.83	1.78	0.33	0.65	-2.14	13.91	-0.95
CRMT Total Correct – SS	-0.99	1.30	0.21	0.92	-1.20	22	-1.08

**$p<0.01$, ***$p<0.001$

Table 14. (cont.)
Group Comparisons of Neuropsychological Test Scores

	TBI Group		OI Group				
	M	*SD*	*M*	*SD*	*t*	df	*d*
Executive Functioning							
DKEFS Trails 4 Switching – SS	7.50	4.27	11.42	2.15	-2.84	16.24	-1.22
DKEFS Verbal Fluency Switching Accuracy – SS	11.42	3.85	14.50	2.61	-2.30	22	-0.95
DKEFS Design Fluency Total Correct – SS	9.83	2.95	14.50	2.32	-4.31***	22	-1.77
DKEFS Color Word Interference – SS	7.92	3.53	12.33	2.74	-3.42**	22	-1.41
DKEFS Color Word Interference/Switching – SS	7.25	3.41	11.92	1.93	-4.12***	22	-0.66
DKEFS 20 Questions – SS	11.17	2.37	10.25	2.86	0.85	22	0.57
DKEFS Word Context - SS	10.58	2.75	12.08	1.88	-1.56	22	-0.65
DKEFS Tower – SS	10.58	2.97	10.67	1.97	-0.08	22	-0.04
DKEFS Proverbs – SS	11.83	1.59	12.42	1.44	-0.94	22	-0.39
Iowa Gambling Task – T score	47.92	7.66	53.83	13.58	-1.32	22	-0.56
WCST-64C Total Errors – T score	49.58	10.7	48.42	8.99	0.06	22	0.12
Gross Motor Speed							
Finger Tapping: Dominant – T score	32.42	12.4	50.83	8.50	-4.24***	22	-1.76
Finger Tapping: Non-Dominant – T score	35.83	9.58	49.42	8.93	-3.59**	22	-1.47

**$p<0.01$, ***$p<0.001$

Table 15.
Group Comparisons of Emotional Functioning, Impulsivity, and Community Integration

	TBI Group		OI Group				
	M	*SD*	*M*	*SD*	*t*	df	*d*
Beck Depression Inventory-II Total (BDI-II)	7.83	7.94	8.83	8.84	-0.292	22	-0.12
Beck Anxiety Inventory Total (BAI)	2.17	2.21	5.17	6.13	-1.594	22	-0.72
Personality Assessment Screen							
Negative Affect (NA)	38.08	15.00	48.25	26.42	-1.159	22	-1.49
Acting Out (AO)	52.18	18.55	49.37	16.86	0.389	22	0.16
Health Problems (HP)	49.56	16.70	50.56	15.84	-0.150	22	-0.06
Psychotic Features (PF)	51.83	22.56	47.95	14.49	0.501	22	0.21
Social Withdrawal (SW)	67.80	24.34	77.55	21.92	-1.031	22	-0.42
Hostile Control (HC)	50.62	6.86	53.32	19.01	-0.919	22	-0.21
Suicidal Thinking (ST)	49.59	19.01	45.25	13.95	0.638	22	0.26
Alienation (AN)	48.18	21.77	48.38	21.90	-0.022	22	-0.01
Alcohol Problem (AP)	43.24	7.06	43.93	9.00	-1.207	22	-0.09
Anger Control (AC)	54.92	19.90	48.43	11.99	0.967	22	0.41
Total	31.87	34.56	43.89	33.63	-0.863	22	-0.35
UPPS-P Impulsive Behavior Scale							
Negative Urgency (NU)	3.60	4.57	2.17	0.53	1.076	22	0.56
Lack of Premeditation (PM)	3.68	5.16	1.78	0.44	1.268	22	0.68

**p<0.01, ***p<0.001

Table 15 (cont.).
Group Comparisons of Emotional Functioning, Impulsivity, and Community Integration

	TBI Group		OI Group				
	M	*SD*	*M*	*SD*	*t*	df	*d*
Lack of Perseverance (PSV)	2.87	3.22	1.76	0.61	1.172	22	0.58
Sensation Seeking (SS)	4.69	6.42	2.73	0.54	1.363	22	0.56
Positive Urgency (PU)	3.37	4.34	1.65	0.67	-0.863	22	0.69
Community Integration Questionnaire							
Home Integration	3.67	1.61	5.33	2.31	-2.049	22	-0.85
Social Integration	9.33	1.67	8.67	1.53	1.030	22	0.41
Productivity	5.42	2.15	5.83	1.53	-0.547	22	-0.22
Total	18.42	4.27	19.83	3.83	-0.855	22	-0.35

**p<0.01, ***p<0.001

Table 16.
Group Comparisons of Accuracy on the DMS Task

	TBI Group		OI Group				
	M	*SD*	*M*	*SD*	*t*	df	*d*
New Match	94.4%	0.08	94.3%	0.05	0.977	22	0.02
Studied Match	96.3%	0.06	96.5%	0.03	0.912	22	-0.04
New Non-match	96.4%	0.08	97.3%	0.03	0.715	22	-0.16
Studied Non-match	94.6%	0.09	95.8%	0.03	0.645	22	-0.20

*p<0.05, **p<0.01, ***p<0.001

Table 17.
MANCOVA: Group Comparison of Reaction Time (Covaried for Dominant and Nondominant Finger Tapping) on the DMS Task

	TBI Group		OI Group				
	M	*SD*†	*M*	*SD*†	*F*	df	*d*
New Match	606.50	136.24	524.16	136.24	3.310	20	0.60
Studied Match	627.94	131.49	516.93	131.49	6.457*	20	0.84
New Non-match	655.96	125.12	563.87	125.12	4.910*	20	0.74
Studied Non-match	657.31	123.70	570.58	123.70	4.453*	20	0.70

*p<0.05, **p<0.01, ***p<0.001, †pooled standard deviation

Table 18.
Description of fMRI Regions of Interest (ROIs)

			x	y	z	Cluster Size† TBI	OI
Frontal Regions							
BA 9	Left	T-T Atlas	-32	33	30	17	48
(Middle Frontal Gyrus)		MNI Atlas	-34	34	32		
	Right	T-T Atlas	32	33	30	24	41
		MNI Atlas	34	34	32		
BA 46	Left	T-T Atlas	-50	38	16	17	12
(Middle Frontal Gyrus)		MNI Atlas	-54	38	16		
	Right	T-T Atlas	50	38	16	24	101
		MNI Atlas	53	38	16		
BA 10	Left	T-T Atlas	-24	56	6	43	323
(Superior Frontal Gyrus)		MNI Atlas	-26	55	3		
	Right	T-T Atlas	24	56	6	112	364
		MNI Atlas	25	55	3		
BA 45	Left	T-T Atlas	-54	23	10	70	8
(Inferior Frontal Gyrus)		MNI Atlas	-58	23	10		
	Right	T-T Atlas	54	23	10	29	101
		MNI Atlas	57	23	10		
BA 47	Left	T-T Atlas	-38	24	-11	346	12
(Inferior Frontal Gyrus)		MNI Atlas	-41	22	-14		
	Right	T-T Atlas	38	24	-11	252	14
		MNI Atlas	40	22	-14		
Temporal							
BA37	Left	T-T Atlas	-48	-55	-7	11	322
(Inferior Temporal Gyrus)		MNI Atlas	-52	-63	-4		
	Right	T-T Atlas	48	-55	-7	34	626
		MNI Atlas	51	-63	-4		
Hippocampus	Left	T-T Atlas	-30	-24	-9	152	11
		MNI Atlas	-32	-31	-8		
	Right	T-T Atlas	30	-24	-9	66	6
		MNI Atlas	32	-31	-8		
Parahippocampus	Left	T-T Atlas	-25	-25	-12	152	11
		MNI Atlas	-27	-32	-11		
	Right	T-T Atlas	25	-25	-12	66	8
		MNI Atlas	26	-32	-11		

T-T Atlas=Talairach-Tournoux Atlas; MNI = Montreal Neurological Institute Atlas
†Cluster size in voxels at a threshold of $p<0.01$ (z-scores)

Table 18 (cont.).						Cluster Size†	
			x	y	z	TBI	OI
Parietal							
BA 7	Left	T-T Atlas	-16	-60	48	>346	17
(Precuneus/Superior Parietal)		MNI Atlas	-17	-64	60		
	Right	T-T Atlas	16	-60	48	>346	6
		MNI Atlas	17	-64	60		
BA 40	Left	T-T Atlas	-51	-40	38	>346	715
(Inferior Parietal)		MNI Atlas	-55	39	47		
	Right	T-T Atlas	51	-40	38	>346	30
		MNI Atlas	54	-44	47		
Cingulate							
Anterior Cingulate	Left	T-T Atlas	-8	32	7	>346	18
		MNI Atlas	-9	32	6		
	Right	T-T Atlas	8	32	7	>346	6
		MNI Atlas	8	32	6		
Posterior Cingulate	Left	T-T Atlas	-10	-54	14	>346	11
		MNI Atlas	-11	-60	20		
	Right	T-T Atlas	10	-54	14	>346	>715
		MNI Atlas	11	-60	20		

T-T Atlas=Talairach-Tournoux Atlas; MNI = Montreal Neurological Institute Atlas
†Cluster size in voxels at a threshold of $p<0.01$ (z-scores)

Table 19.
Frontal Regions – ANOVA: Match Type (match vs. non-match) x Novelty (new vs. studied) x Hemisphere (left vs. right) x Group (TBI vs. OI)

Frontal Region		*df*	*MS*	*F*	*p*	η^2
BA 9	Main effect of Match Type (MT)	22	0.003	1.99	0.171	0.083
	MT x Group	22	2.94E-5	0.017	0.898	0.001
	Main effect of Novelty (Nov)	22	0.009	5.538	0.028*	.0201
	Nov x Group	22	0.002	0.988	0.331	0.043
	Main effect of Hemisphere (Hem)	22	0.000	6.490	0.018*	0.228
	Hem x Group	22	4.60E-6	0.100	0.755	0.005
	MT x Nov	22	0.015	14.52	0.001**	0.398
	MT x Nov x Group	22	0.003	2.750	0.111	0.111
	MT x Hem	22	0.000	2.656	0.117	0.108
	MT x Hem x Group	22	3.99E-6	0.043	0.838	0.002
	Nov x Hem	22	0.000	2.048	0.166	0.085
	Nov x Hem x Group	22	0.000	0.728	0.403	0.032
	MT x Nov x Hem	22	2.65E-5	0.117	0.735	0.005
	MT x Nov x Hem x Group	22	8.17E-6	0.036	0.851	0.002
BA 46	Main effect of Match Type (MT)	22	0.004	3.603	0.071	0.141
	MT x Group	22	3.20E-6	0.003	0.959	0.000
	Main effect of Novelty (Nov)	22	0.011	14.53	0.001**	0.398
	Nov x Group	22	0.001	1.372	0.254	0.059
	Main effect of Hemisphere (Hem)	22	1.69E-5	0.198	0.661	0.009
	Hem x Group	22	0.001	11.55	0.003**	0.344
	MT x Nov	22	0.015	14.76	0.001**	0.402
	MT x Nov x Group	22	2.81E-5	0.027	0.870	0.001
	MT x Hem	22	4.13E-7	0.002	0.968	0.000
	MT x Hem x Group	22	0.000	1.778	0.196	0.075
	Nov x Hem	22	4.23E-5	0.141	0.711	0.006
	Nov x Hem x Group	22	0.000	0.780	0.780	0.034
	MT x Nov x Hem	22	0.000	1.386	0.252	0.059
	MT x Nov x Hem x Group	22	0.001	4.151	0.054	0.159
BA 10	Main effect of Match Type (MT)	22	0.012	7.185	0.014*	0.246
	MT x Group	22	0.001	0.415	0.526	0.018
	Main effect of Novelty (Nov)	22	0.015	12.76	0.002**	0.367
	Nov x Group	22	0.002	1.585	0.221	0.067
	Main effect of Hemisphere (Hem)	22	7.31E-7	0.009	0.926	0.000
	Hem x Group	22	2.59E-5	0.314	0.581	0.014
	MT x Nov	22	0.016	13.87	0.001**	0.387

Table 19 (cont.).

	MT x Nov x Group	22	0.004	3.357	0.081	0.132
	MT x Hem	22	1.39E-7	0.001	0.975	0.000
	MT x Hem x Group	22	8.48E-5	0.592	0.450	0.026
	Nov x Hem	22	0.000	1.383	0.252	0.059
	Nov x Hem x Group	22	7.14E-6	0.059	0.810	0.003
	MT x Nov x Hem	22	0.000	1.968	0.175	0.082
	MT x Nov x Hem x Group	22	0.000	2.599	0.121	0.106
BA 45	Main effect of Match Type (MT)	22	0.005	3.034	0.095	0.121
	MT x Group	22	7.11E-5	0.044	0.836	0.002
	Main effect of Novelty (Nov)	22	0.007	4.762	0.040*	0.178
	Nov x Group	22	0.001	0.460	0.505	0.020
	Main effect of Hemisphere (Hem)	22	0.001	12.596	0.002**	0.364
	Hem x Group	22	0.000	2.443	0.132	0.100
	MT x Nov	22	0.020	10.66	0.004**	0.326
	MT x Nov x Group	22	5.76E-5	0.031	0.862	0.001
	MT x Hem	22	0.001	2.572	0.123	0.105
	MT x Hem x Group	22	1.48E-6	0.005	0.944	0.000
	Nov x Hem	22	0.001	3.611	0.071	0.141
	Nov x Hem x Group	22	0.000	0.574	0.457	0.025
	MT x Nov x Hem	22	0.003	8.798	0.007**	0.286
	MT x Nov x Hem x Group	22	0.000	1.748	0.200	0.074
BA 47	Main effect of Match Type (MT)	22	0.005	5.118	0.034*	0.189
	MT x Group	22	0.001	0.757	0.394	0.033
	Main effect of Novelty (Nov)	22	0.006	9.343	0.006**	0.298
	Nov x Group	22	0.000	0.321	0.577	0.014
	Main effect of Hemisphere (Hem)	22	6.17E-5	1.528	0.229	0.065
	Hem x Group	22	4.92E-5	1.218	0.282	0.052
	MT x Nov	22	0.012	13.52	0.001**	0.381
	MT x Nov x Group	22	0.000	0.230	0.636	0.010
	MT x Hem	22	5.47E-5	0.662	0.424	0.029
	MT x Hem x Group	22	0.000	1.818	0.191	0.076
	Nov x Hem	22	0.000	1.585	0.221	0.067
	Nov x Hem x Group	22	3.43E-5	0.494	0.489	0.022
	MT x Nov x Hem	22	0.000	1.162	0.293	0.050
	MT x Nov x Hem x Group	22	9.99E-4	0.980	0.333	0.043

*p<0.05, **p<0.01, ***p<0.001

Table 20.

Post-Hoc: BA 46 Hemisphere x Group

	TBI Group		OI Group				
	M	*SD*	*M*	*SD*	*t*	df	*d*
Left Hemisphere	-0.0004	0.00592	-0.0004	0.01098	0.011	22	0.00
Right Hemisphere	0.0035	0.00733	-0.0056	0.01091	2.402*	22	-0.23

*p<0.05, **p<0.01, ***p<0.001

Table 21.

Temporal Regions – ANOVA: Match Type (match vs. non-match) x Novelty (new vs. studied) x Hemisphere (left vs. right) x Group (TBI vs. OI)

		df	*MS*	*F*	*p*	η^2
Temporal Region						
BA37	Main effect of Match Type (MT)	22	0.012	8.141	0.009**	0.270
	MT x Group	22	3.52E-5	0.023	0.880	0.001
	Main effect of Novelty (Nov)	22	0.038	24.694	0.000***	0.529
	Nov x Group	22	2.58E-5	0.017	0.898	0.001
	Main effect of Hemisphere (Hem)	22	1.45E-5	0.253	0.620	0.011
	Hem x Group	22	3.24E-5	0.563	0.461	0.025
	MT x Nov	22	0.60	29.78	0.000***	0.575
	MT x Nov x Group	22	0.002	0.753	0.395	0.033
	MT x Hem	22	3.43E-5	0.485	0.493	0.022
	MT x Hem x Group	22	1.00E-6	0.014	0.906	0.001
	Nov x Hem	22	0.000	1.843	0.188	0.077
	Nov x Hem x Group	22	0.001	9.170	0.006**	0.294
	MT x Nov x Hem	22	1.51E-5	0.107	0.746	0.005
	MT x Nov x Hem x Group	22	0.001	6.727	0.017*	0.234
Hippocampus	Main effect of Match Type (MT)	22	3.35E-8	0.000	0.995	0.000
	MT x Group	22	0.000	0.332	0.571	0.015
	Main effect of Novelty (Nov)	22	0.009	15.03	0.001**	0.406
	Nov x Group	22	0.000	0.489	0.492	0.022
	Main effect of Hemisphere (Hem)	22	1.28E-5	0.200	0.659	0.009
	Hem x Group	22	7.41E-6	0.116	0.737	0.005
	MT x Nov	22	0.010	10.71	0.003**	0.327
	MT x Nov x Group	22	0.000	0.467	0.502	0.021
	MT x Hem	22	1.76E-7	0.004	0.949	0.000
	MT x Hem x Group	22	3.73E-5	0.896	0.354	0.039
	Nov x Hem	22	0.000	4.625	0.043*	0.174
	Nov x Hem x Group	22	7.90E-5	1.064	0.314	0.046
	MT x Nov x Hem	22	0.001	10.44	0.004**	0.322
	MT x Nov x Hem x Group	22	3.80E-5	0.474	0.499	0.021
Parahippocampus	Main effect of Match Type (MT)	22	0.000	0.100	0.755	0.005
	MT x Group	22	0.000	0.222	0.642	0.010
	Main effect of Novelty (Nov)	22	0.032	34.15	0.000***	0.608
	Nov x Group	22	0.000	0.126	0.726	0.006

Table 21 (cont.).

	Main effect of Hemisphere (Hem)	22	2.94E-6	0.056	0.815	0.003
	Hem x Group	22	5.13E-6	0.098	0.757	0.004
	MT x Nov	22	0.031	23.57	0.000***	0.517
	MT x Nov x Group	22	0.000	0.134	0.718	0.006
	MT x Hem	22	3.80E-8	0.001	0.971	0.000
	MT x Hem x Group	22	1.32E-6	0.048	0.829	0.002
	Nov x Hem	22	0.001	9.857	0.005**	0.309
	Nov x Hem x Group	22	0.000	2.104	0.161	0.087
	MT x Nov x Hem	22	0.000	1.963	0.175	0.082
	MT x Nov x Hem x Group	22	4.74E-5	0.772	0.389	0.034

*p<0.05, **p<0.01, ***p<0.001

Table 22.

Post-Hoc: BA 37 – ANOVA Novelty x Hemisphere x Group

	Right Hemisphere		Left Hemisphere				
	M	*SD*	*M*	*SD*	*F*	df	η^2
TBI Group							
New Objects	0.010	0.017	0.005	0.018	9.572*	11	0.465
Studied Objects	-0.025	0.014	-0.018	0.016	4.205	11	0.277
OI Group							
New Objects	0.007	0.01	0.009	0.020	0.768	11	0.065
Studied Objects	-0.018	0.019	-0.021	0.022	1.587	11	0.126

*p<0.05, **p<0.01, ***p<0.001

Table 23.

Parietal Regions – ANOVA: Match Type (match vs. non-match) x Novelty (new vs. studied) x Hemisphere (left vs. right) x Group (TBI vs. OI)

Parietal Region		*df*	*MS*	*F*	*p*	η^2
BA 7	Main effect of Match Type (MT)	22	7.06E-5	0.023	0.881	0.001
	MT x Group	22	5.15E-5	0.017	0.898	0.001
	Main effect of Novelty (Nov)	22	0.117	41.11	0.000***	0.651
	Nov x Group	22	0.001	0.350	0.560	0.016
	Main effect of Hemisphere (Hem)	22	0.000	5.442	0.029*	0.198
	Hem x Group	22	0.000	1.914	0.180	0.080
	MT x Nov	22	0.120	45.58	0.000***	0.674
	MT x Nov x Group	22	0.012	4.619	0.043*	0.174
	MT x Hem	22	0.000	0.653	0.428	0.029
	MT x Hem x Group	22	0.000	1.332	0.261	0.057
	Nov x Hem	22	0.000	0.526	0.476	0.023
	Nov x Hem x Group	22	0.002	4.708	0.041*	0.176
	MT x Nov x Hem	22	0.001	2.327	0.141	0.096
	MT x Nov x Hem x Group	22	0.000	0.472	0.499	0.021
BA 40	Main effect of Match Type (MT)	22	0.003	1.364	0.255	0.058
	MT x Group	22	2.22E-5	1.364	0.255	0.000
	Main effect of Novelty (Nov)	22	0.003	2.023	0.169	0.084
	Nov x Group	22	0.000	0.070	0.794	0.003
	Main effect of Hemisphere (Hem)	22	7.13E-5	.579	0.455	0.026
	Hem x Group	22	4.78E-6	0.039	0.846	0.002
	MT x Nov	22	0.009	5.954	0.023*	0.213
	MT x Nov x Group	22	0.001	0.667	0.423	0.029
	MT x Hem	22	0.000	0.672	0.421	0.030
	MT x Hem x Group	22	0.001	1.937	0.178	0.081
	Nov x Hem	22	1.83E-5	0.107	0.747	0.005
	Nov x Hem x Group	22	2.40E-5	0.140	0.712	0.006
	MT x Nov x Hem	22	2.42E-5	0.168	0.686	0.008
	MT x Nov x Hem x Group	22	5.53E-5	0.383	0.542	0.017

*p<0.05, **p<0.01, ***p<0.001

Table 24.

Post-Hoc: BA 7 – ANOVA Novelty x Hemisphere x Group

	Right Hemisphere		Left Hemisphere				
	M	*SD*	*M*	*SD*	*F*	df	η^2
TBI Group							
New Objects	0.024	0.023	0.021	0.021	1.547	11	0.123
Studied Objects	-0.038	0.023	-0.025	0.015	10.06*	11	0.478
OI Group							
New Objects	0.013	0.029	0.019	0.037	1.520	0.243	0.121
Studied Objects	-0.028	0.022	-0.031	0.025	0.261	11	0.023

*p<0.05, **p<0.01, ***p<0.001

Table 25.

Post-Hoc: BA 7 – ANOVA Match Type x Novelty x Group

	New Objects		Studied Objects				
	M	*SD*	*M*	*SD*	*F*	df	η^2
TBI Group							
Match	0.054	0.025	-0.066	0.034	105.5***	11	0.906
Non-match	-0.009	0.030	0.003	0.026	0.665	11	0.057
OI Group							
Match	0.032	0.054	-0.047	0.038	18.06**	11	0.621
Non-match	-0.002	0.032	-0.013	0.038	0.530	11	0.046

*p<0.05, **p<0.01, ***p<0.001

Table 26.

Cingulate Region – ANOVA: Match Type (match vs. non-match) x Novelty (new vs. studied) x Hemisphere (left vs. right) x Group (TBI vs. OI)

		df	*MS*	*F*	*p*	η^2
Cingulate Anterior Cingulate	Main effect of Match Type (MT)	22	0.008	6.233	0.021*	0.221
	MT x Group	22	3.67E-6	0.003	0.958	0.000
	Main effect of Novelty (Nov)	22	0.009	7.751	0.011*	0.261
	Nov x Group	22	8.61E-5	0.078	0.783	0.004
	Main effect of Hemisphere (Hem)	22	2.00E-5	1.047	0.317	0.045
	Hem x Group	22	2.59E-6	0.136	0.716	0.006
	MT x Nov	22	0.008	8.035	0.010*	0.268
	MT x Nov x Group	22	0.002	1.991	0.172	0.083
	MT x Hem	22	0.000	13.59	0.001**	0.382
	MT x Hem x Group	22	1.28E-5	1.018	0.324	0.044
	Nov x Hem	22	0.000	5.673	0.026*	0.205
	Nov x Hem x Group	22	5.59E-8	0.001	0.971	0.000
	MT x Nov x Hem	22	0.000	3.259	0.085	0.129
	MT x Nov x Hem x Group	22	2.34E-5	0.652	0.428	0.029
Posterior Cingulate	Main effect of Match Type (MT)	22	0.000	0.120	0.732	0.005
	MT x Group	22	0.000	0.092	0.764	0.004
	Main effect of Novelty (Nov)	22	0.115	63.06	0.000***	0.741
	Nov x Group	22	0.000	0.163	0.690	0.007
	Main effect of Hemisphere (Hem)	22	0.000	6.860	0.016*	0.238
	Hem x Group	22	7.41E-6	0.133	0.718	0.006
	MT x Nov	22	0.109	38.84	0.000***	0.638
	MT x Nov x Group	22	6.17E-6	0.002	0.963	0.000
	MT x Hem	22	0.000	4.782	0.040*	0.179
	MT x Hem x Group	22	0.000	3.036	0.095	0.121
	Nov x Hem	22	0.001	2.257	0.147	0.093
	Nov x Hem x Group	22	0.000	0.988	0.331	0.043
	MT x Nov x Hem	22	0.002	6.021	0.023*	0.215
	MT x Nov x Hem x Group	22	4.77E-5	0.164	0.689	0.007

*p<0.05, **p<0.01, ***p<0.001

Table 27.
Neural Discrimination: Frontal Regions – ANOVA: Novelty (new vs. studied) x Hemisphere (left vs. right) x Group (TBI vs. OI)

Frontal Region		*df*	*MS*	*F*	*p*	η^2
BA 9	Main effect of Novelty (Nov)	22	0.031	14.54	0.001**	0.398
	Nov x Group	22	0.006	2.750	0.111	0.111
	Main effect of Hemisphere (Hem)	22	0.000	2.656	0.117	0.108
	Hem x Group	22	0.000	0.043	0.838	0.002
	Nov x Hem	22	0.000	0.117	0.735	0.005
	Nov x Hem x Group	22	0.000	0.036	0.851	0.002
BA 46	Main effect of Novelty (Nov)	22	0.030	14.76	0.001**	0.402
	Nov x Group	22	0.000	0.027	0.870	0.001
	Main effect of Hemisphere (Hem)	22	0.000	0.002	0.968	0.000
	Hem x Group	22	0.001	1.778	0.196	0.075
	Nov x Hem	22	0.001	1.386	0.252	0.059
	Nov x Hem x Group	22	0.002	4.151	0.054	0.159
BA 10	Main effect of Novelty (Nov)	22	0.031	13.87	0.001**	0.387
	Nov x Group	22	0.008	3.357	0.081	0.132
	Main effect of Hemisphere (Hem)	22	0.000	0.001	0.975	0.000
	Hem x Group	22	0.000	0.592	0.450	0.026
	Nov x Hem	22	0.001	1.968	0.175	0.082
	Nov x Hem x Group	22	0.001	2.599	0.121	0.106
BA 45	Main effect of Novelty (Nov)	22	0.040	10.66	0.004**	0.326
	Nov x Group	22	0.000	0.031	0.862	0.001
	Main effect of Hemisphere (Hem)	22	0.002	2.572	0.123	0.105
	Hem x Group	22	0.000	0.005	0.944	0.000
	Nov x Hem	22	0.005	8.798	0.007**	0.286
	Nov x Hem x Group	22	0.001	1.748	0.200	0.074
BA 47	Main effect of Novelty (Nov)	22	0.024	13.52	0.001**	0.381
	Nov x Group	22	0.000	0.230	0.636	0.010
	Main effect of Hemisphere (Hem)	22	0.000	0.662	0.424	0.029
	Hem x Group	22	0.000	1.818	0.191	0.076
	Nov x Hem	22	0.000	1.162	0.293	0.050
	Nov x Hem x Group	22	0.000	0.980	0.333	0.043

*p<0.05, **p<0.01, ***p<0.001

Table 28.

Neural Discrimination: Temporal Regions – ANOVA: Novelty (new vs. studied) x Hemisphere (left vs. right) x Group (TBI vs. OI)

		df	*MS*	*F*	*p*	η^2
Temporal Region						
BA 37	Main effect of Novelty (Nov)	22	0.121	29.78	0.000***	0.575
	Nov x Group	22	0.003	0.753	0.395	0.033
	Main effect of Hemisphere (Hem)	22	0.000	0.485	0.493	0.022
	Hem x Group	22	0.000	0.014	0.906	0.001
	Nov x Hem	22	0.000	0.107	0.746	0.005
	Nov x Hem x Group	22	0.002	6.727	0.017*	0.234
Hippocampus	Main effect of Novelty (Nov)	22	0.019	10.71	0.003**	0.327
	Nov x Group	22	0.001	0.467	0.502	0.021
	Main effect of Hemisphere (Hem)	22	0.000	0.004	0.949	0.000
	Hem x Group	22	0.000	0.896	0.354	0.039
	Nov x Hem	22	0.002	10.44	0.004**	0.322
	Nov x Hem x Group	22	0.000	0.474	0.499	0.021
Parahippocampus	Main effect of Novelty (Nov)	22	0.061	23.57	0.000***	0.517
	Nov x Group	22	0.000	0.134	0.718	0.006
	Main effect of Hemisphere (Hem)	22	0.000	0.001	0.971	0.000
	Hem x Group	22	0.000	0.048	0.829	0.002
	Nov x Hem	22	0.000	1.963	0.175	0.082
	Nov x Hem x Group	22	0.000	0.772	0.389	0.034

*p<0.05, **p<0.01, ***p<0.001

Table 29.

Neural Discrimination Post-Hoc: BA 37 – ANOVA Novelty x Hemisphere x Group

	New Object		Studied Object				
	M	*SD*	*M*	*SD*	*F*	df	η^2
TBI Group							
Right Hemisphere	0.032	0.040	-0.061	0.060	12.12**	11	0.524
Left Hemisphere	0.020	0.033	-0.052	0.053	11.53**	11	0.512
OI Group							
Right Hemisphere	0.010	0.033	-0.042	0.044	23.39**	11	0.680
Left Hemisphere	0.016	0.031	-0.052	0.043	25.80**	11	0.701

*p<0.05, **p<0.01, ***p<0.001

Table 30.

Neural Discrimination: Parietal Regions – ANOVA: Novelty (new vs. studied) x Hemisphere (left vs. right) x Group (TBI vs. OI)

		df	*MS*	*F*	*p*	η^2
Parietal Regions						
BA 7	Main effect of Novelty (Nov)	22	0.240	45.58	0.000***	0.674
	Nov x Group	22	0.024	4.619	0.043*	0.174
	Main effect of Hemisphere (Hem)	22	0.000	0.653	0.428	0.029
	Hem x Group	22	0.001	1.332	0.261	0.057
	Nov x Hem	22	0.002	2.327	0.141	0.096
	Nov x Hem x Group	22	0.000	0.472	0.499	0.021
BA 40	Main effect of Novelty (Nov)	22	0.000	5.954	0.023	0.213
	Nov x Group	22	0.001	0.667	0.423	0.029
	Main effect of Hemisphere (Hem)	22	0.018	0.672	0.421	0.030
	Hem x Group	22	0.002	1.937	0.178	0.081
	Nov x Hem	22	0.000	0.168	0.686	0.008
	Nov x Hem x Group	22	0.000	0.383	0.542	0.017

*p<0.05, **p<0.01, ***p<0.001

Table 31.

Neural Discrimination Post-Hoc: BA 7 – Novelty x Group

	New Object		Studied Object				
	M	*SD*	*M*	*SD*	*F*	df	η^2
TBI Group	0.064	0.037	-0.068	0.049	56.75***	11	0.838
OI Group	0.034	0.061	-0.034	0.063	8.133*	11	0.425

*p<0.05, **p<0.01, ***p<0.001

Table 32.

Neural Discrimination: Cingulate – ANOVA: Novelty (new vs. studied) x Hemisphere (left vs. right) x Group (TBI vs. OI)

		df	*MS*	*F*	*p*	η^2
Cingulate						
Anterior Cingulate	Main effect of Novelty (Nov)	22	0.016	8.035	0.010*	0.268
	Nov x Group	22	0.004	1.991	0.172	0.083
	Main effect of Hemisphere (Hem)	22	0.000	13.59	0.001**	0.382
	Hem x Group	22	0.000	1.018	0.324	0.044
	Nov x Hem	22	0.000	3.259	0.085	0.129
	Nov x Hem x Group	22	0.000	0.652	0.428	0.029
Posterior Cingulate	Main effect of Novelty (Nov)	22	0.218	38.84	0.000***	0.638
	Nov x Group	22	0.000	0.002	0.963	0.000
	Main effect of Hemisphere (Hem)	22	0.001	4.782	0.040*	0.179
	Hem x Group	22	0.000	3.036	0.095	0.121
	Nov x Hem	22	0.004	6.021	0.023*	0.215
	Nov x Hem x Group	22	0.000	0.164	0.689	0.007

*p<0.05, **p<0.01, ***p<0.001

Table 33.
Simultaneous Regression Analyses: Regression of Neuropsychological Test Variables onto Activation in Each Hemisphere for BA 46

	Variable	B	SE B	β	*t*	*p*
TBI Group						
Left Hem.	PASAT	0.000	0.000	-0.809	-1.145	0.304
	WAIS-III PSI	0.000	0.000	0.323	0.533	0.617
	CVLT-II SDFR	-0.002	0.002	-0.456	-0.946	0.387
	DKEFS Design Fluency	0.000	0.002	-0.097	-0.123	0.907
	DKEFS CW Interference	0.002	0.001	0.914	1.186	0.289
	DKEFS CW Interference/Switching	0.000	0.001	-0.039	-0.046	0.965
Right Hem.	PASAT	-0.001	0.000	-0.981	-1.687	0.152
	WAIS-III PSI	0.000	0.000	0.850	1.702	0.149
	CVLT-II SDFR	-0.001	0.002	-0.290	-0.730	0.498
	DKEFS Design Fluency	-0.002	0.002	-0.698	-1.071	0.333
	DKEFS CW Interference	0.003	0.001	1.229	1.937	0.111
	DKEFS CW Interference/Switching	0.000	0.001	-0.102	-0.146	0.890
OI Group						
Left Hem.	PASAT	0.000	0.001	-0.051	-0.088	0.933
	WAIS-III PSI	0.001	0.001	0.558	1.022	0.354
	CVLT-II SDFR	-0.005	0.008	-0.321	-0.717	0.506
	DKEFS Design Fluency	0.001	0.002	0.133	0.344	0.745
	DKEFS CW Interference	-0.002	0.002	-0.404	-0.685	0.524
	DKEFS CW Interference/Switching	0.000	0.004	-0.085	-0.128	0.903
Right Hem.	PASAT	-0.001	0.001	-0.469	-0.791	0.465
	WAIS-III PSI	0.001	0.001	0.735	1.311	0.247
	CVLT-II SDFR	-0.006	0.008	-0.374	-0.814	0.453
	DKEFS Design Fluency	0.001	0.002	0.250	0.629	0.557
	DKEFS CW Interference	-0.003	0.002	-0.862	-1.425	0.214
	DKEFS CW Interference/Switching	0.005	0.004	0.815	1.193	0.286

*p<0.05, **p<0.01, ***p<0.001

Table 34.
Simultaneous Regression Analyses: Regression of Neuropsychological Test Variables onto Activation in Each Hemisphere for BA 37

	Variable	B	SE B	β	*t*	*p*
TBI Group						
Left Hem.	PASAT	0.000	0.000	-0.340	-0.601	0.574
	WAIS-III PSI	0.000	0.000	1.067	2.201	0.079
	CVLT-II SDFR	-0.001	0.002	-0.176	-0.457	0.667
	DKEFS Design Fluency	-0.001	0.002	-0.187	-0.296	0.779
	DKEFS CW Interference	0.003	0.002	0.985	1.598	0.171
	DKEFS CW Interference/Switching	-0.002	0.002	-0.770	-1.138	0.307
Right Hem.	PASAT	0.000	0.000	-0.026	-0.053	0.960
	WAIS-III PSI	0.001	0.000	1.255	2.950*	0.032
	CVLT-II SDFR	-0.002	0.002	-0.310	-0.917	0.401
	DKEFS Design Fluency	0.001	0.002	0.257	0.464	0.662
	DKEFS CW Interference	0.002	0.002	0.607	1.122	0.313
	DKEFS CW Interference/Switching	-0.004	0.002	-1.364	-2.296	0.070
OI Group						
Left Hem.	PASAT	-0.002	0.000	-1.161	-8.518***	0.000
	WAIS-III PSI	0.002	0.000	1.504	11.665***	0.000
	CVLT-II SDFR	-0.004	0.002	-0.186	-1.761	0.138
	DKEFS Design Fluency	-0.001	0.000	-0.093	-1.020	0.354
	DKEFS CW Interference	-0.002	0.001	-0.387	-2.781*	0.039
	DKEFS CW Interference/Switching	0.007	0.001	1.115	7.098	0.001
Right Hem.	PASAT	-0.002	0.000	-1.212	-3.996*	0.010
	WAIS-III PSI	0.001	0.000	1.342	4.679**	0.005
	CVLT-II SDFR	-0.001	0.004	-0.039	-0.164	0.876
	DKEFS Design Fluency	-0.002	0.001	-0.341	-1.677	0.154
	DKEFS CW Interference	-0.003	0.001	-0.621	-2.006	0.101
	DKEFS CW Interference/Switching	0.007	0.002	1.243	3.554*	0.016

*p<0.05, **p<0.01, ***p<0.001

Table 35.
Simultaneous Regression Analyses: Regression of Neuropsychological Test Variables onto Activation in Each Hemisphere for BA 7

	Variable	B	SE B	β	*t*	*p*
TBI Group						
Left Hem.	PASAT	0.000	0.000	0.506	0.884	0.417
	WAIS-III PSI	0.001	0.000	1.404	2.857*	0.036
	CVLT-II SDFR	-0.001	0.002	-0.258	-0.662	0.537
	DKEFS Design Fluency	-0.001	0.002	-0.255	-0.398	0.707
	DKEFS CW Interference	0.000	0.001	-0.180	-0.289	0.784
	DKEFS CW Interference/Switching	-0.002	0.002	-0.876	-1.277	0.258
Right Hem.	PASAT	0.000	0.001	0.450	0.792	0.464
	WAIS-III PSI	0.001	0.000	1.326	2.719*	0.042
	CVLT-II SDFR	-0.001	0.003	-0.166	-0.428	0.686
	DKEFS Design Fluency	0.001	0.002	0.257	0.405	0.703
	DKEFS CW Interference	0.000	0.002	-0.010	-0.016	0.988
	DKEFS CW Interference/Switching	-0.004	0.002	-1.322	-1.941	0.110
OI Group						
Left Hem.	PASAT	-0.001	0.001	-0.484	-1.077	0.331
	WAIS-III PSI	0.002	0.001	0.980	2.303	0.069
	CVLT-II SDFR	0.000	0.009	-0.019	-0.053	0.960
	DKEFS Design Fluency	-0.002	0.002	-0.281	-0.933	0.394
	DKEFS CW Interference	-0.006	0.003	-1.076	-2.342	0.066
	DKEFS CW Interference/Switching	0.008	0.004	0.968	1.866	0.121
Right Hem.	PASAT	-0.002	0.001	-0.779	-1.865	0.121
	WAIS-III PSI	0.002	0.001	1.218	3.085*	0.027
	CVLT-II SDFR	-0.003	0.010	-0.084	-0.260	0.805
	DKEFS Design Fluency	-0.002	0.002	-0.215	-0.766	0.478
	DKEFS CW Interference	-0.007	0.003	-0.943	-2.211	0.078
	DKEFS CW Interference/Switching	0.010	0.005	0.984	2.044	0.096

*p<0.05, **p<0.01, ***p<0.001

Table 36.
BA 46 - Hierarchical Logistical Regression

Step	$\chi 2$	$\Delta\chi 2$	R^2	ΔR^2	% correctly predicted
1 DKEFS Design Fluency [1]	15.171*	15.171*	0.625	0.625	83.3%
1 PASAT [1]	19.443*	4.272*	0.740	0.115	91.7%
2 No fMRI Data Added to the Model[2]	--	--	--	--	--
1 Studied Match – Right Hemisphere [2]	5.946*	5.046*	0.293	0.293	70.8%
1 Studied Match – Left Hemisphere [2]	13.952*	8.007*	0.588	0.295	79.2%
2 DKEFS Design Fluency [1]	25.935*	11.983*	0.881	0.293	91.7%

[1] Neuropsychological test variables entered stepwise in this block: PASAT, WAIS-III PSI, DKEFS Design Fluency Total Scaled Score, DKEFS Color-Word Interference Scaled Score, DKEFS Color-Word Interference Switching Scaled Score. [2] fMRI variables entered stepwise in this block: New Match – Right Hemisphere, New Match – Left Hemisphere, Studied Match – Right Hemisphere, Studied Match – Left Hemisphere, New Non-Match – Right Hemisphere, New Non-Match – Left Hemisphere, Studied Non-Match – Right Hemisphere, Studied Non-Match – Left Hemisphere.
Note. R^2 = Nagelkerke R^2.
*$p < 0.05$

Table 37.
BA 37 - Hierarchical Logistical Regression

Step	$\chi 2$	$\Delta\chi 2$	R^2	ΔR^2	% correctly predicted
1 DKEFS Design Fluency [1]	15.171*	15.171*	0.625	0.625	83.3%
1 PASAT [1]	19.443*	4.272*	0.740	0.115	91.7%
2 No fMRI Data Added to the Model[2]	--	--	--	--	--
1 No fMRI Data Added to the Model[2]	--	--	--	--	--
1 DKEFS Design Fluency [1]	15.171*	15.171*	0.625	0.625	83.3%
1 PASAT [1]	19.443*	4.272*	0.740	0.115	91.7%

[1] Neuropsychological test variables entered stepwise in this block: PASAT, WAIS-III PSI, DKEFS Design Fluency Total Scaled Score, DKEFS Color-Word Interference Scaled Score, DKEFS Color-Word Interference Switching Scaled Score. [2] fMRI variables entered stepwise in this block: New Match – Right Hemisphere, New Match – Left Hemisphere, Studied Match – Right Hemisphere, Studied Match – Left Hemisphere, New Non-Match – Right Hemisphere, New Non-Match – Left Hemisphere, Studied Non-Match – Right Hemisphere, Studied Non-Match – Left Hemisphere.
Note. R^2 = Nagelkerke R^2.
*$p < 0.05$

Table 38.
BA 7 - Hierarchical Logistical Regression

Step	$\chi 2$	$\Delta\chi 2$	R^2	ΔR^2	% correctly predicted
1 DKEFS Design Fluency [1]	15.171*	15.171*	0.625	0.625	83.3%
1 PASAT [1]	19.443*	4.272*	0.740	0.115	91.7%
2 No fMRI Data Added to the Model[2]	--	--	--	--	--
1 No fMRI Data Added to the Model[2]	--	--	--	--	--
1 DKEFS Design Fluency [1]	15.171*	15.171*	0.625	0.625	83.3%
1 PASAT [1]	19.443*	4.272*	0.740	0.115	91.7%

[1] Neuropsychological test variables entered stepwise in this block: PASAT, WAIS-III PSI, DKEFS Design Fluency Total Scaled Score, DKEFS Color-Word Interference Scaled Score, DKEFS Color-Word Interference Switching Scaled Score. [2] fMRI variables entered stepwise in this block: New Match – Right Hemisphere, New Match – Left Hemisphere, Studied Match – Right Hemisphere, Studied Match – Left Hemisphere, New Non-Match – Right Hemisphere, New Non-Match – Left Hemisphere, Studied Non-Match – Right Hemisphere, Studied Non-Match – Left Hemisphere.
Note. R^2 = Nagelkerke R^2.
*$p < 0.05$

Figure 13. Comparison of Structural MRI. A representative of the OI control group is presented (top) with a representative of the TBI group (bottom). Participants were matched on gender and similar in age.

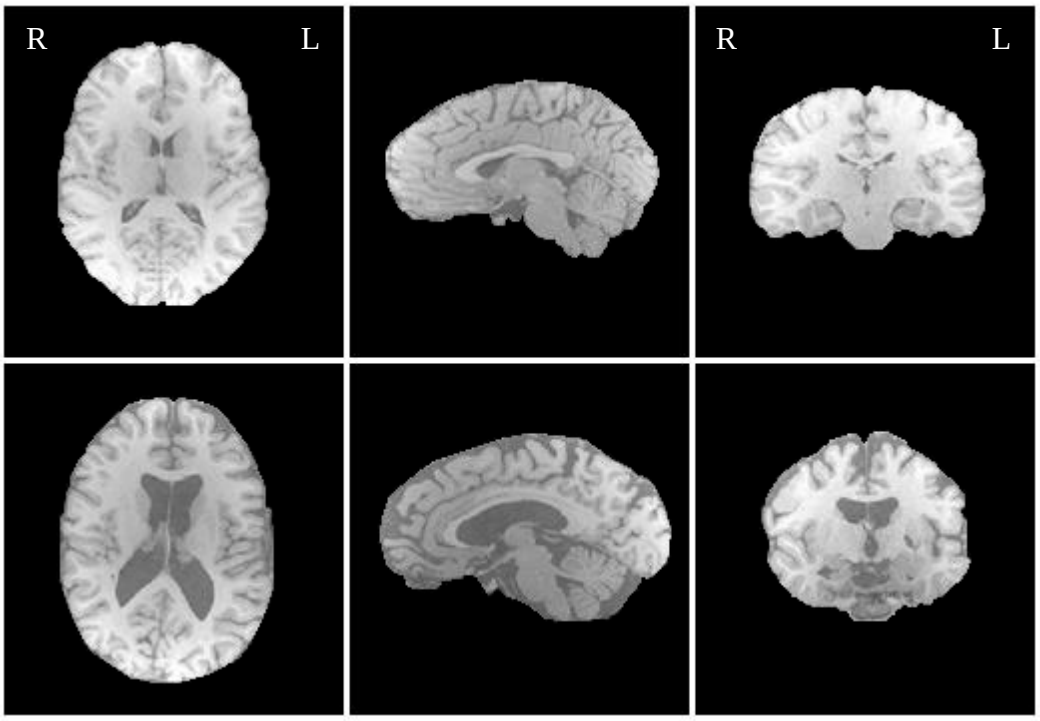


Figure 14. Graph of BA 46 Hemisphere by Group Interaction.

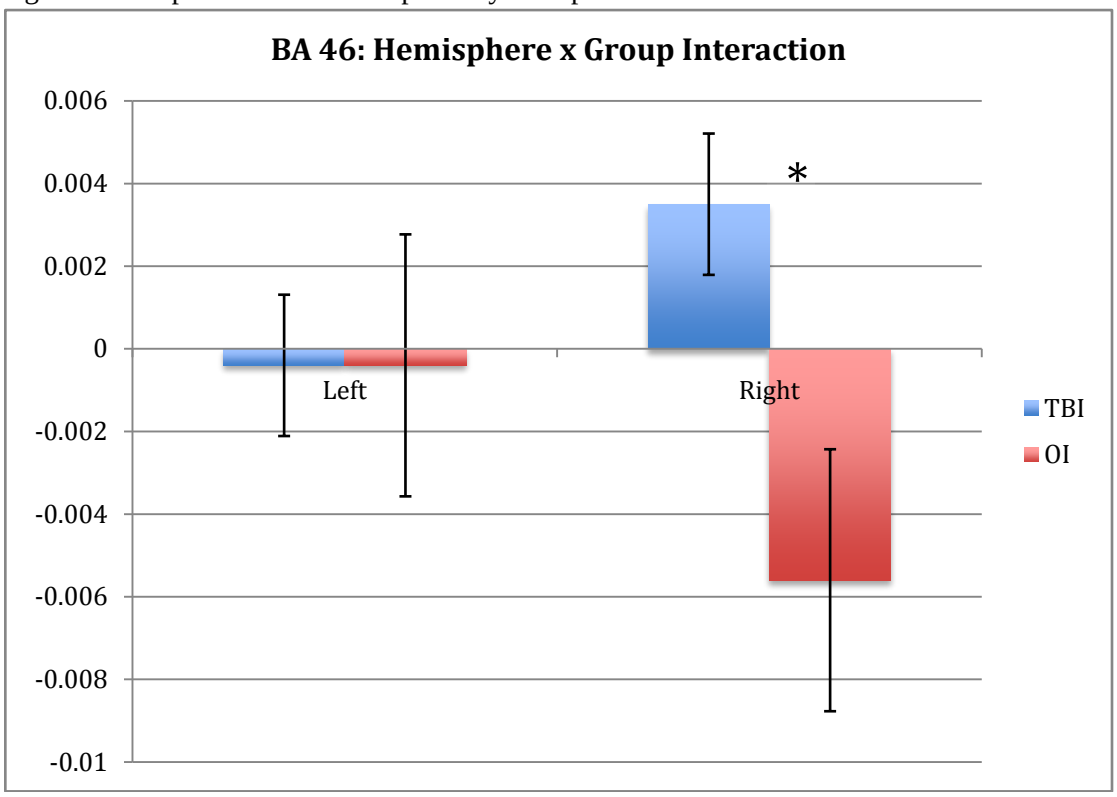


Figure 15. Images of BA 46 Hemisphere by Group Interaction. Participants within the OI group (top) decreased in activation within right BA 46, whereas the TBI group (bottom) increased activation within right BA 46.

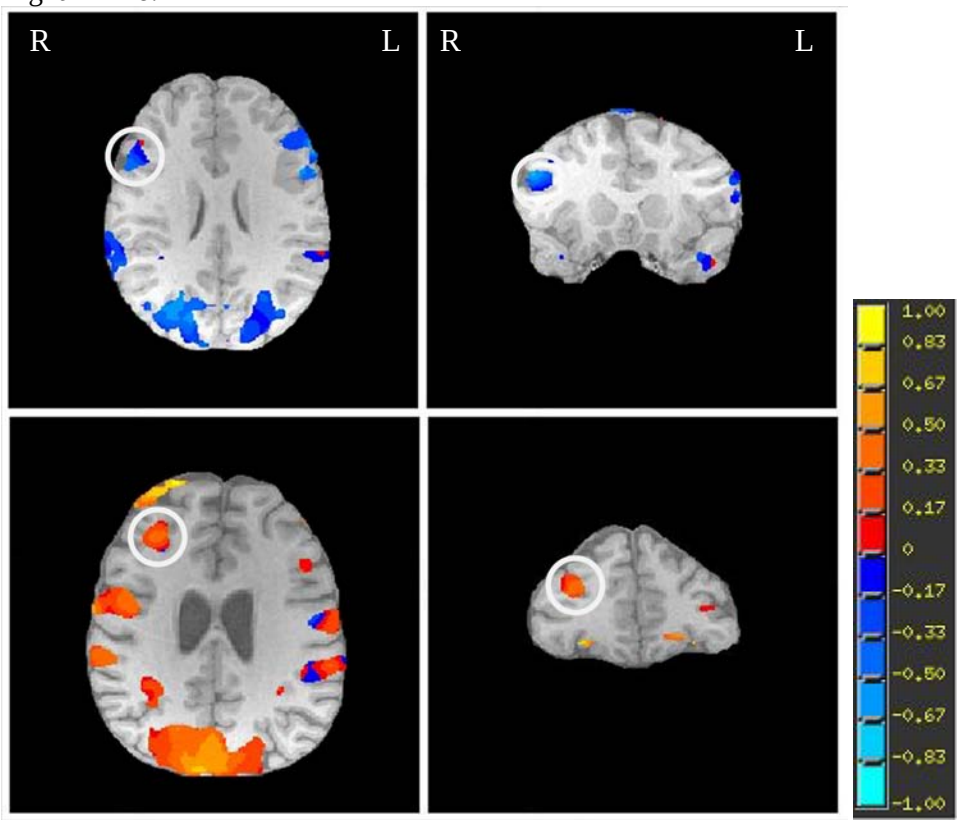


Figure 16. Graph of BA 37 Novelty by Hemisphere Interaction.

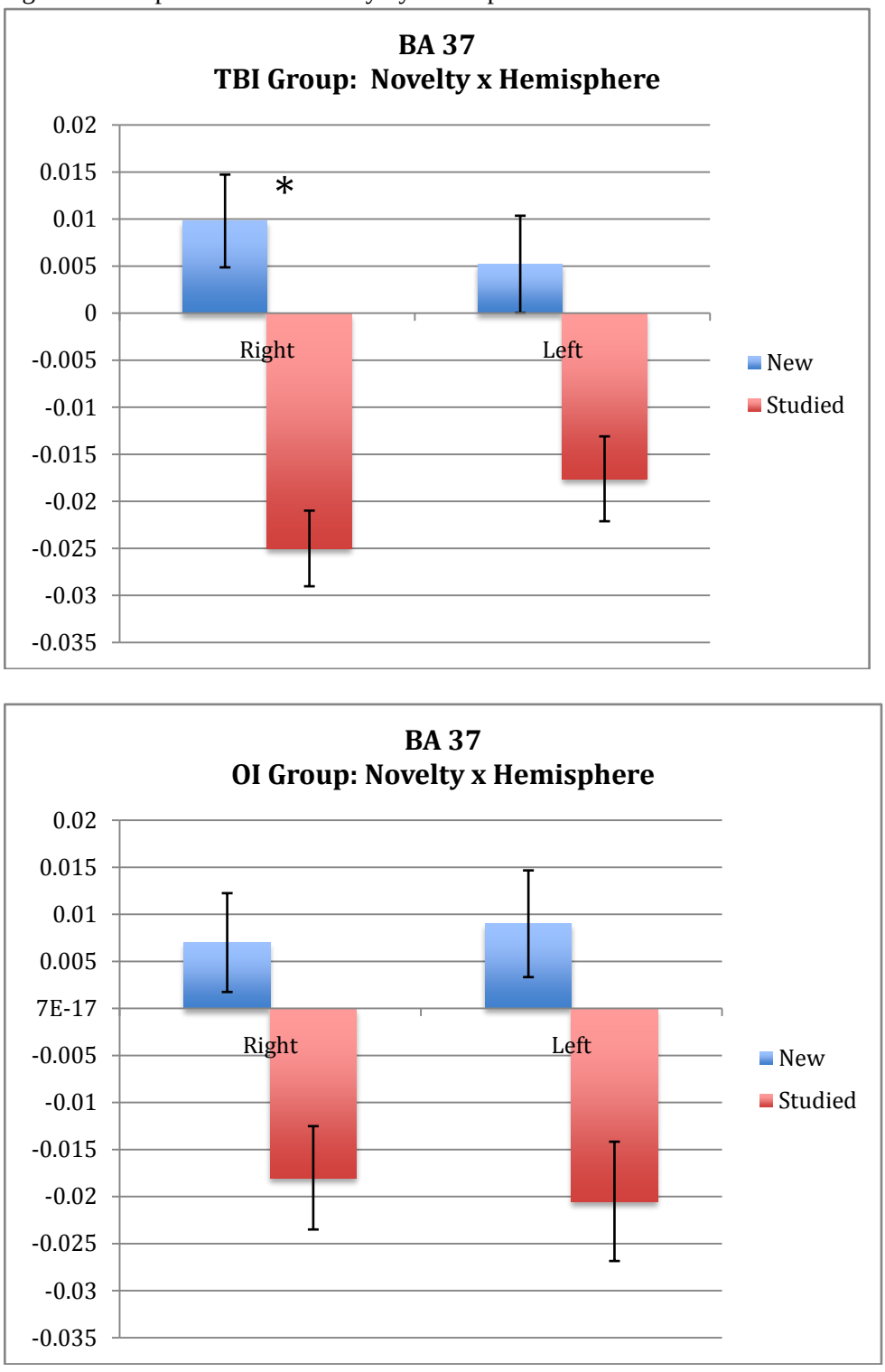
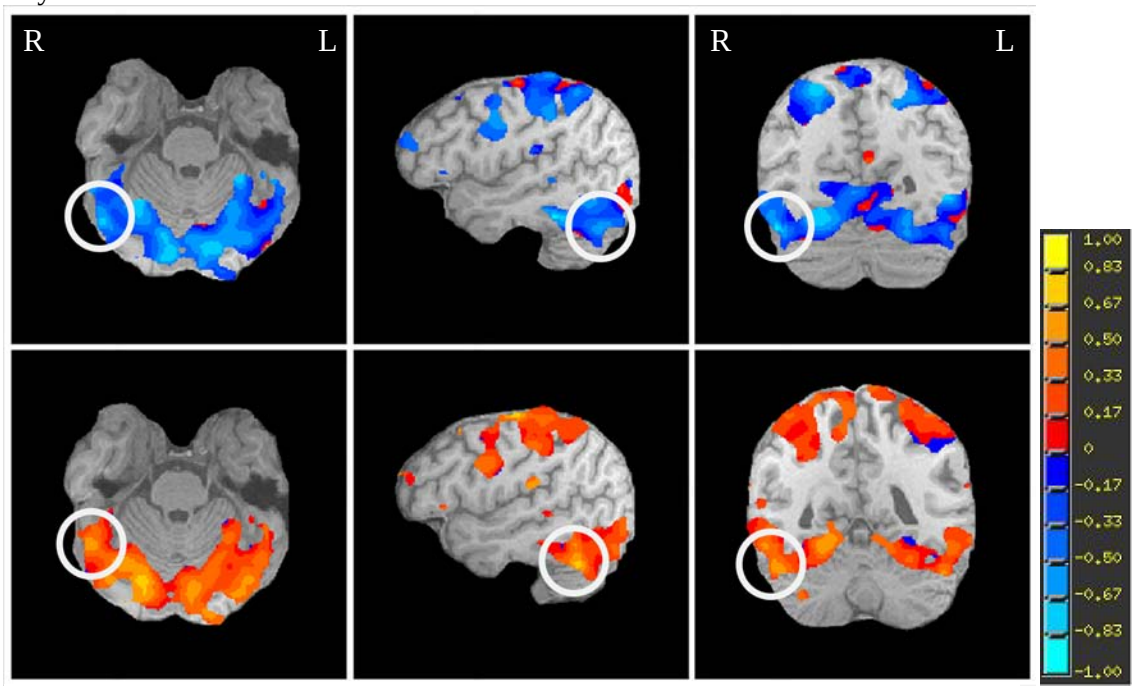


Figure 17. Images of BA 37 Novelty by Hemisphere Interaction. New items demonstrated activation while studied items showed deactivation within bilateral BA 37. The difference between novelty types was statistically significant within the right hemisphere for the TBI group only.



Representative participants from the TBI group (above) and OI group (below) are presented. Neural activation in response to studied items is presented in the top row and response to new items on the bottom.

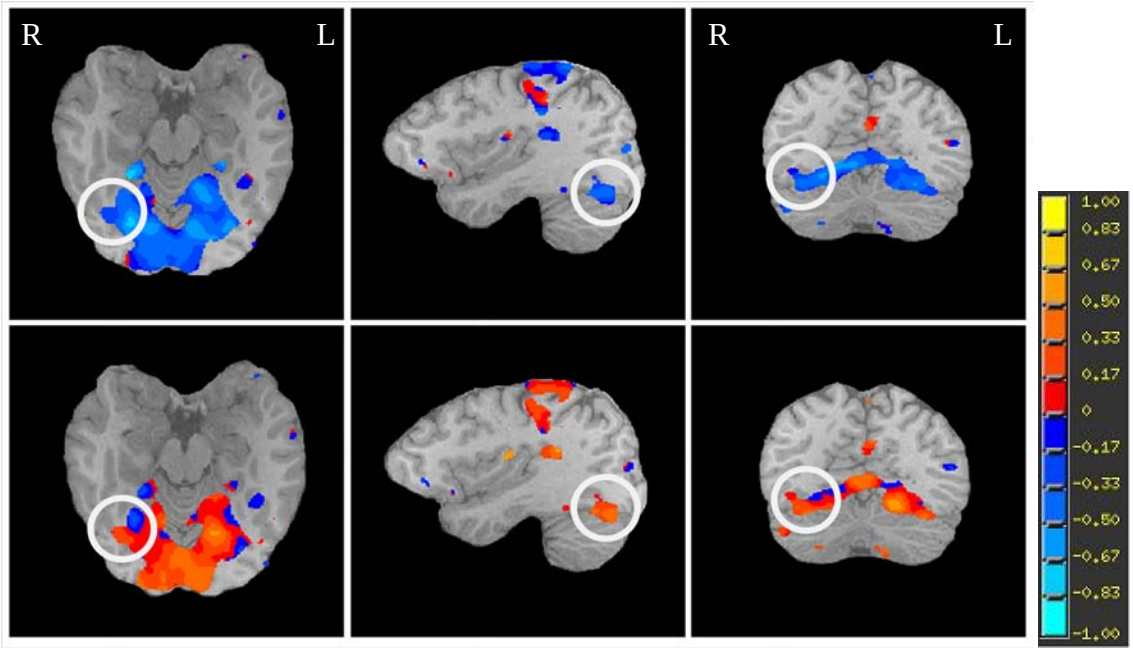


Figure 18. Graph of BA 7 Novelty by Hemisphere Interaction.

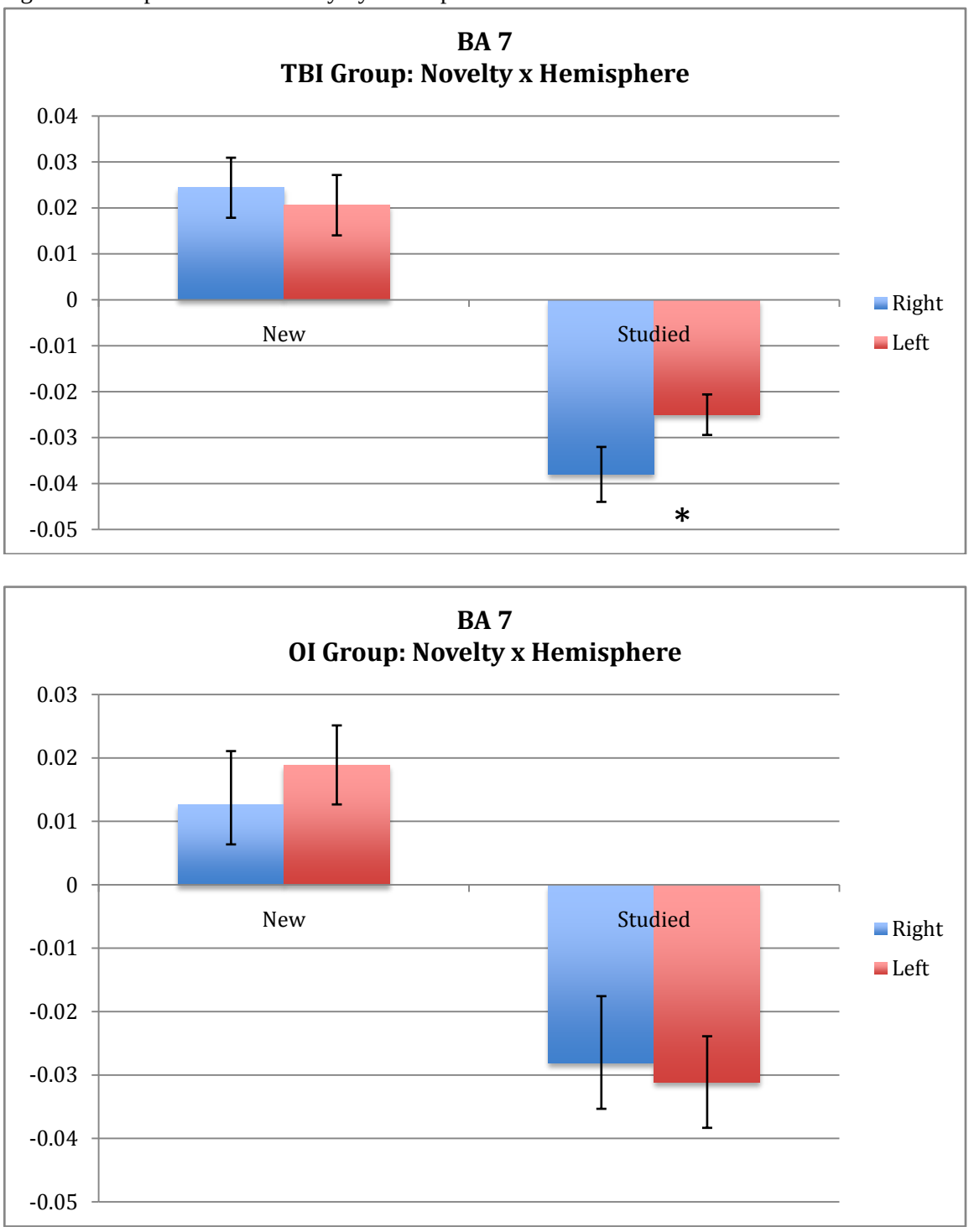


Figure 19. Images of BA 7 Novelty by Hemisphere Interaction. The top row shows significant differences between right and left hemispheres for a TBI participant for studied targets. Statistically significantly greater decreases were found for the right hemisphere compared to the left. An OI control participant is presented in the bottom row, but there were no significant hemispheric differences between hemispheres found for studied items.

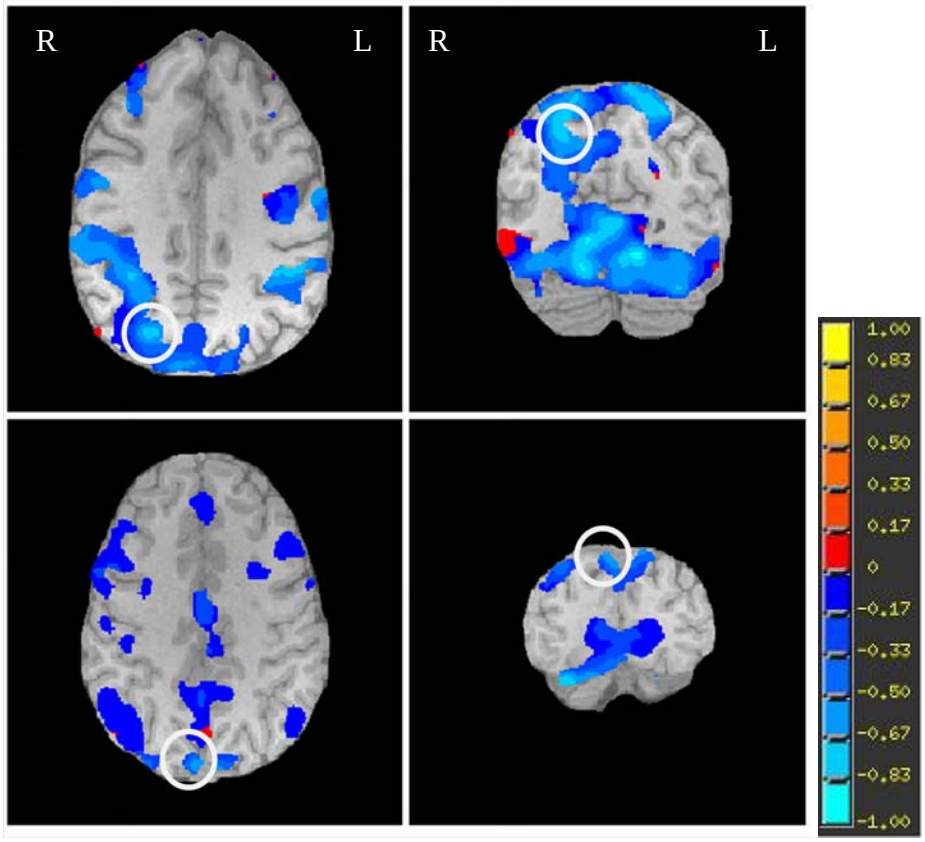


Figure 20. Graph of BA 7 Match Type by Novelty by Group Interaction.

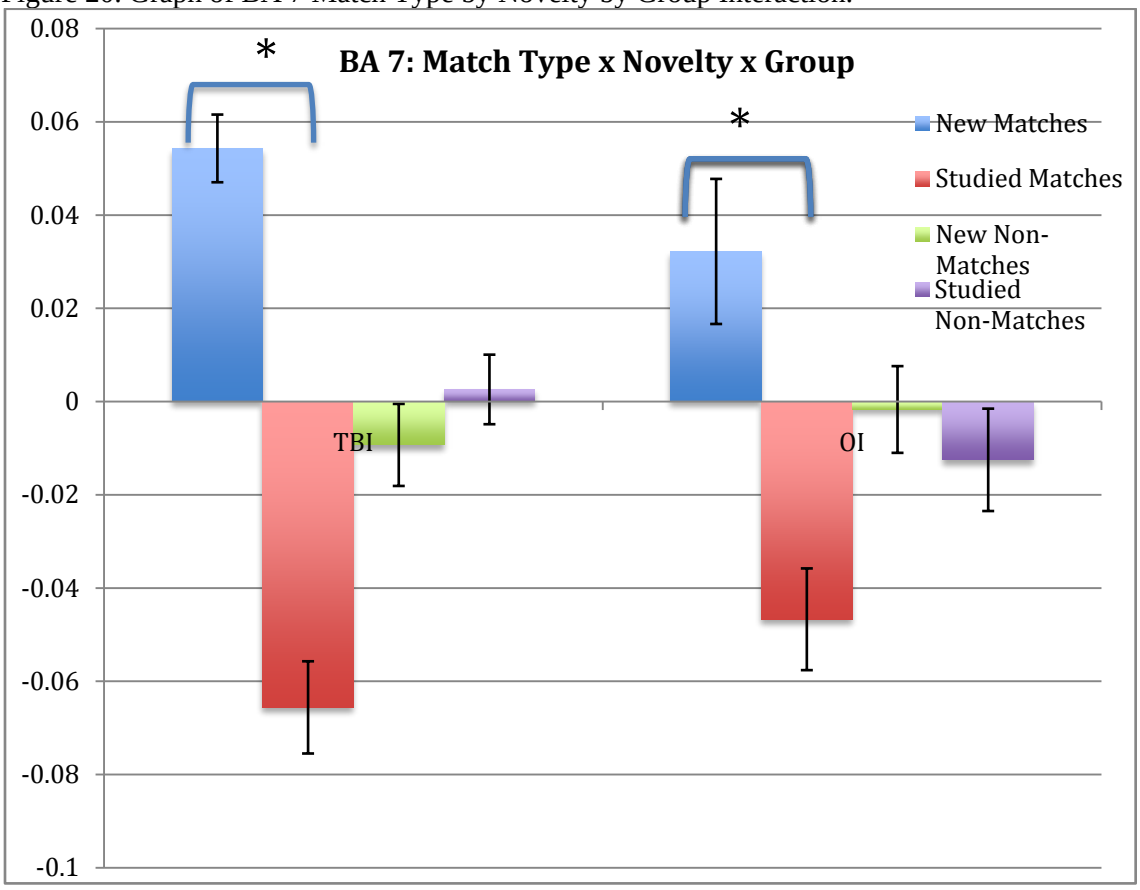
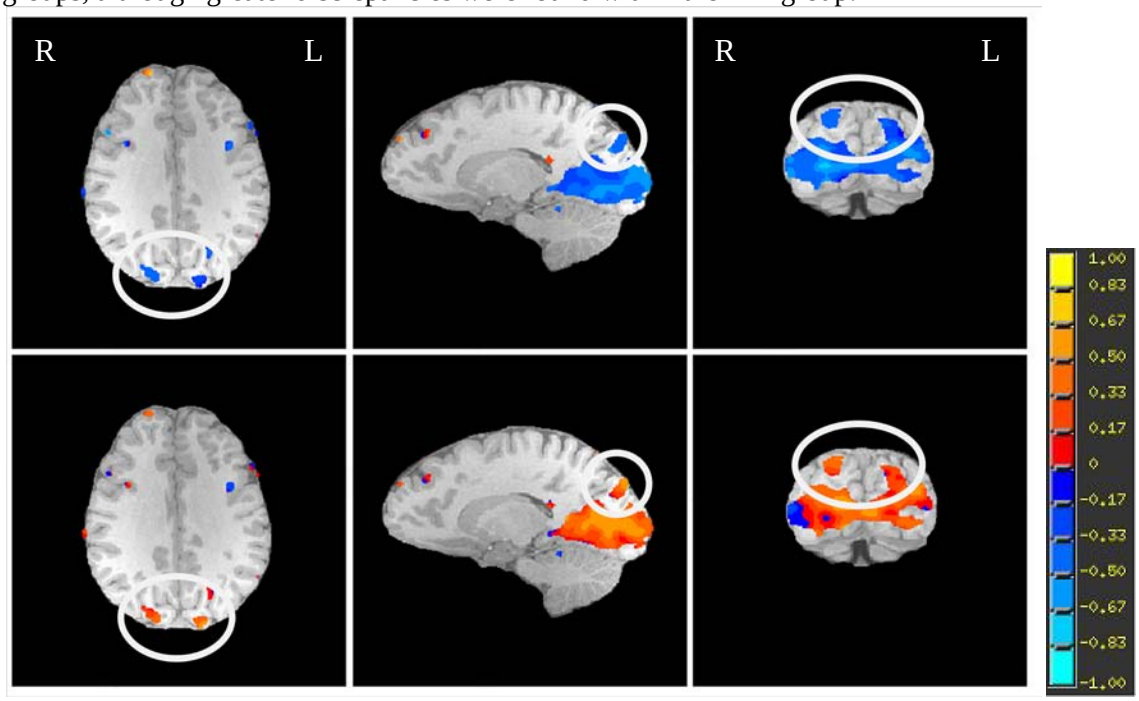


Figure 21. Images of Match Type by Novelty by Group Interaction. Statistically significant differences were found between studied matches and new matches within both the TBI and OI groups, although greater discrepancies were found within the TBI group.



An OI control participant is presented above, and a TBI participant is presented below. Studied matches showed a decrease in activation (top rows) whereas new matches showed an increase in activation. The discrepancy between studied and new matches was of a greater magnitude for the TBI group.

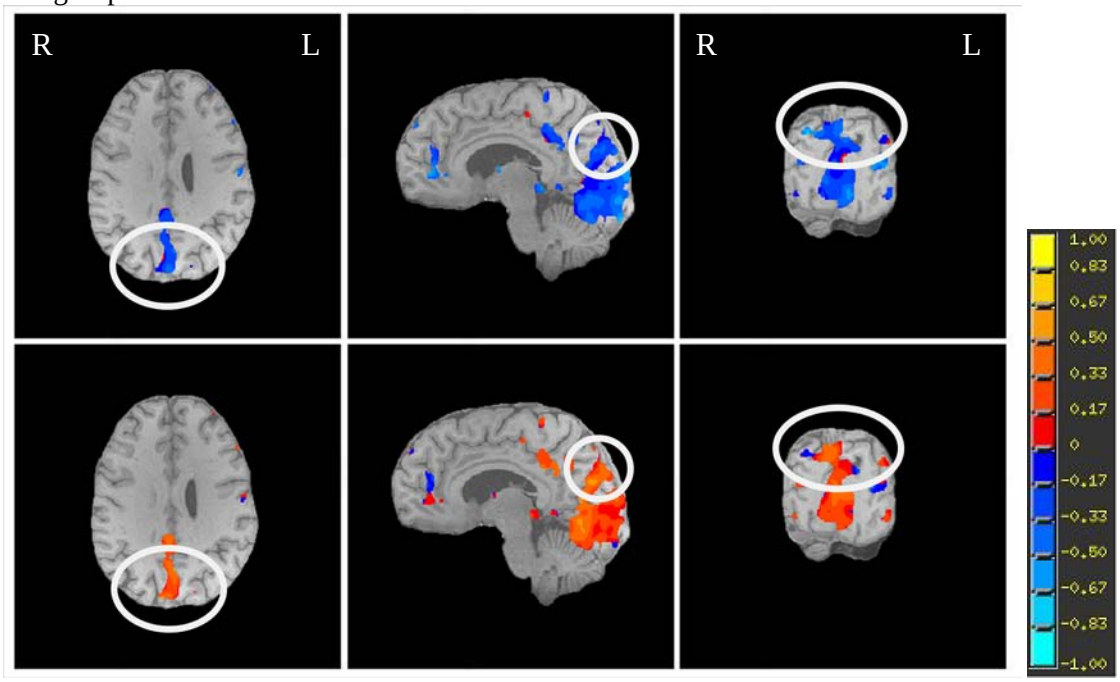


Figure 22. Graph of BA 37 Neural Discrimination Novelty by Hemisphere by Group Interaction.

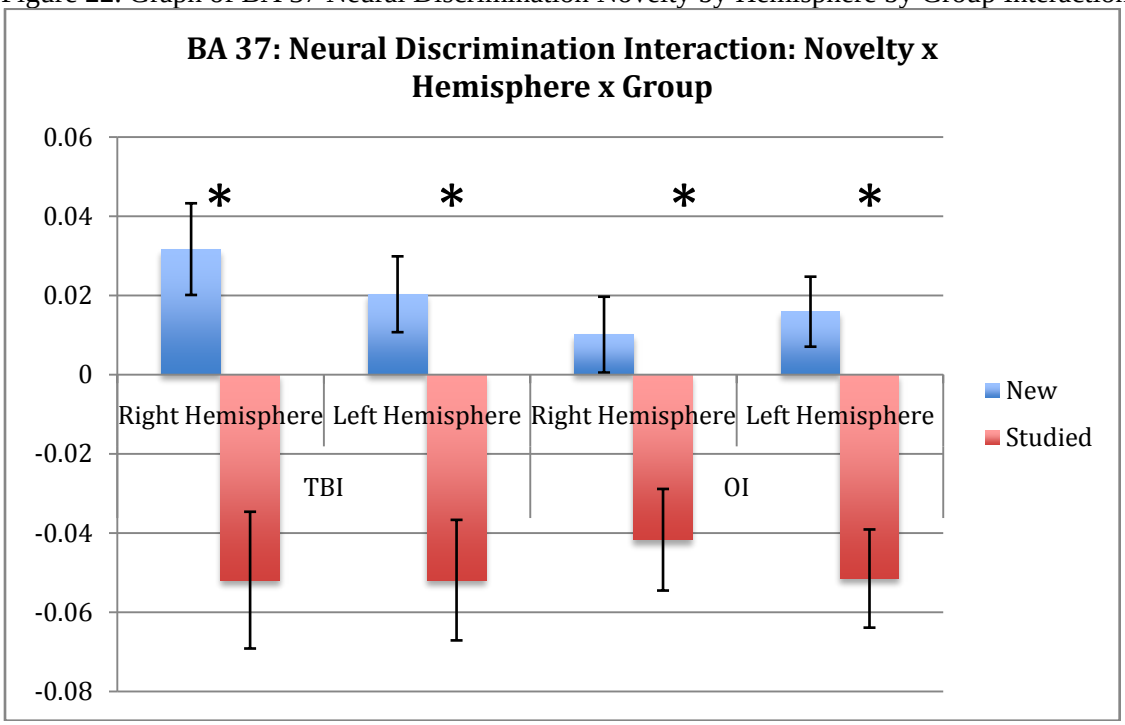
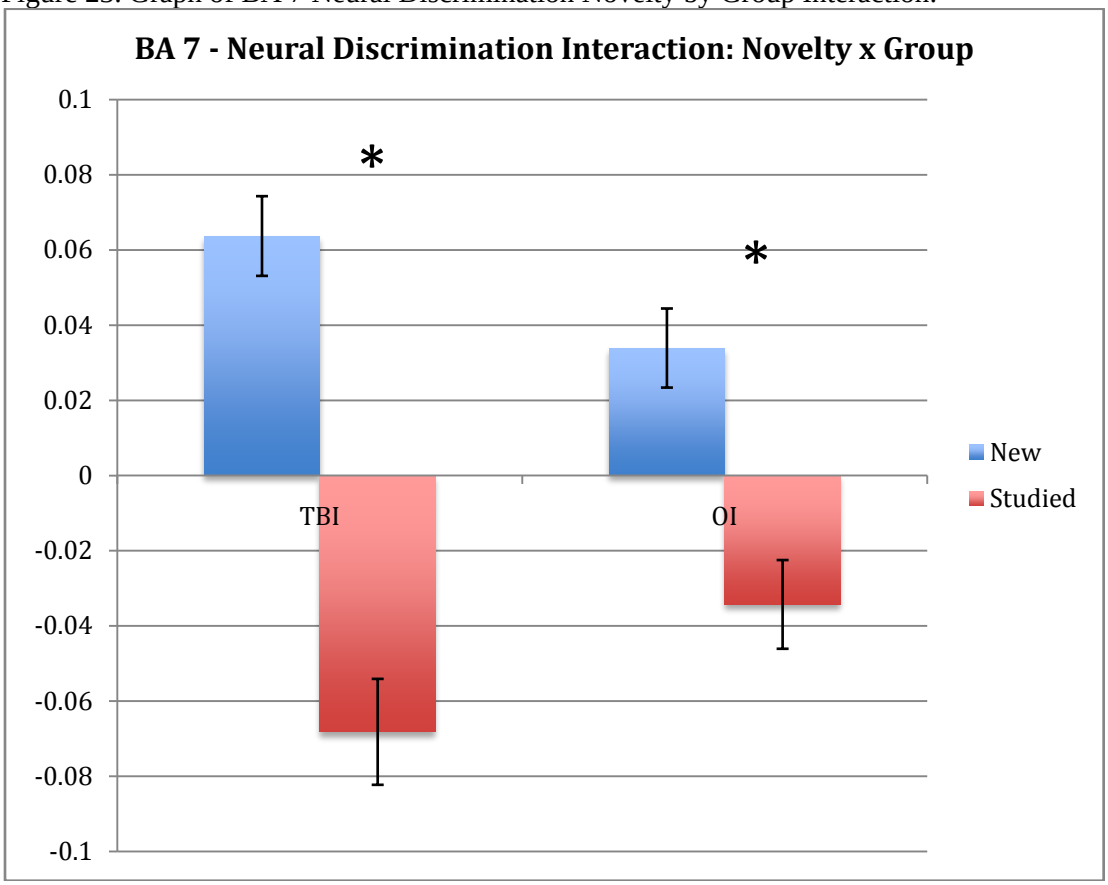


Figure 23. Graph of BA 7 Neural Discrimination Novelty by Group Interaction.



CHAPTER FOUR: DISCUSSION

The purpose of this study was to investigate the cortical activation of working memory in individuals with TBI and the relationship of this activation to paper-and-pencil neuropsychological tests. It utilized event-related methodology, a 3T scanner, and a working memory task different from those used in previous studies, in order to add to a relatively new literature involving fMRI and TBI. It was intended to 1) examine performance on behavioral aspects of the DMS task (accuracy and reaction time) within individuals with TBI and an OI comparison group; 2) compare patterns of neural activation associated with the processing of visual information related to recognition and working memory; and 3) correlate this information with neuropsychological test data.

It was hypothesized that 1) TBI participants would activate areas previously identified in preliminary studies using the current DMS task, namely working memory areas within the frontal cortex (BA 45/47, 46, 9, 10, and anterior cingulate), temporal cortex (fusiform, parahippocampus, and hippocampus), and visual cortex (precuneus and occipital regions). However, it was also thought that TBI individuals would show increased activation compared to controls in the frontal and parietal areas. It was hypothesized that 2) TBI participants would show a positive correlation between neuropsychological test performance and brain activation, with better performance related to increases in activation in frontal and parietal areas. It was hypothesized that 3) controls would show a negative correlation between neuropsychological testing and brain activation, with decreased activity in similar frontal and parietal areas. Exploratory analyses were conducted in order to examine the utility of fMRI as a diagnostic tool above and beyond neuropsychological testing alone.

In order to do this, a number of analyses were conducted. First, potentially confounding variables such as demographic variables, emotional functioning, impulsivity, and community integration were compared between groups and no statistically significant differences were found. Next, neuropsychological test data were compared between groups. Although an alpha of 0.01 was set to account for a large amount of neuropsychological test data, it should be noted that predicted pre-injury IQ as measured by a test of reading ability (WTAR-FSIQ) was significant at an alpha of 0.05. This presents a potential confound that will be discussed later. Both TBI and OI groups were both within the average range of intelligence. Groups were comparable on measures of language functioning, visual-spatial abilities, and sustained attention. However, results suggested that TBI and OI groups differed on measures of processing speed (WAIS-III PSI), working memory (PASAT), recall after an interference task (CVLT-II Short Delay Free Recall), design fluency (DKEFS Design Fluency Total Correct), inhibition (DKEFS Color Word

Interference), and inhibition and switching (DKEFS Color Word Interference/Switching). It is interesting that these tests all require inhibition (of previously learned responses or newly learned but now irrelevant information), and mental flexibility/manipulation of information. Furthermore, most of these tests include a processing speed component.

Although differences were seen on neuropsychological test performance, behavioral data on the DMS task indicated that there were no differences in accuracy between groups. Stated another way, TBI participants were performing just as well as OI control participants in terms of accuracy on the task. This is an important point, as previous literature regarding fMRI within TBI samples highlights differences in patterns of activation depending on the comparability of TBI and control groups on the fMRI task itself (see above for review). Differences were observed on reaction time for the DMS task even when accounting for physical slowing (e.g. covarying for Finger Tapping score). This suggests that the TBI group may have demonstrated slowed processing on the DMS task, especially on studied matching targets.

Discussion of Hypothesis 1:

The next step in analysis was to compare patterns of neural activation associated with the DMS task between groups. The current study adds an additional level of complexity to existing literature because the event-related design allows one to examine specific aspects of each stimulus, instead of blocking all responses together into one response. This permits the examination of new matches, studied matches, new non-matches, and studied non-matches. In general, it appeared that new objects resulted in activation, whereas studied objects(especially studied matches) resulted in deactivation. This deactivation was unexpected, but the patterns of neural responses and potential interpretations will be presented below.

While main effects for the fMRI data were reported in the Results section, no main effect of group was found within any ROI. Group interactions were found within BA 46 (middle frontal gyrus), BA 37 (inferior temporal gyrus), and BA 7 (precuneus/superior parietal). As hypothesized, the TBI group demonstrated a similar pattern of activation as controls; however, disruption of activation was seen within the TBI group as evidenced by exaggerated response patterns in comparison to the OI control group.

BA 46: The hemisphere by group interaction found within BA 46 indicated that the TBI group increased activation within the right hemisphere, while the OI group decreased responses. This is consistent with previous research that has demonstrated increased activation within the right hemisphere by participants with TBI compared to controls (Christodoulou, et al., 2001; Perlstein, et al., 2004; Rasmussen, et al., 2006), and supports the hypothesis that the TBI group would show increased frontal activation in comparison to controls. In addition, this study

provides additional evidence of right lateralization in TBI samples. While previous studies suggesting right lateralization have utilized healthy control samples, which could present a potential limitation, the current study attempted to account for host factors that may impact cognition (e.g., impulsivity, emotional functioning) by using a control sample that had sustained orthopedic injuries.

Furthermore, the increased activation in the dorsolateral prefrontal cortex for TBI participants, in comparison to controls, is consistent with literature highlighting a posterior to anterior shift. Within the cognitive aging literature, the posterior-anterior shift is well documented (Cabeza, 2002). Consistent with compensatory hypotheses, older adults who were able to perform well on a visual-perception task showed increases in frontal activity and decreases in posterior regions such as the occipital cortex (Davis, et al., 2007). This relationship was found when older adults and younger controls had comparable task performance, consistent with the literature on TBI and fMRI. Davis and colleagues (2007) suggest that more posterior regions responsible for sensory input may experience degradation within older adults, and that frontal regions may organize and redirect sensory input in a top-down manner. This may also be the case with individuals with TBI. Another potential explanation stems from the fact that the individuals within the current study are known to differ significantly from controls on tasks of inhibition, mental flexibility, and manipulation of information, which are all tasks largely associated with BA 46. Therefore, the increased activation seen by TBI participants may also be a result of increased efforts to recruit this area for successfully performing the DMS task.

BA 37: The novelty by hemisphere by group interaction within BA 37 indicates that the difference between new and studied objects is statistically significantly different within the right hemisphere for TBI participants only. Although the temporal lobe was not hypothesized to show any group differences, BA 37 was analyzed because it is typically activated in delayed-match-to-sample tasks (Jiang, et al., unpublished data). BA 37 is typically associated with object naming and recognition memory (Stewart, et al., 2001), although there is also evidence to suggest that it plays a part in selective attention and working memory (Zhang, et al., 2008). While a similar pattern of activation (for new objects) and deactivation (for studied objects) is seen within both right and left hemispheres for TBI and OI groups, the pattern appears to be exaggerated for the TBI group in the right hemisphere. In addition, the neural discrimination index (matches – non-matches), revealed a novelty by hemisphere by group interaction. While new objects always resulted in increased activation and studied objects always resulted in decreased activation, the discrepancy between the two was greater for the TBI group, especially within the right hemisphere. This suggests that right BA 37 within the TBI group responds with greater activation

for new material, which is consistent with its role in recognition naming and memory, whereas there is deactivation for previously studied material.

This deactivation was unexpected and somewhat difficult to interpret. However, some theories exist that might lend insight. For instance, there is some evidence to suggest that deactivation may occur when neural resources shift away from ongoing tasks to process increasingly demanding material (Engle, et al., 1995) such as the encoding, maintenance, and retrieval of new information (Habeck, et al., 2005). Other studies have also shown an "old/new" effect within the anterior medial-temporal lobe, in which previously studied ("old") items demonstrate a reduction in activity (Henson, et al., 2003). Another study suggests that decreases in activation within the left anterior medial-temporal lobe are associated with familiarity, as opposed to recollection or implicit priming (Henson, Hornberge, and Rugg, 2005). Although BA 37 is located within the posterior temporal lobe, it is possible that similar processes are occurring. Also, the current study did not examine the effect of repetition of stimuli across time, which may correspond more directly to familiarity as defined by Henson and colleagues (2005), but this may be an interesting avenue of future research to help explain this finding.

BA 7: Parietal patterns included a novelty by hemisphere interaction within BA 7. It was initially stated within hypothesis 1 that activation within parietal regions was expected to increase for TBI participants in comparison to controls. Contrary to that hypothesis, however, it was found that activation within this region actually decreased for both groups. An explanation for this is the fact that BA 7 encompasses a large area within the parietal cortex. While parietal regions are associated with attentional switching and executive functioning, BA 7 is also known to be associated with the "default network" noted among fMRI studies and described earlier. Within this default network, deactivation of BA 7 is typically seen between rest and active states (Raichle, et al., 2000). Activation within BA 7 decreases as other areas become activated. Hemispheric differences were found for studied items (collapsed across match and non-match), in which the right hemisphere showed a greater deactivation than did the left for the TBI group only. Raichle and colleagues (2000) conceptualize the role of BA 7 (precuneus) in the default network as one of vigilance and the continuous gathering of information about the world, with obvious evolutionary ramifications such as the detection of danger within the environment. However, when effort needs to be exerted for successful focused attention on a task, activity in this area is suppressed in order to allow for allocation of resources to other areas. The fact that TBI participants showed a greater decrease than controls within this region may indicate that more resources needed to be reallocated. This may also correspond to increased activation in BA 46 within the frontal regions for the TBI group.

Consistent with this pattern, a match type by novelty by group interaction was also found within BA 7. Again, the general pattern between the TBI and OI groups was similar: new matches resulted in increased activation while studied matches resulted in decreased activation for both groups. Similar to previous analyses, the TBI group appeared to have a more exaggerated response pattern with greater increases for new matches and greater decreases for studied matches. The neural discrimination index, calculated by subtracting non-matches from matches), revealed a pattern in which new objects increased activation for both groups, while studied objects resulted in deactivation for both groups. Yet again, this pattern is more exaggerated for the TBI group. Overall, these patterns suggest that the activation pattern for the TBI group is generally similar to the OI group. However, the TBI group appears to show greater activation than does the OI group for new objects, especially new matches. The TBI group also shows greater deactivation than the OI group for studied objects, especially studied matches.

Discussion of Hypothesis 2 and 3:

Simultaneous regression analyses were conducted to examine the ability of neuropsychological test data to predict percent signal change, as described in hypotheses 2 and 3. It was hypothesized that TBI participants would show a positive correlation between neuropsychological test performance and brain activation, with better performance related to increases in activation in frontal and parietal regions. It was also hypothesized that controls would show a negative correlation between neuropsychological testing and brain activation, with decreased activity in similar frontal and parietal areas, because they were not anticipated to need additional compensation. Before regression analyses were even conducted, it was understood that predictions would have been altered because BA 7 had shown decreased activation, instead of increased activation as initially thought.

ROIs and neuropsychological tests of interest were chosen based on previous analyses. In order to simplify the analyses, only areas that had demonstrated group differences were analyzed. Within BA 46, neuropsychological test data did not predict percent signal change for either the TBI or the OI control group.

For BA 37, WAIS-III Processing Speed Index accounted for a statistically significant amount of variance in percent signal change within the right hemisphere within the TBI group. As hypothesized, this relationship was positive, indicating that activation increased with processing speed, possibly because these individuals were able to successfully recruit neural resources within this area. The OI group demonstrated a similar pattern, with positive associations between PSI and activation in BA 37. Although unexpected, it is possible that even OI control participants were able to recruit additional neural resources and react with faster

processing speeds, although no causal relationship can be inferred. Consistent with a hypothesis of an inverse relationship between neuropsychological testing and brain activation, PASAT, Color Word Interference, and Color Word Interference/Switching were successful predictors of percent signal change. This suggests that the better the neuropsychological test performance, the more efficiently the OI control group was processing information and the fewer resources were needed.

WAIS-III PSI again predicted a statistically significant amount of variance in neural activation within BA 7 for both the TBI and OI groups. As BA 7 showed decreased activation for both groups, the association between neuropsychological testing and neural activity may not seem intuitive. The relationship was positive, which suggests that slower processing speed was associated with greater deactivation. Given the role of BA 7 in the default network, this finding may indicate that those with slower processing speed required a greater reallocation of neural resources away from BA 7to other areas of the brain in order to complete the DMS task.

With regard to hypothesis 2, a positive relationship was found between neuropsychological test data and increased neural activation within the TBI group. However, the relationship was not found within the frontal region, but rather between temporal regions associated with object naming, selective attention and working memory (BA 37). In addition, the hypothesized relationship between neuropsychological testing and BA 7 was indeed positive; however, it was in the opposite direction with poorer performance related to greater deactivation. This again makes sense if the deactivation of BA 7 is related to reallocation of neural resources to other areas, as is consistent with the default network theory. Hypothesis 3 was not supported, as the OI control group showed similar positive relationships between neuropsychological testing and patterns of activation.

It appears that, of all of the neuropsychological tests entered into the model, processing speed (PSI), working memory (PASAT), and executive functioning (Color Word Interference, Color Word Interference/Switching) were most closely correlated to neural activation on the DMS task. These three domains can be conceptualized as overlapping to constitute a model of cognitive control as mentioned in previous literature (Baddeley, 1974; Baddeley, 1981; Sohlberg & Mateer, 1987). This suggests that performance on these measures may lend some insight into the biological underpinnings of cognitive control, including decreased efficiency in those with TBI leading to compensatory recruitment of neural resources (as seen in Discussion of Hypothesis #1).

Exploratory Analyses:

Logistic regression analyses suggest that fMRI data did not add any incremental predictive value beyond neuropsychological testing alone. Although fMRI data would not be used in a clinical setting to diagnose TBI, a scenario such as this could be useful in other settings such as examining mild TBI, especially those with postconcussive syndrome, in future research. Furthermore, the utility of fMRI to predict whether participants belonged to the TBI or OI group, over and above the utility of neuropsychological testing alone, might have contributed to assessing functional reorganization and rehabilitation outcome for rehabilitation in future studies. Unfortunately, this was not found with the current data.

Conclusion:

The current study contributes to the literature on chronic, moderate to severe TBI by using event-related methodology, a 3T scanner, a strong control group, and a working memory task different from those used in previous studies. It also adds to research in neuroscience by examining variations in novelty and match types within a patient population. However, there are limitations to the current study.

The sample size was small, as is typical for fMRI studies due to the cost prohibitive nature of this type of research. As evidenced by Strangman, et al. (2008), however, larger studies may demonstrate more sensitive findings regarding the relationship between behavioral performance and neural activation.

Another limitation is the fact that the TBI group had lower estimated pre-injury IQ scores than the OI control group. Although means for both groups were found to be within the average range, some evidence suggests that lower pre-injury IQ scores may lead to increased activation within midline structures including the posterior cingulate and bilateral thalami (Scheibel, et al., 2009). Of note, although not reported, correlational analyses did not suggest a relationship between premorbid IQ and activation in BA 46, BA 37, or BA 7 in the current sample. Another confound of group differences in preinjury IQ is the effect that this may have on neuropsychological testing. Group differences were found in higher order domains such as working memory and executive functioning, which may be affected by differences in baseline IQ scores. Although it is preferable to avoid this incomparability of group IQ scores, it is nonetheless a limitation of the current sample.

A limitation that is perhaps the greatest cause for concern for the current study, and most fMRI studies in general, is the large number of analyses that were conducted on such a small sample. This would increase the odds of making a Type I error (rejecting the null when the null is true, a “false positive”). Lieberman & Cunningham (2009) suggested addressing this issue within

fMRI research by providing evidence that the findings are theoretically sound and can be replicated. For instance, the ROIs examined within the present study were determined after looking at regions typically activated in DMS studies, combined with altered patterns of activation observed in TBI samples. Though the current study added to the current literature, it also replicated findings such as increased frontal activation and right lateralization for the TBI group. In addition, conservative corrections were used for analyses to minimize the impact of multiple analyses on "false alarms."

Paradoxically, the study is further limited by low power relative to other behavioral studies. Although the sample size of the present study is consistent with that recommended for fMRI research, low power may account for the lack of significant findings when activation was regressed onto neuropsychological test variables within frontal regions. It may also explain why fMRI data did not account for incrementally significant predictive power beyond neuropsychological tests alone when determining group membership.

The aforementioned results may be used as a starting point for future studies. They serve to help establish a pattern of activation for moderate to severe TBI patients. In the future, studies such as this may be conducted to predict outcome following rehabilitation interventions. Patterns of activation within areas such as the frontal and parietal regions may help to determine the most efficacious treatment interventions for patients. Comparisons of traditional neuropsychological testing and fMRI may also be conducted in order to examine any incremental predictive power of one method over another for prediction of functional outcome. More specifically related to the current fMRI task, future research into this area should include analysis of repetition of stimuli on the DMS task used here. Although not within the scope of this study, the DMS task included three presentations of each type of stimuli (new match, studied match, new non-match, studied non-match). Analyses of repetitions may help to elucidate current findings, such as deactivations in response to studied objects. Additionally, neural activation across repetitions may also have far reaching implications, as many cognitive rehabilitation programs rely on the repetition of material as part of retraining.

In conclusion, the current research contributes to a rapidly expanding literature. As additional research is uncovered, patterns of neural activity and its relation to functioning and outcome will be discovered. It is this author's sincere hope that future advances will help individuals with TBI and their families to experience meaningful functional recovery and improve the quality of their lives.

Appendix A:

Neuropsychological Test Battery: Descriptions, Reliability, and Validity

For a thorough review of the following neuropsychological measures, please see Lezak, Howieson, & Loring, 2004. Each test is listed below, along with a brief description and selected citations regarding each test's reliability and validity.

Galveston Orientation and Amnesia Test (GOAT; Levin, O'Donnell, & Grossman, 1979)

The GOAT is a short mental status examination used to determine the extent and duration of posttraumatic amnesia following a brain injury. It has an interrater reliability of 0.99 for trained examiners, and a correlation of 0.85 between GOAT scores and patients own estimates of PTA (Levin, et al., 1979).

Conners' Continuous Performance Test – II (CPT-II; Conners, 2000)

A computerized measure of sustained attention, the CPT-II involves the presentation of letters on a computer screen, at interstimulus intervals of 1, 2, or 4 seconds. Test-takers are to click the mouse or space bar every time a letter appears, except when an "X" appears. Patients are asked to try to be as fast as possible, but also as accurate as possible. The test lasts approximately 15 minutes.

Split-half reliability coefficients were 0.95 for hit rate reaction time, 0.83 for errors of commission, 0.94 for errors of omission and 0.87 for hit rate standard error (Sitarenios, 1998). Test-retest reliability estimates were moderate and varied from 0.55 to 0.84 (Anastasi, 1988). Validity studies show that individuals with ADHD perform statistically significantly lower than those with other clinical conditions (Conners, 1994). In addition, it has been shown to accurately classify 70-75% of those with ADHD when compared to those with other psychiatric diagnosis (Czerny, O'Laughlin, & Griffioen, 1999).

Paced Auditory Serial Addition Task (PASAT; Gronwall, 1977)

This test of working memory requires the serial presentation of randomized numbers. The patient is to add each number to the previously presented number, not to the total. Therefore, the task requires maintaining the last number they heard while attending to incoming information, and calculating the sum. The rate of presentation varies across four trials at a rate of 2.4, 2.0, 1.6, or 1.2 seconds. The task is quite difficult and very sensitive to even mild brain injuries within the

acute phase of recovery (Stuss, et al., 1989), although it has been shown to be quite sensitive to more severe injuries in the chronic stage as well (Stuss, et al., 1989; Ponsford, & Kinsella, 1992).

Delis-Kaplan Executive Functioning System (DKEFS; Delis & Kaplan, 2001)

Rather than a single score for evaluating performance on an executive function task, the D-KEFS intends to isolate and measure fundamental neurocognitive skills, such as attention, perception, and language along with higher-level cognitive functions such as concept formation, inhibition, planning, cognitive flexibility, that might play a role in success at a particular task. An interesting aspect of the DKEFS is that it accounts for more fundamental skills contributing to executive functioning, as well as higher order executive functions. The D-KEFS tests were designed (or modified) for sensitivity to mild brain damage (especially frontal) by incorporating three key features: *switching*, *capture stimuli*, and procedures for *increasing processing* demands. *Switching* features require a subject to shift mental sets and are incorporated in the following tests: Color-Word Interference, Verbal Fluency, Trail Making, and Design Fluency. *Capture stimuli* invite stimulus-bound response and thus challenge a subject's ability to think abstractly. The Trail Making, Twenty Questions, and Proverb Tests include capture stimuli. Both the Sorting Test and the Trail Making test include conditions with a r*aised processing threshold*, which seek the upper limit of a subject's processing ability.

Although the D-KEFS is relatively new measure of executive functioning, studies have linked poor scores on the D-KEFS with damage to the frontal lobes. McDonald, et al. (2005) found that patients with frontal-lobe epilepsy showed deficits in speed and accuracy on the Trail Making Test switching task compared with temporal-lobe epilepsy and control subjects. Neither patient group differed from the control group on the four baseline tasks of the TMT, which assess visual scanning, motor speed, number sequencing, and letter sequencing. Yochim, et al. (2007) found that the D-KEFS Trail Making Test was sensitive to patients with lateral prefrontal cortex lesions. Patients with LPC lesions showed deficits compared to controls on Letter Sequencing, Number-Letter Switching, and Motor Speed subtests.

Wisconsin Card Sorting Test – 64 Card Version (WCST-64; Heaton, 1981; Axelrod, Henry, & Woodard, 1992)

This is a sorting test in which patients are required to match a stack of cards to one of four key cards according to an undisclosed rule (e.g., according to color, shape, etc.). Patients are not told how to sort the cards; rather, they are asked to deduce how to match the cards based on feedback from the examiner. Studies utilizing functional neuroimaging have demonstrated that

the frontal lobes play a prominent in patients' ability to perform the WCST (Berman, et al., 1995; Esposito, et al., 1999, Fallgatter & Strik, 1998; Ragland, et al., 1997). Furthermore, studies have suggested that individuals with frontal lesions make more perseverative and set-loss errors on the WCST than do patients with lesions in other locations (Stuss, Levine, et al., 2000). The test has also been found, however, to be sensirtive to diffuse damage (Axelrod, Goldman, Heaton, et al., 1996). Due to the nature of the test, it has not been found to be highly reliable. As the test is based on problem solving to ascertain the sorting principles, test-takers are not likely to fail the test or even take as long to finish during a repeat testing. An exception is observed in those with neurological impairments, who are evaluated with sufficient time between testings (McCaffrey, Duff & Westervelt, 2000; Basso, et al., 1999). Retest correlations have been found to be 0.63 at best (Bowden, et al., 1998).

Iowa Gambling Task (IGT; Bechara, 2007)

The IGT is a computerized test on which test-takers are select cards from one of 4 decks. Two of these decks yield a high profit, but also involve a high risk of loss. The other two decks involve lower profit, but also have less risk. Patients with damage to the prefrontal cortex tend to select from the more disadvantageous decks, whereas those with lesions in other areas chose from the more advantageous decks (Anderson, et al., 1999; Bechara, et al., 2000; Bechara & Damasio, 2002). Functional neuroimaging studies also suggest that frontal lobe dysfunction is associated with poor performance on the IGT (Bolla, et al., 2003; Windman, et al., 2006). However, research regarding the reliability of the IGT is lacking (Buelow & Suhr, 2009)

California Verbal Learning Test-II (CVLT-II; Delis, Kramer, Kaplan, & Ober, 2000)

A well-known and frequently used test of verbal learning, memory, and recall, the CVLT-II involves the presentation of a word-list containing 16 words. Patients are asked to recall as many of the words as possible, in any order. The list is repeated a total of 5 times, with patients attempting to freely recall the list after each presentation. After this, a new list of words ("List B") is presented once, followed by a free recall trial. Patients are then asked to freely recall the original list without an additional presentation (Short Delay Free Recall). They are also cued according to category, as all words can fit into one of four different groups (i.e. animals; Short Delay Cued Recall). Following a 20-minute delay, patients are again asked to freely recall the original list (Long Delay Free Recall), and are then cued (Long Delay Cued Recall). Finally, patients undergo a yes/no recognition trial in which a longer list of words is presented, including words from the original list and the interference list. An optional trial includes a forced choice

recognition task, in which patients are presented with two words and asked to choose which word was on the original list.

Split-half reliability correlations of the Total score from Trials 1-5 range from 0.87 to 0.89 (Delis, Kaplan, Kramer, & Ober, 2000). Test-retest reliability after a span of 21 days suggests reliability of 0.82 for Total Trials. Both the CVLT-II and the original CVLT have been shown to discriminate between many types of patient groups with memory impairment, including those with TBI (Deshpande, et al., 1996, Kibby, et al., 1998; Delis, Kaplan, Kramer, & Ober, 2000).

Continuous Recognition Memory Test (CRMT; Hannay, Levin, & Grossman, 1979)

Consisting of 120 black and white line drawings of common objects (i.e., various types of plants and animals), the CRMT presents eight targets that are memorized by test-takers. Subsequent pictures are then presented that either match the target or do not match the target. Of the non-matches, some pictures are very similar to the targets, while others are dissimilar. Patients are to say "old" or "new" for each picture presented after the initial targets. Research has suggested that the CRMT was able to identify between 67% and 85% of moderate to severe brain injured patients (Hannay, Levin, & Grossman, 1979).

Finger TappingTest (Halstead, 1947; Reitan & Wolfson, 1993; Spreen & Strauss, 1998)

The Finger Tapping test is a widely used measure requiring patients to tap a lever as quickly as possible over a period of 10 seconds. Five scores are obtained (within a range of five taps from one another) and averaged. The test has been found to be highly reliable, with test-retest reliability estimates varying from 0.86 to 0.94 for healthy individuals (Gill, et al., 1986), and 0.64 to 0.87 for neurological populations (Goldstein & Watson 1989; Dodrill & Troupin, 1975). Evidence suggests that those with head injuries demonstrate slower tapping speed than normal controls (Stuss, et al., 1989; Reitan & Wolfson, 1996). This is typically on the contralateral side of the lesion (Brown, et al., 1989; Reitan & Wolfson, 1994), although those with diffuse axonal injury also demonstrate slowed tapping rates (Haaland, Temkin, Randhahl, & Dikmen, 1994).

Benton Form Discrimination (Benton, Sivan, Hamsher, Varney, & Spreen, 1994)

Within the Form Discrimination test, a figure consisting of two main figures and a third, smaller peripheral figure, is presented to each patient. They are then asked to match this figure to one of four similar figures presented in a multiple-choice format below. Foils may differ in

details, orientation, and/or peripheral figure. Studies suggest that Visual Form Discrimination is closely related to design copy and nonverbal visual memory tasks (Moses, 1986; Moses, 1989), although there is some evidence to suggest that it is also related to attention and concentration (Benton, et al., 1994) and visual neglect (Mendez, et al, 1990)

Line Bisection (Schenkenberg, Bradford, & Ajax, 1980)

During this task, 20 horizontal lines of different lengths are presented on one page. Some are centered, while others are aligned more towards the left or right of midline, and lines are randomized on the page with regard to alignment. Test-takers are asked to cut each line in half by placing a small mark through the middle with their pencil. The test is sensitive to visual inattention, particularly left-sided inattention (Kinsella, et al., 1995; Ferber & Karnath, 2001).

Multilingual Aphasia Examination (MAE; Benton & Hamsher, 1989; Benton, Hamsher, & Sivan, 1994)

Visual Naming (Benton, Hamsher, & Sivan, 1994): The Visual Naming subtest of the MAE is a 30-item confrontation naming test. It has very good concurrent validity with the Boston Naming Test (r=0.86; Axelrod, et al, 1994). Confrontation naming tests are valuable for detecting phonologic paraphasic errors (Knopman, et al, 1984), as well as dysnomia associated with the left temporal lobe and hippocampal dysfunction (Mottaghy, et al., 1999; Sawrie, Martin, et al., 2000).

Sentence Repetition (Benton & Hamsher, 1989): This measure consists of 14 sentences, read one at a time to the patient. The patient is then required to repeat the sentence back to the examiner in full. Sentences vary from three words, to more complex sentences with multiple details. It has been found to be sensitive to mild language deficits in patients who otherwise appear to have intact communication skills (Benton & Hamsher, 1989).

Token Test (Benton, Hamsher, & Sivan, 1994): The Token Test is involves providing single and multistep commands to patients, using chips of various sizes, shapes and colors. It is quite sensitive to aphasic disturbances, and highly correlated with measures of auditory comprehension (Morley, et al., 1979) as well as immediate memory span (Lesser, 1976). It is been shown to have high reliability coefficients, from 0.92 to 0.97 in aphasic patients (Spreen & Strauss, 1998).

Wecshler Adult Intelligence Scale – III (WAIS-III), Processing Speed Index (PSI) (The Psychological Corporation, 1997)

The PSI from the WAIS-III consists of the Digit-Symbol Coding and Symbol Search subtests. In the Digit-Symbol Coding subtest, patients are asked to match a symbol to the numbers presented on the page, according to a key at the top of the page. The Symbol Search subtest requires patients to find one of two target symbols from a row of symbols, checking "yes: if one of the targets is present and "no" if it is not. Each test is restricted to 120", and participants are asked to work as quickly as possible without making mistakes. Although there is a motor component involved in the PSI, it is also associated with visual working memory, planning ability, and speeded processing (Kaufman & Lichtenberger, 1999).

Wechsler Test of Adult Reading (WTAR; The Psychological Corporation, 2001)

The WTAR is simply a list of irregularly pronounced words that patients are asked to read aloud. It is typically used as an estimate of premorbid intelligence, as reading recognition is generally preserved in the presence of cognitive decline or impairment due to injury (Crawford, 1992; Spreen & Strauss, 1998). According to the manual, the test has shown good internal consistency, varying from 0.90 to 0.97 in U.S. samples. Test-retest reliability estimates vary from 0.90 to 0.94. Correlations with other reading measures is generally good, including Wide Range Achievement Test-Revised (WRAT-R) reading scores (0.73) and the National Adult Reading Test (NART; 0.78).

Letter Memory Test (LMT; Inman, Vickery, Berry, Lamb, Edwards, and Smith, 1998)

The LMT is a well-validated test of neurocognitive effort. This test is in reality quite easy; however, it steadily increases in face difficulty as the test progresses. In this forced-choice, computer administered test, 45 items consisting of combinations of consonant letters are presented. After a 5-second delay, the test-taker chooses the target combination from a distractor or group of distractors. The LMT increases in face difficulty by crossing the number of letters in the stimuli to be remembered (3, 4 or 5) with the number of choices from which the target stimulus must be recognized (2, 3 or 4) in 9 blocks of five trials each. Thus, the first block of trials involves a 3-letter stimulus that must be chosen from 2 alternatives, the next a 4-letter stimulus that must be chosen from 2 alternatives, etc. These changes were intended to manipulate face difficulty level without affecting actual difficulty level.

Results from the initial validation study demonstrated a cutting score at or above 93% (< 93% classified as feigning) to have a mean specificity and sensitivity of 100% and 84.3%,

respectively (Inman et al., 1998). This translates into positive and negative predictive powers of 100% and 98% at a 15% base rate, 100% and 95% at a 21% base rate, and 100% and 87% at a 48% base rate (Inman et al., 1998). This cutting score was later cross-validated using a sample of both head injured and analog malingerers (Inman & Berry, 2002), and the LMT was found to have a specificity of 100%, a sensitivity of 73%, and an overall hit rate of 87%. In 2004, Vickery et al. examined the possibility that head-injured patients may be better suited to feign cognitive deficits due to their experience with brain trauma. This study again showed the LMT to be relatively insensitive to the presence of head injury while being quite sensitive to malingering by both analogue malingerers and those with a head injury who were instructed to malinger. Specificity was quite high, sensitivity was moderately high, and head injured patients showed no superiority in feigning cognitive symptoms (Vickery et al., 2004).

Beck Depression Inventory-II (BDI-II; Beck, 1987; Beck, Steer, & Brown, 1996)

The BDI-II is a 21 item measure designed to assess various aspects of depression, including mood, sense of failure, indecisiveness, anhedonia, sleep and appetite. Test-retest reliability coefficients range from 0.74 to 0.93 (Kaszniak & Allender, 1985), and multiple studies have demonstrated concurrent validity (Kivela, 1992; Spreen & Strauss, 1998).

Beck Anxiety Inventory (BAI; Beck et al., 1988)

The BAI is a widely used 21-item inventory designed to access the severity of anxiety symptoms. The BAI has demonstrated high internal consistency and acceptable test-retest reliability (Fydrich, Dowdall, & Chambless, 1992).

Personality Assessment Screener (PAS; Morey, 1999)

Comprised of the most sensitive questions on the Personality Assessment Inventory (PAI), the PAS is a 22-item screening instrument designed to assess clinical problem areas. The domains targeted include: negative affect, hostile control, acting out, suicidal thinking, health problems, alienation, psychotic features, alcohol problems, social withdrawal, and anger control. Alpha coefficients for the total PAS score were modest at 0.63 (Holden, et al., 2001)

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UPPS-P Impulsive Behavior Scale (Whiteside & Lynam, 2003)

The UPPS-P is a measure of behavioral impulsivity, and is characterized by five scales: urgency, (lack of) premeditation, (lack of) perserverance, sensation seeking, and positive urgency. In the initial validation studies, it was found to have a positive predictive power of 0.84 and

negative predictive power of 0.67 when discriminating between individuals with psychopathology (e.g., borderline personality disorder, pathological gambling, alcohol abuse) and those with healthy controls (Whiteside, et al., 2005).

Community Integration Questionnaire (CIQ; Dijkers, 1997)

This measure of community integration consists of 15 items designed to assess home integration, social integration, and participation in productive activities. Reliability studies have been mixed. Internal consistency has been found to be 0.80 or greater (Willer, Linn, & Allen, 1994). The correlation between self and other report on items vary from 0.42 for shopping to 0.94 for school participation. Likewise, Sander, et al. (1997), suggest that home integration differ the most between patients and other reporters.

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JESSICA A. CLARK

Vita

July 2010

Date of Birth: August 26, 1981

Place of Birth: Drexel Hill, Pennsylvania

Education:

2010 (expected) Ph.D., Clinical Psychology (Neuropsychology Specialization)
The University of Kentucky
Lexington, KY
Dissertation Title: *Neuropsychological Correlates and Underlying Cortical Mechanisms of Working Memory in Moderate to Severe Traumatic Brain Injury: An fMRI Study*

2003 B.S., Psychology
The Pennsylvania State University
University Park, PA

2003 B.S., Premedicine
The Pennsylvania State University
University Park, PA

Honors and Awards:

- Kentucky Fellowship, 2003 – 2004
- Graduate School Fellowship, 2006-2007
- Kentucky Graduate Scholarship, 2007-2008
- University of Kentucky Physical Medicine & Rehabilitation 19th Annual Research Day, 1st Place – Best Poster, 2007

Professional and Honor Societies:

- Kentucky Psychological Association (graduate student affiliate)
- International Neuropsychological Society (presenter)

CLINICAL EXPERIENCE:
(See last page for list of assessments utilized)

07/09-06/10 **Neuropsychology Intern**
VA Maryland Health Care System/University of Maryland Psychology Internship Consortium
Baltimore, MD and Perry Point, MD

- **Neuropsychology Service** – Baltimore, MD. (07/09-06/10)
  - Outpatient neuropsychological assessments.
    - Interviewing, report writing, and feedback.
    - Patient population includes veterans with brain injury, dementia, seizures, stroke, ADHD, psychiatric

conditions (PTSD, schizophrenia, anxiety, depression, etc.), substance use, and infectious disease.
        - *Supervisors:* Anjeli Inscore, Psy.D. & S. Marc Testa, Ph.D.
    - Polytrauma Clinic.
        - Interviewing and neuropsychological testing.
        - Work within an interdisciplinary team to ensure appropriate assessment and treatment of returning veterans.
        - Patient population includes veterans from Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) with multiple injuries sustained in combat, typically PTSD and mild traumatic brain injury.
        - *Supervisor:* Patricia Roger, Ph.D.
    - Dementia Clinic.
        - Neuropsychological testing and presentation of test findings to patients and families.
        - Emphasis on differential diagnosis of various types of cognitive impairment, including Alzheimer's disease, vascular/subcortical dementia, mixed disease, frontotemporal dementia, dementia secondary to substance use, mild cognitive impairment, and normal pressure hydrocephalus.
        - Work within an interdisciplinary team to ensure appropriate assessment, treatment planning, and referrals for individuals with memory disorders.
        - *Supervisor:* Anjeli Inscore, Psy.D.
    - Stroke Clinic.
        - Interviewing and neuropsychological testing.
        - Feedback incorporating neuroanatomical lesions and neuropsychological test performance is given to the patient, their family, and the referring neurologist.
        - Emphasis on program development in piloting a new clinic within this VA hospital. This includes the incorporation of clinical work with potential research.
        - *Supervisor:* Alison Cernich, Ph.D., ABPP-CN
    - Cognitive Rehabilitation.
        - Individual treatment of OEF/OIF veterans who are having functional difficulty due to brain injury.
        - Treatment includes goal setting, development of compensatory strategies, cognitive behavioral techniques to manage psychological stress related to deficits.
        - *Supervisor:* Patricia Roger, Ph.D.

- **PTSD Clinical Team/Returning Veterans Outreach, Education and Care Programs** – Perry Point, MD. (11/09-3/10)
    - Treatment of veterans with PTSD, some of which have dual diagnosis substance abuse and other psychiatric disorders.

- Group Co-Facilitator.
  - *Post-Deployment OEF/OIF Group* – Focus on helping veterans adapt and cope with post-deployment issues such as family and role adjustment, changed views, social isolation, and other PTSD symptoms.
  - *Seeking Safety Group* – Developed to simultaneously address issues of PTSD and substance abuse. Helps veterans learn ways to create safe environments for themselves with regard to physical and emotional well-being.
  - *Sleep and Nightmares Group* – Psychoeducational group focused on sleep hygiene, stimulus control and sleep restriction, relaxation, and nightmare rehearsal. Includes tracking of sleep patterns and review of sleep diaries.
  - *Multicultural Group* – Addresses veterans' ability to relate to others of differing cultural backgrounds, including military status, gender, race, socio-economic status, religion, etc. Also helps veterans to process cultural experiences and prejudices related to combat and post-deployment.
- Individual Therapist.
  - Treatment of individual patients using Prolonged Exposure (PE) therapy and Cognitive Processing Therapy (CPT).
- Psychological Assessment.
  - Evaluation of individuals with PTSD and other comorbid Axis I and Axis II disorders in order to ensure appropriate diagnosis and treatment.
- *Supervisors:* Christina Watlington, Ph.D. & Andrew Santanello, Psy.D.

07/07-06/09 **University of Kentucky Department of Physical Medicine & Rehabilitation – Cardinal Hill Rehabilitation Hospital**
Lexington, KY

- Neuropsychological assessments and report writing.
  - Patient population includes patients with brain injury, stroke, dementia, and combat veterans from OEF/OIF with PTSD and blast injury.
- CLIMB (Community Living Independently Moving Beyond) Neuropsychology Group
  - Outpatient psychological services for brain injured patients – group therapy focused on increasing awareness of deficits, social skills, brain injury psychoeducation, etc.
- *Supervisor:* Walter M. High, Jr., Ph.D.

05/04-07/08 **Dr. C. Christopher Allen** (private practice neuropsychologist)
Lexington, KY

- Neuropsychological testing of adults and children.

- Referral questions include brain injury, stroke, neurological disease, learning disability, autism spectrum disorders, giftedness, ADHD, behavioral issues, etc.
- Report writing.
- Brain injury rehabilitation involving attention and memory training of individuals with a history of head injury.
- Cognitive-behavioral therapy with brain injury patients.
- *Supervisor:* C. Christopher Allen, Ph.D.

08/04-09/08 **Jesse G. Harris Psychological Services Center**
University of Kentucky, Lexington, KY

- Individual psychotherapy of adults and children in the Lexington Community. (08/04-09/08)
  - Emphasis on cognitive behavioral therapy, including Dialectical Behavioral Therapy (DBT) with clients with Borderline Personality Disorder.
  - Assessment experience.
  - *Supervisor:* Steven Mangine, Ph.D. (2005-2008), Mary Beth Diener McGavran, Ph.D. (2004-2005)
- **Clinic Coordinator**. (07/06-07/07)
  - Supervisor for undergraduate Clinic Assistants, responsible for teaching a weekly class on various types of psychotherapy and the role of psychologists.
  - Responsible for everyday functioning of the clinic, intakes for new clients, attending to phone calls for individuals seeking services; staffing of new clients.
  - *Supervisor:* David Susman, Ph.D.
- Group psychotherapy and social skills training. (05/05-08/05)
  - Children with ADHD, autism spectrum disorders, and other socially impairing issues.
  - *Supervisor:* Katherine Stone, Ph.D.

05/04-05/05 **Cardinal Hill Rehabilitation Hospital**
Brain Injury and Pulmonary Units
Lexington, KY

- Psychotherapy with brain injured and pulmonary patients (adults and children).
- Family therapy & brain injury education.
- Behavior modification/crisis management.
- Relaxation techniques.
- Bereavement counseling.
- Assessment experience.
- *Supervisor:* Michael S. Lynch, Ph.D.

RESEARCH EXPERIENCE:

07/07-present **University of Kentucky Department of Physical Medicine & Rehabilitation – Cardinal Hill Hospital**
Lexington, KY

- Dissertation: Research into the underlying neural correlates of cognitive control and working memory in moderate to severe TBI patients using fMRI.
  - Responsible for all aspects of the study, including IRB, recruiting, scanning, neuropsychological testing, analyses, and write-up.
  - Additional scans included DTI and spectroscopy.
- Examination of the neuropsychological sequelae of blast injuries and PTSD in returning OEF/OIF combat veterans.
- Research examining community outcome of patients with executive dysfunction.
- *Supervisor:* Walter M. High, Jr., Ph.D.

08/03-present **Neuropsychological Assessment and Malingering Research**
Psychology Department
University of Kentucky, Lexington, KY

- Research involving neuropsychological assessment, the feigning of psychiatric and neurocognitive symptoms, & test validation in a variety of populations (forensic, head injury, mental retardation, etc.).
- Duties included IRB submissions, data collection, analysis, manuscript preparation, etc.
- *Supervisor:* David T. R. Berry, Ph.D.

07/09-06/10 **VA Maryland Health Care System/University of Maryland Psychology Internship Consortium**
Baltimore, MD

- Research examining the differences in TBI symptom reporting and neurocognitive test scores for veterans with mild TBI, with and without PTSD.
- Development of a database for neurocognitive test scores for returning OEF/OIF veterans who have screened positive for TBI.
- Program development for a new Stroke Clinic; involved incorporation of clinical referrals into a research referral stream, including databases set up, as well as developing auto-populated report and chart review templates for use in clinical and research endeavors.
- Assistance with IRB submissions.
- *Supervisor:* Alison Cernich, Ph.D., ABPP-CN

07/05-07/07 **Aging, Brain and Cognition Lab**
Behavioral Sciences Department
University of Kentucky College of Medicine, Lexington, KY

- Research involving working memory and attention using neuroimaging techniques, normal and pathological aging, as well as research into malingering and ERP.

- Work involving EEG and fMRI, analyzing neuroimaging and behavioral data, & manuscript preparation.
- Duties also entailed interacting with participants throughout studies including those with Alzheimer's disease, dementia with Lewy bodies, and Mild Cognitive Impairment (MCI).
- Responsibilities involve working with these patients and their families to ensure adequate training and retention for research protocols, as well as placement and filling of EEG cap and positioning in the MRI scanner.
- Certification received from the University of Kentucky Magnetic Resonance Imaging and Spectroscopy Center (MRISC) to run participants through the scanner independently without assistance from staff physicist or radiologist.
- *Supervisor:* Yang Jiang, Ph.D.

05/04-07/08 **Dr. C. Christopher Allen** (private practice neuropsychologist)
Lexington, KY

- Neuropsychological test validation and development using neurological populations; research into neuropsychological correlates of combat veterans serving in the first Gulf War.
- *Supervisor:* C. Christopher Allen, Ph.D.

05/02-05/03 **Multiple Sclerosis Lab**
Psychology Department
The Pennsylvania State University, University Park, PA

- Research into the neuropsychological correlates of Multiple Sclerosis.
- Duties included scoring and administration of neuropsychological tests, data coding/entry, and collaboration with graduate students.
- *Supervisor:* Peter Arnett, Ph.D.

05/02-05/03 **Clinical Child Development Lab**
Psychology Department
The Pennsylvania State University, University Park, PA

- Longitudinal research into child development and the possible causes of later pathology.
- Duties included observation and coding of parent/child interactions within an experimental setting.
- *Supervisor:* Keith Crnic, Ph.D.

Teaching Assistantships – University of Kentucky:

Graduate Level

- PSY 631: *Personality Assessment* (Spring 2006)
  Duties: Graduate lab instructor – lecture preparation; guidance for MMPI-2, NEO-PI-R, and PAI test scoring, interpretation, and report writing; grading.

Undergraduate Level

- PSY 399: *Clinic Assistant Seminar* (Summer 2006, Fall 2006, Spring 2007, & Summer 2007). Duties: Supervision of undergraduate clinic assistants at the Jesse G. Harris Psychological Services Center. Seminar instructor – lecture preparation, paper

grading, outside mentoring, providing information and training regarding therapy, clinic duties, and professional conduct.

- PSY 215: *Experimental Psychology* (Fall 2004, Spring 2005, & Fall 2005)
  Duties: Undergraduate lab instructor – lecture preparation; teaching APA style; helping students develop, carry out, and write up experiments; paper grading; outside mentoring; providing information about graduate school and research.
- PSY 216: *Applications of Statistics in Psychology* (Summer 2005)
  Duties: Undergraduate lab instructor – lecture preparation; reviewing problem sets; grading; external mentoring.

Publications:

Jasinski, L.J., Berry, D.T.R., Shandera, A., & Clark, J.A. (under review). Use of the Digit Span test for detecting malingered neurocognitive dysfunction: A Meta-Analysis. *Journal of Clinical and Experimental Neuropsychology.* Manuscript submitted for publication in May 2010.

High, W., Briones-Galang, M., **Clark, J.**, Gilkison, C., Mossberg, K., Zqaljardic, D., Masel, B., & Urban, R. (in press). Effect of growth hormone replacement therapy on cognition after traumatic brain injury. Manuscript revised and resubmitted for publication in April 2010.

Berry, D.T.R., Schipper, L.J., & **Clark, J.A.** (in press). Detection of feigned head injury symptoms on the MMPI-2. In C.R. Reynolds (Ed.) Detection of malingering during head injury litigation (2nd Ed.). New York: Plenum Press.

Shandera, A.L., Berry, D.T.R., **Clark, J.A.,** Schipper, L.J., Graue, L.O., & Harp, J.P. (2010). Detecting Malingered Mental Retardation. *Psychological Assessment.*

Berry, D.T.R., Sollman, M.J., Schipper, L.J., **Clark, J.A.**, & Shandera, A.L. (2009). Assessment of feigned psychological symptoms. In J.N. Butcher (Ed.) Handbook of personality and clinical assessment. New York: Oxford University Press.

Alwes, Y.R., **Clark, J.A.**, Berry, D.T.R., & Granacher, R.P. (2008). Screening for feigning in a civil forensic setting, *Journal of Clinical and Experimental Neuropsychology*, 30, 133-140.

Schipper, L.J., Berry, D.T.R., Coen, E., **Clark, J.A.** (2008). Cross-validation of a manual form of the Letter Memory Test using a known-groups methodology. *The Clinical Neuropsychologist*, 22, 345-349.

Vagnini, V., Berry, D., **Clark, J.**, & Jiang, Y. (2008). New measures to detect malingered neurocognitive deficit: Applying reaction time and event-related potentials. *Journal of Clinical and Experimental Neuropsychology*, 30(7), 766-776.

Graue, L. O., Berry, D. T. R., **Clark, J. A.**, Sollman, M. J., Cardi, M., Hopkins, J. & Werline, D. (2007). Identification of feigned mental retardation using the new generation of malingering detection instruments: Preliminary findings. *The Clinical Neuropsychologist*, 20(6), 929-942.

Jiang, Y., Vagnini, V., **Clark, J.**, Zhang, Q. (2007). Reduced sensitivity of affective mismatch in older adults. *TheScientificWorldJOURNAL*, 7, 115.

Vagnini, V. L., Sollman, M. J., Berry, D. T. R., Granacher. R. P., **Clark, J. A.**, Burton, R., O'Brien, M., Bacon, E. & Saier, J. (2006). Known-groups cross-validation of the Letter Memory Test in a compensation-seeking mixed neurologic sample. *The Clinical Neuropsychologist.* 20(2), 289-304.

Presentations:

Kurtz, S.M., Dux, M.C., **Clark, J.A.,** & Cernich, A.N. (2010, June). *Factor structure of the neurobehavioral symptom inventory (NSI) in a veteran population.* Poster to be presented at the annual meeting of the American Academy of Clinical Neuropsychology, Chicago, IL.

Clark, J.A., Shandera, A.L., Harp, J., Schleenbaker, R., & High, Jr., W.M. (2010, February). *Neuropsychological profiles of combat veterans exposed to mild head trauma and combat-related stressful events – a continuation.* Presented at the annual meeting of the International Neuropsychological Society, Acapulco, Mexico.

Harp, J., **Clark, J.A.,** Shandera, A.L., Schleenbaker, R., Berry, D.T.R., & High, Jr., W.M. (2010, February). *Neuropsychological profile patterns of combat veterans feigning mild head trauma.* Presented at the annual meeting of the International Neuropsychological Society, Acapulco, Mexico.

Kurtz, S., **Clark, J.,** Cernich, A. (2010, February). *Differences in TBI symptom reporting for veterans with and without PTSD.* Poster presented at the International Brain Injury Association Conference, Washington, D.C.

Shandera, A.L., Harp, J., **Clark, J.A.,** Schleenbaker, R., & High, Jr., W.M. (2010, February). *Psychological profiles of combat veterans exposed to mild head trauma and combat-related stressful events.* Presented at the annual meeting of the International Neuropsychological Society, Acapulco, Mexico.

Clark, J.A., Shandera, A.L., Harp, J., Schleenbaker, R., & High, Jr., W.M. (2009, February). *Neuropsychological profile of combat veterans exposed to mild head trauma and combat-related stressful events.* Poster presented at the annual meeting of the International Neuropsychological Society, Atlanta, GA.

Shandera, A.L., **Clark, J.A.,** Harp, J., Schleenbaker, R., & High, Jr., W.M. (2009, February). *MMPI-2 profiles of combat veterans exposed to mild head trauma and combat-related stressful events.* Poster presented at the annual meeting of the International Neuropsychological Society, Atlanta, GA.

Jiang, Y., **Clark, J.,** Jicha, G., Schmidt, F., Kiser, S., Gold, B., Powell, D., Andersen, A., & Smith, C. (2008, November). *Individual differences in functional alterations of memory networks among normal older adults.* Talk presented at Neuroscience 2008, sponsored by the Society for Neuroscience, Washington, D.C., Society for Neuroscience Abstracts, 815, 10.

Guo, C., **Clark, J.**, Lawson, A., & Jiang, Y. (2008, June). *Automatic coding of new and studied objects during a working memory task: Evidence from multimodal imaging.* Poster presented at the Human Brain Mapping Conference, Melbourne, Australia.

Jiang, Y., **Clark, J.**, Lawson, A., & Guo, C. (2007, June). *Age related alteration in memory networks among high functioning older adults.* Poster presented at the Human Brain Mapping Conference, Chicago, IL.

Clark, J.A., Lawson, A., Guo, C., Kiser, S., & Jiang, Y. (2007, March). *Cortical alteration in memory networks in young and older adults.* Poster presented at the Neuroscience Day Conference presented by the Bluegrass Society for Neuroscience, Lexington, KY.

Kiser, S., **Clark, J.**, Lawson, A., Guo, C., Jiang, Y. (2007, March). *Age and memory performance during a combined working memory/repetition task.* Poster presented at the Kentucky Psychological Association Conference, Lexington, KY.

Clark, J.A., Alwes, Y., Berry, D. (2007, February). *Evaluation of brief malingering screening instruments in a civil forensic sample.* Poster presented at the annual meeting of the International Neuropsychological Society, Portland, OR.

Graue, L., Berry, D., **Clark, J.**, Sollman, M., Cardi, M., Hopkins, J., & Werline, D. (2007, February). *Detection of malingered mental retardation.* Poster presented at the annual meeting of the International Neuropsychological Society, Portland, OR.

Schipper, L., Berry, D., Coen, E., & **Clark, J.** (2007, February). *Validation of a manual form of the Letter Memory Test*. Poster presented at the annual meeting of the International Neuropsychological Society, Portland, OR.

Jiang, Y., Lawson, A., Guo, C., Vagnini, V., **Clark, J.**, Powell, D., & Anderson, A. (2006, June). *Frontal interaction between repetition effect and working memory.* Poster presented at the Human Brain Mapping Conference, Florence, Italy.

Jiang, Y., Vagnini, V., **Clark, J.**, & Lawson, A. (2006, April). *Age-related changes in brain potentials associated with old/new and repetition effects.* Poster presented at the Cognitive Aging Conference, Atlanta, GA

Wegman, T. J., **Clark, J.** A., Schipper, L. J., & Berry, D. T. R. (2005, February). *Possible contributions of MMPI-2 validity indicators to the detection of malingered neurocognitive dysfunction.* Poster presented at the annual meeting of the International Neuropsychological Society, St. Louis, MO.

Grants:

2010 VA Travel Grant
- Awarded to present poster at the International Neuropsychological Society in Acapulco, Mexico.
- Award amount: $2000

2009 University of Kentucky Research Challenge Trust Fund
- Awarded to support dissertation research efforts
- Award amount: $200

2008 Travel Grant
- Awarded to present poster at the International Neuropsychological Society in Atlanta, GA.
- Award amount: $400

2007 University of Kentucky Psychology Department Grant Proposal Incentive
- Awarded for submission of an NIH-F31: National Research Service Award
- Award amount: $500

2007 Travel Grant
- Awarded to present poster at the International Neuropsychological Society in Portland, OR.
- Award amount: $400

2005 Travel Grant
- Awarded to present poster at the International Neuropsychological Society in St. Louis, MO.
- Award amount: $500

Grant Proposals Submitted:
- NIH-F31: Ruth L. Kirschstein National Research Service Award (scored but not funded)
- Pilot Fund from the University of Kentucky Department of Behavioral Science

Professional Workshops Attended:
- Introduction to the MMPI-2-RF – November 2009, Perry Point, MD
- Supervision Training – October 2009, Baltimore, MD
- Mindfulness-Based Stress Reduction Training – October 2009, Baltimore, MD
- Acceptance and Commitment Therapy (ACT) – August 2008, Louisville, KY

PSYCHOLOGICAL AND NEUROPSYCHOLOGICAL TOOLS UTLIZED
Tests are provided according to the domain assessed. Battery subtests are not recategorized.

Neurocognitive Screens
Dementia Rating Scale (DRS)
Galveston Orientation and Amnesia Test (GOAT)
Mini Mental State Examination (MMSE)
Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)

Language Functioning
Animal Naming Test
Boston Diagnostic Aphasia Examination (BDAE)
Boston Naming Test (BNT)
Controlled Oral Word Association Test (COWAT)
FAS Fluency Test
Multilingual Aphasia Examination (MAE)
Ruff Language Screening Examination
Supermarket Naming Test

Visual/Spatial
Benton Judgment of Line Orientation (JLO)
Benton Visual Forms Discrimination
Clock & Cross Drawing (Dean Woodcock)
Judgment of Line Orientation
Line Bisection/Cancellation Tasks
Rey Complex Figure Test
Three Dimensional Block Construction
Visual Object and Space Perception Battery (VOSP)

Attention
Barkley-Murphy Symptom Checklists
Brief Test of Attention
Conners' Continuous Performance Test
Conners' ADHD Rating Forms
Integrated Visual and Auditory Continuous Performance Test (IVA-CPT)
Paced Auditory Serial Addition Test (PASAT)
Ruff 2 and 7 Selective Attention Test
Trail Making Test A

Sensory & Motor
Dean Woodcock Sensory Motor Battery
Finger Tapping Test
Grip Strength Test
Grooved Pegboard Test
Motor Regulation/Go-No-Go

Learning & Memory
Brief Visual Memory Test (BVMT-R)
California Verbal Learning Test (CVLT-II)
Heaton Story Test
Heaton Figure Memory Test

Hopkins Verbal Learning Test (HVLT-R)
Prospective Memory Test (PMT)
Rey Complex Figure - Retention
Ruff-Light Trail Learning Test
Selective Reminding Test
Tests of Memory and Learning (TOMAL)
Wechsler Memory Scale-III (WMS-III)

Executive Functioning
Behavioural Assessment of Dysexecutive Syndrome (BADS)
BRIEF/BRIEF-A
Controlled Oral Word Association Test (COWAT)
Delis-Kaplan Executive Functioning System (D-KEFS)
Nelson Modified Wisconsin Card Sorting Test
Ruff Figural Fluency Test
Stroop Color-Word
Symbol Digit Modalities Test (SDMT)
Trail Making Test B
Wisconsin Card Sorting Test

Intelligence & Achievement
Hopkins Adult Reading Test (HART)
Kaufman Brief Intelligence Test (K-BIT)
NEPSY-II
North American Reading Test (NART)
Wechsler Abbreviated Scale of Intelligence (WASI)
Wechsler Adult Intelligence Scale-III (WAIS-III)
Wechsler Individual Achievement Test-II (WIAT-II)
Wechsler Intelligence Scale for Children-IV (WISC-IV)
Wechsler Test of Adult Reading (WTAR)
Wide Range Achievement Test (WRAT-IV)
Wonderlic Personnel Test
Woodcock-Johnson-III – Tests of Cognitive Abilities
Woodcock-Johnson-III – Tests of Achievement

Effort/Feigning
B-Test
Digit Memory Test (DMT)
Dot Counting Test
Letter Memory Test (LMT)
Multi-Digit Memory Test (MDMT)
Miller – Forensic Assessment of Symptoms Test (M-FAST)
Structured Inventory of Malingered Symptomatology (SIMS)
Structured Interview of Reported Symptoms (SIRS)
Test of Memory Malingering (TOMM)
Word Memory Test

Emotional, Behavioral, Personality, Psychopathology & Adaptive Functioning
Achenbach Child Behavioral Checklists
Adolescent Psychopathology Scale (APS)
Autism Behavior Checklist (ABC)

Beck Anxiety Inventory (BAI)
Beck Depression Inventory (BDI-II)
Beck Symptom Inventory (BSI)
Clinician-Administered PTSD Scale (CAPS)
Competence Assessment to Stand Trial for Defendants with Mental Retardation (CAST*MR)
Child Depression Inventory (CDI)
Ekman 60 Item Test
Emotional Prosody Test
Geriatric Depression Scale (GDS)
Gilliam Asperger's Rating Scale (GARS)
Katz Adjustment Scale
Minnesota Multiphasic Personality Inventory-2 (MMPI-2)
NEO-Personality Inventory-Revised (NEO-PI-R)
NEO-Five Factor Inventory (NEO-FFI)
Personality Assessment Inventory (PAI)
Personality Assessment Screener (PAS)
Ruff Neurobehavioral Inventory (RNBI)
Sickness Impact Profile (SIP)
SCID-II
Street Survival Skills Questionnaire (SSSQ)
Symptom Checklist – 90 (SCL-90-R)