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QUANTITY AND QUALITY: THE IMPORTANCE OF STRUCTURAL INTEGRITY IN METACOGNITIVE FUNCTIONING FOLLOWING MODERATE AND SEVERE TRAUMATIC BRAIN INJURY

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ABSTRACT

Moderate to severe traumatic brain injury (TBI) often results in residual deficits in cognitive, emotional, and physical functioning. Metacognition, the in-the-moment self-awareness of cognitive performance, has been found to be affected after such injuries. Although deficits in metacognition have been documented, the organization of this domain in the brain is unclear; specifically, the contribution of structural brain tissue integrity to metacognitive functioning has yet to be examined. In the current study, Voxel Based Morphometry (VBM) methods were used to explore two potential contributors to metacognitive functioning after injury: 1) the amount of total brain tissue volume present, and 2) the location of injury. Characteristics of white matter integrity were also examined using Diffusion Tensor Imaging (DTI) methods. A relationship between metacognitive performance and global brain tissue volume was found when performance differences were present between the two sample groups (participants with TBI and non-injured peers). Particular measures of global white matter integrity were also found to be related to metacognitive functioning. Together, findings suggest that global brain tissue volume, rather than specific location of injury, is better associated with metacognitive awareness. Furthermore, there may be a "threshold effect" at which point metacognition and brain tissue volume are not linearly related.

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"Cultivate the habit of being grateful for every good thing that has come to you, and to give thanks continuously. And because all things have contributed to your advancement, you should include all things in your gratitude." --Ralph Waldo Emerson

"Piglet noticed that even though he had a Very Small Heart, it could hold a rather large amount of Gratitude." --A.A. Milne, *Winnie-the-Pooh*

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Chapter 1. INTRODUCTION

Traumatic Brain Injury

Traumatic brain injury (TBI) is an injury resulting from various types of forces inflicted on the brain; it is sustained by nearly 1.7 million Americans every year and leaves 5.3 million living with disabilities (Faul, et al., 2010). Despite prevention and treatment efforts, it is still predicted that in the next ten years, TBI will rise to the third leading cause of disability and morbidity in the world (Murray and Lopez, 1997). TBI occurs within a bimodal distribution of younger (15-24) and older adults (65-75), and occurs more often in men than women at a ratio of about 5:2 (Whyte and Rosenthal, 1993). Motor vehicle accidents account for the leading cause of serious injuries, followed by falls, firearms, and assaults (Whyte and Rosenthal, 1993; Faul, et al., 2010).

TBI is classified based upon the severity of injury; injuries can be labeled as mild, moderate, or severe. There are several measurements that are considered when assigning severity. One of the most commonly used measures of injury severity is the Glasgow Coma Scale (GCS) (Teasdale and Jennett, 1974). The GCS is commonly used to measure the level of consciousness and to track progression of acute coma recovery. The scale evaluates abilities in eye opening, motor response, and verbal response; a composite score of those three areas ranges between 3 and 15. GCS scores of 8 or less indicate severe injuries, scores from 9 to 12 indicate moderate injuries, and scores of 13 or above indicate mild injuries (Teasdale and Jennett, 1974).

The duration of posttraumatic amnesia (PTA) is another variable used to determine injury severity (Russell and Nathan, 1946). PTA refers to the period of time immediately following the injury where the individual is still unable to consolidate new information and has difficulty forming new memories. Generally, PTA duration of less than 5 minutes constitutes a mild

injury, duration of 1 to 24 hours suggests a moderate injury, and 1 or more days signifies a severe injury (Russell, 1971). The Galveston Orientation and Amnesia Test (GOAT) (Levin, O'Donnell, and Grossman, 1979) is an instrument developed to provide a better quantitative description and to assess resolution of PTA by testing for orientation and memory for incidents preceding and following the time of injury.

Advancements in neuroimaging techniques now allow health professionals the ability to identify neuroanatomical and even electrophysiological abnormalities that may be consistent with the different levels of injury severity. For example, brain lesions can be detected using computerized axial tomography and magnetic resonance imaging (MRI) scans. Significant correlations found between injury severity (as measured by GCS scores) and amount of brain tissue lost (identified using MRI scans) suggest that imaging methodologies are sensitive to detecting gross changes after injury that may be predictive of injury severity (Levine, et al., 2008) thus offering information about the pathophysiology of the injury and diagnostic implications. Although these techniques offer a visual illustration of trauma to the brain, imaging alone is typically not considered a method for determining injury severity. Rather, information acquired from imaging provides useful evidence supplementary to the "gold standard" of the duration of loss of consciousness and PTA as determinants of injury severity (Bigler, 1990).

Determination of injury severity is not only important for clinical assessment, but also has implications for patient outcome. Patients who suffer moderate to severe injuries are more likely to have worse functional outcome and are vulnerable to disability (Jennett, 1976; Levin, Benton & Grossman, 1982; Whyte and Rosenthal, 1993). In particular, severity determined by the duration of PTA has been documented to be a reliable predictor of neuropsychological

functioning, employment status, and/or personality alterations (Prigatano, et al., 1986). Injury severity can be indicative of the amount of cognitive recovery and the time course; those with more serious injuries demonstrate worse cognitive performance, and take longer to recover (Novack, Alderson, Bush, Meythaler & Canupp, 2000; Schretlen and Shapiro, 2003).

Cognitive Functioning After TBI: Metacognition

Moderate and severe TBIs often result in persisting cognitive or physical impairments; recovery is most significant during the two years after the injury and but has been found to plateau afterwards (Schretlen and Shapiro, 2003). However, there is still some ambiguity regarding the temporal frame of recovery; a longitudinal study tracking patients from one to five years after sustaining TBI showed that recovery across individuals was variable—while some patients demonstrated recovery in neuropsychological domains, other patients did not (Millis, et al., 2001). Cognitive deficits following injury are usually broad, covering the domains of attention and concentration, learning and memory, judgment and perception, executive and frontal lobe functioning (DeLuca, Schultheis, Madigan, Christodoulou, & Averil, 2000; Draper & Ponsford, 2008; Felmingham, Baguley, & Green, 2004; Goldstein & Levin, 1995; Kersel, Marsh, Havill, & Sleigh, 2001; Madigan, DeLuca, Diamond, Tramontano, & Averill, 2000; Mathias & Mansfield, 2005; Mathias & Wheaton, 2007; McDowell, Whyte, & D'Esposito, 1997; Park, Moscovitch, & Robertson, 1999; Prigatano and Fordyce, 1986; Rapoport, Herrmann, Shammi, Kiss, Phillips, & Feinstein, 2006; Schretlen & Shapiro, 2003; Whyte and Rosenthal 2003).

Anosognosia, or the condition of being unaware of one's deficits, is an area of emerging interest in studies of TBI. Studies of insight oriented processes are proving to be important as it

has been determined that functioning in these domains has great implications for recovery and quality of life following TBI (Evans, Sherer, Nick, Nakase-Richardson, and Yablon, 2005Flashman and McAllister, 2002; Godfrey, Partridge, Knight & Bishara, 1993; Kervick and Kaemingk, 2005; Ownworth and Fleming, 2005; Prigatano, 1997; Sawchyn, Mateer and Suffied, 2005; Sherer, et al., 2003; Trahan, Pépin, & Hopps, 2006).

In this literature examining "self-awareness," investigators have commonly focused on metacognition, a higher-order cognitive process that specifically refers to the ability to have insight about one's own cognitive functioning. For example, studies have commonly examined individuals' judgments about their own memory performance (metamemory), or their own ability to assess their comprehension of material they had read (metacomprehension). In particular, metacognitive experiences refer to online self-appraisal processes that occur while engaged in a cognitive task (Flavell, 1979). These metacognitive processes have been shown to require distinct processing of information about the self that differ from other cognitive domains (Chiou, Carlson, Arnett, Cosentino, & Hillary, 2011; Cosentino, Metcalfe, Steffener, Holmes, & Stern, 2011). In an examination of event related potentials, Skavhaug, Wilding and Donaldson (2010) were able to dissociate the temporal frame of neural activity associated with the metacognitive task and a memory encoding task, further supporting the notion of metacognition as an independent domain.

A well accepted model of metacognition in the current literature suggests that metacognition operates on two levels: the object level and the meta-level (Nelson and Narens, 1990). According to this model, basic primary cognitions operate at the object level; the meta-level then regulates the processes occurring at the object level. Information travels between the two levels through monitoring and control processes. Monitoring processes inform the meta-

level of what is occurring at the object level, while control processes are mechanisms which the meta-level uses to manipulate actions that ultimately affect the object level.

Several different measures have been developed to capture the construct of metacognition. Objective measurements of the metacognitive process can be obtained by collecting both actual performance data and beliefs about performance. Monitoring processes can be categorized into two types: prospective and retrospective, depending on temporal placement of the required judgment. Prospective processes refer to judgments about performance that are made prior to completing an actual test item. These types of processes include ease of learning judgments (EOL), feeling of knowing judgments (FOK), and judgments of learning (JOL). EOLs are judgments of how easy it will be for one to learn something and are made just prior to when they are tested on the material or task. JOLs, in contrast, refer to judgments of how well one has learned the content and how they will perform in the future; these judgments are made either during or after the learning process. FOKs are judgments of how likely one would be able to recognize a correct answer to the test item. The retrospective confidence judgment (RCJ) is a measurement of retrospective monitoring. These judgments are made immediately after an individual performs an item on a cognitive task and is a report of how confident the individual that the answer provided was correct.

The use of imaging studies has established evidence for the existence of several different types of metacognitive monitoring processes. These type of studies indicate that different monitoring processes (e.g., FOK, JOL, RCJ), are associated with different neural substrates. When comparing activation during FOK and RCJ tasks, FOK judgments were associated with greater activation in the medial parietal region, fusiform area, right superior temporal region and hippocampal formation regions (Chua, Schacter, & Sperling, 2009). When RCJs were being

made, areas in the in anterior left inferior prefrontal region were found to have more activation (Chua, Schacter, & Sperling, 2009). These results demonstrate the complexity of monitoring processes and suggest that the differences between them can be dissociated even at a neural level.

Impairments in metacognitive monitoring processes have been observed in multiple neurological populations, including individuals with Alzheimer's disease and Korsakoff's syndrome (Shimamura and Squire, 1986). Most pertinent to this study, deficits in metacognitive accuracy have also been documented in both pediatric and adult populations following TBI. Children with TBI have been found to make less accurate JOL and EOL judgments (Hanten, Bartha, & Levin, 2000). These findings have also been replicated in adult samples. Adults with TBI have been found to make less accurate JOL predictions on memory tasks (Kennedy and Yorkston, 2000; Kennedy, Carney, & Peters, 2003). In another study examining RCJs made during a recognition memory task, the reports made by participants with TBI were significantly less accurate than healthy adults (Chiou, et al., 2011). Interestingly, in another study, adults with TBI did not demonstrate explicit deficits in accuracy of retrospective monitoring processes; RCJs made by adults with TBI in response to a recall memory task did not differ in accuracy compared to healthy adults (Kennedy, 2001). However, differences in the directional quality of the judgments were observed between the two groups; participants with TBI erred on the side of overconfidence (i.e., their ratings of confidence were higher than their actual performance), while healthy adults consistently thought they were performing poorly (Kennedy, 2001). Although impairments in metacognitive functioning have been documented in adults with TBI, it is still not yet well understood how or why this domain becomes compromised.

Mechanisms of TBI and Implications

Familiarity with the mechanisms of injury in TBI and the consequential neurophysiological sequelae is particularly important to the understanding of cognitive functioning after injury because of the established association between brain and behavior. The physiological insults observed following injury are often accompanied by deficits in cognitive functioning. Identification and characterization of these injuries is necessary to determine their role in affecting cognitive processes. Comprehending the relationship between injury and cognitive functioning may ultimately have implications for the understanding of how the brain and cognitive processes are organized, thus offering an explanation for how and why functioning becomes impaired.

In broad terms, focal injuries in TBI may be the result of penetrating or non-penetrating trauma. Penetrating injuries are characterized by lacerations to the scalp and skull, and penetration of brain tissue by skull bone fragments or foreign matter. Penetrating injuries often result in focal injuries due to the path of injury caused by the foreign matter as it lodges into brain tissue. Non-penetrating (or closed head) injuries occur in two stages: primary and secondary. Primary injuries refer to initial injuries sustained upon impact and are often the result of inertial forces. While injury can certainly be sustained from impact with an external object (Hochswender, 1988), it has been shown this is not a prerequisite; serious injury can occur from inertial forces that do not involve the collision of the head and brain against another surface (Ommaya, Fass, and Yarnell, 1968; Ommaya and Corrao, 1969).

An injury that forms at the site of impact (e.g. bruising) is referred to as a *coup* injury; due to the intracranial space in the skull, it is possible that after the initial impact, the brain will forcefully collide with the opposite side of the skull, causing a *contracoup* injury. The

contusions resulting from *coup* and *contracoup* injuries tend to be more focalized to the area of impact, and are commonly found on the undersurface of the frontal and temporal lobes (Whyte and Rosenthal, 2003). The protruding ridge of the sphenoid bone is a major contributor to contusions that occur in this area (Bigler, 2001a). Bruising of the brain is also possible without direct impact and can affect deeper areas such as the basal ganglia, hypothalamus, corpus callosum, and brainstem (Evans, 1992; Gennarelli, Thibault, and Graham, 1998). Although the focal lesions resulting from these mechanisms are usually macroscopic and easily identifiable via modern imaging, there may be underlying pathophysiology affecting functioning that goes undetected (Bigler, 2001a).

Primary injuries in TBI can also include hemorrhaging that leads to hematomas. In addition to bleeding that can occur in cerebral brain tissue (intraparenchymal bleed), depending on the site of bleeding and vascular contribution, there can also be epidural, subdural, and subarachnoid hematomas (pools of blood between the skull and dura matter, between dura mater and arachnoid mater, and in the subarachnoid space, respectively). The continual collection of blood can be problematic; growth in the mass of blood leads to increased intracranial pressure, potentially causing secondary injury. Other forms of secondary injury include cerebral edema (swelling) resulting in ischemic brain damage, brain shift and herniation, and infection (Levin, Benton, and Grossman, 1982). Secondary injuries prolong the effects of the initial injury and increase the overall magnitude and scope of structural brain damage which has important implications for patient outcome. These secondary injuries may also contribute to more diffuse brain injuries.

Diffuse axonal injury (DAI) is a hallmark injury in TBI that is caused by stretching and shearing of the axonals due to acclerative, decelerative, and rotational forces. As its name

implies, DAI is a global effect and may occur in white matter throughout the brain; however, there is higher likelihood that it will occur in the connecting fibers of the frontal and temporal lobes (Holbourn, 1943), pons and corpus callosum (Levin, Benton and Grossman, 1982; Whyte and Rosenthal, 2003). DAI can occur on the microscopic scale and thus can escape detection even when using conventional neuroimaging scans; however, its emergence has been documented to occur as quickly as within one hour of the injury (Gennarelli, et al., 1998). DAI has been classified into four stages of severity (Gennarelli, et al., 1998). In the first stage of axonal injury, the axon remains intact, but there are changes in biochemistry that may prevent action potentials to be propogated. In the second stage, there is noted cytoskeletal change, such as swelling of the axons; however, at this point the changes are still reversible. The third stage of axonal injury involves both previous stages, although at this point, there is higher likelihood that the damage is permanent and irreparable. In rare and very severe cases, the injury causes an immediate and complete tear in the axonal fiber; this is considered the fourth stage, and can occur without injury at the first three stages.

In the past, it was assumed that the cellular mechanisms that are involved in DAI were similar to the pattern of cell death occurring at focalized lesion sites; however, emerging research suggests that there are particular characteristics of DAI that lead to a more complex cellular cascade than previously thought (Büki and Povlishock, 2006; Farkas and Povlishock, 2007). Cell death that results from trauma can be characterized as apoptotic or necrotic. In apoptosis, the neuronal cell membrane remains intact, but the chemical instability within the cell causes the slow death of the neuron; on the other hand, when the cell membrane is disrupted, activation of calpain and caspase causes quick cell death (Povlishock and Katz, 2005). Additionally, it has also been discovered that cell membranes may heal and regain proper functioning and it is

possible for some axons to recover after injury (Povlishock and Katz, 2005). These findings have significant implications for plasticity following brain injury; however, more research is required to determine if biological recovery of brain tissue will translate to functional recovery.

Theories of Brain and Behavior Relationships: What Causes Impaired Cognitive Processes?

The structural integrity of the brain is acknowledged to be of importance in facilitating cognitive function; thus, anatomical compromise, such as those occurring after TBI, often results in impaired functioning. Two theoretical perspectives dominating the field's understanding of how the brain functions to organize and enable cognitive processes can offer explanations for how and what type of changes in the structural integrity of the brain would lead to decreased cognitive functioning. The localists emphasize the specificity of structures and brain areas in the function of cognitive processes; on the other hand, proponents of the generalist theory believe that cognitive processes occur through the integration of various brain structures and regions. Evidence for these theories has been collected in other areas of functioning (e.g., vision, memory), but have yet to be extended to the domain of metacognition. Based on the organization of the brain posed by these two theoretical perspectives, two characteristics of injury emerge as having great potential in understanding how metacognition becomes impaired: 1) the location of an injury and 2) the extent of an injury. The extent to which these variables in structural disruption contribute to deficits in cognitive functioning may differ; a closer examination of such variables is needed to provide a more comprehensive understanding how and why metacognitive deficits occur after injury.

The localist theory.

Beginning in the late eighteenth century, localization began to develop as what would turn out to be one of the most prominent theories in describing the organization of the brain and its effect on cognitive functioning. According to the localist perspective, cognitive functions can be traced to specific locations or structures in the brain. This movement was birthed from the practice of phrenology. Introduced by Franz Josef Gall, practitioners of phrenology believed that the topography of the skull was representative of different areas of functioning and that the features on an individual's skull were telling of performance in these areas (Feinberg & Farah, 2003).

Despite some resistance in response to phrenology, the localist theory continued to gain momentum as an explanation of how the organization of the brain dictates behavior. The theory gained further popularity when findings by Paul Broca in 1861 suggested that the function of speech could be localized to an area in the left frontal region of the brain (Feinberg and Farah, 2003). Using two case studies, Broca was able to demonstrate that a lesion in the specified location rendered the two individuals with identical disturbances in speech (namely, impairments in the expression of speech). Closely following Broca, Carl Wernicke in 1874 documented the existence of another disturbance in language (the inability for language comprehension), but found that it was localized to an area in the left temporal region of the brain (Feinberg and Farah, 2003). Broca's and Wernicke's works posed as landmark studies supporting the localist view that structures in the brain do posses some specificity in function, and disruption to a given site will render a certain functional consequence. The localist perspective thus asserts that function is organized by location in the cortex; this suggests that functioning could be directly predictable based upon the health or damage of specific structures.

Application of the localist theory.

Since Broca and Wernicke's initial discoveries, the localist approach has been applied to areas of functioning other than speech; for example, using an animal model, Fritsch and Hitzig (1870) demonstrated that motor abilities could be effected by manipulations to the anterior cortex. Application of the localist theory has also been extended to more complex cognitive functions and emotional functioning as well. Executive functioning is an example of a higher order cognitive process that is responsible for initiation, planning, and organizing behaviors. It is thought to be a more involved process because it draws from several different components, including abilities for selection/inhibition, maintenance and updating, and set shifting (Miyake, et al., 2000). There is converging evidence that identifies the frontal lobes as neuroanatomical correlates of executive functioning; multiple studies of healthy adults have found activation of this area when participants engage in tasks of executive functioning (Chen, Wei, & Zhou, 2006; Markela-Larenc et al., 2004; Sauseng, Klimesch, Schabus & Doppelmayr, 2005; Wylie, Javitt, & Foxe, 2003). In another review, Stuss and Alexander (2000) summarized that impaired executive abilities were found in individuals who had sustained focal damage to the frontal lobes. Collectively, these studies suggest that the frontal lobes are critical to executive functioning, and that damage to this area will render impairment in this domain.

The gambling task was developed as an assessment of higher order processing that involves decision making and self-regulation. Participants of this task are required to make decisions about how a deck of cards are sorted; furthermore, there is an element of emotional incentive as there are both rewards and losses that are associated with each sort. When self-regulation and decision making abilities are intact, individuals will learn over time how to maximize their winnings. In a study examining these abilities in adults with TBI, it was found

that performance on the gambling task was not related to gross volume of cerebral white and gray matter; however, participants with focal frontal lesions performed worse than participants with lesions that were not focalized (Levine, et al., 2005). Studies investigating more direct emotional processes have also contributed to the support of localization as an organizing principle. In studies of negative affect, symptomology has been found to differ depending on lateralization of injury. Finset and Andersson (2000) were able to dissociate participant reports of apathy and depression. It was found that participant reports of symptoms consistent with apathy (reduction in goal oriented behavior, motivation, and emotional response) correlated with right hemisphere and subcortical lesions; on the other hand, left hemisphere lesions were correlated to reports of depression.

The generalist theory.

In contrast and in response to theories of localization, proponents of the generalist theory contend that cognition and behavior cannot be pinpointed to specific structures; instead, this perspective favors an emphasis on the brain's capability for plasticity and integration. According to the generalists, ultimately it is the magnitude or size of lesions incurred in injury that will predict functioning. Karl Lashley, a pioneer in this approach, made two important contributions in further detailing this perspective. First, he fostered the principle of equipotentiality in the neurological context. Lashley did not deny that certain areas of the brain may be more specialized (e.g., visual areas); however, he did not believe that function was restricted only to these specific areas (i.e., destruction of an area translates to direct impairment). Instead, he argued that functionality can be distributed across the brain, so that different brain areas, regardless of location, have the potential to facilitate functioning (Lashley, 1930; Lashley, 1933). Lashley was able to demonstrate this concept of equipotentiality through extensive lesion studies

of learning and memory in animals. In his early studies, rats were first trained to learn maze patterns; then, the areas of the brain where the learned behavior was thought to be stored were removed. Despite the exclusion of areas previously thought to be associated with memory of the learned behavior, the rats were able to navigate the maze as they had previously learned (Franz and Lashley, 1917). In other similar studies, dogs were trained to retrieve food from "problem boxes" (boxes that required some manipulation such as the pull of a lever to release food). To test the belief at the time that the complex integrated movements (such as those necessary to operate the "problem boxes") were localized to the precentral gyrus, these areas were surgically removed from the dogs. Immediately following operative procedures, the dogs did show some paralysis; however, the dogs were able to regain motor movement and retained their ability to operate the "problem boxes" (Lashley, 1924). The maintenance and recovery of function demonstrated by the animals even after resection of specified brain structures indicated that function was not necessarily isolated to one particular area (Lashley, 1933). Furthermore, Lashley (1933) also observed that even when a supposedly localized area of the brain is damaged, there is rarely complete extinction of a given function; there is still some semblance of organization that exists outside of the specified area. These findings emphasize an organization of the brain that is based on more diffuse and integrated distribution of functionality opposed to the "isolated specificity" supported by localist theories.

Lashley's second important contribution to the generalist theory is the principle of mass action. Instead of relying on structural location as a predictor of cognitive or behavioral functioning, the principle of mass action states that the amount of damage is paramount in affecting function. In his study of lesions in animals, Lashley (1930) observed that the amount of cognitive impairment did not depend on location, but size of the injury; the larger the amount

of cortical injury present, the greater the impairment. Lashley was able to find significant correlations between the amount of lesions and the degree of impaired functioning (Lashley, 1926; Lashley and Wiley, 1933). In select studies of learning, rats would be trained to navigate a maze; however, after each successful learning trial, the rats would receive additional resection of brain matter. Although the rats were capable of learning the navigation accurately after each operation, it was found that progressively more time was needed after each operation (Lashley, 1931). The findings of this study suggest that as more and more brain tissue is removed, the ability to learn also becomes compromised. The principle of mass action can be complemented by Lashley's views of equipotentiality and integration of the brain as a whole to function; he speculates that because the cortex has a more "generalized" function, removing tissue would be like removing reserves that might otherwise be able to subsume functioning (Lashley, 1931). Taking these organizing principles together, the implication for functioning from the generalist perspective is that cognition and behaviors are complex processes in their own right. A generalist perspective does not dispute that there may be regions that are highly specialized; however, human functioning is complex nonetheless and can rarely be distilled into simplistic compartments.

Application of the generalist theory.

The principle of mass action and the generalist theory have been supported by observations of global structural changes and corresponding alterations in cognitive functioning in individuals with TBI. The nature and interaction of the mechanisms involved in TBI are believed to have a cumulative effect that result in overall global and diffuse atrophy (Bigler, 2001a); findings supporting such changes in brain structures have been widely documented. The amount of injury present can easily be measured using volumetric analyses. The occurrence of

brain atrophy can be observed by either measuring gray and/or white matter tissue, or more indirectly by measuring amount of cerebral spinal fluid (CSF), ventricular dilation, or brain to ventricle ratios. The observance of structural change after TBI was elegantly demonstrated in one case study; the individual received a MRI scan before and after an injury, allowing for detection of changes resulting from the injury (Macnamara et al., 1992). The post-injury scan indicated significant dilation of the ventricles (particularly in the third and lateral ventricles). The ventricle to brain ratio had also increased; it was found that there was a 70% enlargement of ventricle size (Macnamara, et al., 1992). Cognitive testing that was done post injury also demonstrated diffuse cognitive impairment (Macnamara et al., 1992). Changes in brain structure appear not only during the immediate stages of recovery, but can continue to occur with time. Sidaros et al. (2009) tracked changes in the brain using tensor based morpohmetry at eight weeks and twelve months post injury. When measured at eight weeks post injury, it was found that brain volume had decreased 8.4 percent; at the year follow up, they had measured between 0.6 to 9.4 percent of change in brain volume (Sidaros et al., 2009). In a separate study following adults with TBI at 4.5 months and 29 months after injury, Ng et al. (2008) had also found an increase in CSF volume, and decrease in hippocampus volume.

Cross sectional imaging studies have confirmed these findings of enlarged ventricles, increased volume of CSF, and widespread decrease in volume of both white and gray matter including areas in the frontal, parietal, and temporal regions, thalamus, cingulate, corpus callosum, hippocampus, and fornix (Blatter et al., 1997; Bigler, 2001b; Kim et al., 2008; Levine et al., 2008; Mamere et al., 2009; Tomaiuolo et al., 2004). Studies have also found evidence of widespread cortical thinning present after injury. Using techniques that analyze the surface of the brain (surface based morphometry), Turken et al. (2009) discovered thinning in the frontal,

temporal, and occipital lobes of adults who had sustained TBI. These findings have also been observed in populations of pediatric TBI; in comparison to healthy children, those who have sustained TBI showed significant cortical thinning (Merkley et al., 2008) of gray matter.

Importantly, relationships between decreased brain volume and compromised cognitive function have been established, providing support for the generalist theory. Lashley's initial discovery of the importance of brain matter was in the domain of memory; since those initial studies, the principle has been extended to other higher order cognitive domains, such as executive functioning. In one sample of pediatric participants with TBI, the volume of frontal lesions alone did not correlate with performance on executive functioning tasks; however, the additive effect of total lesions, including those not in the frontal cortex, did predict performance on an executive functioning task (Slomine, et al., 2002). In another study examining executive functioning performance in children with TBI, researchers found that diffuse lesion severity was predictive of executive functioning, but severity of focal frontal lesions were not (Power, Catroppa, Coleman, Ditchfield & Anderson, 2007).

As described earlier, Lashley believed that the preservation of cognitive processes despite injury to localized areas provided evidence for the dispersion of function across the brain. Lashley's initial findings were based off of animal studies, but the conservation of cognitive abilities after injury has also been documented in human populations. In working with adults who had sustained brain injuries, Kurt Goldstein in the 1940's discovered that not all facets of executive functioning had been impaired. Goldstein (1944) noticed that the adults seemed to possess the motivation and know the steps involved in a goal oriented activity, but then would have difficulty with the actual initiation of the steps. These observations provided evidence that two "types" of symptoms, abstract and concrete, are both involved in deficits of executive type

functions; however, brain injury that is associated with one type of the symptom does not equate to association with the other (Goldstein, 1944; 1959). The finding that all symptoms of executive dysfunction are not simultaneously impaired, and that in fact some functioning seem to have been spared suggests diffusivity.

Plasticity and recovery of functioning observed even after localized injury support the generalist view. If cognitive processes are associated with certain structures, as believed in the localist theory, function should be lost after injury to the structure; however, the ability to regain some of the function despite a localized injury suggests that functional abilities are not limited to focal sites. Evidence of recovered function with focal injury has extended beyond animal lesion studies; emerging literature supports similar findings of recovery in humans. In a longitudinal study of adults with TBI, those that had frontal and fronto-temporal lesions initially performed worse on tasks of executive functioning than individuals with no lesions and non-frontal lesions; however, when the individuals were tested again after one year, the groups had shown significant improvement, and no differences in performance were found between the groups (Lehtonen, et al., 2005). The improvement in performance evidenced over time in the sample with frontal and fronto-temporal lesions suggests that faculties required for executive functioning are not likely to be localized, otherwise, the focal damage should have rendered permanent impairments.

Understanding Metacognition: Localized Function, Brain Matter Dependent, or Both?

The localist and generalist theories each have distinct explanations for the organization of cognition in the brain; they also identify the types of disruptions in the physiology of the brain that may affect cognitive functioning, including the domain of metacognition. According to a localist perspective, metacognitive functioning should be localized to a specific area within the

brain; this emphasizes location as the main injury variable of interest that causes deficits in the ability to make accurate judgments about one's cognitive functioning. In contrast, generalists would argue that metacognitive abilities do not reside in any specific structure, but rather damage to large quantities of brain matter (regardless of location) will lead to impairment. Some evidence exists that support each of the theoretical arguments; however, as will be discussed, the literature to date is still far from clear in its ability to definitively indicate the organization of metacognition in the brain.

The use of functional neuroimaging techniques have helped to elucidate some of the neuroanatomical correlates of metacognition. Studies in healthy adults have identified neural systems that are related to metacognition. In a study comparing activation during metamemory tasks and a non-metamemory task, activation was greater in the medial prefrontal, mid/posterior cingulate, and lateral parietal and temporal regions when making the metamemory judgments (Chua, Schacter, & Sperling, 2009). A related study by the same researchers demonstrated that when making confidence judgments, participants showed greater activation in bilateral lateral parietal region, insula, superior frontal regions, dorsal medial prefrontal regions, and the right orbitofrontal regions than when completing only the memory task (Chua, Schacter, Rand-Giovanetti, & Sperling, 2006). In another study of healthy adults, it was found that greater FOK was related to increased activation in the left dorsolateral, left anterior, bilateral inferior, and medial prefrontal cortices; furthermore, it was found that activation found in the frontal regions were present only when FOKs were being made and not during the accompanying memory task (Kikyo, Ohki, & Miyashita, 2002). While the results of these studies do identify areas of the brain that appear to be associated with metacognitive functioning, it is not known if these structures are essential and to what extent they are necessary for metacognitive accuracy.

Aside from these functional imaging findings, there has been one other lesion study that provides evidence of the association between the frontal lobe functioning and metacognitive performance. Schneyer, et al., (2004) examined FOK judgments in individuals who had sustained lesions in the right medial prefrontal cortex, and found that they made less accurate judgements than healthy adults. This finding infers the importance of the prefrontal cortex as an area needed for metacognitive functioning; as indicated by Scheneyer et al.'s (2004) results, an injury to this particular location in the brain resulted in impaired ability to make accurate metacognitive judgments. However, these results could not be generalized to all measurements of metacognition. While impaired FOK was associated with the focal lesions in the right prefrontal cortex, retrospective confidence judgments were not found to be affected (Schneyer, et al., 2004).

Although these findings provide an alluring argument for the localization of metacognition, there is still some questionability in its ability to fully account for deficits in metacognition. The existence of additional damage that is diffuse across the brain in TBI complicates the possibility that a cognitive deficit can be completely attributed to a focal injury. Another critique of the localist perspective lies in the large number of areas found in the earlier mentioned imaging studies that are thought to be associated with metacognitive functioning. The identification and inclusion of such a wide number of areas being implicated in the process of metacognition weakens the argument for a focalized location of function.

In support of generalist theories, evidence has been found in the current literature that suggests self-reflective processes rely on integration of the whole brain, and deficits in these processes is associated with the amount of injury sustained rather than the location. Impaired awareness has been found to be related to the number of lesions present after injury (Prigatano

and Altman, 1990). More recently, Sherer, et al., 2005 measured awareness using a self-report questionnaire in individuals with TBI; in their sample, they also classified participants into groups depending on location of lesions. It was found that the locations of the lesions did not predict accuracy of awareness; instead, impaired self-awareness was related to the number of lesions present (Sherer, et al., 2005). These findings support the generalist view that there is no focalized location responsible for metacognition, but rather it is the magnitude of injury that predicts functioning. However, these findings were from studies of general self-awareness (e.g., awareness of functioning on activities of daily living) that used subjective questionnaires instead of objective measurements; these findings have yet to be extended to studies specifically investigating metacognition that are traditionally measured using a comparison of metacognitive judgment and actual performance. Further investigations are required in order to determine the effects of additive global injury on metacognition. As discussed earlier, it has been established that global atrophy after TBI has been associated with deficits in cognitive functioning; however, the direct relationship between brain matter and metacognitive functioning has yet to be formally tested.

Historically, the localist and generalist theories have opposed each other; however modern neuropsychology has worked to integrate contributions from both perspectives. Alexander Luria (1973) argued that it was highly unlikely that the function of mental processes, especially those that are higher order in nature, could be pinpointed to one particular structure; but on the other hand, Luria also believed that the lack of specificity in organization argued by extreme generalists was too crude of an explanation for complex human cognitive processes. Luria proposed that higher order cognitive processes should be seen as "functional systems" that have different contributing components that are located in different areas of the brain; thus,

integration of the various parts of the brain is needed (Luria, 1973). Modern day expansion of these ideas has resulted in neural network theories; according to Mesulam (1990), complex behaviors are thought to rely on multifocal networks across the brain. Rather than focus on any particular structure, function is based upon the coordinated involvement of not only local networks, but large widespread networks whose centers may be far from one another. This conceptualization of brain organization allows for explanatory contributions from both localist and generalist perspectives to coexist.

The examination of specific variables of injury, notably location and quantity, provides a more comprehensive understanding of how cognitive processes are organized in the brain and how they become impaired. Currently, the organization of metacognition is not well comprehended, and the evidence that exists remains divided. An issue that remains to be addressed in this literature is the determination of which injury variable best predicts metacognitive impairment; this then has implications as to the theoretical orientation, localist or generalist that best explains how metacognition is organized. Additionally, it is important the potential interactions between the influences of location and quantity of damaged tissue be examined; as integration is becoming increasingly accepted, an examination of the interface between localist and generalist variables may provide a more comprehensive answer.

Novel Methods of Examining Structural Brain Change After TBI

The mechanisms of TBI lead to the emergence of both focal and diffuse injuries. These types of injuries can be of significant importance in helping to determine which theory of organization best accommodates an understanding of metacognitive functioning. Impairments that are found to be associated with specified focal lesions from injury would support the localist

views; on the other hand, if it is determined that the magnitude of injury that predicts metacognitive functioning, then the generalist view is confirmed. What is critical in making these determinations is the ability to observe such lesions. In order to appreciate and capture the full extent of focal and diffuse brain matter lost in injury, methods that are highly sensitive to detecting both pronounced and minute changes in brain structure need to be considered.

There are currently two methods that could address the needs for high sensitivity in the measurement of brain structure. The first approach is voxel based morphometry (VBM). This method is well suited because it consists of a whole brain analysis of voxels, resulting in a comprehensive survey of areas where damage could occur. In addition to providing information about total brain volume, it is possible to obtain measurements of volume in particular brain tissue types. The second method is diffusion tensor imaging (DTI), which is a method that is very sensitive to detecting microscopic injuries in white matter that might otherwise remain undetected. Of significant pertinence to the current study, DTI can be used to make determinations about the integrity of white matter tissue and tracts after injury.

Voxel based morphometry.

Introduced by Wright et al. (1995), VBM is a technique used to quantify total brain volume, gray matter, white matter, and CSF concentration/density and volume. Using T1 weighted MRI scans, VBM consists of several preprocessing steps and a final statistical analysis at the voxel level to determine differences in tissue concentration between groups. In the first step of preprocessing, the images are spatially normalized, meaning that scanned images are fit to a template image, making them comparable to each other. After normalization, the images are then segmented, or separated into gray matter, white matter, and CSF. A third smoothing step is then used to maximize the normal distribution of the voxels for use in statistical analyses (fully

detailed explanations of these preprocessing steps can be found in Asburner and Friston (2000); in addition, for technical summaries of methods and application, see: Ashburner and Friston, 2001; Mechelli, Price, Friston & Ashburner, 2005; Whitwell, 2009). Finally, after the images have been preprocessed, the data from groups are compared statistically on a voxel by voxel basis to identify differences. VBM is a departure from older region of interest (ROI) tracing methodologies, where the ROIs would be manually traced onto structural images, and gross measurements would be made based on the traced masks.

This methodology of using voxel wise comparisons affords several advantages over ROI tracing methods. First, due to the normalization procedure, VBM allows for meaningful group comparisons; the confounds of individual differences in brain shape and size are accounted for—the brains are fitted into a common space, but variations are accounted for during the preprocessing steps. Secondly, the results of the analyses are more "data driven" in comparison to ROI tracing methods. In VBM, an extensive number of comparisons between voxels are made, and a final result is produced based upon these automated comparisons; ROI tracing methods, on the other hand, require the researcher to make *a priori* decisions of "where to search" for potential differences. The analysis used in VBM is more comprehensive as it encompasses the whole brain, and is potentially more precise as it uses comparisons of voxels instead of gross measurements that have been used in previous studies. Thus, VBM is a method that accommodates examining questions from both a generalist and localist approach; if impairment of cognition is dictated by global changes and the principle of mass action, then it is a well suited method that has high sensitivity to maximize detection of tissue loss in the whole brain. VBM is also ideal for testing the localist approach; because it has a component of spatial mapping, focalized lesions can be identified using this method.

Examination of TBI using VBM methods have shown decreases in both gray and white matter. Nine individuals with mild to severe head injury were scanned in a study by Gale, Baxter, Roundy, and Johnson (2005). The researchers found that the adults with TBI had decreased gray matter in the bilateral frontal, temporal, parietal, and right mesial temporal regions compared to healthy adults; gray matter in the cerebellum was also found to be decreased in the sample of adults with TBI (Gale et al., 2005). Consistent with the generalist theory, these widespread areas of decreased gray matter (bilateral frontal, temporal, parietal and left cingulate regions) were correlated with poor performance on a cognitive task of attention (Gale et al., 2005). In another recent study utilizing VMB techniques, individuals with TBI were shown to have decreased white matter in the frontal lobes, limbic region, corpus callosum, cingulate, thalamus, parahippocampal region, and cerebellum (Vannorsdall, et al., 2010). Additionally, these individuals also had decreased gray matter along the temporal poles, the central portions of the frontal, parietal and occipital lobes, cingulate cortex, thalamus and cerebellum (Vannorsdall, et al., 2010). In this sample, poor performance in the domains of psychomotor speed, attention, memory, and executive functioning was related to a lower white matter to total intracranial volume ratio (Vannorsdall, et al., 2010). Declines in brain volume detected by VBM have also been observed to continue over the time of recovery. Bendlin, et al. (2008) tracked changes in brain tissue within individuals during acute and chronic stages of recovery (average of 2 and 13 months after injury, respectively) and found that there was white matter volume decline in the frontal, temporal, parietal and occipital areas. Decreases in gray matter volume were found in the thalamus, bilateral pallidum, cingulum, right post central gyrus, supplementary motor area, right precentral gyrus, and bilateral putamen (Bendlin, et al., 2008). Interestingly, despite the loss of brain volume over time, Bendlin et al. (2008) found that memory functioning improved

between the two timepoints; however, even at the second time point, individuals with TBI still demonstrated impaired cognitive performance in comparison to the healthy adults. The collective findings from these studies indicate that VBM is sensitive to detecting diffuse loss of brain volume, and these losses in volume are indeed related to worse cognitive outcome.

Diffusion tensor imaging.

Due to the heterogeneity of injury present after TBI, not all changes in brain tissue may be observed using traditional clinical scanning methods; a methodology such as DTI that is highly sensitive to detecting changes in white matter is not only advantageous but crucial. In addition, the information gained from DTI provides another dimension from which to describe injury and how it may be related to functioning. Thus far, the location and quantity of injury have been suggested as potentially important predictors of cognitive functioning; however, little is known about effect of other injury characteristics (e.g., lesions reflective of complete axonal degradation).

The development of diffusion tensor imaging (DTI) has afforded researchers the ability to investigate the integrity of white matter in the brain. The functionality of DTI is based upon the Brownian motion of water, which refers to the observation that water molecules appear to move in random directions as they collide with one another. When there is nothing to impede the diffusion of water and the molecules are equally diffused, diffusion is said to be isotropic. In contrast, anisotropic diffusion occurs in the presence of interference with diffusion. In the brain, the physiological architecture of axons and fiber tracts act as barriers that prevent isotropic diffusion; as the water diffuses, it runs up against the tracts and is prevented from moving in random directions. Intact axons and fibers result in more barriers to random water diffusion and create more anisotropic diffusion. When axons and fibers are damaged, the barriers break down

and water molecules are permitted to diffuse equally and randomly once again, becoming isotropic. Thus, DTI is not a direct measure of the axons and fiber tracts in white matter; rather, it is a measure of water diffusion in the brain which allows inferences to be made about the integrity of the white matter (for more technical reviews of DTI methodology, please refer to: Assaf and Parsternak, 2008; Basser, 1995; Basser and Pierpaoli, 1996; Le Bihan et al., 2001, Huisman, 2003).

DTI techniques are capable of quantifying the amount of diffusion. There are several ways of reporting diffusion. The most commonly reported measure is the fractional anisotropy (FA) value. This is a number between zero and one, representing a ratio of the magnitude of diffusion that is anisotropic; values closer to zero are indicative of isotropic diffusion and those closer to one suggest anisotropic diffusion (Basser, 1995, Basser and Pierpaoli, 1996). Another measurement, although at this point less understood, is the apparent diffusion coefficient (ADC); this value is used to report the rate of diffusion. Although these values are reported numerically, they can also be rendered onto spatial representations (e.g., a FA map where areas with higher values appear brighter). In addition, there are also studies that utilize measurements of diffusivity that are said to be parallel to the axon fibers (axial diffusivity) and that which are perpendicular to the axons (radial diffusivity). Axial and radial diffusivity have been used to make inferences about the microstructure of the fibers—a reduction in axial diffusivity may be attributed to axonal injury, where a decrease in radial diffusivity may be indicative of demyelination (Song et al., 2002). Measurements of diffusivity can be applied to the whole brain or restricted to ROIs; more recently, DTI has been used to isolate major axonal tracts (Mori, et al., 2002; Wakana, Jiang, Nagae-Poetscher, van Zijl, & Mori, 2003), of which quantitative measurements can also be made.

The methodology of DTI has been applied successfully to examine white matter after TBI because of the hallmark presence of diffuse axonal injury in TBI physiopathology. DTI has been found to be useful in quantifying observable white matter lesions after TBI (de la Plata, et al., 2007); but more importantly it has capabilities of identifying microscopic injuries in white matter that are often time visually missed in conventional structural MRI scans (e.g., T1-weighted image) (Nakayama, et al., 2006). DTI offers impressive sensitivity to also having the ability to detect lesions in mild TBI; decreased FA values have been observed in the corpus callosum, internal capsule, and centrum semiovale (Inglese, et al., 2005). Interestingly, the level of injury severity has been found to influence the health of white matter (Kraus, et al., 2007). Individuals with moderate and severe TBI have more areas of decreased FA; additionally, while decreased axial and radial diffusivity has been found after both mild and moderate/severe injuries, these diffusivities remain low only in moderate/severe cases suggesting more permanent physiological damage (Kraus, et al., 2007). Reductions in FA values after TBI is well documented and affects the following areas: cerebral peduncles, corticopontine tract, portions of the thalamus, anterior and posterior corona radiate, cortices spinal tracts, cingulum fiber bundles, external capsule, superior longitudinal fasciculus, saggital stratum, forceps minor and major, genu, corpus callosum, and inferior fronto-occipital fasciculus (Bendlin, et al., 2008; Kraus, et al., 2007; Kumar, et al., 2009; Sidaros, et al., 2008; Xu, Rasmussen, Lagopoulos, & Håberg, 2007), although interestingly on study by Greenberg, et al. (2008) did not find a change in FA values for the corpus callosum.

Importantly, these changes in FA values following injuries are associated with cognitive functioning. An examination of memory and learning abilities following TBI illustrated that impaired functioning in this area was related to increases in diffusivity (Salamond, et al., 2006).

Kraus, et al., (2007) chose thirteen ROIs as areas of focus and found that diffusivity in the individual ROIs were slightly related to impairments in the domains of attention, memory, and executive functioning following. However, a combination of diffusivity values from all the ROIs (thus creating a more "global" score) resulted in strong negative correlations between diffusivity and memory and executive functioning (Kraus, et al., 2007). Contrary to these findings, Bendlin, et al., 2008 documented improvements in the area of memory despite increases in FA values over time in individuals with TBI; however, it is noted that both FA values and cognitive functioning of individuals with TBI were depressed compared to healthy adults. These studies confirm that axonal contributions are important and damage to these areas indeed influences cognitive functioning.

The Proposed Study

Metacognition is a domain of cognitive functioning that has been observed to be impaired following moderate to severe TBI; however, explanations for the neuroanatomical correlates to these deficits remain elusive. Two foundational theories of organization, localization and generalization, highlight two types of injury variables (location and quantity) that could play crucial roles in influencing metacognitive functioning. What remains unknown however, is how exactly these injury variables may contribute to impairments; further, these variables could be telling of how metacognition is organized in the brain. The localist perspective argues that structures in the brain are specified for distinct functions; thus injury to a specific brain area will cause a corresponding deficit in function. Studies of functional imaging have suggested that the prefrontal cortex is involved in the making of metacognitive judgments; however, this literature lacks further specificity--there are several brain structures within the frontal cortex that were

found to be associated with metacognition. Furthermore, there is limited knowledge as to the contribution of these localized regions to metacognitive functioning after it has sustained injury. In contrast, the generalist perspective asserts that the brain works in an integrated fashion so damage to the brain in one location may not initially cause extensive impairment, but as the damages increase, greater function is lost. Loss of brain tissue as evidenced by global trophy after TBI that has been linked to poor cognitive performance has been established; however, it is not known whether this pattern would extend to the domain of metacognition. A handful of studies indicate that impairments in self-reflective processes do correlate with magnitude of tissue damage, but these studies utilized subjective self report questionnaires, yet, this remains to be replicated using objective item-by-item measurements of metacognition. To date, it remains unknown whether impairments in metacognition are the result of injury to a specialized area (or network) responsible for the domain, or if it is a result of accumulated injury that affects the brain's ability to work cohesively as an integrated whole.

This study seeks to clarify the relationship between brain and metacognitive functioning. By examining how alterations in brain physiology contribute to the loss of metacognitive accuracy after TBI, some conclusions can also be made about how metacognition is organized. A crucial part of this study will involve examination of the lesions present in TBI; but detection of these potentially microscopic injuries can be difficult, thus, it is crucial that techniques that are highly sensitive to pathophysiological changes in the brain (VBM and DTI) be used to accomplish such a task. Expanding the understanding of metacognitive functioning will occur by addressing these aims:

1. Using quantitative MRI methods, it is a goal to identify and measure two characteristics of injury after TBI: location and volume. Using VBM, areas in the

brain where the tissue density is lower in participants with TBI than healthy adults will be identified. The total amount of brain volume will also be determined using VBM.

Hypothesis: It is hypothesized that participants with TBI will have a decreased amount of total brain volume compared to healthy adults; based upon and consistent with previous studies in the literature, it is anticipated that areas of decreased volume will include the frontal, temporal, and parietal regions, cingulate, and corpus callosum.

2. Determine the extent to which injury characteristics predict metacognitive functioning, using measurements of injury location and brain volume quantity as independent predictor variables. Based upon the results of the analyses, conclusions can be made to regarding the organization of metacognitive processes in the brain.

   Hypothesis: Finding impairments in metacognition that can be fully accounted for by measuring the location of the injury would suggest that metacognitive processes are localized to specific area, and that damage to these areas causes impairment. In contrast, finding impairments in metacognition that are fully accounted for by a measure of total brain volume would suggest that these processes are not dependent on any structure in particular, but how much brain tissue is available. It is anticipated that more realistically, both location and quantity will account for some of the variance in metacogntive functioning; an important goal is to be the premier study in the field identifying the contribution of each injury variable to metacognitive functioning.

3. Explore other dimensions or qualities of injury that can potentially affect metacognitive impairment.
    a. Determine if there is an effect of specific tissue type (gray or white matter loss) on metacognitive functioning.
    b. Determine the effect of different axonal injuries (demylination or axonal breaks) on metacognitive functioning.

    Hypothesis: White matter tracts have been established to be highly influential in facilitating communication in the brain. Whether it be limited to a specific subset of structures or across the whole brain, it is hypothesized that white matter integrity will have an important role in its functioning; specifically, lower FA values will be associated with worse metacognitive functioning. Furthermore, it is hypothesized that decreased axial diffusivity (suggesting axonal breaks) will be associated with worse metacognitive functioning than demylination.

Chapter 2. METHODS

Participants

Thirty-five adults with moderate to severe TBI were recruited for this study. Injury severity was defined by a GCS score between 3 and 12 at time of admittance to the emergency room, and medical chart documentation of a positive neuroradiological scan (e.g., positive CT or MRI scan). Twenty-six healthy adults were also recruited. Exclusion criteria for both groups included a history of color blindness, and/or psychiatric illness (including alcohol/substance abuse and dependence) that required inpatient treatment or hospitalization. The demographics of both groups are shown in Table 1. There was no significant difference in the years of education held by the participants ($t(60)=-1.53$, $p=0.13$); however, the adults with TBI were slightly older in age ($t(60)=2.09$, $p=0.41$). All participants provided written informed consent prior to beginning the study.

Neuropsychological Test Battery

Participants completed the battery of paper and pencil neuropsychological test after being scanned. Paper and pencil testing occurred in a well-lit, quiet room with minimal visual and auditory distraction. Each participant received the same battery of tests. Tests were administered and scored by trained researchers and researcher assistants. Analyses of results from paper and pencil neuropsychological test measures were carried out using IBM Statistical Package for the Social Sciences version 19 (SPSS) software.

Measures of Metacognition.

Measurements of metacognitive monitoring were collected by requiring participants to report retrospective confidence judgments (RCJs) after each item on the tests described in this

section. Following each item of these tests, participants reported their confidence that the answer they provided was correct. Immediately after giving their answer to the item, they were instructed to complete the statement: "I am _____my answer is correct." Six Likert scale choices were provided: completely certain, certain, somewhat certain, somewhat uncertain, uncertain, and completely uncertain. These were coded into numerical value for calculation of the gamma coefficient (described below).

To measure metamemory, manipulations were made to the Hopkins Verbal Learning Test-Revised (HVLT-R) (Benedict, Schretlen, Gronigner, & Brandt, 1998). First, to discourage learning and increase variance in RCJs, only one learning trial was administered. Participants were be read the list of words once, and then asked to repeat words they remembered. After a brief delay, the recognition trial was administered. A RCJ was verbally obtained following each query in the recognition task.

Assessments of metacognition during tasks of abstract reasoning (meta-abstract reasoning) were obtained through the use of two manipulated tests, the Matrix Reasoning subtest of the Wechsler's Adult Intelligence Scale-III (WAIS-III) (Wechsler, 1997) and the Abstraction subtest of the Shipley's Institute of Living scale (Shipley, 1946). On the Matrix subtest, all 26 stimuli were used, without adherence to discontinuation rules. The stimuli were also divided into two sets by selecting every other item. In one set, Matrix Order, the stimuli were left in order as published so that the level of difficulty progressed from easy to difficult. In contrast, the stimuli were randomized in the other set, Matrix Random, so that there was not a linear progression of difficulty as the task advanced. After each item these tasks, participants were required to verbally report their confidence in the manner described above. The Abstraction subtest

consisted of a written task where participants completed logic patterns by filling in blanks. Following each item, they provided a written response of their confidence.

The Goodman and Kruskal gamma coefficient (Goodman and Kruskal, 1954) served as a quantitative measure for metacognition. A pair of scores was obtained for each item on a task: a score indicating accuracy of the response (correct or incorrect) and a confidence judgment (Likert scale rating). The gamma coefficient was calculated by comparing these paired scores against one another (a dyad, meaning, two pairs of scores) for all the items of the task. These dyads can be concordant, discordant, or tied. In a concordant dyad, the confidence scores of both pairs consistently reflect a relatively more accurate judgment. A disconcordant dyad indicates a less accurate confident judgment. The gamma coefficient is calculated as the surplus of concordant to disconcordant dyads. The numerical value of the gamma coefficient ranges from negative one to one; values closer to negative one suggest less metacognitive accuracy, and values closer to one suggest higher metacognitive accuracy. Tied dyads are comparisons in which both performance and confidence judgments are equal; these types of dyads can be misleading (Gonzalez and Nelson, 1996) and thus are eliminated when the gamma coefficient is calculated. The means from the sample of healthy adults will be used for standardization of scores on tests of metacognition.

Assessment of basic cognition.

In addition to the measurements of metacognition, the following tests were also administered to assess for basic cognitive performance:

- Digit Span subtest of the WAIS-III (Wechsler, 1997) was administered to examine attention and working memory.

- Stroop Color-Word test (Trenerry, Crosson, DeBoe & Leber, 1989) was administered to assess inhibition and executive functioning.
- The Letter Fluency subtest of the Delis-Kaplan Executive Functioning System (DKEFS) (Delis, Kaplan & Kramer, 2001) test was used to measure verbal fluency.
- Trailmaking Tests A and B (Army Individual Test Batter, 1944; Reitan & Wolfson, 1985) assessed for visual scanning attention as well as speeded set shifting skills.

  In addition to measuring metacognition, the actual performance scores on the HVLT-R provided an assessment of memory, while the Matrix Reasoning and Shipley's Abstraction tasks provided additional measures of executive function.

Structural Imaging

Scanner Parameters.

Structural imaging data were acquired using 3Tesla scanners at the Pennsylvania State University, University Park campus and Hershey Medical Center. Participants were instructed to relax and to lie as still as possible for the duration of the scans. A high resolution MPRAGE (T1) image and diffusion weighted data were collected during the scan. The following scanner parameters were used to obtain the T1 images: 150 slices, 1 mm slice thickness, 1 X 1 X 1 voxel size, TR= 9.8 ms, flip angle= 9°, field of view (FOV) of 256, 204, 150. Diffusion weighted images were collected using the following parameters: 56 slices, 2.5 mm slice thickness, 3.13 X 3.13 X 2.50 voxel size, TR= 6882.6, FOV of 250, 250, 140.

Pre-processing procedures.

The VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm/) and Statistical Parametric Mapping 8 (SPM8) software (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) were used for

pre-processing and analyses of volumetrics. In the optimized pre-processing steps, the T1 images were first segmented by tissue class, resulting in a set of gray matter, white matter, and cerebrospinal fluid maps. These segmented images from each individual were then aligned to a template brain (Montreal Neurological Institute (MNI) space) during a normalization step. The effect of different size brains and manipulation of the images into the MNI template space was eliminated by choosing a non-linear modulation option during normalization. These pre-processing steps provided a quantitative measure (mL/cc) of global (whole brain) gray matter, white matter, and cerebrospinal fluid volumes, and also rendered the images ready for second level statistical analyses. The quantitative values were entered into SPSS for further statistical analyses, and SPM8 was used for statistical analyses of imaging data.

Diffusion tensor imaging data were processed using the DTI Track module of the MedInria software (http://www-sop.inria.fr/asclepios/software/MedINRIA/). The file type of the raw diffusion weighted data collected from the two study sites differed where the scanner at one site output the data in a "dicom" format, and the other packaged it in a "par/rec" format. Both formats were transformed into "analyze" format required by MedInria; dicom data were transformed using an option in the SPM8 software, while par/rec data were transformed using the dcm2nii program in MRIcron (http://www.mccauslandcenter.sc.edu/mricro/mricron/dcm2nii.html). Due to the difference in initial file type, gradient tables that list the directions of diffusion weights, were also acquired differently. As part of the dicom to analyze transformation, a gradient table is automatically created by SPM8; however, the table was manually created for the par/rec files by using a gradient converter code (http://godzilla.kennedykrieger.org/~jfarrell/OTHERphilips/GUI.html) developed by Farrell, et al. (2007). To maximize processing efficiency, the following parameters

were used to isolate white matter tracts in the brain: minimum FA threshold=0.2, smoothness=20, minimum fiber length=20, and sampling =10. Using the binding box feature, excessive fibers formed from artifact were eliminated. The remaining fibers were selected as bundles of interest. Statistics of the bundle of interest were computed, yielding whole brain fractional anisotropy (FA), apparent diffusion coefficient (ADC), lambda (λ) 1, 2, and 3 values. Radial diffusivity values were calculated by computing the average of the λ2 and λ3 values. These values were then entered into a SPSS database for statistical analyses.

Chapter 3. RESULTS

Behavioral Data

Independent samples t-tests were conducted using the raw scores from the neuropsychological measures to examine group differences in cognitive performance. Participants with TBI were found to perform significantly worse on all measures of cognitive functioning except for the Forward Digit Span. The means, standard deviations, *t* scores, and significance values are reported in Table 2.

Independent samples t-tests were also performed on the gamma coefficients from each metacognitive task to examine performance differences in metacognitive accuracy between groups. On the task of metamemory, no differences in metacognitive accuracy were found between the participants with TBI and the healthy adults. Participants with TBI did not demonstrate any difference in metacognitive accuracy compared to healthy peers on two of the meta-abstract reasoning tasks (the modified Shipley's Abstraction task and Randomized Matrix Reasoning task). However, the difference in accuracy between groups on the Ordered Matrix Reasoning task was close to reaching statistical significance at the $p=0.05$ level ($p=0.059$). Results of one-tailed t-tests based on the assumption that participants with TBI should have worse metacognitive performance indicated that the difference in accuracy between groups on the Ordered Matrix Reasoning task did reach statistical significance ($p=0.03$). Table 3 lists the mean gamma coefficient values, standard deviations, *t* scores, and significance values of the two-tailed tests.

Differences in Global Brain Tissue Volume

Differences in global intracranial gray and white matter volume, as well as total volume of cerebral spinal fluid (CSF) between participants with TBI and healthy adults were examined using independent samples t-tests. Adults with TBI had less total gray matter (*mean*= 633.0 mL, *standard deviation(SD)*=70.6) than the healthy adults (*mean*=677.3 mL, *SD*=84.1); the difference in gray matter volumes between groups was statistically significant ($t(59)=-2.2$, $p=0.03$). The participants with TBI as a group also had less total white matter (*mean*=474.8 mL, *SD*=77.9) compared to the healthy participants (*mean*=512.6 mL, *SD*=62.9). This difference in amount of white matter present was statistically significant ($t(59)=-2.0$, $p=0.047$). Total brain CSF volume was found to be statistically different between the two groups ($t(52.1)=3.6$, $p=0.001$). The participants with TBI had greater total CSF volume (*mean*=273.7 mL, *SD*=61.0) than their healthy peers (*mean*=231.3mL, *SD*=30.0).

Relationship between Global Brain Volume and Metacognitive Functioning

The relationship between metacognitive functioning and global brain tissue volume was determined using correlation analyses. For each participant group, correlation analyses were conducted using the raw global gray matter, white matter, and CSF volumes computed from the VBM processing procedures, and the gamma coefficients calculated from the four measures of metacognition. In this sample of participants with TBI, no relationships were found between the amount of brain tissue volume and metacognitive performance. The Pearson's *r* coefficient and significance values are noted in Table 4.

In contrast, several significant relationships were found between metacognitive performance and global brain tissue and CSF volumes in the sample of healthy adults. A

statistically significant negative correlation was found between the metacognitive accuracy of the Shipley's Abstraction task and the amount of total CSF (r=-0.43, p=0.03). Additionally, statistically significant positive correlations were found between the metacognitive accuracy of the Ordered Matrix Reasoning task and total gray matter (r=0.44, p=0.03) and white matter (r=0.53, p=0.005) volumes. No significant relationships were found between brain tissue or CSF volumes and metacognitive performance on the Random Matrix Reasoning and metamemory tasks. Calculated Pearson's r coefficients and significance values are listed in Table 4.

For comparison purposes, correlation analyses were also completed in each participant group examining the relationship between brain tissue volumes and performance on tasks in other cognitive domains. In the sample of participants with TBI, significant relationships were found between CSF volume and 3 measures of executive functioning. Higher amounts of CSF were found to be related with lower scores on the Ordered Matrix Reasoning task (r=-0.37, p=0.03), lower scores on the Shipley's Abstraction task (r=-0.35, p=0.04), and increased time (indicating poorer performance) taken to complete both the Trail Making A test (r=0.44, p=0.01) and the Trailmaking B test (r=0.41, p=0.02). Only one significant relationship between tissue volume and performance in executive functioning was found; gray matter volume in adults with TBI was positively correlated with the Stroop task (r=0.36, p=0.04). In healthy adults, the volume of CSF present was not related to performance on any tasks of basic cognition. Only one set of tasks, the Digit Span Forward and Backward, was found to be significantly correlated with brain tissue volume. The results of the correlation analyses for both groups are presented in Table 4.

Localized Volumetric Gray Matter Differences Between Participant Groups

Areas of difference in gray matter volume between participants with TBI and healthy adults were identified by completing an independent samples t-test in SPM8. The segmented gray matter maps obtained from VBM processing were entered and grouped based on group membership for comparison. An uncorrected p=0.001 and 20 voxel cluster size threshold was applied. When a contrast identifying areas where healthy adults had greater gray matter volume compared to the participants with TBI was used, the clusters showing the greatest difference were in areas of the thalamus, caudate, right medial frontal gyrus, left cerebellum, right postcentral gyrus, and left middle temporal gyrus.

Gray Matter Structural Correlates of Metacognitive Functioning

Correlations analyses were conducted for each participant group to determine whether metacognitive performance was related to the volume of gray matter at specific locations. Gamma coefficients from each test of metacognition were entered as covariates in the analyses, and contrasts were applied to identify areas in the gray matter segmentation maps that were positively correlated to metacognitive performance. Initially, analyses were set with thresholding criteria of FWE and FDR corrected p-values of 0.05, as well as uncorrected p-values of 0.0001 were used. When using these criteria, no areas of gray matter were found to be correlated with metacognitive performance.

In an exploratory analysis, a more liberal p-value was set to 0.01 uncorrected, with a 20 voxel extent threshold. For efficiency of reporting and discussion purposes, the top clusters of each activation map obtained using the more liberal threshold criteria are discussed here. Greater volume in the left precuneus, right orbitofrontal areas, left medial frontal gyrus, and right

inferior frontal gyrus was found to be related to higher accuracy in metamemory (modified HVLT task) for participants with TBI. Areas of the left posterior cerebellum, left inferior frontal gyrus, left subgyral frontal, and left brainstem were found to be positively correlated with the meta-abstract reasoning task of Ordered Matrix Reasoning. Areas positively correlated with the meta-abstract reasoning Random Matrix Reasoning task included the right uncus, right middle frontal gyrus, and the left superior frontal gyrus. Finally, higher metacognitive accuracy on the Shipley's task was found in participants with greater volume in the left inferior parietal lobe, right fusiform gyrus, and cerebellum.

In healthy individuals, higher accuracy in the metamemory task was positively correlated with areas of the left superior frontal gyrus, left subgyral frontal area, left precentral gyrus, and right posterior cerebellum. Accuracy on the meta-abstract reasoning Matrix Ordered task was higher for individuals with greater volume in the left middle frontal gyrus, right superior frontal gyrus, right inferior frontal gyrus, left anterior cerebellum, and left precentral gyrus. Meanwhile, greater volume in the right insula, right superior frontal gyrus, right parahippocampal gyrus, left cingulate gyrus, and left middle temporal gyrus in healthy adults was associated with greater accuracy on the metacognitive Matrix Random task. A positive relationship was found between metacognitive performance of the Shipley task and volume in the left subgyral areas, left anterior cingulate, right superior frontal gyrus, and left insula.

Gray Matter Structural Correlates of Other Domains of Cognition

Areas of gray matter that were associated with performance in other cognitive domains were also identified using correlation analyses. On a task of basic attention (Forward Digit Span of WAIS-III), healthy adults who had higher scores also had higher gray matter volume in the

left inferior occipital areas, left subgyral parietal areas, left middle occipital areas, right uncus, and right lingual gyrus. For adults with TBI, better performance on this task was associated with greater gray volume in bilateral precuneus and left superior temporal gyrus. When visual search and attention was involved (Trail Making Test Part A), better performance for healthy adults was related to greater volume in right precentral areas. In contrast, adults with TBI performed better on this same task when they had greater gray matter volume in areas of the right anterior cerebellum, left posterior cerebellum, right paracentral lobule, right medial frontal gyrus, and right postcentral gyrus.

On a working memory task (Backwards Digit Span from WAIS-III), greater volume in the areas in the right and left middle temporal lobes, right pons, right middle frontal gyrus, and right superior frontal gyrus of the healthy adult sample was associated with better performance. Greater volume in the left precuneus, right precentral gyrus, and right post-central gyrus in the adults with TBI were found to be associated with performance on the same task. Higher scores on a verbal recognition memory task (HVLT recognition trial) was associated with greater gray matter volume in the left middle occipital areas, left post central gyrus, left inferior occipital areas, and left precuneus in healthy adults. In adults with TBI, high recognition scores were associated with greater gray matter volume in the left middle frontal gyrus, left occipital areas, right middle temporal gyrus, left precentral gyrus, and right subgyral temporal areas.

On the Ordered Matrix Reasoning task of executive functioning, performance by the healthy adults was positively related to gray matter volume in the right subgyral temporal areas, right superior frontal areas, left insula, right caudate, and right middle frontal areas. In contrast, for adults with TBI, performance on the same task was related to gray matter volume in the left and right precentral gyri, and the left medial frontal gyrus. Different areas were associated with

performance on the Random Matrix Reasoning executive functioning task. For healthy adults, performance on this measure was positively associated with volume in the left anterior cerebellum, right lingual gyrus, left middle occipital gyrus, left inferior occipital area, and right precuneus, whereas volume in the left and right middle frontal areas as well as the right superior temporal areas was associated with performance for the adults with TBI. Healthy adults' performance on the Shipley's Abstraction test was positively correlated with the right cingulate, left medial frontal areas, right subgyral parietal areas, and right cuneus. For the adults with TBI, performance on the same task was associated with the right precentral gyrus, right subgyral temporal area, right limbic lobe, right superior temporal area, and right putamen. Higher scores on the measure of executive inhibition (Stroop Color Word Test) in healthy adults was associated with greater volume in the right inferior frontal gyrus, right posterior cingulate, and right lingual gyrus. High scores on the Stroop in the adults with TBI were positively correlated with volume in the right precuneus, left posterior cerebellum, right middle frontal gyrus, right superior frontal gyrus, and right subgyral frontal areas. Finally, on the speeded set-shifting Trail Making Test (Part B), better performance in the healthy adults was related to greater volume in the right cingulate, left subgyral temporal areas, and right occipital subgyral areas. The results from the adults with TBI also showed a positive correlation between performance and the left subgyral temporal areas, in addition to the left subgyral parietal and the right inferior occipital areas.

Differences in White Matter Integrity Between Groups

Mean FA, ADC, axial diffusivity, and radial diffusivity values were calculated for each participant group (means and standard deviations reported in Table 5) and tested for between group differences. Additionally, as described earlier, the DTI images were processed slightly

differently based upon the original file type; thus, to determine whether there were any effects due to these different file types and related processing procedures, four separate factorial analysis of variance (ANOVA) were conducted. In the first analysis, participant FA values were entered as the dependent variable, while group membership and file type were dummy coded and entered as fixed factors. An effect of group membership (F (1,50)=15.6, p<0.000) was found where healthy adults had higher FA values than the adults with TBI. There was also an effect of file type indicating that dicom processed data yielded higher FA values than the par/rec processed data (F (1,50)=57.5, p<0.000). No significant interaction was found between the two variables (F (1, 50)=0.23, p=0.64).

In the second analysis, participant ADC values were entered as the dependent variable, while group membership and file type were entered as fixed factors. A significant effect of group membership was found where healthy adults had lower ADC values than the adults with TBI (F (1, 50)=29.8, p<0.000), and the dicom processed data yielded lower ADC values than the par/rec processed data (F (1, 50)=8.4, p=0.006). The interaction between these variables was not statistically significant (F (1, 50)=0.57, p=0.45).

In the third analysis, measures of axial diffusivity (Lambda (λ) 1) were entered as the dependent variable, group membership and processing procedure as fixed factors. No significant effect of group membership was found (F (1, 50)=1.96, p=0.17), indicating no difference in axial diffusivity between participants with TBI and healthy participants. There was also no difference in axial diffusivity measures based on file type (F (1, 50)=0.06, p=0.80). No significant interaction was found between the variables (F (1, 50)=0.42, p=0.52).

Finally, measures of radial diffusivity (the average of λ2 and λ3) were entered as dependent variables, with group membership and file type as the fixed factors. A main effect for

group membership was found where healthy adults had significantly lower radial diffusivity values than the participants with TBI (F (1, 50)=4.26, p=0.044). No significant effect of file type of radial diffusivity value was found (F (1, 50)=3.02, p=0.089). There was no significant interaction between these two variables (F (1, 50)=1.20, p=0.279).

Relationships Between Metacognition and White Matter Integrity

Separate analyses were conducted for each participant group (TBI and healthy adults) to investigate the relationships between metacognitive performance and characteristics of white matter integrity. The results of the factorial ANOVAs from the preceding section indicated that the type of file used had an effect on measures of FA and ADC; thus semi-partial (or part) correlations were used to control for this effect and to avoid introduction of a confounding variable into the analyses. For each participant group, a series of semi-partial correlations was executed using performance from each of the four metacognitive test and two characteristics of white matter integrity, FA and ADC, as the variables. Zero-order correlations were conducted using performance from the four metacognition measures and the remaining two measures of white matter, axial and radial diffusivity.

In the adults with TBI, only radial diffusivity values were significantly related with metacognitive performance. Specifically, higher radial diffusivity measures were related to higher accuracy on the meta-abstract reasoning Matrix Random task (r=0.42, p=0.01). A positive correlation between radial diffusivity and metamemory accuracy was found to be close to reaching statistical significance (r=0.28, p=0.07). No other significant relationships between measures of white matter integrity (FA, ADC, or axial diffusivity) and metacognitive accuracy were found.

The data from healthy adults also indicated a significant relationship between measures of radial diffusivity and metacognitive performance. However, in contrast to the participants with TBI, a negative correlation was found between radial diffusivity values and the meta-abstract reasoning Matrix Order task (r=-0.47, p=0.01). A negative correlation between radial diffusivity and performance on the meta-abstract reasoning Matrix Random task was also close to reaching significance (r=-0.30, p=0.08). Additionally, data from the healthy adults also revealed significant relationships between metacognitive performance and two other measures of white matter integrity: FA and ADC. High FA values were significantly related to more accurate metacognition on the Matrix Random task when using a zero-order correlation (r=0.37, p=0.04), however, the correlation coefficient dropped dramatically to only 0.07 when using a semi-partial correlation. A significant negative correlation was found between ADC values and metacognitive performance on the Matrix Order task (r=-0.45, p=0.02) when using a zero-order correlation; the correlations coefficient decreased when using a semi-partial correlation, but at -0.33, remained moderate in size. The results of both zero-order and semi-partial correlations for each participant group and significance values are reported in Table 6a and Table 6b.

Relationship Between White Matter Integrity and Other Cognitive Domains

The relationship between white matter integrity and performance in other domains of cognition was also examined. Again, semi-partial correlations were examined to investigate the relationship between measures of white matter integrity (FA, ADC, radial and axial diffusivity) and performance on cognitive tests while controlling for type of file. The only statistically significant relationship identified between all measures of white matter integrity and cognition

(other than metacognitive performance) for adults with TBI was a positive correlation between performance on the Random Matrix Reasoning task and radial diffusivity (r=0.46, p=0.004).

In contrast, performance on several cognitive tasks was found to be associated with different measures of white matter integrity in the sample of healthy adults. Interestingly, statistically significant negative correlations were found between FA values and performance on Verbal Fluency (r=-0.27, p=0.03), Random Matrix Reasoning (r=-0.18, p=0.05), and Part B of the Trail Making Test (r=-0.09, p=0.05). Values of axial diffusivity were found to be negatively correlated to performance on the Stroop task (r=-0.41, p=-0.04), and the Ordered Matrix Reasoning task (r=-0.45, p=0.02). Finally, values of radial diffusivity were correlated to performance on Part A of the Trail Making Test (r=0.10, p=0.05) and Forward Digit Span (r=-0.53, p=0.03).

Chapter 4. DISCUSSION

Structural change in the brain occurring due to moderate or severe injury can lead to severe cognitive consequences for survivors of TBI. Although relationships between the deterioration of brain tissue and cognitive domains have been observed, this association has yet to be established for the domain of metacognition. This study used VBM and DTI methodologies to determine the influence of global atrophy, localized areas of volume loss, and white matter integrity on two domains of metacognition.

Metacognition and Global Brain Volume: Amount Matters

As expected, the participants with TBI in this study experienced atrophy of brain tissue as evidenced by significantly lower quantities of global gray and white matter tissue, and larger amounts of CSF in comparison to the healthy participants. Although gray and white matter volumes in participants with TBI were not related to any domains of basic cognition tested in this study (executive function, attention and memory), negative correlations were found between CSF volumes and several measures of executive functioning. The elevated amount of CSF in the participants with TBI indicate the occurrence of brain atrophy, and the results here suggest that executive functioning performance is negatively affected by the loss of brain tissue. Surprisingly, this finding was not consistently replicated in the domain of metacognition. In fact, a difference in the pattern of relationships between total brain volume and metacognition was found between the two groups (TBI and health). A positive relationship was found between both types of brain tissue (white and gray matter) and metacognitive performance in healthy adults, but not in the participants with TBI. Importantly, this differential result occurred in the one domain, the meta-Ordered Matrix Reasoning task, where the two groups had significant

performance differences. The meta-Ordered Matrix Reasoning task was the only measure where healthy adults were significantly more accurate in their metacognitive judgments than the adults with TBI. The finding here that greater amounts of tissue volume is associated with better metacognitive performance provides support for the generalist theory, suggesting that larger quantities of neural substrate is advantageous for performance on metacognitive tasks.

This finding also raises the possibility that there is a threshold that must be reached at which point relationships between tissue volume and metacognitive performance can be detected. In the meta-Ordered Matrix Reasoning task, there was a distinction between groups where a benefit of having more total tissue volume was demonstrated in healthy adults having significantly more or "enough" metacognitive accuracy. Interestingly, a similar pattern is found when examining metacognitive accuracy on the meta-Shipley Abstraction test and global brain volume. Although the metacognitive accuracy of healthy adults was not significantly different from that of the adults with TBI when using strict statistical standards (p=0.05), the average gamma coefficient for this task obtained by healthy adults is *quantitatively greater* than that obtained by the participants with TBI on the same task, and the highest gamma obtained by healthy adults on the meta-Ordered Matrix Reasoning task (i.e., gamma coefficients from this task were the highest out of all 4 metacognitive tasks and between the 2 groups). This high gamma coefficient was negatively correlated with cerebrospinal fluid volume, suggesting reduced global brain volume (as indicated by larger amounts of CSF) is associated with poorer metacognitive performance. To reiterate, these significant relationships were observed only on the two metacognitive tasks where metacognitive accuracy was the greatest. It is possible then, that performance of both participant groups in the two other metacognitive measures (metamemory, meta-Random Matrix Reasoning) did not reach a required performance threshold,

and thus neither group demonstrated relationships between total tissue volume and metacognitive performance.

The potential of an existing "threshold effect" suggests that the amount of brain tissue present is important in predicting metacognitive performance; thus, consideration should be given to additional related factors that could also affect tissue volume. One specific factor related to TBI that could affect tissue volume is chronicity of injury; there may be potential differences between participants in the acute phases of recovery and those who have lived with their injury for years. The influence of this variable was explored in *post hoc* analyses. A subset of the original 35 participants with TBI was created by excluding participants who had sustained injuries for less than one year. Correlation analyses were repeated with this subset of 27 participants with "chronic" injuries. Again, relationships between metacognitive performance and brain tissue volume were not observed. Interestingly, a positive correlation was found between CSF volume and the meta Shipley Abstraction task (r=0.42, p=0.03). The direction of this relationship is opposite of that found in the healthy adults, but there was no between group difference in metacognitive accuracy. The lack of metacognitive performance difference complicates the interpretation of such results. Future studies would benefit from increased recruitment to maintain the statistical power needed to either control for these factors or to examine them independently as variables of interest.

Contributions of White Matter to Metacognitive Performance After TBI: Specificity of Measures Matters

As expected, results from the DTI analyses indicated that adults with TBI had lower whole brain FA values and higher ADC values than healthy adults, suggesting compromised

white matter integrity after injury. Interestingly, neither whole brain FA nor ADC values were associated with metacognitive performance. However, investigation of more specific diffusivity measures indicated that adults with TBI had higher values of radial diffusivity than the healthy adults. This is consistent with findings in the literature that higher values radial diffusivity, a measure believed to reflect abnormalities in mylenation, is related to injury severity, and thus is more likely to be found in samples with moderate to severe TBI (Kraus, et al. 2007). Importantly, values of radial diffusivity were positively correlated with the meta-Matrix Random and metamemory tasks in adults with TBI, and were negatively correlated with the meta-Matrix Ordered task.

The findings suggest that more detailed examination of diffusivity properties at the microstructural level (radial and axial diffusivities) may be more sensitive than averaged ADC or FA measures in identifying performance differences. Curiously, the two groups (TBI and healthy adults) had opposing directionality in relationship between radial diffusivity values and performance on the meta-Matrix Random task. Results from the healthy adults were consistent with expectations; higher radial diffusivity values, indicative of poorer white matter integrity, was related to worse accuracy on metacognitive measures. In contrast, poorer white matter integrity was related to better metacognitive accuracy in the adults with TBI. Although the correlations found here are statistically significant, the meaningfulness of these opposing results is less clear, given that there were no significant differences in metacognitive performance on the meta-Matrix Random task. More variability is needed to determine if there is a threshold of white matter integrity that must be breached before performance differences would occur.

An alternative interpretation of the finding of a negative relationship between radial diffusivity and metacognitive performance is that adults with TBI may benefit from a

speed/accuracy trade off. The demylination observed in this sample of adults with TBI may serve to "slow" down the process of making a metacognitive judgment, allowing the individual more time to reflect on the cognitive task and come to a more accurate judgment. The lack of difference in axial diffusivity suggests that the axonal tracts between networks subserving metacognition are intact, so that the framework for communication still exists; however, the demylination may serve to slow down the rate of communication so that the individual can take the time needed to make an accurate judgment when using compromised faculties. Examining a variable of timing in making metacognitive measurements will be of great interest to test this hypothesis in the future.

Metacognition and Localized Areas of Decreased Volume

Metacognitive performance was not found to be related to gray matter volume in any specific location of the brain when using conservative corrective thresholds in VBM analyses (FWE, FDR, and even uncorrected p=0.001 criteria). The lack of relationship between performance and any particular structure would suggest that metacognition is not localized to any one part of the brain. While it has been shown that metacognition is a unique and separate entity from other higher order constructs of executive functioning such as cognitive inhibition, or novel word initiation/letter fluency (Chiou, et al., 2011), it is still possible that metacognition may rely on an interaction of "basic" cognitive processes such as attention or working memory. The potential involvement of one or more of these other processes would likely require the engagement of multiple related neural systems rather than one single structure.

The lack of localized, structural correlates may also be explained by thresholding issues. It is a possibility that the sample used in this study did not have enough atrophy or damage to

specific structures to cause impairment in metacognition. Another possibility is that the correction threshold used the in the analyses was too stringent and insensitive to detecting correlates. As an exploratory endeavor, a more liberal correction criteria was used (uncorrected p=0.01) that resulted in localization of multiple structures, many of which were scattered throughout the frontal region. Even when considering these results, patterns of localization were not explicitly clear as there were inconsistencies dependent upon participant group membership (TBI or healthy), cognitive domain (metacognition or basic cognition), and between metacognitive domains (metamemory or meta-abstract reasoning). Figure 1 lists the areas that were found to be associated with metacognitive performance for each participant group, and is coded to highlight areas of overlap between groups, between metacognitive domains, and with tests of executive functioning. Figure 2 provides a visualization of these results, highlighting areas associated with different cognitive functions. It is evident that there are multiple areas related to metacognitive performance, and the identification of a single, distinct structure that is exclusively involved with metacognition is unlikely.

When considering the results of these more liberal analyses, it is also curious that the structures associated with performance for each group were different even when no metacognitive performance differences were found between adults with TBI and healthy participants (except for the meta-Matrix Ordered task). This is counter-intuitive to the expectation that if metacognition is localized to specific structures, performance should "map" onto similar, if not identical areas in both groups, especially in light of a lack of difference in performance. The inconsistency of structures correlated to metacognitive performance even within the frontal region suggests that the specificity to which metacognition can be localized remains at the "network level," rather than at an isolated, specific structural level. Furthermore,

the inconsistent overlap in structures correlating to similar performance between two groups may allude to the possibility that the two groups are relying on different structures to perform the same task. This suggests that there may be flexibility, and potentially plasticity, in these different structures that can still "maintain" metacognitive functioning despite surrounding tissue loss.

Although the results from more liberal analyses provide weak support of strict localization of metacognition, there does appear to be a trend of frontal involvement that is consistent with well-established findings that the frontal cortices are associated with higher order cognitive functions that is worthy of discussion. In particular, the relationship identified in this study mirrors more recent findings that link anterior and lateral frontal structures specifically to self-referential processes such as performance monitoring, and the integration and maintenance of information related to decision-making (Fleming & Dolan, 2012). Indeed, as a process that involves self-reference, metacognitive performance in healthy adults has been found in previous studies to correlate with activation and gray matter volume of the right anterior prefrontal area (Fleming, Weil, Nagy, Dolan & Rees, 2010; Fleming, Huijen, & Dolan, 2012; Yokoyama, et al., 2010).

Using more liberal threshold criteria, areas in the right orbitofrontal and left medial frontal were found to be related specifically to metamemory performance in the adults with TBI. These regions overlap with findings from a functional neuroimaging study by Chua et al. (2009) demonstrating the activation of medial prefrontal areas while engaged in a metacognitive task. The same study by Chua et al. (2009) also distinguished areas of activation associated with the type of metacognitive judgment made (feeling-of-knowing versus retrospective confidence judgments). When making feeling of knowing judgments, greater activation was found in the

left anterior prefrontal, bilateral occipital, fusiform, hippocampal formation, medial parietal, and right superior temporal regions; however, greater activation was also seen in some of these structures (right and left fusiform, right hippocampal formation, and right superior temporal gyrus) when participants had high confidence ratings (Chua, et al., 2009). This documented functional involvement of the fusiform areas on tasks where high confidence judgments were made may help explain our finding that gray matter volume in the fusiform was associated with performance on the meta-Shipley's Abstraction task.

The relationship between metacognitive performance and gray matter volume of both the insula and cingulate identified in this study helps to highlight these two structures as substrates of growing importance in processes of self-awareness. This finding is consistent with recent investigations of insula and cingulate function. In a recent review, Craig (2009) outlined several ways in which the insula has been found to be involved in processes of self-awareness. In addition to contributing to awareness of physiological states (e.g., awareness of heart rate, body movements), the insula has also been linked with awareness of subjective, emotional states. It has also recently been hypothesized that the insula coordinates the interactions between externally-oriented and internally (self)-oriented attentional processes, thus playing a role in decisions made about the self (Menon and Uddin, 2010). The anterior cingulate is another structure that has been implicated in higher order cognitive control and self-referential processes of performance monitoring. Indeed, impaired performance monitoring following TBI was found in an earlier study to be related to weaker error-negativity event related potentials, a signal generated by the anterior cingulate (Larson, Kaufman, Schmalfuss, & Perlstein, 2007).

Importantly, the insula together with the anterior cingulate (with connections to limbic and subcortical structures) form a "salience network" that identifies and responds to information

that is most pertinent (to the self) (Seeley, et al., 2007; Menon and Uddin, 2010). Structures of this salience network may be recruited during metacognitive functioning as such processes require individuals to reflect and attune to salient, subjective feelings that cue their judgment. It has also been postulated that metacognitive processes involve an executive control network (mediated by dorsolateral frontal regions) complementary to the salience network (Fleming & Dolan, 2012).

Gray matter volume in areas of the cerebellum was identified as a structural correlate of metacognitive performance (along with the domain of executive functioning), providing evidence of its role in higher order cognitive processes. Initially regarded for its role primarily in timing and movement, the cerebellum has steadily gained attention as a contributor to higher order cognition (Schmahmann, 1991) especially through its functional connectivity with areas that have traditionally been associated with such processes (i.e., prefrontal cortex) (Dreher & Grafman, 2002). Complementary to the functional relationship between the cerebellum and higher order cognition, the structural size of the cerebellum has also been found to be an important factor in executive performance. In one pediatric study, children with greater cerebellar volume were found to perform better on memory and executive functioning tasks (Bauer, Hanson, Pierson, Davidson, & Pollak, 2009). Results from the current study parallel those findings, supporting both ideas that the cerebellum has a role beyond motor and temporal control, and that "bigger" or "more" (physical) brain tissue in this area is better.

Although the results of these liberally thresholded analyses yield patterns of neural involvement that are consistent with other findings in the literature, these should be interpreted with caution. A goal of replication in future studies with bigger sample size, greater variability

in performance, and the use of more stringent thresholding criteria is necessary to establish the authenticity of the localized, structural relationships.

Limitations, Big Picture Considerations, and Future Directions

This study presents a novel examination of brain volume tissue and metacognitive functioning in a sample of patients with moderate and severe TBI; however, the study is not without limitations and considerations to take into account when making conclusions. While trends were observed in the results of this study, there were also some surprising findings across groups and tasks that were inconsistent with expectations. One prime example is the finding that this sample of participants with TBI did not demonstrate consistent metacognitive deficits compared to the healthy adults. There was only one metacognitive task (meta-Ordered Matrix Reasoning) on which the participants with TBI had less accurate judgments. This was surprising considering a subset of participants for this study was recruited from a previous study (Chiou, et al., 2011) where clear deficits were observed in other metacognitive domains (e.g., metamemory). This suggests that there is variability in metacognitive performance after injury; that is, there is likely a spectrum of levels of metacognitive accuracy on which an individual with brain injury may perform at. The presence of variability in the sample of TBI confronts a bias that often occurs when clinical populations are grouped artificially based on assumptions of pathology or performance difference (e.g., patient versus healthy controls). Embracing this heterogeneity and examining the differences that exist within the group may prove to be an advantageous strategy to understanding the true nature of functioning in clinical populations. Important extensions of this type of research will be to then determine factors that account for the variability within group. This approach could have great rehabilitative implications for

metacognition research. If researchers are able to distill factors that contribute to better metacognitive functioning after injury, strategies specifically designed to address such factors may result in greater success in improving performance. A future extension of this study may be to continue recruiting enough participants with TBI so that a factor analysis can be conducted to identify if certain demographic, biomarkers, or patterns of performance variables contribute to differing metacognitive ability within the TBI groups.

A practical limitation to consider in the context of the inconsistencies in associated structures found across tasks and groups is the correction and threshold parameters used for the imaging data in this study. As noted in the results section, the study employed an uncorrected threshold of p=0.001 and 20 voxels. While significant findings emerged, the study could be improved and expanded upon through replication and increased sample size. This would allow for the application of more stringent corrections (family-wise error, false discovery rate) providing further, more robust evidence that structures that surviving these thresholds were not false positive errors.

Although the regions found to be associated with metacognitive performance in this study are consistent with the same neural networks identified in previous functional imaging studies, there should be caution in assuming causality between structural and functional contributors to metacognitive performance. The exact effect of structural volume of this functional network remains unclear. This issue can be addressed by future research by using a region of interest (ROI) approach. ROIs can be identified based upon functional applications maps, and voxel counting methods may be applied to determine the volumetrics of the ROIs.

Finally, one more consideration for future directions of research concerns the functional and clinical utility of metacognitive measures. Self-awareness, broadly, has been found to be

associated with functional outcome, but such relationships are yet to be determined with metacognition specifically. Thus far, a crucial advantage of using metacognitive measurements such as the gamma coefficient is that it provides an objective and quantifiable measure of self-awareness. However, it is unclear if these numerical values translate to any functional deficits in real life, daily living situations; that is, how does an individual with a gamma coefficient of 0.20 function at home or work, and does that differ from the functioning of an individual who has a gamma coefficient of 0.70? An important goal of future research will be to determine if these quantifiable metacognitive measures (e.g., gamma coefficients) are predictive of functional outcome. Such findings could have implications for our understanding of the ecological impact of metacognitive functioning (measured in this way), and the utility of metacognition in rehabilitation efforts. A natural extension of the research thus far then, is to include questionnaires/measures of outcome and independent functioning in addition to collecting metacognitive judgments.

Chapter 5. CONCLUSION

Metacognitive deficits have been documented after the occurrence of moderate to severe TBI, but the neuroanatomical correlates are poorly understood. This novel study examined the contribution of structural brain tissue integrity to metacognitive functioning after TBI. Using VBM methods, a positive correlation was found between global brain tissue volume and metacognitive performance when performance differences existed between groups, supporting a generalist theory. Furthermore, a particular attribute of global white matter integrity, radial diffusivity, was found to be related to metacognitive functioning. Exploratory analyses using liberal thresholds identified certain areas of the frontal lobes that were correlated with metacognitive functioning; however, the inconsistencies of structures associated with performance across tasks and between groups suggest that metacognitive processes are not precisely localized. The lack of localization specificity of metacognitive processes beyond the level of a gross, frontal neural system, suggests that deficits in this domain are affected by a threshold of tissue volume loss rather than location.

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APPENDIX

TABLES AND FIGURES

Table 1. Demographics of Participants

	Group	
	TBI	Healthy
Gender	20 m, 15 f	11m, 15 f
Age (in years)	34.4 (13.4)	27.7 (11.0)
Education (in years)	13.5 (2.2)	14.3 (2.3)
GCS Score	5.5 (3.5)	--
Time Since Injury (in months)	75. 5 (82.7)	--

Table 2. Between Group Differences on Measures of Basic Cognitive Functioning

	TBI	Healthy	*t* score	*p*-value
Executive Functioning				
Stroop	92.5 (22.2)	105.7 (9.8)	*t*(47.9)=-3.1	0.004
Verbal Fluency	31.9 (10.6)	37.7 (9.0)	*t*(59)=-2.2	0.029
Matrix-Ordered	9.1 (2.1)	10.3 (1.9)	*t*(59)=-2.4	0.018
Matrix-Random	7.7 (1.6)	8.7 (2.1)	*t*(59)=-2.2	0.030
Shipley's Abstraction	24.1 (7.7)	29.5 (7.3)	*t*(59)=-2.8	0.007
Trailmaking B	75.5 (38.8)	53.7 (23.0)	*t*(53.3)=2.7	0.010
Attention				
Trailmaking A	32.1 (19.5)	21.9 (9.7)	*t*(57)=2.4	0.018
Digit Span Forward	10.1 (2.3)	10.7 (1.9)	*t*(59)=-1.1	0.278
Working Memory				
Digit Span Backward	6.5 (2.1)	7.7 (2.1)	*t*(59)=-2.1	0.039
Memory				
HVLT recognition	7.0 (2.9)	9.0 (2.2)	*t*(59)=-3.0	0.005

Table 3. Difference in Metacognitive Accuracy Between Groups

	TBI	Healthy	*t* score	*p* value
Meta-Abstract Reasoning				
Ordered Matrix Reasoning	0.73 (0.2)	0.84 (0.2)	*t*(59)=-1.9	0.059
Random Matrix Reasoning	0.45 (0.4)	0.46 (0.5)	*t*(59)=-0.1	0.889
Shipley's Abstraction	0.80 (0.4)	0.91 (0.1)	*t*(58)=-1.5	0.131
Metamemory				
HVLT Recognition	0.28 (0.6)	0.40 (0.6)	*t*(58)=-0.8	0.449

Table 4a. Relationship Between Metacognitive Performance and Global Brain Tissue Volumes (Raw Scores)

	Gray Matter				White Matter				CSF			
	TBI		Healthy		TBI		Healthy		TBI		Healthy	
	r	*p*-value										
Metamemory												
HVLT Recognition	0.12	0.50	0.17	0.42	0.15	0.39	-0.03	0.88	-0.02	0.89	0.00	0.99
Meta-Abstract Reasoning												
Ordered Matrix Reasoning	-0.10	-.057	0.43	0.03	-0.15	0.39	0.53	0.005	-0.04	0.80	0.10	0.63
Random Matrix Reasoning	0.15	0.39	0.14	0.50	0.25	0.15	0.23	0.22	0.05	0.76	-0.01	0.97
Shipley's Abstraction	0.18	0.31	-0.03	0.90	0.19	0.27	0.04	0.85	0.32	0.07	-0.43	0.03
Executive Functioning												
Stroop Task	0.36	0.04	0.13	0.54	0.22	0.22	0.05	0.79	-0.29	0.09	0.04	0.84
Verbal Fluency	0.26	0.13	0.04	0.84	0.21	0.23	0.02	0.92	-0.13	0.45	0.02	0.92
Ordered Matrix Reasoning	0.05	0.76	0.26	0.20	-0.11	0.53	0.18	0.38	-0.37	0.03	-0.31	0.13
Random Matrix Reasoning	0.14	0.42	0.24	0.24	0.18	0.31	0.14	0.50	-0.05	0.76	-0.10	0.50
Shipley's Abstraction	0.19	0.27	0.36	0.07	0.01	0.97	0.28	0.17	-0.35	0.04	-0.06	0.77
Trailmaking B	-0.21	0.24	-0.13	0.50	-0.11	0.55	-0.05	0.82	0.41	0.02	0.22	0.29
Attention												
Trailmaking A	-0.08	0.65	-0.14	0.50	-0.20	0.27	-0.07	0.73	0.44	0.01	0.09	0.66
Digit Span Forward	0.33	0.06	0.47	0.02	0.19	0.29	0.55	0.004	-0.14	0.42	-0.09	0.65
Working Memory												
Digit Span Backward	0.21	0.23	0.50	0.009	-0.02	0.91	0.50	0.009	-0.30	0.08	0.14	0.49
Memory												
HVLT Recognition	-0.08	0.64	0.04	0.84	-0.17	0.33	-0.01	0.95	-0.24	0.16	-0.19	0.36

Table 4b. Relationship Between Metacognitive Performance and Global Brain Tissue Volumes (z scores)

	Gray Matter				White Matter				CSF			
	TBI		Healthy		TBI		Healthy		TBI		Healthy	
	r	*p*-value										
Metamemory												
HVLT Recognition	0.12	0.50	0.17	0.42	0.15	0.39	-0.03	0.88	-0.02	0.89	0.00	0.99
Meta-Abstract Reasoning												
Ordered Matrix Reasoning	-0.10	0.57	0.43	0.03	-0.04	0.80	0.53	0.005	-0.04	0.80	0.10	0.63
Random Matrix Reasoning	0.15	0.39	0.14	0.50	0.05	0.15	0.25	0.22	0.05	0.76	-0.01	0.97
Shipley's Abstraction	0.18	0.31	-0.03	0.90	0.19	0.27	0.04	0.85	0.32	0.07	-0.43	0.03
Executive Functioning												
Stroop Task	0.36	0.04	0.13	0.54	0.22	-0.29	0.05	0.79	-0.29	0.09	0.04	0.84
Verbal Fluency	0.26	0.13	0.04	0.84	0.21	-0.13	0.02	0.92	-0.13	0.45	-0.20	0.34
Ordered Matrix Reasoning	0.05	0.76	0.26	0.20	-0.11	0.53	0.18	0.38	-0.37	0.03	-0.31	0.13
Random Matrix Reasoning	0.14	0.42	0.24	0.24	0.18	0.31	0.14	0.50	-0.05	0.76		
Shipley's Abstraction	0.19	0.27	0.36	0.07	0.01	0.97	0.28	0.17	-0.35	0.04	-0.10	0.61
Trailmaking B	0.21	0.24	0.13	0.54	-0.11	0.55	0.05	0.82	-0.41	0.02	-0.22	0.29
Attention												
Trailmaking A	0.08	0.65	0.14	0.50	-0.20	-.27	0.07	0.73	-0.44	0.01	-0.09	0.66
Digit Span Forward	0.33	0.06	0.47	0.015	0.19	0.29	0.55	0.004	-0.14	0.42	-0.09	0.65
Working Memory												
Digit Span Backward	0.21	0.23	0.51	0.008	-0.02	0.91	0.50	0.009	-0.30	0.08	0.14	0.49
Memory												
HVLT Recognition	-0.08	0.64	0.04	0.84	-0.11	0.53	-0.01	0.95	-0.24	0.16	-0.19	0.36

Table 5. Between Group Differences in Diffusivity Measures (*Mean, SD, t-test*)

	TBI		Healthy		T-test	
	Mean	*SD*	Mean	*SD*	*t* value	*p*
All						
FA	0.38	0.04	0.40	0.04	*t*(52)=-1.56	0.13
ADC	2.76	0.29	2.47	0.12	*t*(41.7)=5.05	0.00
λ1 (Axial Diffusivity)	1.28	0.11	1.22	0.16	*t*(52)=1.48	0.14
Average of λ2 & λ3 (Radial)	0.71	0.15	0.65	0.07	*t*(52)=1.80	0.08
Dicom						
FA	0.40	0.04	0.44	0.04	*t*(29)=-2.60	0.02
ADC	2.69	0.30	2.39	0.10	*t*(27.6)=4.06	0.00
λ1 (Axial Diffusivity)	1.28	0.09	1.20	0.02	*t*(23.7)=4.04	0.00
Average of λ2 & λ3 (Radial)	0.70	0.11	0.60	0.05	*t*(28.9)=3.77	0.00
Par/Rec						
FA	0.34	0.01	0.37	0.01	*t*(21)=-5.57	0.00
ADC	2.92	0.23	2.52	0.09	*t*(11.3)=5.11	0.00
λ1 (Axial Diffusivity)	1.27	0.16	1.24	0.21	*t*(21)=0.36	0.72
Average of λ2 & λ3 (Radial)	0.73	0.22	0.69	0.05	*t*(21)=0.53	0.60

Table 6a. Adult TBI Sample: Relationship Between Cognitive Performance and White Matter Tract Characteristics (z scores)

	FA Value			ADC			λ 1			(λ 2 & λ 3)/2		
	Zero Order	Semi Partial	Sig. *(p)*	Zero Order	Semi Partial	Sig. *(p)*	Zero Order	Semi Partial	Sig. *(p)*	Zero Order	Semi Partial	Sig. *(p)*
TBI												
Metamemory	0.08	-0.15	0.33	-0.15	-0.05	0.21	-0.11	-0.12	0.29	0.28	0.30	0.07
MetaOrder	-0.07	-0.01	0.35	0.17	0.14	0.18	0.22	0.23	0.11	0.07	0.06	0.36
MetaRandom	0.19	0.07	0.15	-0.16	-0.09	0.20	0.19	0.17	0.16	0.42	0.44	0.01
MetaShipley	-0.05	-0.13	0.34	0.13	0.16	0.26	0.15	0.14	0.22	0.17	0.17	0.19
Exec fxn												
Stroop	0.16	0.18	0.20	-0.06	-0.05	0.38	0.19	0.19	0.16	0.01	0.01	0.48
Verbal fluency	0.23	0.15	0.11	-0.28	-0.23	0.07	-0.30	-0.31	0.05	-0.11	-0.10	0.28
Matrix Order	-0.07	0.20	0.35	-0.08	-0.22	0.33	-0.06	-0.04	0.37	0.15	0.13	0.21
Matrix Random	-0.00	0.05	0.49	-0.14	-0.17	0.23	-0.04	-0.04	0.41	0.47	0.46	0.004
Shipley	0.01	0.15	0.49	-0.20	-0.27	0.15	-0.15	-0.14	0.21	0.26	0.25	0.08
Trails B	0.18	0.28	0.17	-0.30	-0.33	0.06	-0.23	-0.23	0.11	-0.05	-0.05	0.41
Attention												
Trails A	0.14	0.11	0.24	-0.11	-0.08	0.28	-0.11	-0.11	0.29	0.12	0.13	0.26
Digits Forward	-0.05	0.03	0.39	-0.14	-0.19	0.23	-0.15	-0.15	0.21	0.17	0.17	0.29
Memory												
Digts Backward	-0.06	0.07	0.38	-0.20	-0.27	0.15	-0.20	-0.19	0.14	0.18	0.17	0.17
HVLT	-0.07	-0.35	0.36	0.15	0.27	0.22	0.17	0.16	0.18	0.09	0.11	0.31

Table 6b. Healthy Adult Sample: Relationship Between Cognitive Performance and White Matter Characteristics (z scores)

	FA Value			ADC			λ 1			(λ 2 & λ 3)/2		
	Zero Order	Semi Partial	Sig. *(p)*	Zero Order	Semi Partial	Sig. *(p)*	Zero Order	Semi Partial	Sig. *(p)*	Zero Order	Semi Partial	Sig. *(p)*
Healthy												
Metamemory	-0.14	0.36	0.27	0.14	-0.14	0.26	0.11	0.06	0.31	0.12	-0.27	0.30
MetaOrder	0.25	-0.00	0.13	-0.45	-0.33	0.02	-0.13	-0.10	0.28	-0.47	-0.34	0.01
MetaRandom	0.37	0.07	0.04	-0.08	0.20	0.36	0.15	0.20	0.25	-0.30	-0.03	0.08
MetaShipley	0.13	0.34	0.27	0.06	0.00	0.40	0.23	0.22	0.15	-0.08	-0.21	0.35
Exec fxn												
Stroop	-0.28	-0.12	0.10	0.08	-0.09	0.37	-0.37	-0.41	0.04	-0.06	-0.33	0.39
Verbal Fluency	-0.41	-0.27	0.03	0.25	0.08	0.13	-0.24	-0.27	0.14	0.24	0.04	0.13
Matrix Order	-0.24	-0.07	0.14	-0.01	-0.18	0.49	-0.42	-0.45	0.02	0.18	0.01	0.21
Matrix Random	-0.35	-0.18	0.05	0.19	0.01	0.19	-0.11	-0.14	0.31	0.18	-0.05	0.21
Shipley	-0.31	-0.43	0.07	0.26	0.27	0.12	0.13	0.13	0.27	0.07	0.03	0.38
Trails B	-0.35	-0.09	0.05	0.16	-0.07	0.24	-0.18	-0.23	0.20	0.15	-0.14	0.25
Attention												
Trails A	-0.48	-0.28	0.01	0.37	0.18	0.04	-0.05	-0.09	0.42	0.34	0.10	0.05
Digits Forward	-0.04	-0.08	0.44	-0.12	-0.14	0.29	0.00	0.00	0.50	-0.40	-0.53	0.03
Memory												
Digits Backward	-0.04	0.00	0.43	-0.18	-0.18	0.30	-0.10	-0.11	0.32	-0.23	-0.40	0.12
HVLT Recognition	-0.39	-0.13	0.04	0.10	-0.15	0.33	0.01	-0.03	0.48	0.07	-0.27	0.38

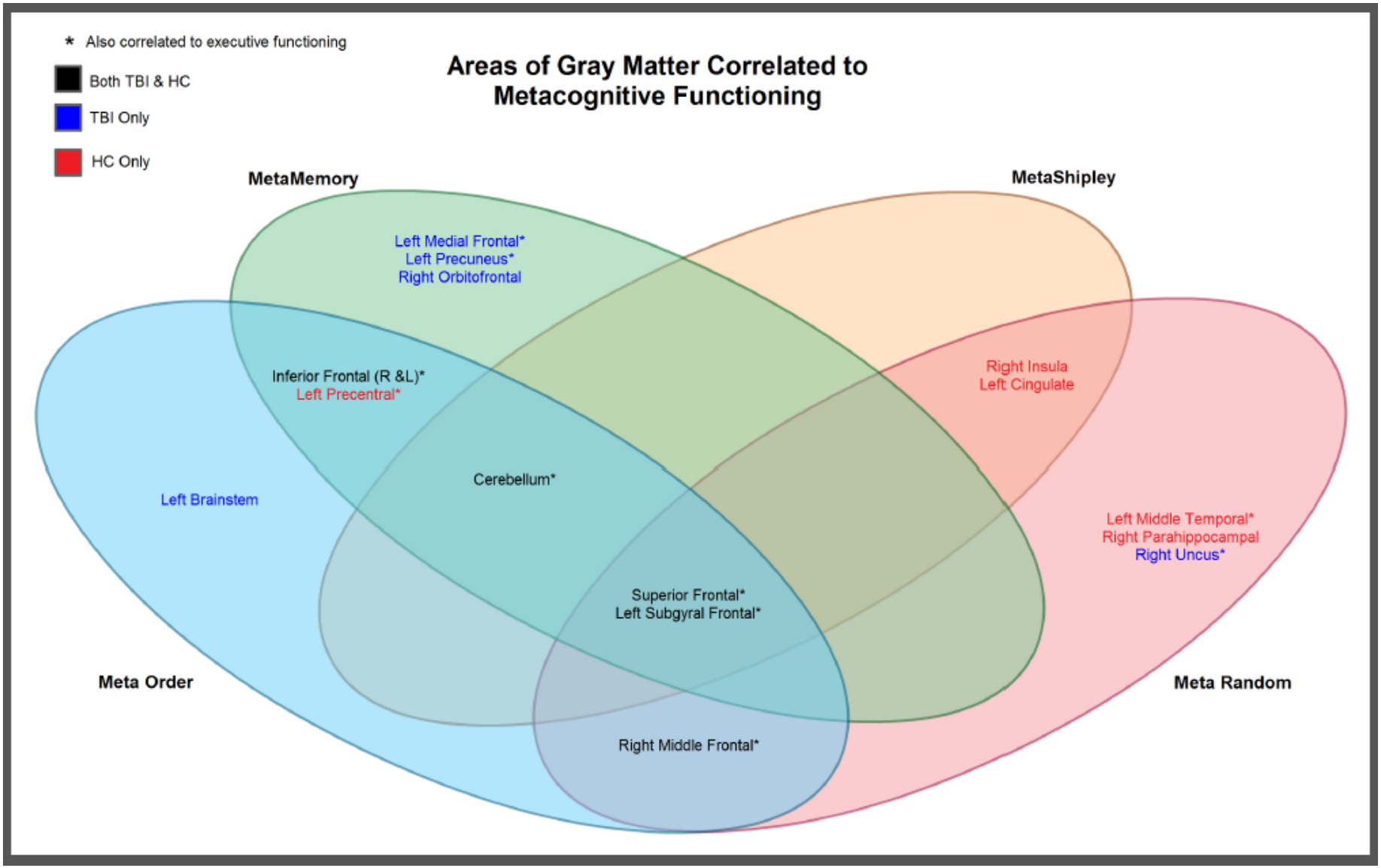
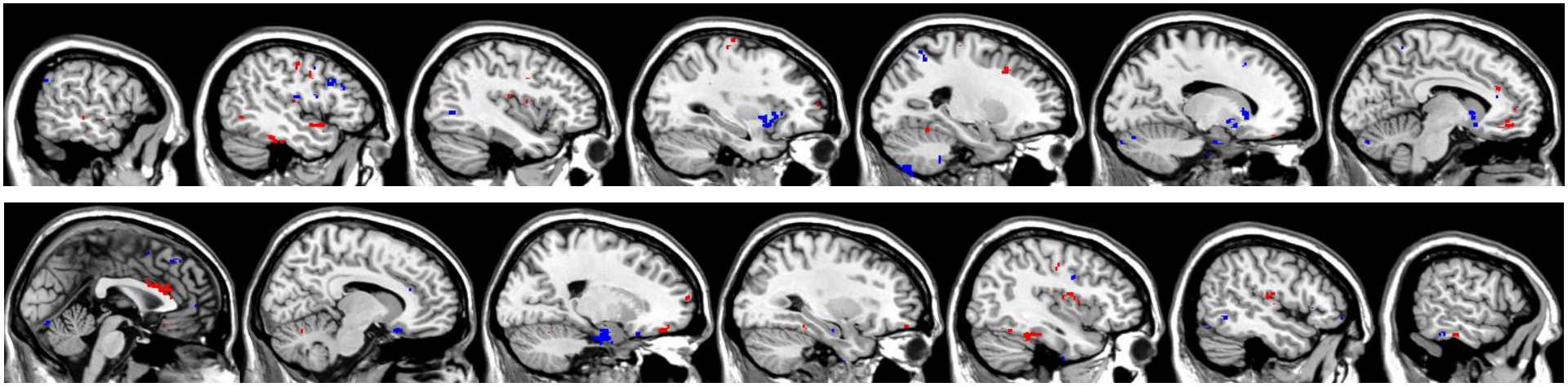
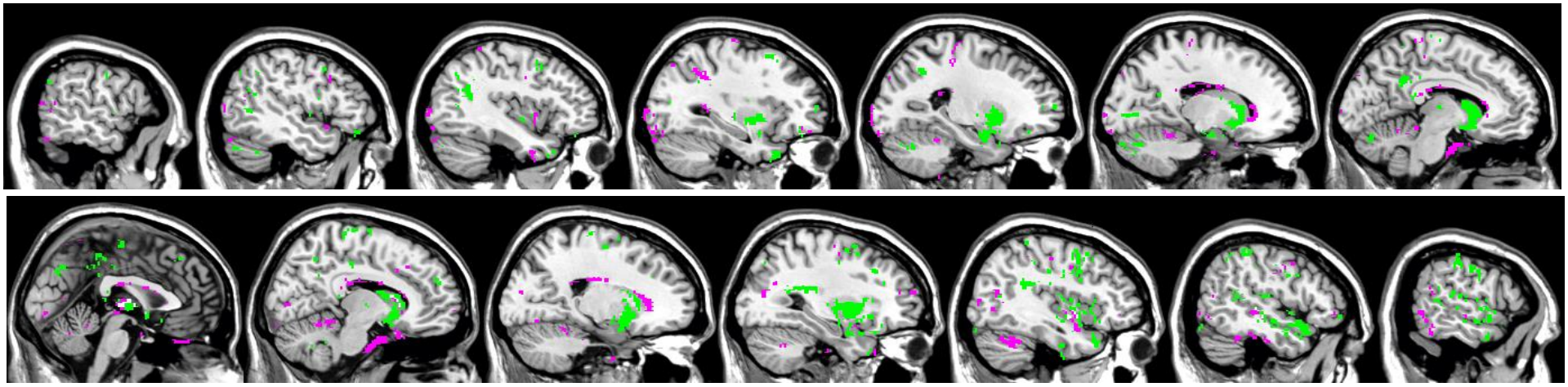


Figure 1. Neuroanatomical correlates of metacognitive functioning. Figure listing areas of gray matter correlated to metacognitive functioning by domain and participant group.



Structures Correlated with Metacognition (all metacognitive domains)
Red=Healthy Controls, Blue=TBI



Structures Correlated with Executive and Basic Functioning
Purple=Healthy Controls, Green=TBI

Figure 2. Comparison of neuroanatomical correlates of metacognitive functioning and executive functioning. Figure shows areas of gray matter tissue that are correlated with cognitive functioning.

VITA

Kathy S. Chiou was born in Houston, TX to Dr. Wen-An Chiou, a professor in Materials Science, and Mrs. Nae-Shiang Chiou, a former math teacher. Kathy grew up in Wilmette, IL and graduated from New Trier High School. She then attended the University of California, Berkeley, where she majored in Psychology and minored in Education. There, she completed an honor's thesis with Dr. Richard Ivry and graduated with honors. After graduating, Kathy spent a year working as a psychosocial rehabilitation coordinator at Albany Care in Evanston, IL. She came to the Pennsylvania State University to pursue her doctorate degree in Psychology under the mentorship of Dr. Frank Hillary. She obtained a master's degree by completing a thesis examining the relationship between executive functioning and metacognition after traumatic brain injury. Kathy completed her clinical internship in neuropsychology at the University of Florida Health Science Center under the supervision of Drs. Russell Bauer, Dawn Bowers, Duane Dede, Catherine Price, and Shelly Heaton.

While at Penn State, Kathy's involvement in research activities resulted in numerous presentations at national and internationally recognized conferences and 5 publications. She has been awarded multiple awards at the Departmental and College levels, including a grant from the Research and Graduate Studies Office to fund her dissertation work. Additionally, Kathy has served and participated in extracurricular departmental programs supporting neuroscience (AXONS) and diversity (BRIDGE).