

Functional Neuroimaging of Traumatic Brain Injury

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Traumatic Brain Injury

An estimated 1.5 million people sustain traumatic brain injury (TBI) in the United States each year (Guerrero, Thurman, & Sniezek, 2000). On average, 230,000 people are hospitalized with a TBI, 80,000-90,000 people sustain long-term disabilities, and 50,000 of these TBI incidences are fatal (Jager et al., 2000; Sosin, Sacks & Smith, 1989; Sosin, Sniezek & Waxweiler 1995; Thurman et al., 1999). The consequences of TBI are widespread, affecting any areas of cognitive, emotional, sensory or motor functioning, and the long-term disabilities associated with TBI are often permanent.

Trauma related brain damage has traditionally been conceptualized as having two forms: primary injury and secondary injury. Primary injury is nonreversible damage to neural tissue occurring during periods of significant acceleration/deceleration or head-versus-obstacle contact taking the form of cerebral contusion, hemorrhage and/or axonal shear injury. Extensive work examining primary injury in animal models has established the biomechanical thresholds for the various injury subtypes observed following TBI (Ommaya & Hirsch, 1971; Gennarelli, 1982; McIntosh et al., 1996). Secondary injury is associated with the pathophysiological processes occurring hours to days after the trauma, including a host of inter-related factors such as blood brain barrier disruption, mitochondrial dysfunction, and metabolic crisis (for a comprehensive review see Unterberg, 2004). In brief, immediately following brain trauma, excessive neuronal firing in the absence of appropriate O₂ metabolism leads to dependence upon anaerobic cellular respiration which may result in lactate elevations and ischemia (Katayama et al.,

1990) and is associated with poor prognosis (Yamaki et al., 1996). In addition, stimulation of glutamate receptors results in an influx of water binding ions, such as Ca^{+2} , into the cell body resulting in widespread edema, increased intracranial pressure, and further ischemic cell death (glutamate and hyperglycolysis are covered again when this chapter focuses on neurometabolism). Early disruption of basic neurophysiology has long-term implications for baseline cerebral blood flow and oxygen metabolism following TBI. Taken together, these early factors have proven crucial for understanding both acute and long-term consequences of TBI and several imaging techniques discussed herein offer critical insights into the basic pathophysiology associated with acute and chronic TBI.

As noted, the disabilities caused by TBI range from mild to severe and symptoms can be physical, cognitive, and/or psychiatric in nature. These varied and, often, overlapping deficits have widespread implications for a patient's everyday functioning and often affect both the individual sustaining the injury as well as family members/caregivers providing support. Functional neuroimaging provides the unique opportunity to examine and characterize the influences of TBI on basic alterations in neurophysiology and the associated changes in neural networks accounting for the myriad of behavioral deficits evident following TBI in humans.

Overview of Functional Imaging and TBI

Functional neuroimaging has been used to investigate both metabolic and functional alterations in the brain and provide insight into the neural substrates of the behavioral deficits observed following TBI (Ricker, Hillary & DeLuca, 2001). A variety

of imaging techniques have been employed over the past two decades to examine TBI. To date, positron emission tomography (PET), single photon emission tomography (SPECT), functional magnetic resonance imaging (fMRI) and proton magnetic resonance spectroscopy (pMRS), have all been employed to varying degrees in the examination of TBI. To a lesser extent, electroencephalography (EEG) and magnetoencephalography (MEG) have also been employed in the examination of TBI. An important goal of this chapter is to examine how functional neuroimaging has influenced our understanding of the pathophysiology of trauma, the basic changes in neural networks responsible for brain functioning in TBI, and the behavioral deficits associated with adult TBI. Also, we focus on studies of *adult* TBI for two reasons. First, the functional imaging literature examining infant, child and adolescent TBI is quite extensive and an exhaustive review of adult and child TBI is, therefore, not possible here. Second, because TBI at younger ages occurs in a developing brain, the goals and methods of examination and models predicting brain function are often quite different. For a review of functional imaging in child and adolescent TBI, we refer the interested reader to Munson, Schroth & Ernst (2006). Also, while animal models of TBI have proven invaluable for understanding pathophysiology and recovery mechanisms following TBI, this chapter predominantly reflects the human work over the past two decades.

In the following, the applications of resting/baseline studies are first considered. Resting or baseline studies will include those providing a measurement of an identifiable neurophysiological parameter at a given moment in time, or a “snap-shot” of brain functioning. We then review dynamic functional imaging or “time series” measurements and how such methods have been used to examine a variety of deficits associated with

TBI. Finally, we consider the methodological issues facing researchers using functional imaging to examine TBI and the future directions for this form of research.

Proton Magnetic Resonance Spectroscopy in TBI

One technique providing a “snap-shot” of neurometabolic status that has proven useful in characterizing acute and chronic TBI is proton magnetic resonance spectroscopy (pMRS). pMRS is based on the same basic physical principles as conventional MRI sequences, however, the signal source comes from larger macromolecules that have distinct local magnetic properties. Each of these larger nuclei maintains discrete orientations when placed within the MR field and can be localized and quantified. The data collected through the use of pMRS do not create a contrast image, instead appearing as a spectrum and individual signals, or metabolites, can be found at predictable locations in the spectrum (see Figure 1). The primary signals of interest in pMRS arise from N-acetylaspartate (NAA), creatine/phosphocreatine (Cre), choline-containing compounds (Cho), glutamate (Glu), and lactate. NAA is found only in the central nervous system, it is the second most abundant compound in the brain (only Glu is more abundant), and it is produced in the neuron’s mitochondria. While its role in neural recovery following injury remains a topic of investigation, NAA is thought to be involved in a variety of neurometabolic processes and it has been the focus of brain injury literature because of it is a marker for axonal repair, mitochondrial dysfunction and cell death. The choline peak (which is elevated when concentrations of phosphocholine, glycerophosphocholine, and choline increase) has been shown to be elevated for weeks following injury in areas of

local tissue breakdown and edema or repair. For a comprehensive review of pMRS and its use in the study of neurotrauma, see Brooks, Friedman, & Gasparovic (2001).

As noted above, a host of neurometabolic alterations exist following brain trauma, and pMRS provides the unique opportunity to examine baseline alterations in neurometabolism noninvasively. For example, diminished cerebral NAA concentrations have been documented using pMRS and correlated with brain injury in both animals (Smith et al., 1998) and humans (Brooks et al., 2000; Garnett et al., 2000; Friedman et al., 1999). Research using pMRS has shown NAA reductions following TBI as early as 1 hour post injury (Smith et al., 1998) and examination of metabolism in humans has revealed that NAA depression may continue for months prior to metabolic rebound (Brooks, Friedman & Gasparovic, 2001; Friedman et al., 1999). Examiners have used pMRS to document altered neurometabolism in both acute (Ross et al., 1998) and chronic TBI (Friedman et al., 1998; Friedman et al., 1999) and there is evidence of significant correlation with injury severity and cognitive outcome (Friedman et al., 1998; Friedman et al., 1999, Garnett et al., 2000). For example, in the case of chronic TBI, concentrations of metabolic markers such as NAA and Cho have been shown to be predictive of cognitive performance and outcome at 1.5, 3, and 6 months following the injury (Friedman et al., 1999). Moreover, research acquiring pMRS data within the first two weeks of injury and at six months following injury revealed it to be sensitive to neurometabolic changes over time (Garnett et al., 2000). For many of these studies, diminished NAA and elevations in Cho have been the most common findings following moderate and severe TBI and these metabolic alterations have shown the greatest relationship to clinical outcome variables.

Researchers have also used pMRS methods to characterize persistent vegetative state (PVS) following TBI. For example, Carpentier and colleagues very recently examined the influence of “invisible” brain stem lesions on PVS by combining spectroscopy and structural MRI data (T2* and FLAIR) (2006). Other examiners have used pMRS to document metabolic alterations in thalamic nuclei in individuals in a PVS at the time of scanning (Uzan et al., 2003). Importantly, structural MRI detected no thalamic abnormality, yet NAA/Cr values in the thalamus discriminated between individuals emerging from PVS (n=6) and individuals remaining in PVS (n=8). Taken together, these findings reveal the sensitivity of pMRS in detecting altered neurometabolism following severe TBI and the potential for characterizing general brain status even when sampling discrete areas of tissue via region of interest (ROI) analysis.

One important area of future exploration is the use of pMRS to examine glutamate as a catalyst for secondary injury (e.g., hyperglycolysis). As noted above, the term hyperglycolysis has been used to describe neuronal firing during periods of metabolic crisis resulting in reliance upon anaerobic respiration and the potential for further neuronal death. In experimental TBI, regional hyperglycolysis has been observed within hours of the injury and may occur regardless of the pathophysiology (e.g., subdural hematoma, cerebral contusion) (Inglis, Kuroda & Bullock, 1992; Sunami et al., 1989; Katayama et al., 1990; and for review see Hovda, Katayama, 1992). Therefore, Glu has repeatedly been observed to play a critical role in the exacerbation of primary injury, and, recently, through the use of noninvasive pMRS methods, investigators have examined the relationship between early Glu elevations and patient outcome. For example, Shutter, Tong & Holhouser 2004, examined glutamate/glutamine (Glx) and Cho

elevations in 42 patients at approximately 7 days post injury, finding a significant relationship between these values and patient outcome at 6-12 months post injury. This work by Shutter and colleagues provided evidence linking early glutamate elevations to long-term functional recovery. Related work examined Glx in children, and although Glx in occipital regions was elevated, these examiners failed to detect a relationship between Glx and outcome (Ashwal et al., 2004). The authors noted that data collection may not have occurred early enough during time periods post injury when Glx would be peaking in this sample.

The role of Glu in secondary injury early following moderate and severe TBI is critical to understand, yet to date, there has been little examination of Glu using pMRS during the first days following injury in severe TBI. This gap in the literature is most likely attributable to previous software limitations for pMRS data analysis, the use of low field magnets, and difficulty isolating Glu in the spectra (glutamate and, another amino acid glutamine, are very difficult to distinguish). However, understanding the role of Glu in human neurotrauma may now be advanced through the serial application of pMRS at high magnetic field strength and measurement of absolute as opposed to relative metabolic concentrations during acute recovery.

Overall, pMRS has proven to be a promising technique for examining neurometabolic disruption following TBI. It is noninvasive and can be used repeatedly over a protracted recovery course to document basic brain changes following TBI. As noted, however, there remains little application of pMRS to very acute TBI (i.e., within 24-48 hours of injury) and findings for adults, the samples remain somewhat small, and, occasionally, findings for adults and children have been interpreted in conjunction (Ross

et al., 1998). Further work employing pMRS to examine TBI is required to standardize the optimal post-injury time period for data acquisition; there remains surprisingly little longitudinal work documenting the evolution of neurometabolism over the recovery course following TBI. Finally, in the case of severe TBI, investigations using pMRS should include analyses of important neurometabolites (e.g., glutamate, lactate) that have not been the focus of examinations to date, yet may aid in characterizing the progression of secondary injury in TBI and associated cognitive and functional outcomes.

Imaging Baseline Functioning following TBI

Because TBI disrupts a host of basic metabolic processes, examiners have worked to develop novel methods that allow for whole brain analysis of trauma-induced alterations in neurometabolism. Compared to other functional imaging techniques, PET is the gold standard for examining baseline neurometabolism, and has been used most extensively to quantify cerebral metabolic rate of oxygen (CMRO₂) and cerebral metabolic rate of glucose (CMR_{glc}) following TBI. There is a large literature using PET to examine baseline neurometabolic phenomenon after TBI and the following review is not exhaustive, but attempts to integrate the major findings occurring over the past two decades.

Like pMRS, baseline PET measurements of neurometabolism require no overt response by patients and, because of this, can be used during the very early stages of recovery from TBI. The primary focus of early PET studies in TBI was to determine if information about brain metabolism provided additional information about brain injury that was not available in traditional structural imaging techniques such as CT/MRI.

Examiners were able to verify that metabolic abnormalities documented via PET were more extensive than the focal areas apparent on structural imaging (Langfitt et al., 1986; Jansen et al., 1996) and sensitive to injury in mTBI where no focal injury was evident (Ruff et al., 1994; Gross et al., 1996). These early studies confirmed that PET was capable of detecting TBI-related brain changes and demonstrated the importance of examining the neurometabolic markers of injury associated with observable alterations in brain structure.

Based upon the baseline differences in neurometabolism observed using PET, other examiners set out to investigate the relationship between cognitive deficits and neurometabolic alterations. For example, using PET Ruff et al., (1994) examined whole brain glucose metabolism and correlated findings with cognitive performance outside the scanner. Ruff and colleagues demonstrated a relationship between cognitive deficits and metabolic disturbance in frontal and anterior temporal areas (1994). Similar methods were used by Fontaine and colleagues to demonstrate the relationship between cognitive deficits and metabolic derangements in prefrontal and cingulated areas using (18F)-fluorodeoxyglucose (1999). While there are important methodological shortcomings in these early studies, with the most salient being the temporal disconnect between PET measurement and cognitive assessment (which was performed outside the scanner and in the case of Ruff et al, separated by up to a month of scanning), these findings are important for two reasons. First, they further established the sensitivity in using PET to document brain areas outside of visible lesion sites that are commonly influenced by TBI. Second, these studies represent the first work to connect the metabolic alterations evident using PET with the behavioral consequences of TBI.

An important contribution by Bergsneider, Hovda and colleagues (1997) represented the first work using PET to document hyperglycolysis in humans. These examiners employed fluorodeoxyglucose-PET (FDG-PET) to examine glucose utilization as a marker for hyperglycolysis, when similar investigation of secondary injury had been previously relegated animal models of TBI. This seminal research was a precursor to a decade of widespread application of PET to examine the metabolic alterations associated with TBI.

Over that past two decades, PET has been used in a variety of ways to examine pathophysiology following TBI including changes cerebrovascular parameters in acute neurotrauma. As described below, by using PET, examiners have been able to verify, in humans and animals, a host of cerebrovascular abnormalities including decoupling of $CMRO_2$ and $CMRO_{glc}$, diminished cerebral blood flow (CBF), and compensatory increases in oxygen extraction fraction (OEF). For example, a critical research application using PET to study TBI has been the examination of ischemia during secondary injury. Due to widespread disruption in basic cerebrovascular parameters, ischemic cell death has been thought to be common following severe TBI, but the physiologic thresholds for ischemia have proven difficult to establish. However, baseline O^{15} PET measurements have been used successfully to examine ischemic thresholds following TBI (Cunningham et al., 2005; Dinger et al., 2002; Steiner et al., 2003) and, in one study, examiners observed that persistent metabolic crisis and “classic” indicators of ischemia (e.g., elevated lactate/pyruvate ratio) may actually occur in the absence of frank ischemic cell death (Vespa et al., 2005). Similarly, using O^{15} PET, Coles et al. (2004) investigated mechanisms of cerebral ischemia and the relationship between

ischemic cell death and outcome following severe TBI. Data from this work showed that within 24 hours of severe TBI, ischemic brain volume correlated with poorer outcome at 6 months post-injury, as indicated by poor Glasgow Outcome Score (Coles et al., 2004).

Other work has shown that PET compares favorably to invasive surgical procedures when examining basic neurometabolic parameters. For example, research by Hutchinson et al. revealed that O¹⁵ PET can be used to complement invasive measurements such as jugular bulb oximetry and microdialysis for examining cerebrovascular reactivity in severe TBI (2002). Importantly, this study showed that PET imaging was more sensitive in detecting ischemia than bedside monitoring procedures, such as jugular bulb oximetry.

In parallel with work using functional imaging techniques to investigate acute TBI, other researchers have used imaging to explore the influence of brain trauma on chronic metabolic functioning. For example, PET has been used to investigate altered neurometabolism in the cerebral white matter of individuals sustaining TBI. In this study, investigators noted pervasive abnormalities across subjects allowing them to conclude that cases of moderate and severe TBI are likely most accurately conceptualized as diffuse or focal and diffuse (Wu et al., 2004). That is, irrespective of what is observable on traditional structural MRI (i.e., contusion, subdural hematoma), these PET findings indicate that the pathophysiology following more severe neurotrauma rarely results in an isolated focal injury.

Other examiners have focused on both acute and chronic alterations in cerebrovascular parameters following TBI such as CBF and CMRO₂. Reduced baseline CBF has been well documented in both humans and animal models of TBI (Bouma et al.,

1991; Kochanek et al., 2002; Schroder et al., 1996; Yamaki, 1996) and, near lesion sites, reduced CBF is evident at one year following the injury (Kochanek et al., 2002). Based upon this literature, PET has proven invaluable for examining the baseline alterations in CBF, the relationship between CBF and oxygen utilization, and the association between cerebrovascular parameters and injury severity and outcome (for a comprehensive review of this literature see Golding, 2002).

Using a combination of FDG-PET and whole brain MEG during presentation of sensory stimulation, other examiners have been able to characterize baseline neurometabolism and brain response in patients in a persistent vegetative state (PVS) (Schiff et al., 2002). This study provided important evidence that brain activity in this small sample of individuals in PVS (n=5) was typically characterized, not as random activity, but as discrete and identifiable neural networks representing organized brain function.

Other examiners have used PET to examine the efficacy of clinical interventions designed to minimize the influence of secondary injury following severe TBI. For example, PET methods afford the ability to track neurometabolism following clinical interventions such as hyperventilation (Coles et al., 2002; Diringier et al., 2002), cerebral perfusion pressure (CPP) manipulation (Steiner et al., 2003; Johnston et al., 2005), and the influence of medications on glucose uptake (Kraus et al., 2005). For example, using O¹⁵ PET, Steiner and colleagues investigated the efficacy of elevating cerebral perfusion pressure (CPP) to treat hypoperfusion in areas surrounding cerebral contusion (2003). This study successfully increased CBF in peri-lesional areas by manipulating CPP and highlighted the use of PET to examine the efficacy of interventions designed to treat

ischemia following TBI.

Finally, while quite dissimilar from PET in its method (see Chapter 3 of this volume), MEG has also been used to examine aberrant resting activity following mild TBI (mTBI). Lewine and colleagues used MRI and MEG methods in combination to examine postconcussive symptomatology in a sample of individuals with mTBI (1999). These examiners successfully demonstrated the sensitivity of combining structural MRI and MEG data in order to discriminate between healthy adults, individuals with resolved mTBI, and individuals with ongoing symptomatology following mTBI. These data revealed the sensitivity and specificity in using MEG to detect symptoms following even mild brain injuries. While it maintains several important methodological advantages compared to other imaging techniques (the most significant being its superior temporal resolution) there remains a paucity of work using MEG to examine the behavioral deficits associated with TBI. The very small MEG literature in this area is attributable to its expense and the limited number of current MEG facilities for conducting this work.

Application of Functional Imaging Techniques in TBI

Functional neuroimaging techniques now provide researchers with the opportunity to study changes in the neural networks associated with the behavioral deficits observed following TBI. Clinical researchers have emphasized that dynamic neuroimaging techniques hold significant promise for assessing outcomes and the success of novel TBI treatments and interventions (Levin, 1992; Ricker, Hillary, & DeLuca, 2001). For example, fMRI has recently enjoyed widespread application in clinical studies primarily due to the accessibility of MR technology, its non-invasiveness, and its

low cost compared to positron emission tomography. Application of fMRI to the study of TBI is still novel, however, and much work remains to be done before its potential can be realized.

With the exception of work examining finger oscillation (Prigatano, Jounson & Gale, 2004) and hand-grasp movements (Jang et al., 2005) in chronic TBI and a serial MRI study of early motor recovery (Lotze, et al., 2006) there has been little work using functional imaging to examine motor and sensory impairment. Because of this, the following several sections focus on the literature examining discrete areas of cognitive dysfunction typically observed following TBI. Much of the work discussed herein represents cross sectional data where comparisons have been made between a prototypical response (i.e., healthy control sample) and the response provided by individuals with TBI. While such designs have limitations, these studies represent important first work using functional imaging techniques to characterize behavioral deficits following TBI.

Executive Dysfunction

The term “executive dysfunction” is used to describe a constellation of cognitive deficits in the areas of reasoning, planning, mental flexibility, concept formation, and other higher order cognitive processes. Because of the link between executive functions and frontal lobe connections, and in particular the dorsolateral prefrontal circuits (see Cummings, 1993) and the ubiquity of frontal lobe injury in TBI, impairments in executive functioning are nearly universal following TBI (Brooks et al., 1999; Gentilini et al., 1985; Leon-Carrion et al., 1998; Gutentag, Nuglieri & Yeates, 1998; Shallice &

Burgess, 1991; Rieger & Gauggel, 2002; McDonald, Flashman, & Saykin, 2002; Cicerone & Giacino, 1992).

Investigators are now using functional imaging techniques to examine the neural correlates of executive dysfunction following TBI. One of the most well studied neuropsychological tests for the assessment of executive functioning is the Wisconsin Card Sorting Task (WCST) (Berg, 1948; Grant & Berg, 1948). The WCST requires subjects to decipher a set of rules in order to accurately sort a deck of cards. The task instructions for the WCST provide minimal structure and, throughout the test, the rules change requiring the subject to inhibit previously learned responses. Because of this, the WCST demands significant mental flexibility and problem solving skills. Executive dysfunction in TBI has been substantiated using the WCST by multiple investigators (Martzke, Swan and Varney, 1991; Leon-Carrion et al., 1998).

Using O¹⁵ PET during WCST performance, Kirkby et al. examined executive dysfunction in a single case of moderately severe TBI (1996). To control for genetic determinants of baseline cerebral blood flow, the subject with TBI was compared to his monozygotic twin, who had not sustained a brain injury. Also included were 10 pairs of monozygotic twins to serve as additional controls. The investigators found that during performance of the WCST, the subject with TBI showed reduced regional cerebral blood flow in inferior portion of the left inferior frontal gyrus and increased regional cerebral blood flow in the left hippocampus compared to the uninjured twin. Because the performance between the twins was comparable, the authors interpreted the increased hippocampal involvement of the injured twin as compensatory and perhaps engaging long-term memory networks due to disruption of prefrontal working memory networks.

While these data are difficult to generalize to other samples, this case study represents an early example of the potential for using functional imaging to document basic brain changes responsible for executive dysfunction in TBI.

More recently, Lombardi et al. (1999) examined the relationship between regional brain metabolism and performance on the WCST in a group of 8 individuals with mixed TBI severity. These examiners did not directly examine WCST performance during PET data collection; they used an auditory continuous performance test in the scanner and correlated the relationship between PET activation on this test and perseverative responses on the WCST performed within 1 month of PET imaging. The results indicated that perseverative errors were negatively correlated with right (but not left) dorsolateral PFC and caudate nucleus activation. The authors concluded that this dorsolateral frontal-caudate circuit was critical for performance of the WCST. While there are clear shortcomings to the method used by Lombardi and colleagues (1999), including the temporal disconnect between behavioral and functional data, this study represents an important early attempt to examine perseveration following TBI and may serve as the basis for more specific hypothesis testing in future studies of perseveration in TBI. For example, future work may include ROI analysis of the right dorsolateral PFC and caudate nucleus, as well as other neural substrates in this network, in order to clarify the nature of perseverative deficits in TBI

Attention/Concentration and Inhibition

It is well established that individuals with TBI often show impairments on tasks of attention and concentration (Oddy et al., 1985; van Zomeren & van den Burg,

1985; Ponsford & Kinsella, 1992; Stuss et al., 1989) and functional neuroimaging has been recently used to examine basic deficits in attention and concentration following TBI. Early work by Humayun and colleagues employed FDG-PET to examine visual vigilance following mild-moderate TBI (1989). The study included 3 individuals with TBI between 3-12 months post-injury and 3 matched healthy adults. The study findings indicate that, on average, the TBI sample showed increased regional CMRglc in anterior temporal and anterior frontal cortices relative to controls. Decreased glucose metabolism was also observed in subjects with TBI in posterior temporal cortex, posterior frontal cortex, and left caudate nucleus. While the sample size was small, these early PET findings are consistent with the traditional experimental models of head injury and what is observed clinically in TBI; the frontal and temporal systems are the most commonly affected areas in cases of closed head trauma.

Recently, Soeda et al., (2005) adapted the Stroop task (Stroop, 1935) to the fMRI environment in order to investigate impairments in attention and response inhibition in individuals with TBI. These investigators were specifically interested in the role of the anterior cingulate cortex (ACC) in mediating attentional resources following TBI. Findings indicated that healthy controls showed activation in the anterior cingulate, replicating findings of other neuroimaging tasks utilizing the Stroop and individuals with TBI, exhibited less activation in the ACC, and specifically the “ACed”, or the “affective division” of the ACC. The ACed has been linked to attention switching and the deficits specific to ADHD during this task. Because of its hypothesized role in attention, the authors concluded that the observed deficits were due to deficiencies in the neuronal network responsible for attention, as opposed to difficulty with response inhibition or

other related cognitive deficit. Interestingly, the TBI group performed worse in this sample, but not significantly worse than HCs ($p = .51$). Even so, the authors concluded that failure to integrate the anterior cingulate into the neural network on the part of individuals with TBI resulted in poorer attentional performance. These findings appear to corroborate what has been known of the ACC on tasks of attention in a sample of individuals with TBI; the cingulate thus appears to provide critical resources in this neural network allowing for controlled responses to stimuli. This is apparent in the healthy adults sample here and individuals with TBI specifically showing diminished activity in the ACC on this task. Of note, relationship between activation and performance in this study remains somewhat unclear and this has important implications for interpreting the meaning of the differential brain activation observed between individuals with TBI and healthy adults (discussed in greater detail later).

Working Memory

Working memory is considered to be a fundamental component that influences most areas of general cognitive functioning (Courtney, 2004) and basic information processing efficiency in human cognition is influenced by the interaction between processing speed and the size and flexibility of the WM buffer (Demaree et al., 1999; Salthouse 1996; Salthouse and Coon 1993). Because working memory functioning is largely mediated by networks in lateral prefrontal cortex and these same areas are highly susceptible to disruption following TBI, WM impairment is one of the single most common deficits following TBI (Hamm et al., 1996; McDowell, Whyte & D'Esposito, 1997; Stuss et al., 1985, Levin et al., 1990). Because it is so often disrupted, WM is the

cognitive domain that has been most extensively investigated in TBI using functional neuroimaging.

One of the most commonly used tests to assess WM is a visual or auditory “n-back” task. The n-back is a WM task requiring continual monitoring and maintenance of individually presented items (e.g., letters) that are to be recalled when prompted. The first examination using fMRI to examine cognitive functioning in mTBI was performed by McAllister and colleagues (1999) who investigated a group of individuals within one month of their injury. Using the n-back, these examiners, hypothesized that, compared to healthy adults, individuals with mTBI would show greater alterations in the neural networks associated with WM in response to changes in task load. While reaction times were not measured, the authors noted that there were no between group differences in task accuracy in any of the n-back conditions (e.g, 0, 1, or 2). Functional imaging results revealed increased right prefrontal activation in individuals with TBI in response to increasing task load. This activation/task load response was greater for individuals with TBI compared to healthy controls when task load increased from 1-back to 2-back. The authors interpreted this increased activation as compensatory recruitment of additional cerebral resources that healthy adults do not require.

In a follow-up study, McAllister et al. (2001) again examined mTBI using the n-back (1, 2, and 3-back) to examine task load effects. The results revealed that in the moderate load condition (2-back), the mTBI group showed higher activation than healthy adults. In the highest working memory load (3-back), the mTBI group showed less activation than healthy controls. The authors interpreted this finding as a ceiling effect in the TBI sample; individuals with TBI reached a threshold where no additional resources

were available for recruitment from the 2-back to the 3-back. What is important to consider regarding this interpretation, is the method used to create these contrast images (“2-back” was 2-back minus 1-back and “3-back” was 3-back minus 2-back). Because the mTBI sample showed a more elaborate neural network compared to healthy adults during the 2-back task, a more extensive neural network was eliminated in order to create the 3-back contrast image. That is, in mTBI, the 3-back contrast eliminated much of the neural network responsible for responding to increasing task load because, in the mTBI sample because this network was already evident at 2-back. This is a basic problem with cognitive subtraction in functional imaging studies (see Chapter 4 of this volume) and this issue is magnified when examining clinical samples where there may be a fundamental difference between groups in the networks “removed” to create contrast effects.

Even considering the methodological shortcomings covered here, the studies by McAllister and colleagues have provided reliable evidence that the neural networks representing WM in healthy adults and a mildly brain injured TBI sample can be dissociated using fMRI. Also, regardless of the interpretation of the divergent activation patterns between groups, work by McAllister and colleagues generally demonstrated that, during tasks of WM, a disrupted neural network is associated with *increased* brain activation in prefrontal, temporal, and parietal areas.

Christodoulou and colleagues later conducted the first examination of WM deficits using fMRI in a group of individuals with moderate and severe TBI (2001). To examine the neural networks associated with working memory, Christodoulou and colleagues used a modified version of the PASAT (mPASAT) in the scanner. The

mPASAT is a widely used and demanding WM task requiring rapid rehearsal and mental calculation of single digits. The mPASAT has been shown to be sensitive to WM and speeded processing impairments in TBI (Brooks et al., 1999). In this study, Christodoulou et al., hypothesized that the individuals with TBI would show increased activation in conjunction with diminished performance on this WM task. Although the healthy controls and individuals with TBI demonstrated overlapping regions of activation (i.e. middle frontal gyrus, superior and middle temporal gyrus, and inferior parietal gyrus), individuals with TBI consistently showed greater right hemisphere activation, whereas healthy adults exhibited a neural network lateralized to the left hemisphere. Unfortunately, the design employed by these investigators did not allow for parametric manipulation of working memory load. Even so, the TBI sample performed significantly worse on the mPASAT task, so the observed increase in right hemisphere activation was associated with poorer performance. These findings were consistent with work by McAllister and colleagues and, again, indicate that during WM tasks, individuals with TBI show a neural network requiring greater PFC involvement compared to healthy adults. However, unlike McAllister et al., the findings by Christodoulou and colleagues revealed important negative relationship between brain activation and task performance. Similar performance/activation relationships in TBI were more recently observed in a case study by Scheibel and colleagues (2003) and in the most recent study of working memory in moderate and severe TBI where investigators manipulated WM load using the n-back (Perlstein et al., 2004). In fact, the work by Perlstein and colleagues (2004) revealed WM impairments both inside and outside the scanner, and, similar to the findings by Christodoulou and colleagues, individuals with TBI showed greater right dorsolateral prefrontal cortex activation.

While many WM tasks used in imaging studies have use verbally mediated materials, Chen and colleagues recently conducted a study of spatial working memory in mTBI (2003). These investigators used PET to examine neural networks during a spatial working memory task in a group of individuals with mTBI. Interestingly, they found that when examining symptomatic patients as a group, individuals with mTBI had a smaller percentage change in regional cerebral blood flow than controls in the right inferior frontal gyrus. While the sample size in this study was quite small (n= 5 TBI, 5 controls), these data are consistent with prior work in humans and animals documenting reductions in CBF values.

In a more comprehensive investigation of mTBI, Chen et al., (2004) examined 16 concussed athletes, using both a visual and verbal working memory task during fMRI. Importantly, the subjects did not differ significantly in their performance and displayed brain activation patterns similar to HCs. The concussed athletes, however, showed less task-related activation in the right mid-dorsolateral prefrontal cortex and a negative relationship between the BOLD signal change and post concussive symptom severity. Because of the negative relationship between the BOLD signal and degree of symptomatology, these findings are inconsistent with prior work examining WM dysfunction in more severely injured populations. While difficult to reconcile with the literature, the divergent findings in Chen et al. (2004) may be due to the type of task used or the mild nature of the injury in this sample.

Learning and Memory

Disturbed recognition memory for shapes following TBI was documented over

three decades ago (Levin, Grossman, and Kelly, 1976) and “forgetfulness” has long been the most common deficit reported by patients with TBI (van Zomeren & van den Burg, 1985). Since that time, episodic memory deficits following TBI have been repeatedly observed and examiners now maintain that most individuals with moderate and severe TBI experience some degree of memory disturbance (Levin, 1990; Rosenthal & Ricker, 1999). Surprisingly, the emphasis on examining new learning deficits in TBI has not transferred to the imaging literature, where much of the work thus far in TBI has focused on WM deficits.

In one study of episodic memory following TBI, Levine and colleagues used O¹⁵ PET to examine an individual with severe TBI and isolated retrograde amnesia (1998). The examiners hypothesized that, given the role of right prefrontal areas in episodic retrieval, the subject would show right frontal dysfunction compared to healthy adults. The healthy controls showed activation patterns typical of encoding and retrieval: greater left prefrontal activation was observed during encoding, whereas greater right prefrontal was observed during retrieval. However, in the patient with severe retrograde amnesia, decreased activation in right frontal regions was observed during retrieval, as well as increases in activation in posterior cortical areas during cued free recall. This case study is illustrative of trauma-induced alterations in traditionally well-established networks representing episodic memory.

Separately, Ricker et al. were the first to use O¹⁵ PET to examine regional cerebral blood flow (rCBF) changes during verbal recall and recognition in TBI (2001). Using a small TBI sample size (n=5), this study examined word recognition following a list learning trial. The data revealed that, during word recall, frontal lobe regional cerebral

blood flow was reduced in individuals with TBI compared to HCs, however there were increases in CBF in several posterior brain regions in cases of TBI. During recognition trials, both groups demonstrated bifrontal increases in activation. These findings corroborate what has been observed in behavioral studies examining episodic memory deficits following TBI; acquisition of novel material is often slowed or reduced, but individuals with TBI often show relatively spared recognition for recently presented material (DeLuca et al., 2000).

More recently, Levine et al., (2002) once again examined the functional organization of memory in six subjects with moderate to severe TBI using O¹⁵ PET. The goal of the study was to document activation differences in individuals with TBI relative to controls using a previously studied learning and retrieval paradigm. The investigators predicted that, when compared to healthy adults, participants with TBI would show additional activation due to functional reorganization of function following the injury. Behaviorally, the subjects performed worse, but not significantly worse, than the healthy controls. In regards to functional imaging data, healthy adults and subjects with TBI showed a right-lateralized fronto-temporal network, however participants with TBI also exhibited a neural network that extended to areas contralateral and homologous to those regions active in the baseline neural network. In order to examine the influence of localized lesions on the findings, the investigators removed three subjects with focal sites of injury and, after re-analysis, the results remained largely the same. These findings were important because they illustrate that individuals with TBI, regardless of lesion size or location, tend to show similar patterns of activation as healthy individuals, which may imply that diffuse axonal injury may cause the altered activation patterns in this

population. The consistency in these findings across individuals in what has classically been considered a heterogeneous sample is an important contribution by imaging and is discussed again in greater degree later in the chapter (see section titled *Integrating the Findings*).

Summary of functional imaging studies to date:

This chapter has provided an overview of the current functional imaging studies examining cognitive dysfunction following TBI. It is important to remember that the neuroimaging studies covered here are designed to establish a basic pattern of brain activation in HCs, which become the standard for comparison for individuals with TBI. These “normal” activation patterns are used to determine abnormality in the TBI sample, and any differences in the basic neural network are commonly attributed to the trauma. However, the nature of these basic brain activation patterns may vary from study to study, from group to group, and, in some cases, even within groups of healthy adults. This variability in basic neural networks (especially when occurring during roughly equivalent levels of behavioral performance) is important to consider and has implications for interpreting the “aberrant” activation observed in any single case of TBI. Moreover, conclusions, to date, are limited by the very small sample sizes; only the work by McAllister and colleagues have had a sample size of at least 20. The studies conducted thus far have focused largely on the neural networks of cognitive domains known to be impaired in TBI (see Table 1 for description of important baseline and functional studies in TBI). Although various cognitive domains have been assessed, there are some commonalities across findings and these are discussed below.

Integrating the findings

A review of the current literature indicates that, very generally speaking, functional neuroimaging is sensitive to the basic brain alterations evident following TBI. This sensitivity has been consistently documented across studies, and, critically, the basic brain differences observed via functional imaging have typically been linked to specific performance decrements. The directionality of these activation/performance relationships is the basis for understanding how distinct brain structures, and even entire neural networks, contribute to the cognitive deficits observed in TBI.

Altered brain activation in TBI samples compared to HCs has been occasionally interpreted as *compensatory* or indicative of *brain reorganization*. The term “compensation”, as it has been used in the functional imaging literature to date, implies that brain activation observed in individuals with TBI operates to bolster the subject’s performance. However, without directly examining the relationship between performance and activation (specifically using reaction time), it is difficult to determine if altered brain activation facilitates performance or is an indicator of an inefficient neural system. In several studies reviewed above, a negative relationship between performance and activation was observed (see Christodoulou et al., 2001; Perlstein et al., 2004). This negative relationship between neural activity and task performance indicates that the observed neural networks are either directly contributing to poor performance (e.g., neural disinhibition) or they represent a network that is brought online due to diminishing performance (e.g., cognitive control mechanisms). Because of this, increases in brain activation that can be directly linked to performance decrements should not be interpreted

as facilitative and certainly not indicative of “brain reorganization”. Moreover, it is important to note that on tasks of WM, there is evidence that even healthy adults recruit prefrontal cortical networks occurs during periods of increased task load (Braver et al., 1997; Culham, Cavanagh, & Kanwisher, 2001; Manoach et al., 1997; Rypma & D’Esposito, 1999; Rypma et al., 1999). These findings indicate that increased neural activity during periods of poor performance may reflect basic mechanisms in place to tolerate fluctuating increases in task load and are not necessarily directly related to the injury. Because of this, the task/performance relationship has critical implications for interpreting activation in TBI. For a comprehensive review of this issue see Hillary et al., (2006).

While the findings from studies examining attention, WM and episodic memory reveal negative task performance/activation relationships, studies examining other cognitive domains such as response inhibition and sustained attention have shown positive activation/task performance relationships. Appropriate interpretation of imaging results thus requires information about the prototypical performance (i.e., HC performance), and the directionality of activation/performance relationships in the TBI sample. In the case of TBI, prefrontal areas have often shown increases in activation as performance diminishes, however, as noted by Scheibel et al., failure to integrate (or “activate”) the ACC during a task of sustained attention was associated with poorer task performance (2003). This positive relationship between performance and activation was also observed in investigations of more “hard-wired” functions, such as motor skills (Lotze et al., 2006; Prigatano, Johnson, Gale, 2004), further indicating that activation/performance relationships may be dissociable across the various

neuroanatomical substrates and behaviors.

Future Directions for Functional Imaging and TBI

The application of functional imaging techniques to examine TBI thus far has been promising, yet there remain a great number of phenomena to be studied and methodological shortcomings to be addressed. First, at the most fundamental level, future work should continue to document the basic relationships between observable deficits and the neural substrate responsible for those specific deficits. As noted repeatedly, the directionality of the activation/performance relationships is the basis for understanding how distinct brain structures, and even entire neural networks, contribute to the cognitive deficits observed in TBI. Because of this, future work should not aim to simply document the *existence* of altered patterns of activation in TBI, because for any between group comparison, some differences likely exist. What is essential to characterize is the relationship between task performance and the specific neural network associated with that performance; such efforts allow for analysis of discrete cognitive deficits and their specific neurofunctional correlates.

The next generation of functional imaging studies in TBI should aim to examine a broader range of the basic trauma-induced deficits. Such examinations should include motor and sensory deficits, as well as a broader range of cognitive deficits commonly observed following TBI including basic speed of information processing deficits and the varied manifestations of frontal lobe dysfunction including perseveration, impulsivity, planning/problem solving. Future work should focus less on ROI analysis and work to examine basic cognitive deficits in the context of understanding how complete neural

networks are altered following trauma. Approaches using whole brain analyses also permit the opportunity to test models of connectivity to discern how neural networks operate in concert during any cognitive, sensory, or motor task (e.g., independent or principle components analysis). Connectivity analyses such as ICA and PCA provide information not only about alterations at one area of a distributed neural network may influence functioning in connected, but distant, components of the same network (for a more complete review of connectivity methods see Chapter 5 of this volume). As noted, future work will require parametric manipulations in order to better characterize activation/performance relationships.

One important consideration when using functional imaging to examine brain injury and disease is the influence pathology may have directly on the imaging method. For example, while many of the current imaging techniques provide direct measurement of neural activity (e.g., MEG, EEG) or related neurophysiology (e.g., glucose uptake, oxygen utilization), because it is an indirect measure of neuronal firing, fMRI does not enjoy the same advantages. Because of this, there remain important obstacles for investigators attempting to use fMRI to reliably examine the subtypes of TBI and the various stages of recovery. First, there has been no systematic examination of the effects of changes in cerebrovascular physiology on the fMRI signal over the course of recovery from TBI. As documented above, TBI results in widespread disruption of baseline cerebrovascular parameters and recent work in humans has shown that the basic components of the fMRI signal (e.g., CBF, OEF, and blood flow transit time) are influenced in brain areas adjacent to brain lesion (Hillary & Biswal, 2007; see Figure 3). To date, however, there has been no systematic examination of the influence of focal or

diffuse brain lesions on the fMRI signal in humans. Moreover, the relationship between the fMRI signal and various clinical factors such as time since injury, injury severity, and lesion presence remain unknown. In order to more precisely examine the cognitive, motor, and emotional consequences of TBI using fMRI it will be critical to determine the influence of these clinical factors on the fMRI signal.

Summary and Conclusion:

Functional imaging has provided important insights into the basic brain changes commonly occurring following brain trauma. Through the use of multiple technologies, imaging now provides the opportunity to integrate information about the structural, metabolic, and functional brain changes associated with brain trauma. Findings have been instrumental in documenting baseline alterations in cerebrovascular reactivity in humans in areas adjacent to and distant from focal lesions. Examinations of neurometabolism via pMRS methods have been used to isolate important predictors of later cognitive and functional outcomes. Recent work using PET and fMRI methods have isolated localized and whole brain alterations to the basic neural networks associated with attentional, memorial, and higher order functioning. The next generation of studies should also work to examine other areas of deficit following TBI including sensory and motor deficits, psychiatric problems, and common cognitive deficits not yet studied (e.g., speed of information processing, problem solving, impulsivity). Future work requires greater methodological precision by linking behavioral performance to brain activation through parametric manipulation of task load. Such methods allow examiners to directly examine the relationship between basic changes in the neural

network and task performance as the task varies in demand. By including whole brain and network analyses and continually refining current methods, functional imaging has the flexibility necessary for examining the various influences of brain trauma on human behavior.

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Table 1

Single Shot/Baseline						
First Author	Year	Imaging Modality	Regions of Interest	Sample Size	Control Sample Size	Summary of Findings
Coles	2004	O-15 PET	Whole Brain	15 TBI participants	10 matched controls	24 hours after TBI, an increase in ischemic brain volume correlated with poor Glasgow Outcome Scores 6 months after injury; also, PET was more sensitive in detecting ischemia than bedside monitoring procedures
Steiner	2003	O-15 PET	Pericontusional Areas	18 TBI participants	18 non-lesioned areas in same TBI participants	Increasing cerebral perfusion pressure in lesioned areas increased regional cerebral blood flow in those areas
Brooks	2000	MRS	Occipitoparietal grey & white matter	19 TBI, longitudinally over 6 months	28 controls	Poor neuropsychological performance was correlated with decreased NAA and increased choline; NAA levels at 1.5 months were correlated with outcome after 6 months.
Ross	1998	MRS	Lesioned Areas	12 children, 13 adults with acute TBI	None	Reductions in NAA after injury in lesioned areas; in children, detectible lipid/lactate levels and/or decreased NAA/creatine level correlated negatively with outcome
Garnett	2000	MRS	Lesioned Areas	19 TBI participants 3-38 days post-injury	None	NAA decreases and choline increased in the days and weeks post-injury; the severity of the injury & the decline of the ratio of NAA to creatine was significantly correlated
Friedman	1998	MRS	Normal-appearing occipitoparietal white and occipital grey matter	12 TBI	14 controls	TBI participants indicated reduced NAA in white matter and increased choline in grey matter; NAA and creatine levels in the grey matter significantly correlated with neuropsychological performance
Friedman	1999	MRS	Occipitoparietal white & grey matter	14 TBI at 1.5 and 6 months post-injury	14 matched controls	NAA levels correlated with neuropsychological testing performance and Glasgow Outcome Score (GOS)
Carpentier	2006	MRS	Consciousness areas of brain stem	40 severe TBI participants 17.5 ± 6.4 days after injury	None	MRS detected severe brain stem damage where T2 star & FLAIR imaging did not; also found that combining MRS and T2 star/FLAIR data provided clear and distinct boundaries between increasing levels of injury as assessed by the GOS
Uzan	2003	MRS	Thalamus	14 TBI individuals; 8 in a persistent vegetative state, 6 who had recovered from a vegetative state	5 controls	MRS detected severe brain damage in the thalamus by detecting NAA/CR ratios, where conventional MRI did not. Further, NAA/CR ratios were correlated with group prediction on persistent vegetative or emergent status
Shutter	2004	MRS	Normal appearing brain tissue	42 TBI individuals 7 days out from injury	None	Glutamate/Glutamine and Choline were elevated in occipital grey and parietal white matter in those participants with poor outcomes. Further, MRS was more accurate in predicting outcome than somatosensory evoked potentials
Ashwal	2004	MRS	Occipital grey and parietal white matter	38 children with TBI; mean age 11, mean 7 days post-injury	10 Matched controls	Found elevated Glutamate/Glutamine levels, but could not correlate those levels with outcome
Langfitt	1986	Xe-133 PET	Lesioned areas	3 TBI participants with significant intracranial pressure	None	Xe-133 PET detected greater cerebral damage than did MRI or CT, especially in the anterior temporal lobe
Jansen	1996	Co-55 PET	Lesioned areas	5 TBI participants with moderate injuries	None	Co-55 PET again detected greater cerebral damage than did MRI or CT, and detected damage in perilesional areas also detected by EEG
Bergsneider	1997	18-FDG PET	Whole brain, with focus on lesioned areas	28 TBI participants with severe injures	None	First study to document hyperglycolysis after TBI; documented hyperglycolysis in lesioned areas, perilesioned areas, and globally
Cunningham	2005	O-15 PET	Lesioned and non-lesioned regions of interest	14 TBI participants with identified lesions on late-stage MRI	None	Concluded that the level of cerebral blood flow (CBF) at which there is consistent brain damage in TBI differs from the level of CBF at which there is consistent damage in stroke.
Hutchinson	2002	Triple	Frontal areas	17 TBI	None	Significant relationship documented between the

		Oxygen PET	defined by microdialysis	participants with severe injuries		lactate/pyruvate ratio and Oxygen Extraction Fraction (OEF). Combining PET and microdialysis was effective and safe, but complex in setup
Wu	2004	O-15 and 18-FDG PET	Grey & white matter in non-lesioned areas	10 TBI participants with moderate-severe injuries 13 TBI participants with severe injuries; 9 underwent moderate hyperventilation, 4 underwent severe hyperventilation	16 healthy volunteers	Decreases in the global white matter oxygen-to-glucose metabolism ratio indicated that TBI tends to have diffuse effects in addition to foci
Diringer	2002	O-15 PET	Whole brain	30 TBI	None	Hyperventilation caused decreases in oxygen and CBF, however these changes did not translate to energy failure due to increased OEF and lower baseline metabolic rate
Vespa	2003	O-15 PET	Whole brain	186 TBI with GCS of 8 or less	None	Extracellular glucose levels were associated with poor outcome on the GOS, but were not associated with ischemia
Bouma	1991	Xe-133 PET	Whole brain	33 TBI with GCS of 8 or less 3 months post-injury	None	Ischemia occurs in the first 24 hours post-injury; treatments of hyperventilation to reduce edema may therefore be harmful
Schroder	1996	O-15 PET	Whole brain	33 TBI within 7 days of injury	None	Early CBF indications did not correlate with measures of atrophy; later CBF values did correlate with outcome
Coles	2002	O-15 PET	Whole brain	22 total TBI; only 6 underwent PET	14 healthy volunteers	Hyperventilation led to increases in intracranial perfusion pressure, but also were correlated with ischemic brain tissue
Kraus	2005	18-FDG PET	Pre-frontal cortex		None	Usage of amantidine, an NMDA antagonist, post-injury increased left pre-frontal cortex glucose metabolism

Functional Imaging						
First Author	Year	Imaging Modality	Regions of Interest	Sample Size	Control Sample Size	Summary of Findings
Kirkby	1996	O-15 PET	Frontal lobe; hippocampus	1 TBI patient; his uninjured MZ twin	10 pairs of uninjured MZ twins	Injured MZ twin had more activation in the hippocampus and less activation in the inferior portion of the left inferior frontal gyrus than his twin during the WCST; controls showed no augmented rCBF in the hippocampus Inverse relationship found between perseverative responses and metabolism in the right but not left dorsolateral prefrontal cortex and caudate nucleus
Lombardi	1999	18-FDG PET	Frontal lobe	8 TBI participants	None	Decreases in glucose metabolic rates in medial temporal, posterior temporal, posterior frontal areas and the left caudate nucleus compared to controls; increases in anterior temporal and anterior frontal areas
Humayun	1989	18-FDG PET	Whole brain	3 TBI participants	3 matched controls	PET confirmed positive neuropsychological test results where conventional MRI and CT did not
Ruff	1994	18-FDG PET	Various regions	9 TBI participants	24 controls	Bilateral activation of PFC during a response inhibition task and a working memory task where healthy controls were unilateral
Scheibel	2003	fMRI	Pre-frontal cortex	1 TBI participants	4 controls	
Soeda	2005	fMRI	Anterior cingulate cortex	5 TBI participants	11 controls	TBI participants had less ACC activation during the Stroop task than did the healthy controls
McAllister	1999	fMRI	Whole brain	12 TBI participants	11 matched controls	Mild TBI participants exhibited disproportionately increased activation in working memory areas of the brain with increasing task load compared to controls despite insignificantly different task performance
McAllister	2001	fMRI	Whole brain	18 TBI participants (including the 12 from above)	12 matched controls	Healthy control participants could proportionally increase working memory activation in increasing task loads whereas TBI participants showed greater increase from 1-2 back and less from 2-3 back
Christodoulou	2001	fMRI	Whole brain	9 TBI participants	7 matched controls	TBI participants showed more right prefrontal activation during a modified version of the mPASAT, whereas controls showed more left prefrontal activation.
Chen	2003	18-FDG PET	Inferior frontal gyrus	5 TBI participants	5 controls	Individuals with mild TBI had a smaller % increase in regional CBF during a spatial working memory task than did controls in the inferior frontal gyrus
Chen	2004	fMRI	Whole brain	16 mild TBI participants	8 controls	TBI participants showed less activation in the right mid-dorsolateral prefrontal cortex and a negative relationship between the BOLD signal change and post concussive symptom severity
Levine	1998	O-15 PET	Areas involved in memory retrieval	1 amnesic participant	5 moderate to severe TBI w/o amnesia; 12 controls	Amnesic participant had decreased right prefrontal activation during episodic memory retrieval than did the other two groups, and had increased activation in posterior cortical areas
Ricker	2001	O-15 PET	Whole brain	5 TBI participants	4 matched controls	TBI participants had decreased frontal activation during verbal memory recall, and increases in posterior cortical regions
Levine	2002	O-15 PET	Whole brain	6 moderate to severe TBI participants	11 matched controls	TBI participants and controls both had a right fronto-temporal network, but TBIs also had a similar activation in the contralateral homologue

Table 2

