FUNCTIONAL IMPLICATIONS OF CORTICAL DAMAGE

by

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Traumatic brain injury has reached epidemic levels, and yet there are still large

questions that need to be addressed regarding the underlying pathology and the related

behavioral deficits. Adequately measuring the neurological sequelae associated with TBI

in vivo requires the use of sophisticated imaging procedures, while quantifying behavioral

deficits requires precise, sensitive testing procedures. The current analysis examined

three potential biomarkers of TBI using MRI technology, as well as examining both fine

motor and psychological function on a cohort of TBI participants at least 12 months post-

injury. Ten participants with a history of traumatic brain injury and ten matched controls

were recruited for the present analysis. All participants completed a series of four MRI

scans, as well as a simple motor task and a cognitive test battery. Between group analysis

revealed that the two groups could be differentiated based on two MRI measures (BOLD

and FA), and on three behavioral measures (Fitts motor task, self-reported symptoms, and

impulse control). A within group correlation analysis of the TBI participants did not reveal any significant relationship between the MRI data and behavioral deficits. A group-wide regression analysis, however, revealed that MRI markers of cortical damage significantly predicted deterioration in the Fitts motor task performance. The results of the current study suggest that the long-term effects of TBI are not confined to executive function, and that one's performance of a fine motor task has diagnostic potential.

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CHAPTER I

INTRODUCTION

Analyses on central nervous system function are as numerous and variable as the

people performing the research. The breadth of this body of literature, however, is

conjoined by two fundamental topics of investigation: Behavior and / or its underlying

neural function. That is, how is the former a result of the latter? Documenting this

interplay has been a cardinal aspect of modern neuroscience research. Having established

a rudimentary understanding, a tertiary field of research has emerged that seeks to

document the behavioral implications of pathology in the central nervous system. The

following is an account of the current neuroscience literature relating to, 1) The behavior

of the manual motor system, 2) The motor functions of cortical structures, and 3) The

disruption of this interplay as a result of microscopic mechanical damage.

Why should one use the manual motor system to examine the link between

behavior and the CNS? The simple answer lies in the nature of the motor system: Motor

behavior is largely consistent across sex, race, culture, language, etc. That is, researchers

are provided with an unbiased glimpse into a behavior common to all people. To use a

simple illustration, if one were to take a sample of people from different regions of the

world, each person would behave the same from a fine motor perspective. In addition to

human movements being highly stereotyped, this form of behavior can be viewed from a

completely quantitative perspective using modern kinematic analysis. These traits inherent to the manual motor system offer a simple, yet precise view of the health of a human being.

1.1 MOTOR BEHAVIOR AND THE TASK OF REACHING

There is no absence of literature concerning human motor behavior. The 20th century teemed with reports and hypotheses concerning how people chose to move. R. S. Woodworth published the seminal monograph concerning human motor behavior in 1899. Although instrumentation was primitive by today's standards, Woodworth's proposal of a two-part reach plan is still held as a central component of most motor control models. In the most widely cited experiment, participants were required to make reciprocal aiming movements between two horizontally opposed targets by sliding a pencil across a piece of paper. The paper was affixed to a large metal drum, rotating at a constant speed. Analysis of this paper-and-pencil test was quite simple: Woodworth simply examined the trace of lead as it crossed from one edge of the paper to the other.

The data, posited Woodworth, seemed to be composed of two very unique portions. The first part of each movement was remarkably stereotyped not only within each trial but also between subjects. This first phase was subsequently termed the initial, or propulsive phase of movement. During this segment of a reaching movement, participants were simply accelerating their limb towards the target. As the pencil moved closer to the target, the movement slowed considerably and lost its previous consistency: During this second, or "homing in" phase of movement, the kinematic profile of the aiming movement was not only slower, but characterized by sudden accelerations and

decelerations. Woodworth, therefore, posited that each time one initiates an arm movement the motor plan is assembled in two parts. The first part is simply designed to get within the vicinity of the target, while the second, or most important part, required that one use visual feedback of both the hand and the target in order to successfully complete the movement.

In addition to establishing the two-component model of reaching, Woodworth continued to examine the second phase of movement by estimating the time required to use visual feedback. Using the same apparatus as before, participants slid a pencil from one end of a piece of paper to the other to the beat of a metronome. As the speed of the movement increased, the overall accuracy (how often the pencil landed inside the target region) decreased. Participants then performed the same task with their eyes closed at the same time intervals. At movement times requiring less than .45 seconds to complete, there were no differences in accuracy between the two conditions. Woodworth claimed, therefore, that to make use of visual feedback one required at least .45 seconds in full vision of the target to make a significant contribution to accuracy.

These two findings were incredibly influential, and remained largely unchallenged for the better part of 50 years. The largest refinement to Woodworth's proposals was not to the premise of a two-component model of reaching, but to the role of the visual system in movement. One criticism of the Woodworth experiment was that because movements were being made in immediate succession, one would be planning a movement during the deceleration phase of the previous movement. Steve Keele and

Michael Posner (1968) refined the classic Woodworth task, and dramatically decreased the time estimate for using visual feedback mechanisms.

In their 1968 study, Keele and Posner employed a reaching paradigm in which participants would make discrete aiming movements – simple, single movements from one location to another – of defined duration. That is, movement time was predefined so that a variety of speeds would be required. During some trials, the room lights would be extinguished at movement onset. Analysis of movement accuracy (i.e., did the participant hit the target) revealed that during movements lasting less than .26 seconds there was no difference in accuracy with either full vision or no vision of the target. Keele and Posner subsequently argued that given .26 seconds of visual information, one could successfully "home in" on the target using visual feedback. This estimate of visual feedback time was substantially less than the one proposed by Woodworth, but the process of refinement did not end here. Some pundits argued that by randomly removing vision during some trials, it was possible that participants were planning their movements very conservatively. If the element of surprise was eliminated, could the time to use vision change further?

The estimate of time required to use visual feedback was reduced a second time in 1983 when Zelaznik, Hawkins, and Kissleburgh performed a blocked-design version of the Keele and Posner paradigm (1968). Participants again performed small amplitude aiming movements of different speeds in both full vision of targets, and in the absence of visual information. Given the blocked design, the estimate of time was further reduced to some level of less than .1 second. That is, there were accuracy differences between the vision and no-vision trials even at extremely rapid movement times.

In addition to challenging the initial visual-feedback time constraint proposed by Woodworth, there have also been some refinements on his proposal of a dual-by-nature model of limb movements. These changes, however, have been more concerned with providing further description of the phases as opposed to disputing their contributions to movement. Several groups of authors would subsequently use the initial concept of a two-component model of limb movement as the basis for a more *sophisticated* theory.

Among the first major elaborations concerning the first phase of movement (or the *initial impulse* phase) was the *Impulse Variability Model* (IVM) (Schmidt, Zelaznik, and Frank, 1978). The idea behind this report was that some movements, presumably, would require no or virtually no corrective feedback. The need for a second phase of movement, therefore, is largely determined by the idiosyncrasies of the first phase. According to the IVM, neuromuscular noise/variability is a product of the force required to propel the limb to the target. Longer or more forceful movements, therefore, would be inherently more variable, thus requiring corrective feedback mechanisms to ensure accuracy. Shorter movements, the authors argued, might not require any corrective submovements. Although these arguments are rather intuitive, it was the first time they were articulated. The publication of the IVM would give rise to another refinement of the initial Woodworth treatise.

In arguably the most influential publication on motor behavior in the late 20th Century, Meyer and colleagues published a report designed to fully explain discrete arm movements (1988). The *Optimized Submovement Model* (OSM), built on the success of the IVM, but further elucidated the entire process of movement execution. According to

the OSM, each movement begins with a primary propulsive movement, with the variability proportional to muscular force/speed. Based on sensory feedback, submovements are planned based on the *predicted* end point of the initial impulse. If a movement requires fine-tuning, subsequent movements are done in a discontinuous manner: Each movement has to be near completion before the next one can be initiated. According to the OSM, therefore, movements that require large amounts of force will also require a greater number of corrective submovements in order to maintain accuracy. Further, movements that demand high precision will normally exhibit low levels of force in order to avoid high amounts of neuromuscular noise. This final point confirmed other work done in the area of speed-accuracy trade offs (Fitts, 1954).

In addition to the above research, considerable work has been done in the area of modeling discrete hand movements with respect to error detection and correction. That is, we know that during the second phase of a reaching motion corrective submovements exist, but the mechanism by which they occur has been the source of some controversy. Two of the more prominent hypotheses were concerned with either feedback or feedforward models of correction. Feedback was thought of as a reaction to errors perceived by visual and kinesthetic systems. Proponents of this hypothesis would argue that the most powerful error detection system one possesses would be sensory feedback. Corrective submovements, therefore, would reflect an ongoing, conscious refinement of movement based on vision of the target and limb combined with proprioception. Proponents of the feedforward hypothesis, by contrast, asserted that the error correction system *predicted* errors based on a stored representation of the motor program (or

efference copy), and a continuously updated store of sensory information. Corrective submovements, therefore, were predictive in nature as opposed to reactive. The two hypotheses in question proved, however, to be less predictive in isolation than in unity with each other.

Hybrid models have since emerged from the modeling literature, designed to combine the more helpful aspects of both feedback and feedforward mechanisms (for a review, see Desmurget and Grafton, 2000). In essence, these hybrid models assert that all discrete movements begin with sensorimotor cortical areas integrating both internal sensory (from the limbs) and external sensory (predominantly vision) information. A movement plan reflecting the desired displacement of the limb is then specified based on this information; this movement blueprint is then converted to a series of kinetic muscle commands using inverse modeling. The movement is then refined using the following error correction system (Figure 1.1). As the movement is being carried out, information regarding the current target location is combined with a blueprint copy of the motor program and the proprioceptive feedback from the effector. This information is then combined in an error correction detection system, which allows errors to be predicted and corrected before they occur. Hybrid models such as these have also been mapped to certain cortical locations, such as the parietal cortex for the sensory integration, and the cerebellum for the error detection system (Desmurget and Grafton, 2000).
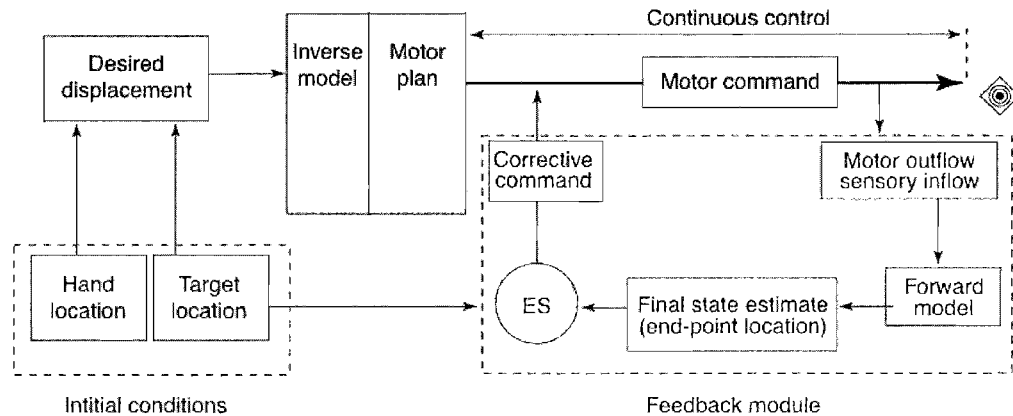
Figure 1.1. Error correction hybrid model. Error detection is a function of both feedforward and feedback mechanisms, computed at location ES.

The initial two-component model proposed by Woodworth more than a century ago has undergone several refinements, but the foundation of a two-component model of limb movement has remained. Modern kinematic evidence further entrenches this theory: In the presence of normal sensory feedback, displacement of a limb can be subdivided into two phases. The first phase is highly stereotyped, while the second is more variable, often exhibiting pronounced epochs of acceleration and deceleration (for a review, see Elliott, Helsen, & Chua, 2001). The simple act of reaching to an object, however, belies the number of cortical computations required to perform the simplest task. Additionally, the central nervous system employs a host of distributed sensory and other cortical regions during interaction with one's environment. Focal injury to any one region or pathway could severely disrupt this fine motor behavior. Diffuse injury to the system might also compromise the efficacy of reaching movements. Because of the consistency exhibited by the motor system, upper limb movements as described above could

theoretically be used as a diagnostic marker of injury in the central nervous system. The following discussion will outline the cortical network responsible for visually guided arm movements.

1.2 CORTICAL SUBSTRATE OF REACHING MOVEMENTS: THE MOTOR CIRCUIT

The planning of a movement in the cerebral cortex makes use of a diverse and distributed network of cortical areas, each of which ultimately contributes to stereotyped motor behavior. A movement made in response to an environmental stimulus, for example, begins with internal (somatosensation) and external (auditory and visual) sensory information arriving at the parietal cortex (Perenin & Vighetto, 1988; Revol et al., 2003). This information then undergoes a process of refinement often referred to as a frame of reference transformation. The ultimate goal of this process is to take neural signals intended to transmit sensory information, and convert them into action potentials designed to perform movement.

Unfortunately for the motor system, this is not a simple task. Sensory information arriving in the parietal cortex is coded in different ways. Auditory information codes object location with reference to one's head, visual information is encoded in retinal-based coordinates, and somatosensory information is coded using a body-centered map. This begets what has been termed a *Problem of Integration* (Anderson & Buneo, 2002): Multiple sensory systems ostensibly "dump" information into the parietal cortex from completely different coordinate maps. This information must also be rendered useful for the manual motor system. The theorized solution to this problem lies in establishing a common and frame of reference from all of these modalities.

A series of studies have been carried out in non-human primate laboratories to address this theory of a common, distributed frame of reference (for a review, see Anderson & Buneo, 2002). The lateral intraparietal area (LIP) is known to be involved in the planning of saccades based on any environmental stimulus. To demonstrate this, Stricane, Anderson, and Mazzoni examined how neurons in a monkey's LIP responded to a task requiring that a saccade be performed to either an auditory tone or visual cue (1996). When compared to neuronal activity generated based on visual input, neuronal discharge in many recorded cells remained the same in the presence of an auditory cue. Further, neurons responding to the auditory saccade task seemed to be modulated by eye position. The authors claim that this pattern of activity would be accounted for by the following situation: Environmental information arrives at area LIP in an external or environmental frame of reference. This information is transformed by neurons in the LIP into a retinal frame of reference that is subsequently 'read out' by the saccadic system to drive a saccade. Given this series of events, Anderson & Buneo describe a similar paradigm using a visually guided pointing task.

If one were to predict what might happen when an arm movement occurred in a comparable region of the parietal lobe, it would be reasonable to expect cells to discharge, regardless of sensory modality, in limb-centered coordinates. The meta-analysis of Anderson and Buneo reported that a percentage of recorded neurons in area PRR – or the parietal reach region—did not discharge in a manner consistent with a limb-centered frame of reference during a visually-guided pointing task, but with a retinal centered frame of reference (2002). Cohen and Anderson demonstrated further evidence

of motor planning occurring in eye-centered coordinates in 2000. This particular study required that a reaching movement be performed based on an auditory cue. Neurons recorded in PRR discharged in a manner that was heavily modulated by eye position. Cohen and Anderson, not surprisingly, attributed this finding to PRR neurons preferentially planning movements of limbs in eye-centered coordinates.

Based on mounting single-cell recording evidence, it can be asserted that a common, retinal based coordinate frame of reference serves as the primary output for the visuomotor system from the parietal cortex. Although the proposed reference frame is retinotopically centered, the general frame of reference can be modified by what is known as a gain field (Anderson & Buneo, 2002). A gain field can be thought of as a progressive switch that shifts the firing pattern of neurons in either the LIP or PRR in response to changes in eye, body, or limb position. The established parietal frame of reference, hence, is not a static construct. As the position of the eyes change, so to does the retinotopic frame of reference through gain field modulation; the frame of reference in the PRR has also been shown to adapt based on learning (Buneo & Anderson, 2006).

Once the parietal cortex processes pertinent sensory information, this information is passed on to the frontal lobe, where a movement plan is finalized. While a host of other brain regions (e.g., cerebrocerebellum, basal ganglia, supplementary motor area) aid in the production of movement, two areas play the defining roles in producing visually guided movements: The premotor cortex and the primary motor cortex. These two regions will now be examined, as the final steps in the motor circuit.

1.3 PREMOTOR CORTEX

While it is commonly held that the primary motor cortex encodes movement commands, there are a variety of cortical areas that perform assistive functions. In other words, there is a great deal of information processing that must occur before motor neurons send movement commands. The premotor cortex plays the leading role for this function. An examination of the premotor cortex (PMC) reveals several key points: 1) It receives input from both the parietal and pre-frontal cortices, 2) Peak activity in the PMC precedes activity in the primary motor cortex, and 3) The PMC seems to further translate sensory information and movement intentions. Given these three functions, it appears self evident that the premotor cortex is the next sequential area of information processing for motor output.

The PMC indeed acts as a relay station of sorts: Movement intention from the prefrontal cortical areas such as the dorsal-lateral prefrontal cortex delivers information about movement intent and motivation (Faw, 2003). At the same time, projections from the parietal cortex regarding auditory, visual, and somatosensory information arrive in retinal-based coordinates. While there is a constant stream of information arriving at the PMC, activity peaks approximately 800 – 1000 ms prior to movement initiation (Bear, Connors, & Paradiso, 2007). This increase in activity is thought to represent one's conscious decision to initiate movement planning. The peak in activity, however, can be attributed to the advanced computations required to complete the integration of intent with incoming sensory information.

While the contribution of the parietal cortex is substantial, it is well established that a further frame of reference transformation must occur before overt limb movement. Specifically, the dorsal Pre Motor Cortex (PMd) is implicated in this process (Chouinard & Paus, 2006). A study by van Donkelaar, Lee, and Drew used a TMS paradigm to observe the contributions of the PMd to frame of reference transformations. Participants were asked to perform an eye-hand movement task where they eye movements were either the same amplitude as arm movement, or various degrees larger. In normal conditions, the movements were made with a high degree of accuracy. That is, the larger eye amplitude movement did not influence the arm trajectory. If the same task was repeated in the presence of a TMS pulse 200 msec. before the onset of movement, arm amplitude varied corresponding to visual amplitude. The authors claim that this effect is due to a disruption in a further frame of reference transformation occurring in the PMC. That is, retinal-based information from the parietal cortex could not be modulated before a motor program was sent out. All arm movements, therefore, would be inherently susceptible to variations in eye movements.

In a study reported by Graziano (2006), a single-cell recording paradigm documented multiple frames of reference existing in the PMC. During a reaching task, each neuron's firing pattern was active during reaches made to a particular response field; that is, each neuron seemed to be coding for a particular region of space. Interestingly, these regions were not dependent on a limb-centered frame of reference or on a retinal frame of reference. The firing rate of each neuron was a function of, "...of the spatial relationship between the target and the eye, the target and the hand, and the eye and the

hand," (page 8). That is, while neurons in the PMC are involved in integrating limb-centered coordinates into a reaching plan, it is not a simple measure of translating from eye to hand. Graziano speculates that at this juncture, it might be appropriate to expand one's view of the PMC to spatial or error-based transformations. Once the movement plan is assembled and the necessary reference frames are encoded, the PMC communicates the movement plan to the primary motor cortex.

1.4 PRIMARY MOTOR CORTEX

The Primary Motor Cortex (M1) is irrefutably the control center for motor output to skeletal muscle. While premotor and cerebellar nuclei make indirect, desultory projections down the spinal cord, no single area can affect movement to the same degree as M1. Traditionally, M1 has been described as controlling movement using three mutually exclusive parameters: Force, direction, and amplitude. Although this evidence is well established, more recent work with respect to M1 suggests that in addition to these three aforementioned parameters, the primary motor cortex performs more advanced calculations in order to perform accurate movement.

Using non-human primate studies, neurons in M1 directly modulated their firing rate to reflect task requirements with respect to force: Greater amounts of force requires a higher rate of neuronal discharge (Krakauer & Ghez, 2000). Lower force levels were also associated with a decrease in neuronal discharge. Additionally, when monkeys were trained to move a robotic arm in 8 different directions, a population of neurons modulated their activity such that certain neurons would depolarize based on a preferred direction. This same group of neurons, interestingly, would hyperpolarize if the movement occurred

in the opposite direction. Finally, a third reported study examined single-cell recordings during movements of constant direction, but varied amplitude. The results indicated that as movements were directed further from peripersonal space, neurons increased their firing frequency. This wealth of information has allowed for a very simple viewpoint with respect to M1: Voluntary movement is reduced to three parameters in order to be carried out in a parsimonious way. A recent meta-analysis, however, challenges this simplistic outlook.

While the idea of movements controlled by a somatotopically mapped motor cortex is still roughly accepted, Marc Scheiber has offered a commentary that expands this viewpoint significantly (2001). According to Scheiber, the simplistic view that *neuron A is responsible for action B* is far to simplistic. A more accurate description would incorporate the ideas of both convergence and divergence. Specifically, many different regions of the motor cortex can operate in synchrony to produce a simply action. Further, a single population of motor cortex neurons can be responsible for innervating several different skeletal muscle groups. In addition to the constructs of convergence and divergence, plasticity plays a role in reorganization in short term (motor learning), and long term (disease states) circumstances. Finally, given the distributed network of the motor cortex, it has also been implicated in performing subtle frame of reference transformations that might be incomplete.

The task of successfully performing any goal directed movement requires the coordination of the body's sensory systems with the brain's motor circuit. This coordination makes use of no fewer than six different cortical locations. In the presence

of small, diffuse, cortical damage it might be predicted that the manual motor system might be profoundly influenced. Diffuse axonal injury, a sequela of traumatic brain injury, is an example of this microscopic damage. While the mechanism of this injury has been elucidated, the behavioral consequences remain unclear.

1.5 TRAUMATIC BRAIN INJURY

In general terms, TBI is the product of cerebral rotation within the cranium during rapid accelerations and decelerations of the head (for a general review, see Ropper & Gorson, 2007). As an illustration, consider the motion of the brain within the skull of a boxer receiving a hard blow. Because there are no ligaments that hold the brain in place, the soft tissue moves and deforms in a manner similar to the movement of gelatin in a bowl. Unlike gelatin, however, cortical tissue is full of micro-structural elements that can be irreparably damaged during movement. The shearing forces associated with this movement often lead to micro-structural damage in various regions of the cortex (Blistein & Tung, 2007). The important clinical feature of this injury is that there can be severe damage without focal contusions or hematomae, and because of this, some forms of TBI are not usually considered life threatening even though the diffuse damage can lead to prolonged coma (Smith, Meaney, & Schull, 2003).

Current literature has documented the specific pathology of diffuse TBI in vitro. Consider the case of the prototypical motor neuron: A dendritic arbor leading to a cell body that gives rise to an axon, which ends with an axonal terminal. This neuronal shape is maintained via a delicate cytoskeleton that is designed not only to provide structural integrity, but to provide transportation of chemical neurotransmitters from the site of

production (the soma) to the axon terminal (Schwartz 1995). During the rapid

accelerations and decelerations of the cerebrum, the cytoskeleton (Bazarian, Blyth, &

Cimpello, 2006) as well as the microvasculature of the axons (Blistein & Tung, 2007)

sustains damage. When the cytoskeleton becomes damaged, the neuron will eventually

lose the ability to communicate distally because of compromised anterograde transport of

neurotransmitters. The cytoskeleton damage will often lead to either immediate cell

death, or programmed cell death due to ineffective communication (Bazarian, Blyth, &

Cimpello, 2006). The compromised microvasculature within the white matter tracts

further compounds this problem by decreasing overall perfusion. Given the host of

potential problems in the presence of TBI, it comes as little surprise that so many

behavioral deficits have been documented post concussion.

Individuals that experience mild concussion often suffer from attentional deficits

as a result of the injury. Research has illustrated that individuals suffering from an mTBI

have deficits in their ability to maintain and effectively divide their attention within and

between tasks (Felmingham et al., 2004; Cicerone, 1996; Chan et al., 2003). A series of

recent publications from our group at the University of Oregon sides with the evidence

for specific deficits in attention after a mild concussion. Using the attention network test

(designed to look at alerting, orienting, and executive components of a task) van

Donkelaar and colleagues compared a cohort of mTBI participants within 48 hours of

their injury to a control group (2005). The results demonstrated that concussed

individuals had normal alerting behavior, but were significantly disrupted in terms of

their orienting and executive functioning. Further, whereas the orienting deficit

normalized after 1 week, the detriments in executive function remained for the duration of the testing period (Halterman et al., 2006). Similar behavioral disruptions were observed in the ability to initially disengage attention (Drew et al., 2007), distribute attention across time (McIntire et al., 2006), or countermand motor output when cued to do so (DeHaan et al., 2007). The behavioral deficits that we have observed, however, are not confined to cognitive tasks. Several accounts of balance and gait impairments post mTBI offer corroborating evidence.

In a well-designed study by Guskiewicz, Perrin, and Gansneder, 19 mTBI patients were examined on their ability to maintain posture in a variety of conditions (1996). Using computerized dynamic posturography, subjects were compared on 9 different tasks. These tasks used a combination of visual conditions (eyes open, closed, & visual conflict) and stance conditions (perturbed stance & foam block stance) in an attempt to elucidate how mTBI patients integrate sensory information. The results indicated that post mTBI, patients displayed significantly more postural sway than either their own baseline (5 days to recovery) or to a normative baseline (10 days to recovery) during the postural control tasks. Further, these differences were exacerbated by the complexity of the task.

A second recently published report examined a relatively homogenous group of concussed individuals using several gait parameters 48 hours after a grade-2 concussion (Parker et al., 2005). Each subject performed two gait conditions: Normal, and divided attention. During the divided attention task, participants were given a secondary cognitive task (e.g., spelling five letter words backwards) to perform while walking. Center of mass

(COM) and center of pressure (COP) measurements were then compared across groups. The group of subjects afflicted with an mTBI displayed a significant decrease in gait velocity during both regular gait and dual task gait. Further, during the divided attention gait task, concussion subjects had increased mediolateral sway of COM, and a decreased anterior COM/COP difference. The last two results, according to the authors, seem to indicate that when a patient is still in the acute phase of a grade-2 concussion, he/she does not have the attentional resources available to perform regular movement. Using a similar paradigm, a second study was conducted that examined the exact time course associated with such movement parameters.

With a slightly increased sample size, Parker, Osternig, van Donkelaar, and Chou (2006) examined the exact time course of recovery of function in mild TBI. Fifteen concussion subjects, all of whom suffered a grade-2 concussion, performed the identical tasks: Normal gait, and dual-task gait. Unlike the previous study, however, concussion subjects and demographically-matched controls were examined 48 hours post concussion, as well as 5, 14, and 28 day post injury. TBI patients at the first testing session (48 hours post injury) displayed significantly slower self-selected gait, consistent with the previous study. Self selected gait speed during simple gait resolved in concussion subjects within 5 days post-concussion. When analysis was performed comparing gait speed as a function of single or dual task gait, concussion subjects displayed significant impairment during all testing sessions. Further, the distance between COM and COP during gait displayed a significant reduction 48 hours post concussion, as well as five and 28 day post

concussion. Finally, medial-lateral displacement during dual-task was negatively affected by concussion 48 hours post concussion as well as five and 28-day post concussion.

The above studies highlight the profound implications of traumatic brain injury. Not only are there alterations to one's cognitive faculties, but also to one's ability to move through the environment. All of the above studies, however, examined the short-term effects of mTBI. Less research has been published using data from patients in the chronic stages of TBI. Recently, increased attention has been given to the clinical diagnosis of Persistent Post Concussion Syndrome or PPCS. The majority of work performed in the area of PPCS has been on moderate to severe TBI (see Guerts et al, 1996; Vallee et al., 2006). While this work has proven valuable, a report by Bigler (2008) suggests that PPCS should be viewed as a continuum diagnosis. That is, PPCS is known to exist in both those who have suffered a severe TBI, as well as those who have experienced a single mild concussion. Research on the later, however, is lacking.

Among the current methodological problems in PPCS research is that many of the symptoms most commonly associated with the pathology are not unique to the etiology of TBI: A study by Iverson suggests that PPCS is often misdiagnosed in a people suffering from depression (2006). This can be traced, according to the author, to the primary symptoms ascribed to PPCS. These include fatigue, disordered sleep, headache, dizziness, and irritability. What are needed are new determinant markers, both behavioral and biological, that would aid in the correct diagnosis of PPCS. As stated earlier, motor tasks allow for a more unbiased view of CNS function and damage and could be of great

use in this context. Further, recent advances in MRI technology might further abet the diagnosis of PPCS.

Recent technological advances in the field of magnetic resonance imaging has allowed for specific pulse sequences to be tuned to specific pathologies (Roberts, 2007). Given the diverse nature of concussion, a multifaceted approach would prove most beneficial. The following section will approach diffuse cortical damage from both structural and functional perspectives.

1.6 MAGNETIC RESONANCE IMAGING

Traditional brain imaging techniques, such as computed tomography scanning (CT), are used in emergency rooms all over the world as a manner to rapidly detect life-threatening conditions such as sub-dural hematoma after a brain injury (Bazarian, Blyth, & Cimpello, 2006). This type of scanning represents the first level of diagnostic imaging: A detailed, albeit static, structural examination of a patient's brain. In other words, the first challenge is to document the degree to which tissue integrity is maintained after closed head injury. While this type of analysis provides no information of the functionality of the tissue, it allows the clinicians and researchers insight into the potential for recovery. As a simple illustration, consider a patient in a coma with a negative CT scan (i.e., no abnormalities): This patient would have a better prognosis than a patient with a massive cortical contusion. All of this information can be rapidly collected using CT technology, but this form of imaging focuses on major damage; it lacks the refinement necessary to detect micro-vascular damage.

Given that our present analysis seeks to document this micro-trauma *in vivo*, a good place to begin would be to look for the presence of cerebral micro-hemorrhage. The brain is an extremely vascular region of the body, with approximately 15% of all cardiac output arriving via the carotid and vertebral arteries (Nolte, 2002). Further, much of this volume is flowing at a constant rate through a dense series of capillary beds. During a closed head injury, the shearing forces around the thalamic and gray-white matter regions often result in the rupturing of these capillary beds (Blistein & Tung, 2007). After the microhemorrhage, small iron deposits –remnants of red blood cells—called hemosiderin can be identified within cortical tissue. Because iron is a ferromagnetic element, these iron deposits affect the homogeneity of magnetic fields, and can be detected using gradient echo T2*-weighted imaging (Roberts, 2007). The aforementioned iron atoms disrupt the magnetic field, and alter the image in such a way as to provide stark contrast between the surrounding tissues. Gradient-echo (GRE) scanning is simply a type of T2*-weighted imaging sequence that is able to detect the presence of these hemosiderin deposits after microhemorrhage (Kinoshita et al., 2005).

While the use of GRE sequences in not yet commonplace in the clinical world, there have been attempts to use this technology in some forms of TBI. Among the first known published accounts of GRE scanning in TBI, Millt and colleagues examined a cohort of patients suffering from mild TBI (1994). The patients were unique, insofar as their CT scans displayed no tissue trauma. Using the T2* weighted images, these authors documented evidence of small hemorrhagic lesions in 20% of these patients. Hughes and colleagues have provided recent corroborating evidence (2004): using a cohort of TBI

patients, two different scanning modalities were used to determine the best method of

determining micro hemorrhaging. GRE T2* weighted imaging consistently displayed

small damage whereas another imaging modality sensitive to levels of microhemorrhage

(fluid attenuated inversion recovery [FLAIR]) did so less consistently. One particular

caveat must be stated with respect to these findings: In both cases, the detection rate of

T2* artifacts was extremely low. In the Millt and colleagues report, only 20% of patients

presented with artifacts, and in the Hughes publication, the number dropped to 3 %. More

research clearly needs to be performed to fully evaluate the potential of T2* weighted

imaging as a marker for diffuse cortical injury.

Microhemorrhage is only one facet of sub/cortical damage in TBI: Recall that in

addition to capillary bed damage, there is also an insult incurred by the cytoskeleton of

the axon (i.e., non-vascular damage). A healthy cytoskeleton acts as a transportation

vessel within the neuron, carrying solutes and water both away from and towards the cell

body: Disruption of this transportation can be monitored using Diffusion Tensor Imaging

(DTI). Depending on the time course of the insult, as well as the exact etiology of the

injury one can observe two types of edema: Vasogenic and cytotoxic (for an excellent

review, see Barzo and colleagues, 1997). Vasogenic swelling occurs in the extracellular

matrix, and usually increases measured diffusion while cytotoxic swelling occurs within

the axons and produces a decrease in overall diffusion. As one can see, therefore, any

deviation from baseline diffusivity (either increased or decreased) is a function of

cytoskeleton damage. In the case of TBI, the cytotoxic swelling is normally confined to

the acute phase of injury, while vasogenic swelling accompanies the chronic phase of

injury. The present analysis will, therefore, examine the presence or absence of vasogenic swelling.

The remaining task is to identify how MR perturbations quantify this type of increased diffusion. Fortunately, there has been a recent proliferation of this type of inquiry in various other populations. Using pulse sequences that *label* water molecules using magnetic gradients, one can monitor the overall diffusivity of a given brain region (Huettel, Song, & McCarthy, 2004). This labeling provides researchers with a quantifiable measure of overall diffusivity with relatively high spatial resolution. These "diffusivity maps" are known as *apparent diffusion coefficient* maps (or ADC), and monitor the overall diffusivity of tissue. For example, water molecules in the lateral ventricles are not tightly constrained and therefore have a great amount of diffusivity; on an ADC map, the ventricles will have a high degree of signal return. In the case of old axonal damage, there could be small areas of increased diffusion within tissues, which would be indicative of vasogenic pooling (and a subsequently high degree of signal return).

Recently, DTI has been used as a predictive measure to approximate functional recovery of TBI patients (Hou et al., 2007). Further, DTI has been used to monitor the degeneration of white matter tracts in other CNS diseases such as Parkinson's (Scherfler et al., 2006). However, to our knowledge there has only been a single instance where a research group has examined both the extent of microhemorrhage and apparent diffusivity (using DTI) on the same patient cohort (Zheng, Liu, Li, & Wu, 2007). In this study, Zheng and colleagues demonstrated that MR technology must be tuned to specific

pathology: In 74 TBI patients, DTI scanning sequences were found to be the most effective contrast for detecting non-hemorrhagic lesions within white matter. This re-states the importance for using more than one imaging modality after TBI. Using a single modality could grossly underestimate the extent of the cortical injury.

For a moment, let us consider this research as absolute truth regarding TBI: That in the presence of moderate/mild TBI there is diffuse damage to neurons and vasculature. It would then stand to reason that cell death and/or apoptosis would ultimately re-organize established cortical circuitry (for a review of specific mechanisms, see Bach-y-Rita, 2003). Given this scenario –and based on the wealth of prior research this appears highly likely—one would predict a deviation from established patterns of neural recruitment for any given task. Evidence from both the GRE-T2* and DTI research presented above suggest that common sites of axonal injury include the corpus callosum, basal ganglia, gray-white matter interface, as well as internal capsule. Because of damage to these specific locations, one cortical circuit that could be affected would be the reach circuit that underlies limb movements. Recent MR technology has allowed researchers a chance to view such cortical coordination patterns. It becomes possible, therefore, to examine the cortical correlates of human motor behavior in a population of TBI patients.

Several decades of multi-disciplinary research has documented set patterns of neural activation during limb movements (For reviews, see Rushworth, Johansen-Berg, Gobel, & Devlin, 2003; Andersen & Buneo, 2002): These cortical networks are imaged *in vivo* using a scanning procedure known as Blood Oxygenation Level Dependence (or BOLD) contrast. The premise behind BOLD imaging lies in its ability to detect the

percentage of oxygenated hemoglobin present in a given region of the brain. During an increase in neural activity, astrocytes within a given brain region send an electrical signal to local arterioles in an attempt to increase overall blood perfusion (Takano et al., 2006). This increase in perfusion is the foundation for BOLD MR contrast: In normal tissue, there is a given ratio of de/saturated hemoglobin within cortical blood. The de-saturated hemoglobin is paramagnetic, meaning that it disrupts the magnetic field in such a way as to decrease local signal intensity. The increase in overall perfusion during an increase in neuronal activity, therefore, increases MR signal within active brain regions. An increase in BOLD signal, hence, is indicative of an increase in overall blood requirements (Roberts & Mikulis, 2007).

Returning to the possibility of disrupted motor circuitry, one might predict a change in baseline BOLD contrast in motor regions of the brain. Unfortunately, this hypothesis remains largely untested. To date –with one notable exception- most imaging research in TBI focuses on cognitive sequelae (e.g., Scheibel et al., 2003) rather than motor deficits. The exception was a publication by Lotze and colleagues in 2006: From a cohort of 34 patients, the acquired data suggested that there was an overall decrease in signal change in motor regions during a single-hand flexion task. Put another way, while a TBI patient is able to perform a task in the same way as a normal healthy subject, he/she will not be able to activate the same quantity of neurons to perform the task comparably. The TBI participant will be required to recruit different neurons from different brain areas to accomplish the task. This has been termed damage-induced plasticity. From a speculative standpoint, this could be the result of mass apoptosis in

motor regions of the brain (e.g., Chistyakov, 1998). What is needed to reduce the

uncertainty is a series of research studies that combine structural and functional measures

associated with TBI.

CHAPTER II

HYPOTHESES

2.1 HYPOTHESIS 1

The first hypothesis relates to the first of the three imaging techniques. Using two neuro-radiologists as consultants, we hypothesize that PPCS participants will have an increased number of hemosiderin-induced artifacts using T2*-weighted imaging.

2.2 HYPOTHESIS 2

Consistent with past research using DTI in other pathologies, we hypothesize that the PPCS group will exhibit greater diffusivity in two region of interest white matter tracts (e.g., corpus callosum, internal capsule, etc), indicative of vasogenic swelling, compared to the matched control group.

2.3 HYPOTHESIS 3

We hypothesize that the PPCS group will show a reduction in activity in M1 when compared to the matched control group during the BOLD contrast. In contrast to the Lotze and colleagues 2006 study, however, this study will employ a visuomotor task as opposed to simple hand-flexion.

2.4 HYPOTHESIS 4

The penultimate hypothesis relates to the behavior of post concussion participants outside an MRI environment. We hypothesize that there will be significant performance

detriments on the following tasks: 1) Visuomotor processing speed as measured by an eye-hand coordination task, 2) Short term memory 3) Reaction time 4) Impulse control, and 5) Self-reported symptoms.

2.5 HYPOTHESIS 5

Finally, we hypothesize that there will be some relationship between these behavioral measures listed in the previous hypothesis and MRI markers of PPCS. Accordingly, we will perform correlation and regression analyses.

CHAPTER III

METHODS

3.1 PARTICIPANTS

A total of 22 participants were recruited for this experiment: Eleven experimental subjects with a history of concussion were matched to eleven control subjects based on sex, height, weight, physical activity, and education. A single participant was removed from the analysis due to severity of injury (focal contusion), leaving 10 participants per group.

The experimental subjects were recruited from the community, and had to conform to the following criteria: A history of concussion, with the most recent event occurring no sooner than 12 months prior to testing. In addition, participants had to have sought medical attention for at least one concussive event, and presently be complaining of persistent symptoms (See Table 3.1). All TBI subjects were living independently in the community. Further, no subjects were currently seeking treatment for post-concussion symptoms. Control subjects were screened for a history of concussion. Finally, all participants were screened for the following factors:

1) A past medical history with significant upper-limb orthopedic involvement (i.e. amputation, joint replacement, joint fusions).

2) Speech deficits that would limit communication during scanning.

3) Moderate to severe vision loss or neglect

4) Psychological involvement

5) Placement of any medical hardware or other imbedded metal that would limit the ability of the subject to participate in an MRI study.

Table 3.1. Experimental group demographics

TBI Participant						
Sub.	Age	Height (In.)	Weight (Lb)	Method of Injury	Injuries	Time Post
1	49	68	160	Fall / MVA	2	36 Months
2	20	68	170	Fall / Rec. Sports	4	24 Months
3	22	72	180	Lacrosse	8	13 Months
4	22	75	215	Fall / Rec. Sports	6	12 Months
5	21	76	195	Football / Soccer	2	13 Months
6	48	74	253	MVA / Rec. Sports	4	> 36 Months
7	21	70	165	Rec. Sports	3	24 Months
8	33	70	155	Martial Arts	10	36 Months
9	22	74	225	Skiing/Football	2	24 Months
10	24	75	275	Football	4	12 Months

All subjects signed an informed consent form and were compensated monetarily for their participation in the study. The Institutional Review Board of the University of Oregon approved the study.

3.2. IMAGING PROTOCOLS AND DATA ANALYSIS

All imaging procedures were performed using a Siemen's 3T Allegra head-only scanner at the Lewis Center for Neuroimaging. All analysis was performed using FSL version 4.0.1 and other in-house software (e.g., file conversion).

3.2.1 T2* WEIGHTED GRE

The GRE scan is a diagnostic image with resolution formatted to the axial plane

performed while the subject lies still with their eyes closed. The imaging procedure

collects data using the following parameters: TR/TE – 798ms/22ms; FOV – 256mm; 30

axial slices of 7 mm thickness with no gap, and a 30 degree flip angle. The total scan time

for this sequence is 6 minutes and 54 seconds.

The data analysis was performed in two stages: 1) Identification of lesions, and 2)

statistical comparison of counts. A neuro-radiologist and one senior resident performed

the first phase of the analysis: Consistent with past research (e.g., Hughes et al, 2004) the

two clinicians individually scored each scan by simply counting the lesions. In the event

that disparities emerged in the counts, both clinicians arrived at a consensus by scoring

the scans together. Both neuro-radiologists were blinded to the group from which the

scans were taken (TBI or control). Counts were entered into a spreadsheet and compared

using an independent sample t-test, with a significance value set to 0.05.

3.2.2 DIFFUSION TENSOR IMAGING

During this sequence, participants were required to lay still with their eyes closed.

Diffusion imaging was collected using the following parameter settings: TR/TE –

10900ms/113ms; FOV – 256mm; 60 contiguous axial slices of 2mm thickness, no gap

with a 2 x 2 in-plane resolution. Total scan time for this sequence is 12 minutes 54

seconds.

Fractional anisotropy (FA) values were extracted in regions of interest previously

correlated with moderate / severe TBI (Sidaros et al., 2008). The FA values were

extracted by creating a defined mask in high-resolution anatomical space for each individual subject (Figure 3.1). The mask was then applied to a FA map, and mean scores were subsequently extracted for off-line statistical analysis. Each set of values was filtered for voxels below 0.2, to counteract partial-volume effects. Extraction of Corpus Callosum (CC) values began by defining the midline of the cortex, and then applying a mask on two adjacent slices (sagittal plane) on either side of the midline, for a total of four slices. The Cerebral Peduncle (CP) was sampled such that the point at which the optic radiation was seen crossing in a posterior direction was slice 1; three other slices immediately below the previous (axial plane) were also used to finalize a participants' FA profile. Each participant, therefore, had a numeric score for both the CC and the CP; these values were entered into a spreadsheet and compared using an independent student's t-test, with significance level set to 0.05.

Figure 3.1. Masks of the corpus callosum and cerebral peduncles.

3.2.3 BLOOD OXYGENATION LEVEL DEPENDENT SIGNAL

During the BOLD contrast, participants performed a modified version of the Fitts motor task. Briefly, participants were required to perform back-and-forth movements between two horizontally opposed targets. Participants were able to view their hands and the targets via a mirror-projector system that displayed a real-time image of the pointing movements. Participants were given practice trials before commencing data collection. The overall movement time was paced via a computer-generated metronome to control for any force variability known to influence cortical activation (Toma & Nakai, 2002). The pacing resulted in subjects producing each movement segment in the back-and-forth cycle in one second. Review of each subjects' movements revealed a stereotyped behavior: Movements were characterized by consistent, smooth motion.

Data was collected using a blocked design: Each active period lasted 20 seconds, and was interspersed with 20 seconds of rest. Whole-brain functional scans were collected during this time using a gradient-echo T2*-weighted sequence. The functional scans used the following parameter settings: TR/TE – 2000ms/30ms; flip angle – 80°; FOV – 256mm; 32 contiguous axial slices of 4mm thickness, interleaved, no gap, 3 x 3mm in-plane resolution. The functional sequence included prospective acquisition correction (PACE) for head motion (Thesen et al., 2000). PACE adjusts slice position and orientation in real time during data acquisition, thus reducing motion-induced artifacts on magnetization history. A whole-brain anatomical scan (for registration purposes) was also collected using a T1-weighted MPRAGE sequence. The anatomical scans used the

following parameter settings: TR/TE – 2530ms/30ms; flip angle – 7°; FOV – 256mm; voxel size – 1.3 x 1.3 x 1mm.

Image analysis was performed using FSL software available in the Center for Neuroimaging. The functional scans were co-registered with the T1 weighted anatomical image normalized to Montreal Neurological Institute (MNI) space. These normalized scans were subsequently smoothed with a 8mm kernel full width at half maximum. The preprocessed functional scans were then statistically modeled for each participant using delta functions convolved with a canonical hemodynamic response function (HRF) with limb movement within each run as a predictor variable and rest as a null variable. The resulting beta weights of the model were tested for each voxel in a Z-test against zero for each subject. To identify differences in cortical patterns of activation associated with the task, group means were calculated and then contrasted with each other.

3.2.3.1 COVARIATE ANALYSIS

The covariate analysis was conducted using all 20 subjects' first-level BOLD analysis, while adding behavioral covariates from the laboratory tests (description below). These activation maps allow for inferences to be made regarding brain regions common to subjects who score similarly on behavioral measures. That is, if several subjects score poorly on a Fitts behavioral task, will there be a common cortical location active in each subject? Individual covariate analyses were conducted using behavioural scores that were different between groups.

3.3 BEHAVIORAL FITTS TASK

All behavioral testing was completed within 48 hours of the MRI scanning in a separate laboratory. The behavioral task consisted of participants making continuous back-and-forth pointing movements between two horizontally opposed targets (Fitts, 1954). The targets were positioned between 20 and 35 centimeters apart, and ranged from 0.5 to 4 centimeters in width. In total, there were 7 combinations of target width and amplitude. Overall difficulty was calculated as a function of movement distance, and target size. The indices of difficulty ranged between 2 (simple) and 7 (extremely difficult). Before data collection, participants were given practice trials to familiarize themselves with the testing protocol.

Each trial began with the researcher affixing one of the 7 randomly selected target arrays in front of the participant. The participant was then instructed to perform a continuous back and forth pointing movement with the dominant hand between the targets for a total of 20 seconds. In the event that accuracy was compromised (greater than 5% of movements made outside the target area), the trial was repeated until sufficient accuracy was maintained.

3.3.1 APPARATUS

Participants were seated at a table, positioned such that all reaching movements were made in peripersonal space. The stimuli were affixed to the table, approximately 20 centimeters away from the participant. Stimuli consisted of targets (vertical rectangles of varying widths and amplitudes) printed in black ink on white paper. The movement of the

tip of a pointing stylus was monitored using an infrared motion-tracking device operating at 200 Hz (Optotrak; Waterloo ON).

3.3.2 DATA ANALYSIS

From each array, an average movement time was computed. Because every array was completed twice, the average of the two movement times was used for further analysis. From the combination of movement times and ID, the data from each participant was used to produce a graph with a slope and y-intercept value. These values were summed, and represented an individual's visuomotor capacity. Results were analyzed using the general linear model. A two-way, repeated measures ANOVA (Group x Index of Difficulty) was used to establish a potential main effect of group, and elucidate any significant interaction effects. All analysis was completed using SPSS version 15 for Windows.

3.4 NEUROPSYCHOLOGICAL TESTING

In addition to collecting visuomotor data, a cognitive test battery previously used in acute TBI was also administered to all subjects: The ImPACT test (Schatz et al., 2006). In short, this computer-based test uses 6 separate tests to document attention capacity, memory, processing speed, and reaction time. From these tests, four composite scores emerge representing verbal memory, visual memory, visuomotor speed, and reaction time respectively. The ImPACT test has been shown to be a sensitive and reliable tool for measuring the deficits associated with acute concussion. In addition, this test also allows a self-report of 21 individual symptoms on a Likert scale allowing a subjective

compliment to the composite scores. Between-group analysis will employ independent students t-test to determine significant group differences.

3.5 CORRELATION AND REGRESSION ANALYSIS

A total-subject correlation matrix was computed on all behavioural variables and the MRI variables that exhibited group differences. Calculating individual scores for most tasks was simple, however, the extraction of BOLD data warrants some description. Obtaining individual BOLD scores began with the formulation of the group contrasts: Several areas were shown to be statistically different between the two groups. These areas, therefore, were used as regions of interest for further analysis. Each region of interest served as a mask, and was applied to individual statistical maps. Z-scores were extracted for each subject from each mask and then entered into an independent t-test. This additional statistical test ensured that all regions of interest truly reflected differences on a subject-by-subject basis. Regions that exhibited significantly different z-scores were then entered into the correlation matrix. A liberal significance level of 0.05 was adopted in order to determine significance in this exploratory analysis.

In addition to the correlation, regression analyses were performed. Individual behavioral measures that exhibited group differences served as dependent variables, while the MRI elements correlated with TBI acted as regressors. A forward selection model was employed for this analysis, in which the independent variable with the highest correlation that meets criteria is entered first, with other variables entered in order of decreasing partial correlation to the dependent variable. The entry criterion was set to a probability of $F = 0.1$, and the exit criterion was set to a probability of $F = 0.2$.

CHAPTER IV

RESULTS

Statistical analysis was performed on participant demographics prior to running group comparisons. Independent student t-tests revealed no significant group differences based on age $t(18) = -0.45$, $p = 0.32$, education $t(18) = -1.05$, $p = 0.15$, height $t(18) = 1.08$, $p = 0.14$, or weight $t(18) = 1.03$, $p = 0.15$. One TBI subject was removed from the analysis based on neuroradiological analysis. Participant KB presented with significant areas of right frontal focal damage, as well as over 50 individual loci of artifacts consistent with hemosiderin deposits (Figure 4.1). A different TBI participant was recruited, and replaced patient KB in the analysis.
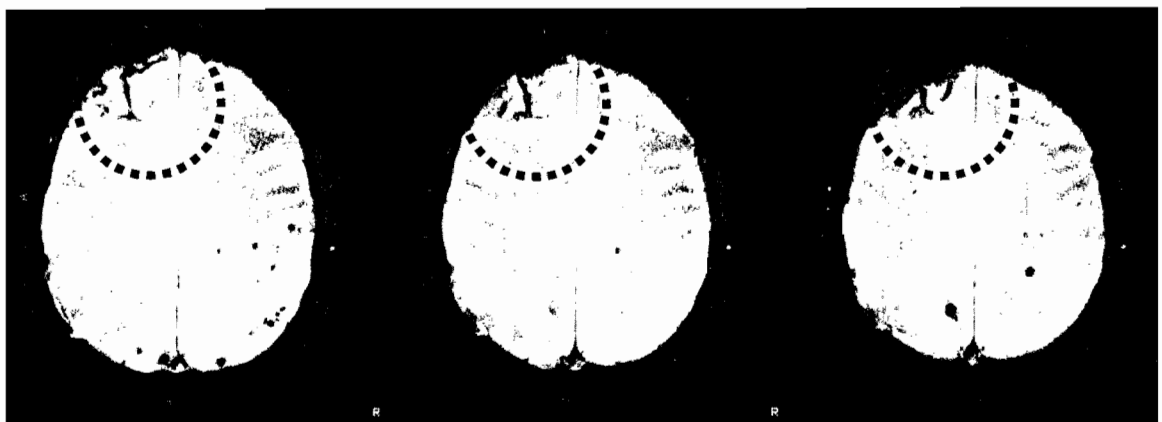

Figure 4.1. Patient removed from the analysis.

4.1 BEHAVIORAL DATA

Analysis of movement time data from the Fitts task (Figure 4.2) revealed a significant effect of group $F(1, 18) = 7.025$, $p = 0.016$, as well as a significant group by index of difficulty interaction $F(6, 108) = 3.402$, $p = 0.0041$. The interactive effect appears to be driven primarily by the data corresponding to the most difficult index of difficulty; by analyzing the data without this condition, the main effect remains $[F(1, 18) = 5.92$, $p = 0.025]$, while the interaction does not reach statistical significance $F(5, 90) = .543$, $p = 0.743$. Given the overall main effect of group, individual mean scores for slope and y-intercept were extracted from each individual and combined to produce a single Fitts score: A higher score indicates either a steeper slope, a higher y-intercept, or some combination of both factors. Both an increased slope and an increased y-intercept are considered detrimental to overall visuomotor performance.

Statistical analysis of the individual extracted Fitts scores also reached statistical significance $t(18)$, $= 2.18$, $p = 0.02$. Given the significant difference between both the group analysis, and individual Fitts score differences, the TBI group could be said to have significantly impaired visuomotor performance of the task. This difference reflects a diminished ability to make accurate arm movements as quickly as a healthy control subject. When accuracy is consistent across groups, therefore, the participants with a history of concussion had to sacrifice overall movement speed.
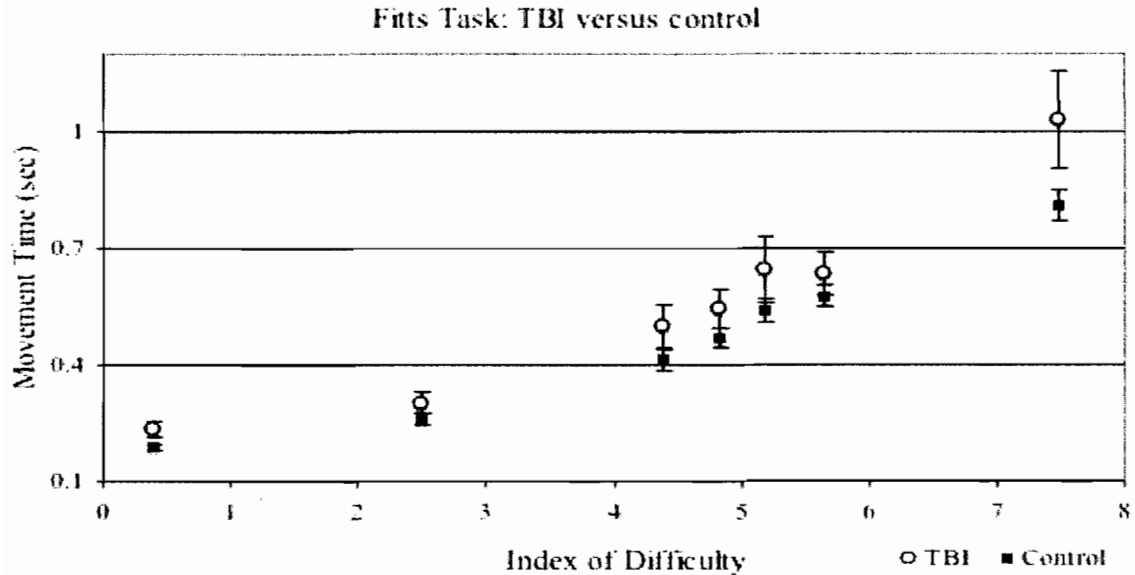
Figure 4.2. Mean movement times plotted as a function of index of difficulty. Error bars denote standard deviation within group.

Analysis of the behavioral composite scores from the ImPACT test revealed significant group effects in Self reported symptom score (SRS) $t(18) = 4.762, p < 0.001$, and impulse control $t(18) = 0.893, p = 0.037$. Verbal memory composite, visual memory composite, visuomotor speed, and reaction time all failed to reach statistical significance (see Table 4.1). Participants classified in the PPCS group, therefore, self-identified as having far more symptoms and had greater difficulty inhibiting a response when required during the ImPact testing. The two groups, however, did not differ in terms of working memory tasks or reaction time. These measures lacked the sensitivity or specificity to differentiate between groups.

Table 4.1. Summary statistics and significance level associated with the IMPACT composite scores.

	TBI Mean (SD)	Control Mean (SD)	Significance p
SRS	**23 (13.66)**	**1.9 (3.10)**	**< 0.001**
Impulse	**10.5 (6.77)**	**6.0 (3.26)**	**0.04**
VM Composite	40.7 (7.45)	43.19 (8.06)	0.24
Verbal Memory	85.8 (7.96)	90.7 (7.01)	0.08
Spatial Memory	74.5 (14.81)	81.9 (8.22)	0.09
Reaction Time	0.51 (0.08)	0.522 (0.056)	0.46

4.2 MRI DATA

4.2.1. SUSCEPTIBILITY WEIGHTED IMAGING

Neuroradiological analysis of the susceptibility-weighted images revealed no hemosiderin-induced artifacts in either group, after patient KB was removed (Figure 4.3). Based on the complete absence of artifacts, no statistical testing was performed.
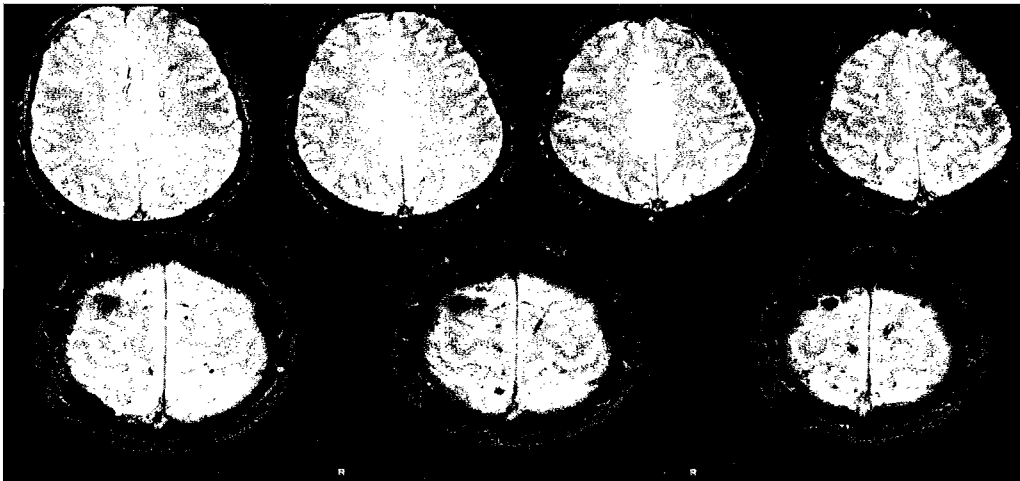
Figure 4.3. Example of two TBI participants. The top row represents patient JE, an individual with 3 separately diagnosed concussions. The bottom row is patient KB, who was identified as having more than 50 distinct focal artifacts.

4.2.2 DTI AND FRACTIONAL ANISOTROPY

Extracted fractional anisotropy values revealed a significant group effect in both the Corpus Callosum $t(18) = 3.30$, $p = 0.002$, and in the Cerebral Peduncle $t(18) = 4.23$, $p < 0.001$ (see Figure 3.4). The decreased values are consistent with the hypothesis that in the chronic stage of TBI, white matter damage presents as decreased anisotropy in areas of highly homogenous white matter. Given the significant group difference, individual FA values were extracted for the regression analysis.
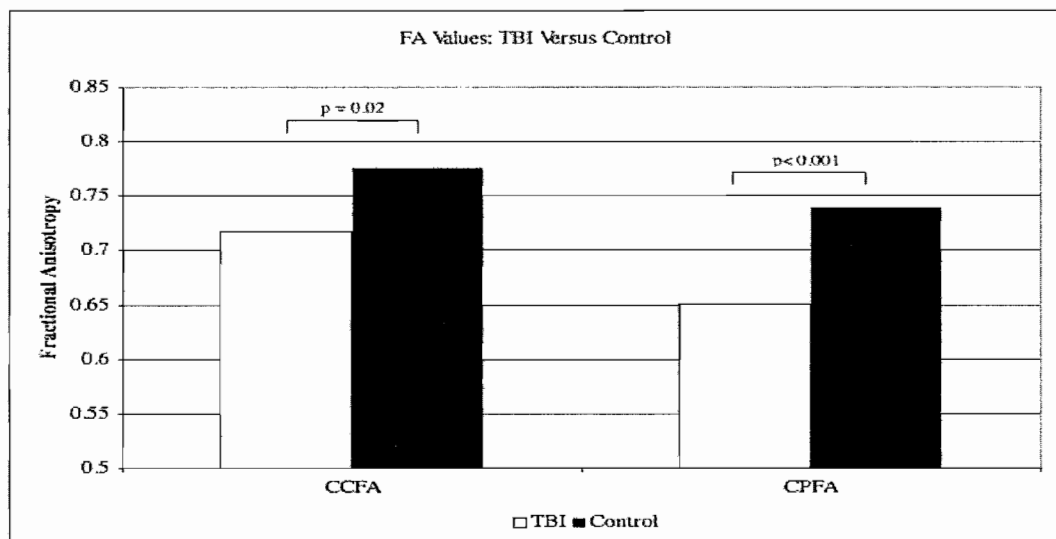
Figure 4.4. Fractional anisotropy ROI analysis.

4.2.3. BOLD ANALYSIS

Within group analysis of BOLD data in controls performing the visuomotor task revealed significant activity extending from the primary visual cortex to the left parietal / motor / premotor region through to the right motor / premotor area (See Figure 4.5 and Table 4.2). Further, there was significant activity bilaterally in the cerebellum, in the left

basal ganglia, and right occipital-parietal region. Within group analysis of the TBI group revealed a similar pattern of activity (Figure 4.6 and Table 4.3): A pattern of significantly active voxels included the left occipital-to-frontal circuit. Activity was also recorded in the cerebellum, as well as in the right occipital-parietal region. These groups means confirm what prior work has established: An occipital-frontal network of activity, predominantly in the left hemisphere, served as a circuit for the completion of the task.

Between-group BOLD analysis yielded areas with significantly greater activity in both the controls relative to participants with mTBI and vice-versa. The control group displayed significantly more activity localized to the cerebellum, and left hemispheric motor regions (Figure 4.7 and Table 4.4). The same between group contrast displayed increased cortical activity in the TBI group localized to the left parietal, bilateral precuneus / cingulate gyrus, right parietal and temporal regions (Figure 4.8 and Table 4.5). These results demonstrate that participants with TBI differentially activate a number of cortical and subcortical sites when performing this task. Because there were differences between controls and TBI in the contralateral motor area, z-values were extracted from all participants for further analysis.

The regions displaying group differences were subject to a region of interest analysis: Significantly active voxels were used as masks to extract z-scores from individual subjects, and compared using an independent samples t-test (Table 4.6). Of the 9 areas displaying significant differences based on the group contrast, only the Left Motor Cortex (LMC), Right Intraparietal Sulcus (RIP), Left Somatosensory Cortex (LSC), and Right Superior Temporal Gyrus (RST) were significantly active on a subject-

by-subject basis. The LMC was significantly more active in the control group, while area RIP, RST, and LSC were significantly more active in the PPCS group. These results indicate that in the presence of decreased activity in the contralateral motor cortex, other cortical regions have to increase their level of activity to perform the same task.

Table 4.2. Summary of BOLD activation in control group

Cluster Index	Voxels	P	Z-MAX	Z-MAX X	Z-MAX Y	Z-MAX Z
Within group contrast: Control group activity						
Left Sensorimotor cortex	11261	3.11E-28	5.37	-36	-38	60
Bilateral Cerebellum	7262	9.05E-21	5.41	32	-42	-36
Basal ganglia /Opercular Cortex	3197	1.63E-11	4.62	-50	4	4
Left Occipital/V5	1072	0.0000619	3.76	-46	-82	10
Right Parietal cortex	1037	0.0000843	3.7	14	-62	70
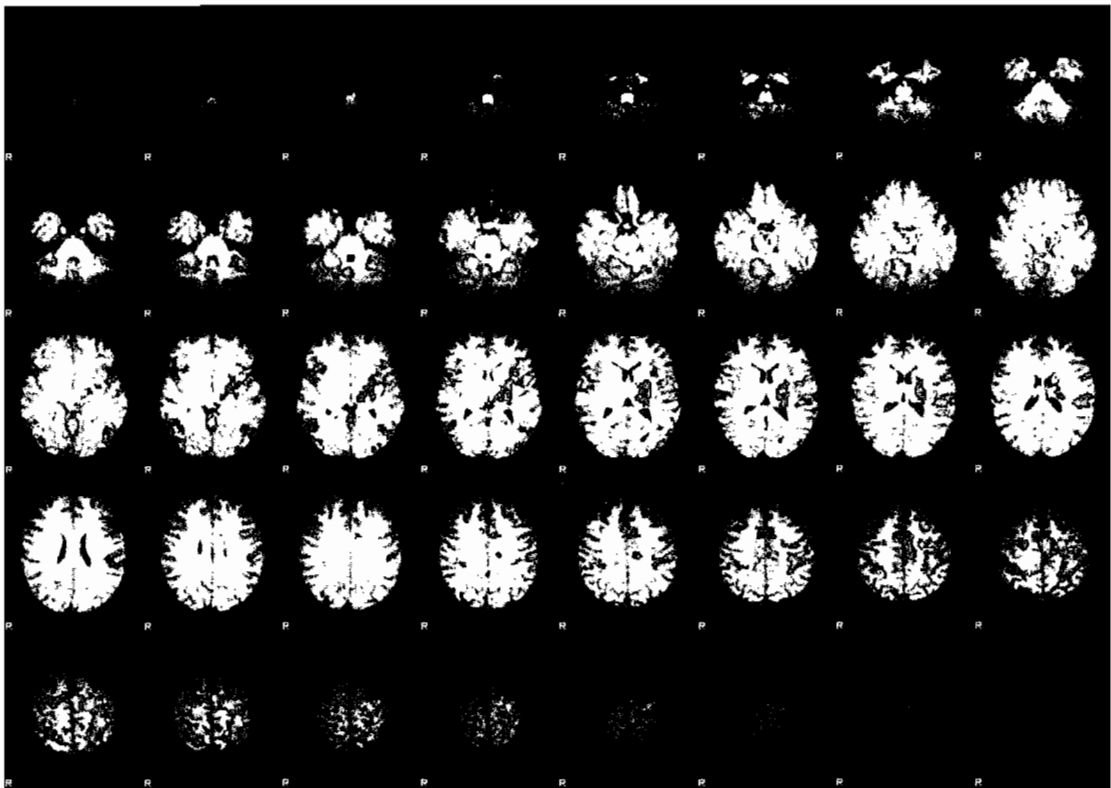
Figure 4.5. Control group activation during the visuomotor MRI task.

Table 4.3. Summary of BOLD activation in TBI group

Within group contrast: TBI group activity						
Cluster Index	Voxels	P	Z-MAX	Z-MAX X (mm)	Z-MAX Y (mm)	Z-MAX Z (mm)
Right/Bilateral cerebellum	23924	0	4.23	30	-34	-36
Left Occipital / Parietal cortex	1197	0.0000148	3.75	-42	-90	-2
Left Inferior Temporal Gyrus	786	0.000673	3.47	-68	-36	-10
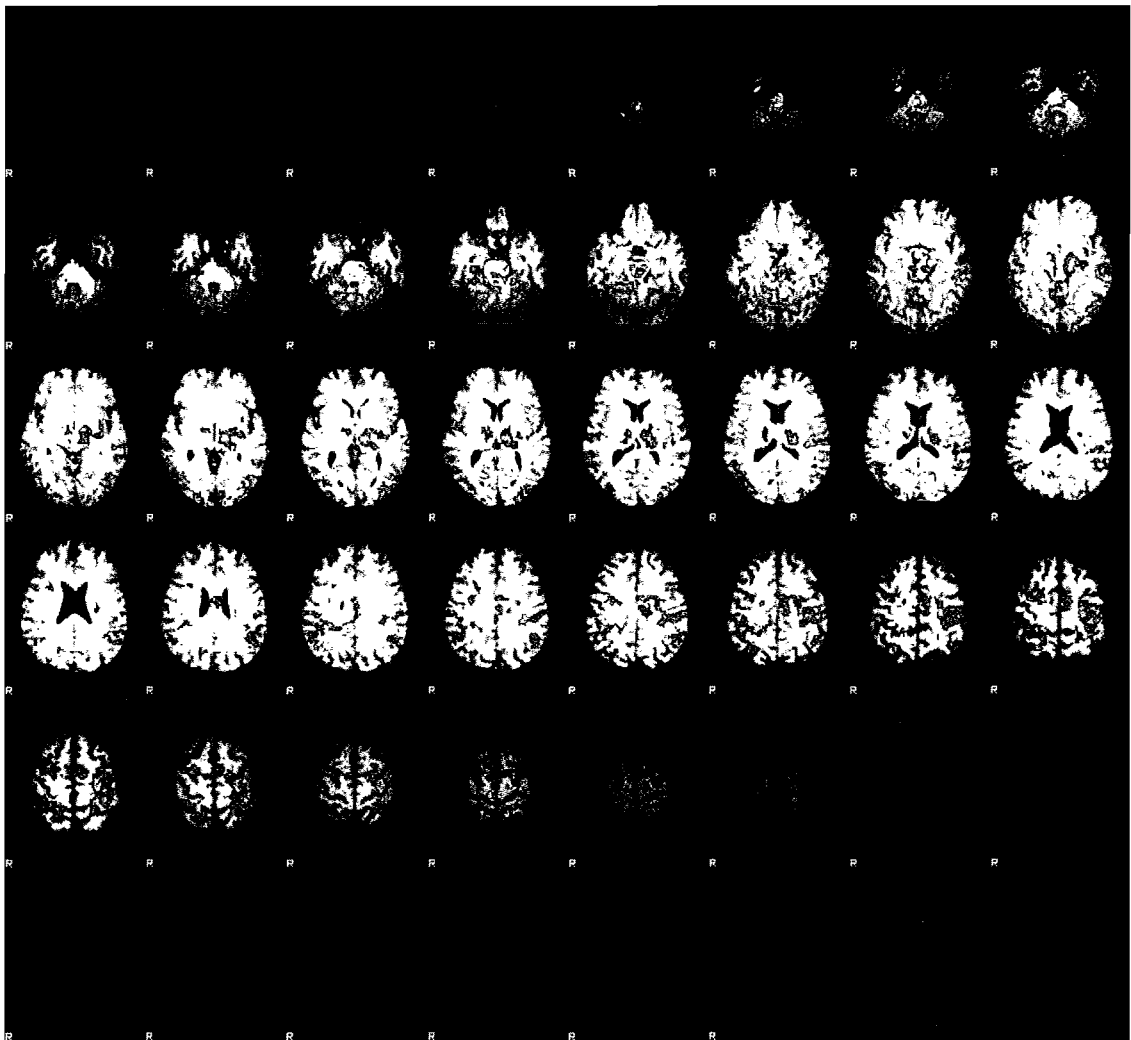
Figure 4.6. TBI group activation during the visuomotor MRI task.

Table 4.4. Significant activity in control group after group contrast.

Between group contrast: Control group activity					
Cortical Location	Voxel Count	Mean Z-Value	Z-max X	Z-max Y	Z-max Z
Vermis / Superior Cerebellum	318	5.48	4	-66	-10
Left Premotor Cortex / Primary motor cortex	291	6.02	-44	-6	56
Left Supplementary Motor Area	92	5.401	-4	-6	66
Left Primary Somatosensory Region	74	5.613	-60	-16	38
Left Extrastriate cortex / V5	53	5.516	-48	-64	-2
Inferior Cerebellum	35	5.556	4	-72	-38
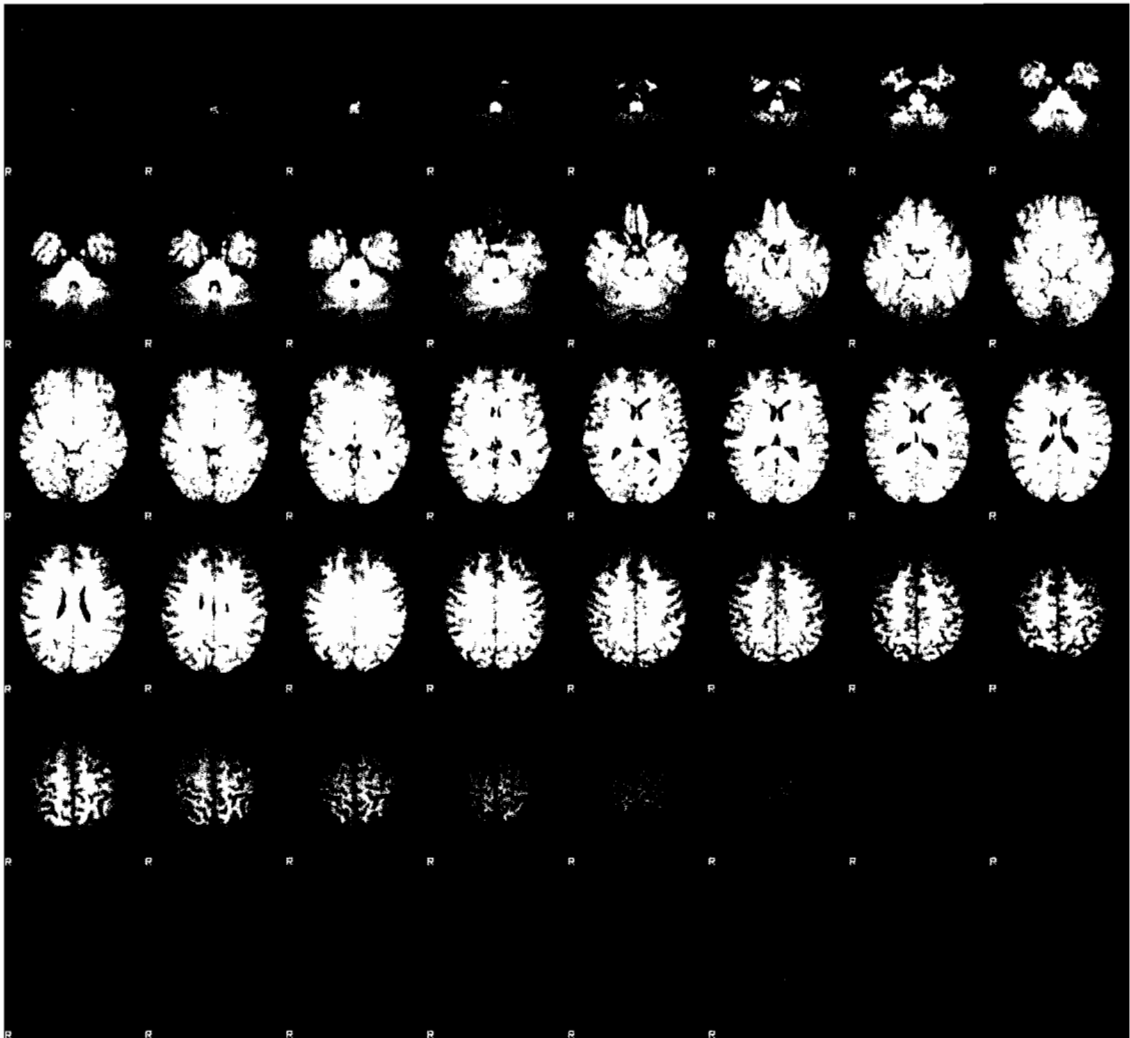
Figure 4.7. Significant activity in controls after group contrast.

Table 4.5. Significant activity in TBI group after group contrast.

Between group contrast: Unique TBI group activity					
Cortical Location	Voxel Count	Mean Z-Value	Z-max X	Z-max Y	Z-max Z
Right Intraparietal sulcus	216	5.217	48	-50	48
Right Superior Temporal Gyrus	208	5.35	54	-44	14
Left Precuneus	84	5.166	0	-50	38
Left Primary Somatosensory Cortex	69	5.67	-50	-30	56
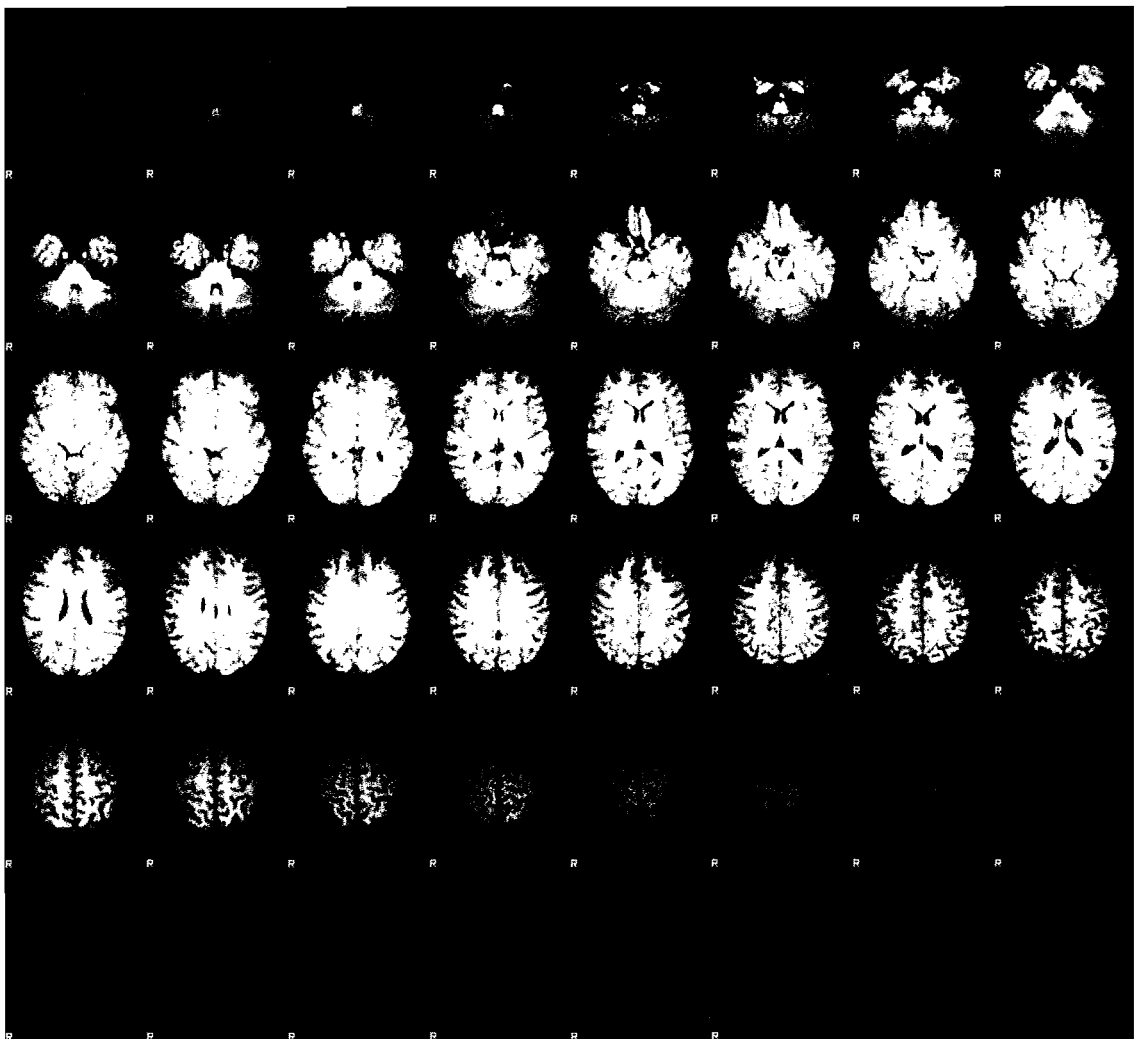
Figure 4.8. Significant activity in TBI participants after group contrast.

Table 4.6. ROI analysis of extracted z-scores.

|	Mean Control Z-Score (St. Dev.)	Mean TBI Z-Score (St. Dev.)	P value
Left Motor Cortex	**4.360 (2.036)**	**2.641 (1.351)**	**p=0.01**
Superior Cerebellum	3.236 (1.491)	2.192 (1.784)	p=0.08
Right Intraparietal Sulcus	**0.338 (0.469)**	**2.004 (1.298)**	**p<0.001**
Precuneus	0.000 (0.000)	0.288 (0.783)	p=0.11
Left Somatosensory Cortex	**2.545 (2.532)**	**5.818 (2.800)**	**p=0.006**
Inferior Cerebellum	3.606 (3.364)	2.852 (2.412)	p=0.286
Visual area 5	3.204 (2.411)	1.693 (1.375)	p=0.102
Supplementary Motor Area	3.727 (1.727)	3.225 (1.229)	p=0.230
Right Superior Temporal Gyrus	**1.018 (0.625)**	**2.577 (1.345)**	**p=0.004**

4.2.4. COVARIANCE ANALYSIS

A total subject covariance analysis was also performed, to determine whether adding a behavioral correlate to the BOLD analysis would elucidate any further patterns of cortical activity. Based on the results of the behavioral analyses, a total of three covariate contrasts were performed: One each for Fitts task performance, SRS, and Impulse Control. Each subject's first level analysis was entered into the model along with his or her respective behavioral score as orthogonal variables. The behavioral data is ordered such that a low score is indicative of normal performance: That is, in all three behavioral tasks, the control group scores were significantly lower than TBI scores. The covariate analysis maps, therefore, represent the areas that displayed increased hemodynamic response in the presence of poor behavior, and decreased hemodynamic response during improved behavior. The activation maps can be seen in Figures 4.9 – 4.11.

The Fitts covariate analysis revealed a single active cluster, beginning in the right temporal cortex and extending through to the right intraparietal sulcus. This is similar to the findings generated by the initial BOLD analysis: TBI participants were more likely to show significant levels of activity in the right temporal and parietal areas. The Impulse control analysis did not yield any significant effects. While impulse control did show a significant group difference in the laboratory, the effect was quite small and the data was highly variable. These two factors, coupled with a conservative covariate analysis might account for this absence of activation. The covariate analyses for self reported symptoms, however, displayed significant activity in the anterior cingulate, right precentral gyrus, right intraparietal sulcus, and inferior cerebellum. Of these regions, only the right intraparietal sulcus could have been anticipated based on the previous BOLD contrast: While the Inferior cerebellum was different between the two groups, the increased significance was localized to the control group. Further, the anterior cingulate cortex and right precentral gyrus displayed no group differences in the preliminary BOLD analysis. This analysis lends considerable support for the hypothesis that in the presence of diffuse cortical damage, the cortex reorganizes itself to compensate for damaged white matter pathways and systemic neuronal injury. The damaged-induced plasticity, in the case of the PPCS participants, seems to implicate the right intraparietal sulcus as the most likely candidate for plasticity.
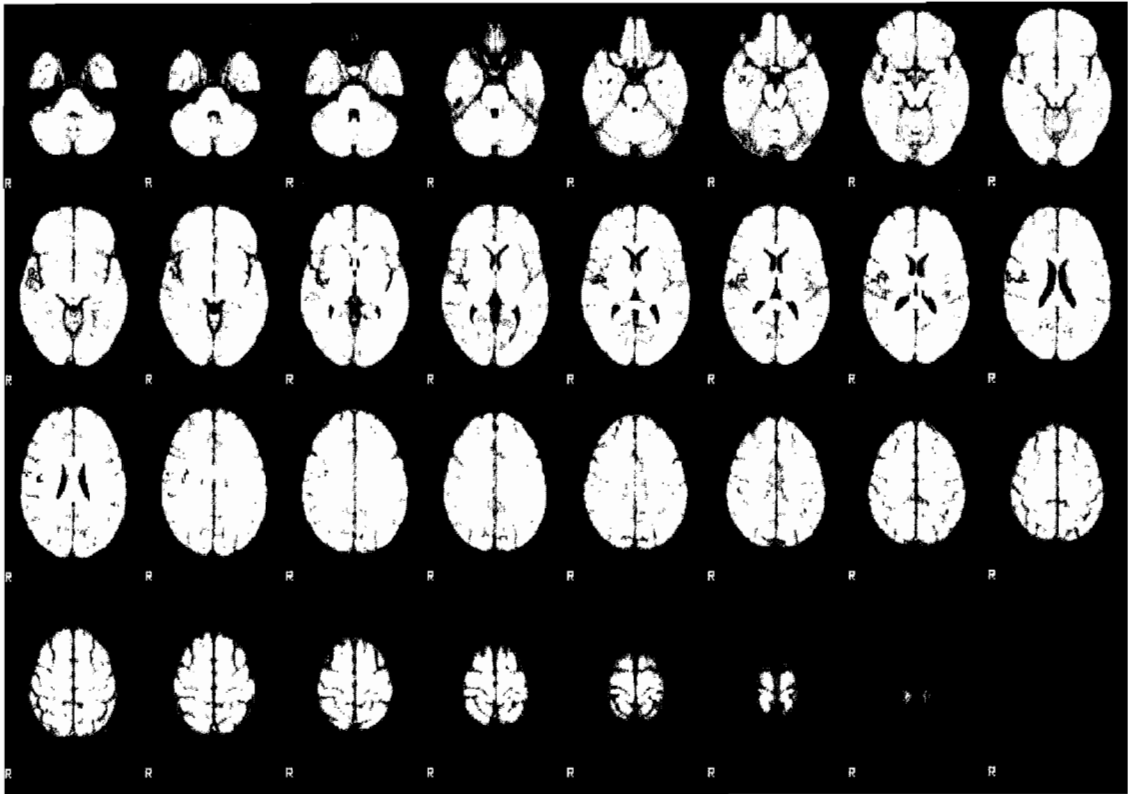
Cluster Index	Voxels	P	Z-Max - X	Z-Max - Y	Z-Max - Z
R. Parietal/Temporal Cortex	776	0.0013	42	-8	12

Figure 4.9. Covariate analysis of Fitts task. Significantly active voxels are associated with decreased performance of the task.
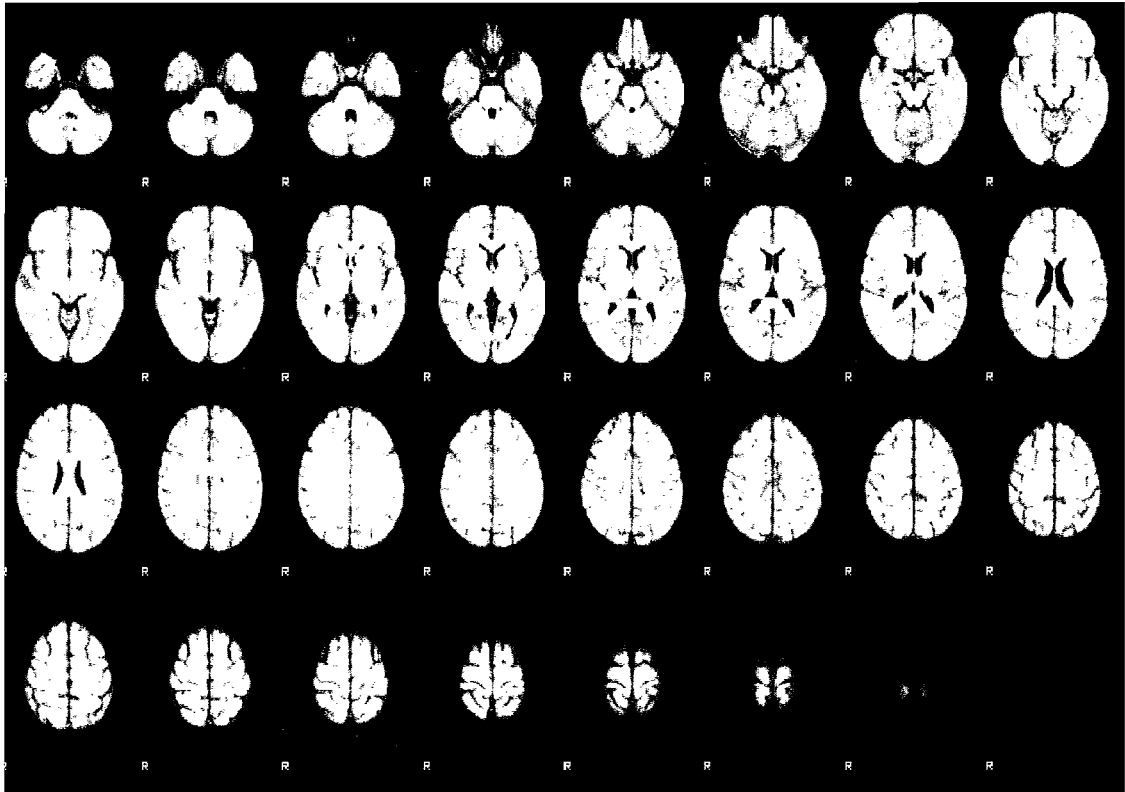
Cluster Index	Voxels	P	Z-Max - X	Z-Max - Y	Z-Max - Z
-	-	-	-	-	-

Figure 4.10. Covariate analysis of Impulse Control. Significantly active voxels are associated with decreased performance of the task.

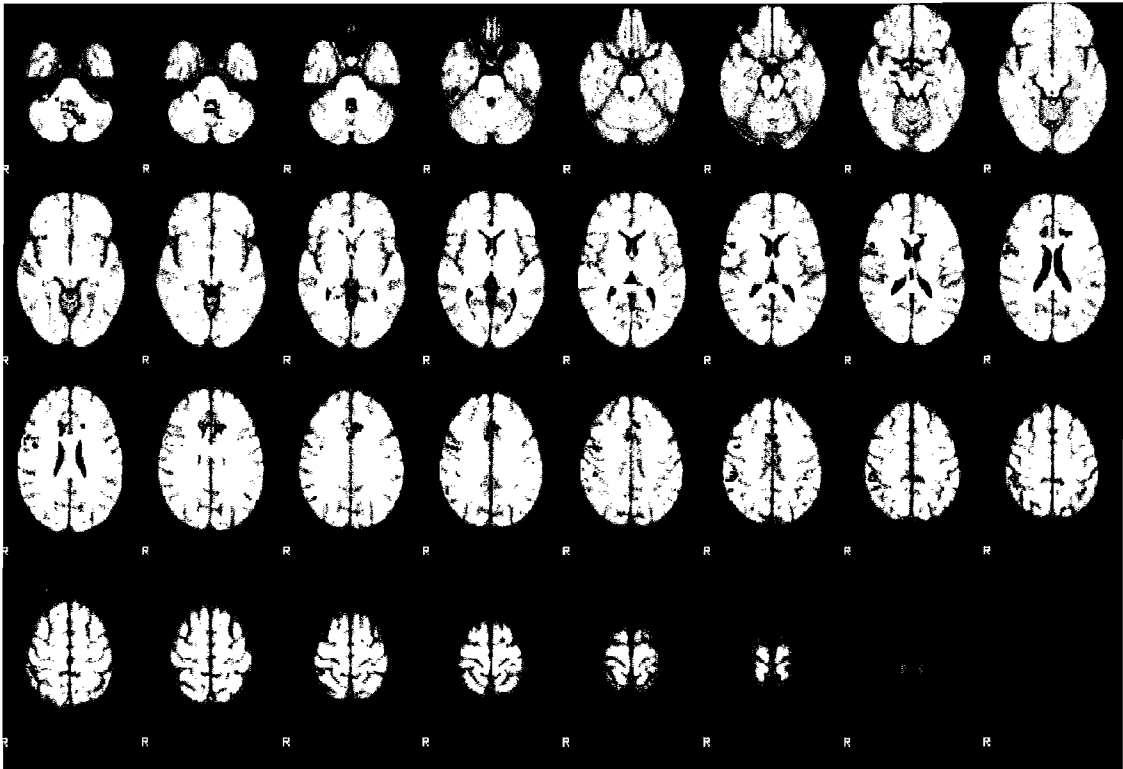| Cluster Index	Voxels	P	Z-Max - X	Z-Max - Y	Z-Max - Z
Bilateral Anterior Cingulate	812	0.000901	3.05	3.89	12
Right Precentral Gyrus	484	0.0244	1.61	3.77	62
Right Intraparietal Sulcus	465	0.0301	1.52	4.6	52
Inferior Cerebellum	429	0.0449	1.35	3.77	-14

Figure 4.11. Covariate analysis of Self Report Symptoms. Significantly active voxels are associated with decreased performance of the task.

4.3 CORRELATION AND REGRESSION ANALYSIS

The behavioral measures (Fitts Score, ImPact variables) were entered into a

correlation matrix with the MRI measures that exhibited group differences (Table 4.7).

Of all the behavioural measures, only two significantly correlated with any MRI markers

of PPCS. The Fitts behavioural task correlated with two of the BOLD measures, as well

as one measure of anisotropy. The correlations, however, were not very strong as

indicated by the probability of a type 1 error. Given the smaller predictive value of the

MRI scores on Fitts performance, it would be safe to assert that there are other factors

that make significant contributions to predicting motor behavior.

Self reported symptoms had three weaker correlations to BOLD values, as well as

two more robust relationships: BOLD activity in the right intraparietal sulcus, as well as

the anisotropy value in the corpus callosum exhibited higher r values, as well as a

probability of a type 1 error less than 0.01. The most significant behavioral difference as

measured in the laboratory part of the testing, hence, might be predicted by more

Table 4.7. Correlation matrix of all behavioral measures and significant MRI markers
of PPCS.

	RST	LM1	RIP	LS1	CCFA	CPFA
Fitts Task	0.218	-0.142	-0.078	**.403 ***	**.384***	**-0.385 ***
SRS	**.429 ***	**-.402 ***	**.623 ****	**.450 ***	**-.559***	-.369
Impulse	.205	-.364	.268	.348	-.187	.039
V. M. Speed	-.230	-.109	..036	-.117	.253	-.038
Verbal Mem.	-.136	-.147	-.016	-.242	.342	0.194
Spatial Mem.	-.180	-.344	-.298	-.236	.158	.188
RT	.358	.375	.026	.181	-.159	-.073

Bold values indicate a significant correlation: * denotes significance at the $p < 0.05$
level, and ** denotes significance at the $p < 0.01$ level.

objective MRI measures. Finally, the behavioral measure of impulse control failed to significantly correlate with any MRI measure of TBI, even though the values were statistically different between the two groups. This could in part be due to the high within-group variability of the scores, as well as the weaker significance of the measure.

Only two regression analyses were performed, as the other behavioural measures were not significantly correlated to any MRI marker of TBI. A forward selection model was employed on both the Fitts score and self-report symptoms. Based on the entry and exit criteria, only a single variable (Right Intraparietal Sulcus) was able to enter the Fitts predictive model. The model, unfortunately, did not reach significance $F(1, 18) = 3.483$, $p = 0.078$. The second regression saw two MRI variables regress on Self Reported Symptoms. A combination of Right Intraparietal Sulcus and Corpus Callosum FA values significantly predicted SRS $F(2, 17) = 9.763$, $p = 0.02$. The model had an $r^2 = .535$. Results of this analysis suggest that a combination of MRI measures might significantly predict how one reports feeling in the chronic stages of TBI. It might be suggested, therefore, that how a subject with PPCS feels is the best reflection of underlying cortical changes post TBI.

CHAPTER V

DISCUSSION

There are long-term behavioural deficits associated with mild traumatic brain

injury, and yet there are still large questions that need to be addressed. Adequately

measuring the neurological sequelae associated with TBI *in vivo* requires the use of

sophisticated imaging procedures, while quantifying behavioural deficits requires precise,

sensitive testing procedures. The current analysis examined three potential biomarkers of

TBI using MRI technology, as well as examining both fine motor and psychological

function on a cohort of PPCS participants. The results have the potential to serve as

diagnostic markers in terms of severity ratings, or perhaps as return to play guidelines for

sport.

5.1 BEHAVIORAL OUTCOMES

5.1.1 FITTS PERFORMANCE

PPCS participants and control subjects were compared using both a fine motor

task (Fitts tapping task) as well as a psychological test battery known as the ImPact. The

Fitts task required that participants perform an eye-hand coordination task as quickly and

accurately as possible in varying difficulty conditions. In the Fitts task, PPCS participants

had significantly slower movement times when averaged across index of difficulty, and

performed progressively worse relative to the controls as task difficulty increased. As a

post-hoc analysis, a second ANOVA was conducted to determine whether the group main effect would still be present if the final level of difficulty was removed. Although the effect was reduced, the group difference was still significant. The interaction, however, was no longer significant.

Upon visual inspection of the data, at every level of difficulty the PPCS group displayed greater variability compared to controls. This is most likely attributable to the within group variability of the PPCS participants. That is, within the PPCS group one can expect to see a range of symptoms and a subsequent range of behavioral impairment. This was corroborated by the significant correlation between Fitts performance and CCFA: Participants with greater white matter damage in the corpus callosum had significantly slower movement times. The relative homogeneity of the control group also contributes to this group difference in variability. The effect might be negated given a more homogenous group of PPCS participants, although without better grading criteria for PPCS, this is not possible. In spite of this higher inherent variability, there was still a main effect and interaction for the Fitts task.

The main effect of group can be attributed to a general slowing of cortical processing time for the visuomotor task (McCrea & Eng, 2005). That is, to produce a highly accurate and fast movement, the cortex must be able to integrate external and internal sensory representations and translate this information into motor commands quickly. After repeated mTBI, this ability is reduced. During completion of the Fitts task, PPCS participants adopted a conservative strategy resulting in an increased movement time. In order to preserve movement accuracy, therefore, PPCS participants sacrificed

movement speed. As the level of difficulty increased, PPCS participants become progressively more conservative, resulting in a group by ID interaction.

The Fitts task had an increasingly larger effect size as the difficulty of the task increased. While the present study only examined an index of difficulty up to 7.48 bits, the group differences could perhaps have shown a greater effect if the difficulty was further increased. Also, one might speculate that a bimanual coordination task such as bimanual finger tapping might have shown group differences as well, given the disruption of the corpus callosum as measured by fractional anisotropy. Alternately, the same task could be performed with the non-dominant hand to artificially increase difficulty. Future studies ought to improve upon the present results by developing a task with a greater range of difficulty, and incorporate both hands. With or without modification, however, tasks such as the one performed by this cohort could be used as a diagnostic marker of PPCS.

A Fitts motor task has been successfully used to differentiate other patient populations from controls in the past. The alterations in task performance have proven robust enough to use on other cortically impaired populations such as stroke (McCrea & Eng, 2005) and cerebral palsy (Gump, LeGare, & Hunt, 2002). In these two populations, there were pronounced differences in the speed with which patients were able to perform the task (stroke), and the manner in which patients managed the increased complexity of the task (CP) The present results lend further credence to using fine motor control as an indicator of cortical damage. One difference between our cohort and the above to populations, however, is that the PPCS participants were highly functioning and

possessed normal musculoskeletal function. A further question arising from this line of research is whether or not a more difficult task is required for highly functioning individuals? Would more severely PPCS patients exhibit greater differences at lower levels of task difficulty?

The group differences in the performance of the Fitts task were observed in conjunction with group changes in BOLD activity during a similar visuomotor task performed in the MRI. While the two results were not highly correlated ($r = 0.403$) on a subject-by-subject basis, one might speculate that if the tasks were more similar, the relationship would be far more predictive. Specifically, the task in the scanner had a very low index of difficulty, with movement time standardized across subjects. This was necessary to avoid movement artifacts that would produce false areas of activation. In future research, an MRI specific motor task should be employed that would both tax the visuomotor system, and not induce whole-body movements.

5.1.2 IMPACT TEST

The ImPact test examined many psychological variables known to make use of executive brain regions, but only SRS and impulse control were shown to be significantly different between groups. Interestingly, SRS showed a very large group difference, and was the only behavioral variable that could be predicted using MRI measures of PPCS. One potential criticism of SRS is that it is very subjective. That is, different subjects could score comparable symptoms differently on the Likert scale. While there is no solution to this problem, SRS has demonstrated a high degree of sensitivity to degree of cortical changes post TBI. In conjunction with more objective measures such as motor

tasks and MRI measures, SRS ought to be employed in all classification systems for PPCS patients.

The other composite scores from the ImPact test battery failed to be sensitive to the changes associated with PPCS. The most likely reason for this is that the ImPact test battery was initially designed for use in acute concussion. During acute concussion, the etiology behind the symptoms is markedly different than in PPCS. In PPCS, one is dealing with the lasting effects of cell death and subsequent reorganization, while during acute concussion, there is more pervasive widespread disruption of function due to axonal permeability and transport (Hall et al., 2005). As healing occurs in mTBI, this disruption diminishes and a return to baseline function is possible. This return to pre-injury behavior has been previously demonstrated in several populations (e.g., Parker, 2007). The true sensitivity, therefore, of the ImPact test is not for PPCS, but for acute concussion. Future studies should employ different cognitive tasks designed to monitor working memory and executive functions such as conflict resolution in a dual-task paradigm.

While PPCS is becoming increasingly recognized as a diagnosis, there appears to be a broad spectrum of psychological deficits within PPCS, ranging from slight to severe. A recent study by Sterr, Herron, Hayward, and Montaldi (2006) examined a cohort of 38 patients who were diagnosed with some form of mild-to-moderate TBI at least 12 months post-event. Participants were matched to a control group, and tested on self-reported symptoms as well as two computer-based testing batteries designed to elucidate the functioning of the frontal lobe. Specifically, the tests measured constructs such as

alertness, working memory, go / no-go tasks, reaction time, and attention. Of the 38 TBI

participants, only 11 could be classified as having post-concussion-like symptoms. The

largest predictive factor was self-reported symptoms, followed by visual information

processing and divided attention tasks.

These results were not dissimilar to those reported in our cohort: The self-reported

symptom score was the largest main effect between our groups, with impulse control

contributing as a significant difference. Further, it appears as though our population of

TBI patients was similar in terms of the range of symptoms reported by Sterr and

colleagues (2006). Of the 10 TBI participants that we analyzed, the range of scores was

expansive: The mean self-report symptom score in the TBI group was 23, with a standard

deviation of 14. The control group, by contrast, had a mean score of 1.9 and a standard

deviation of 3.1. These results suggest that a history of medically diagnosed concussions

predisposes one to long-term symptoms, but is not perfectly correlated.

5.2 IMAGING OUTCOMES

Quantifying TBI-related changes in cerebral structure and function is a difficult

task *in vivo*. Recent advances in both clinical and research-related MRI methods have

allowed for a more complete picture to emerge. This study made use of both clinical

interpretation of T2*-weighted scanning by two neuroradiologists, as well as two

measures of dynamic aspects of brain function (DTI and BOLD). By triangulating the

approach to imaging, one is able to appreciate a greater array of changes that accompany

TBI. The MRI analysis was conducted in three parts: The first analysis was an arithmetic

count of susceptibility artifacts attributed to microvascular damage. The second analysis

was the statistical comparison of Fractional anisotropy values extracted from DTI scanning. The final analysis was a group comparison of regions of activity associated with a visuomotor task. To the best of our knowledge, this is the first analysis that combined all three types of analysis on a single cohort of TBI participants. The results suggest that there are significant group differences between control and TBI participants in both fractional anisotropy and BOLD activity, but not in detectable microvascular damage.

5.2.1. SUSCEPTIBILITY WEIGHTED IMAGING

Previous published reports have concluded that microvascular damage can be detected following TBI using T2*/susceptibility-weighted imaging (Blistein & Tung, 2007). In the present analysis, T2* weighted images were interpreted by two trained neuroradiologists for artifacts consistent with hemosiderin deposits. Out of 11 TBI patients, only a single case was reported as having any of these artifacts. Unfortunately, this participant also had a significant frontal lobe contusion, and was subsequently excluded from the analysis. Given the complete absence of any detectable artifacts, results cannot be correlated with vascular damage. Based on these results, T2* weighted imaging does not seem like a sensitive marker of protracted concussion symptoms within our sample.

One caveat to bear in mind is that previous research has considered T2*-weighted artifacts as secondary evidence of axonal injury. That is, the underlying assumption is that microvascular damage implies axonal damage as well (Blistein & Tung, 2007). Our results cannot dispute this, but suggests that axonal damage can be present in the absence

of hemosiderin-induced artifacts. Given that our population were categorized as having either repeated mild or moderate events, the level of trauma might not have been sufficient to induce microvascular damage. This would agree with the analysis of the subject excluded from the present analysis; Subject KB had a loss of consciousness of 18 days, and had surgical intervention to relieve intracranial pressure. This neurosurgical involvement speaks to the severity of the injury; this level of injury was not reflective of other subjects. Another potential explanation regarding the absence of findings is that in 3 of the subjects, more than 3 years had elapsed since the last mTBI event. As time post injury increases, one might speculate that the probability of detecting vascular damage via hemosiderin decreases. For these three participants, enough time may have elapsed to fully clear the cerebrum of waste products. Finally, while the present results were contrary to our hypothesis regarding elevated counts, prior research has stated that hemosiderin-induced artifacts occur in a minority of mTBI cases (Millt et al., 1994; Hughes et al., 2004). Given a larger sample size, the probability of finding artifacts would increase. At present, however, use of susceptibility-weighted imaging does not appear to be well suited to describing the signs and symptoms of PPCS.

5.2.2. DTI IMAGING

While T2* weighted imaging did not differentiate TBI and controls within our sample, the fractional anisotropy measures proved to be sensitive to the effects of the injury. FA values were significantly lower in both the corpus callosum and cerebral peduncle. Both of these locations were selected based on previous work, and on speculative neurophysiology: The aforementioned locations exhibit extreme invariance in

white-matter fiber direction (Bigler, 2008) and are particularly susceptible to the mechanical deformations common to coup-countercoup injuries. Extreme damage to these fiber tracts will ultimately degrade the ability of the CNS to communicate both between hemispheres (corpus callosum), and with the spinal cord (cerebral peduncle), while less extreme damage can be interpreted as more of a global measure of injury severity. Even though DTI is becoming increasingly common for analysis of TBI, very few studies have examined the diagnostic value of this MRI modality.

While diffusion weighted imaging is undoubtedly a powerful MRI tool, it is not without its caveats in the case of TBI patients. Until recently, it remained unclear whether diffuse damage to white matter tracts can be defined as static, permanent pathology: As the time from injury increases, diffusivity values could change. Recently, a set of authors has examined some particular nuances of the technology within a population of TBI patients (Sidaros et al., 2008). Using a longitudinal design, the authors tracked the diffusion characteristics of several brain regions following TBI. Compared to a control group, diffusion characteristics were found to be significantly different in many cortical locations at 8 weeks post-injury. Further, in the chronic stage of TBI (operationally defined at 12 months post-injury), diffusivity measures were still significantly different in both the corpus callosum and cerebral peduncles. Two points of emphasis emerged from this study: First, white matter damage persists in a population of TBI patients in brain regions consistently identified as prone to axonal injury. In spite of the central nervous system's ability to adapt to injury, diffuse axonal injury can be imaged using MRI technology beyond 12 months post injury. Secondly, these changes in diffusivity arise

from the presence of vasogenic pooling of CSF within highly homogenous tracts of white matter (Barzo et al., 1997).

In the present study, FA values were examined in two a-priori areas as measures of cortical damage. This should not be interpreted as damage to only two regions of the cortex. Rather, the decreased FA values in the corpus callosum and cerebral peduncle should be considered as two markers of global damage. These two regions are particularly susceptible to torsional forces during acceleration/deceleration during a traumatic event, and are the most likely to exhibit group differences using FA values (Bigler, 2008). During acceleration and deceleration of the cortex within the cranium, however, is likely to damage not only white matter within these two tracts, but also other white matter tracts and gray matter. FA, therefore, might be appropriately considered a marker of lasting cortical damage in PPCS.

Many questions remain as to the appropriate use of FA as a marker of PPCS. The most obvious of these is simply what amount of damage is required to induce behavioral changes? In the present study, there was no baseline data to use as a comparison so it is difficult to speculate whether or not there is a criterion point after which one becomes impaired. One potential solution to this is the creation of a normative distribution of FA values in healthy normal populations of various ages. If a PPCS subject were to present with FA values below the normal, it could serve as a useful diagnostic tool for physicians attempting to determine return-to-play guidelines for sport, or return-to-work guidelines for industry. The potential use for FA as a diagnostic/predictive marker in TBI is extremely high, and warrants much more investigation.

5.2.3. BOLD IMAGING

While T2* weighted imaging and FA analysis both examine more structural aspects of the brain, BOLD imaging examines more transient patterns of activity during a set period of behavior. In the present study, participants performed a very simple back and forth visually guided movement. All participants performed the task in an identical manner (both movement amplitude and speed were held constant), as confirmed by visual examination of movements by the PI (TR). Results of the within-group contrast revealed that both groups activated the canonical reach circuit. That is, a continuous cluster of activity was formed from the cerebellum/visual cortex to the motor and premotor areas in the left hemisphere, accompanied by significant activity in both the right motor and parietal regions. Results from the between-group contrast, however, revealed significantly greater levels of activity in the right superior temporal, bilateral precuneal/posterior cingulate gyrus, and bilateral parietal cortices in TBI participants. Further, control subjects exhibited significantly greater levels of activity than TBI subjects in more typically activated motor structures (cerebellum and left motor cortex).

After extracting individual values from the masks created by the group contrast, four regions were classified as significantly altered in PPCS: The left somatosensory cortex, right superior temporal gyrus, and right intraparietal sulcus were all significantly more active in PPCS participants, while the left motor cortex was significantly more active in the control group. In addition, when a group analysis was performed using the significant behavioral measures as covariates, the RTG and RIP were both associated with decreased performance of the Fitts task and increased SRS respectively. Based on

these results, it appears as though the participants in the PPCS group were recruiting a network of right temporal/parietal regions to abet the movement task. The involvement of area RIP, although not traditionally considered highly associated with ipsilateral arm movements, has been reported in previous fMRI studies as a prime contributor to planning movements (Mars et al., 2007). The large increase in activity in PPCS participants, therefore, might reflect more intensive motor planning before each movement occurs. One might further speculate that due to damage in the corpus callosum, a greater number of neurons might have to be active to deliver the same signal to the contralateral hemisphere during movement planning.

Involvement of the right superior temporal gyrus in the task in PPCS participants, however, is not as easily explained. Area RST, from a motor perspective is traditionally viewed from the perspective of the mirror neuron system (Engel et al., 2008; Villarreal et al., 2008)). Briefly, this temporal-frontal network of areas is active when one views actions performed by a member of his/her own species. The mirror neuron system involves bilateral premotor and parietal areas, in addition to the right superior temporal gyrus. As such, many of these cortical regions are shared by the motor system. The possibility exists that in the presence of substantial damage to cortical networks, the mirror neuron system might abet in the planning and the visual monitoring of movements.

The final two regions implicated involve very similar cortical locations: In the control group, there was significantly more activity in the left motor cortex, while in the PPCS group, there was significantly more activity in the left somatosensory cortex. One

possible explanation for these results lies in the reduced activity in the motor cortex of PPCS participants: It is possible that altered white matter tracts specific to the cerebral peduncles have necessitated changes in cortical networking in the PPCS group. That is, because cellular communication has been disrupted, the motor cortex can no longer perform in the same manner as a matched control. This hypothesis has found some corroborating evidence from TMS literature. In a study by Chistyakov and colleagues, 39 patients were examined approximately 2-weeks after admittance to hospital for a minor TBI (1998). Motor evoked potentials were compared between the experimental participants, and 21 control subjects. The TBI participants required a greater amount of stimulation to achieve the same level of motor activity compared with their control counterparts. The authors attributed this to *motor fatigue*. It is possible that this *motor fatigue* is simply a reduced efficacy of the motor cortex due to axonal damage. In the case of PPCS participants, it might be possible that the reduced output of the motor cortex is compensated for by increased activation in the adjacent somatosensory cortex.

The results of the BOLD analysis seem to suggest that in people suffering with PPCS, there is a cortical re-mapping that occurs that involves area RIP, RST, and the left somatosensory cortex. This TBI-induced plasticity seems to be consistent across all 10 PPCS participants, but due to a limited sample size, only the largest effects of reorganization will be detected. More research is warranted in this area, as BOLD scanning provides valuable information regarding gray matter function not attainable through DTI scanning alone. Taken together, these two MRI procedures offer an objective compliment to SRS and Fitts performance.

5.2.4. FUTURE DIRECTION OF IMAGING AND PPCS

Although there have been documented changes in structural imaging, diffusion

tensor imaging, and BOLD imaging following TBI, no composite index has been formed;

as of yet there are also no definitive biomarkers present that can identify severity of TBI,

or sufficiently predict behavior. In addition to the above modalities, a recent study has

proposed a single, definitive MRI procedure to determine severity of injury: Systemic

brain volume change (Levine et al., 2008). This study examined 69 TBI participants one

year after injury using regular structural MRI imaging techniques. These participants

were matched with a control group of 12 people without history of brain injury, and

compared based on gray matter volume, white matter volume, and cerebrospinal fluid.

Results indicated that it was possible to statistically differentiate severity of TBI based

purely on the overall reduction in brain volume, regardless of vascular damage or focal

contusions.

Conceptually, a global decrease in brain parenchyma would lead to profound

deficits in cognitive and sensorimotor performance: Both the ability to perform

computations (gray matter) and communicate between different brain regions (white

matter) would be negatively affected. This method, however, is not without a few

caveats. The first consideration is that small areas of focal damage might contribute more

to global atrophy than more diffuse damage. That is, inducing gray matter damage might

have different effects than diffuse white matter damage. More importantly, however, is

determining what normal brain volume is: The Levine and colleagues study only

measured 12 control subjects to define normal brain volume. While the results are

promising, the relationship between total brain parenchyma, DTI, and BOLD reorganization should be further elucidated.

5.3 CORRELATION AND REGRESSION OUTCOMES

The ultimate goal of using MRI in clinical populations is to better understand how structural and cortical changes impact behavior. To this end, the present analysis chose to examine the relationship between behaviour as measured by Fitts performance and ImPact variables and MRI markers of PPCS. A group-wide correlation analysis was conducted on all behavioural variables, and several significant relationships emerged. Fitts performance was significantly correlated with area RIP and LS1 activity, and negatively correlated with CCFA. This holds intuitive appeal: Participants with higher RIP and LS1 activity performed poorly on a Fitts task, while having decreased FA values in the corpus callosum. While these correlations were not particularly robust (r values of approximately 0.4), the significance lends credence to the hypothesis that fine motor task performance is influenced by changes in brain activity and structural integrity. A regression was carried out with Fitts performance as the dependent variable, but no combination of MRI measures could significantly predict behavior.

The second behavioral measure in the correlation analysis, SRS, was significantly correlated to most MRI markers of PPCS. While the relationship between activity in area RST, LM1, and LS1 were modestly correlated (r of approximately 0.4), two stronger relationships emerged from the analysis: BOLD activity in area RIP and CCFA. Activity associated with area RIP had an $r = 0.623$, while CCFA held a relationship of $r = -0.559$. Both of these were significant at the $p<0.01$ level. These results, taken together with the

BOLD analysis and the FA analysis strengthens the argument that changes in these two measures can be used as predictors of the symptoms associated with PPCS. Indeed, a regression using SRS as the dependent measure, a model using RIP activity and CCFA levels significantly accounted for over 50% of the variance in SRS ($r^2 = 0.535$). The most subjective measure in the study proved to be a sensitive marker of cortical changes in the presence of PPCS. The other variable in question, Impulse Control, did not significantly correlate with any MRI markers and therefore was not analyzed via regression.

The present results add to a small, but compelling body of literature that suggests that changes in brain activity and structural integrity as measured by MRI can indeed predict altered patterns of behavior. Recently, Kraus and colleagues published a report in which the FA values of 37 participants with varying levels of TBI were significantly correlated (negatively) with cognitive scores representing memory, executive function, and attention (2007). The authors suggested that when correlating FA values with behavior, a global score representing total white matter damage ought to be used as opposed to a region of interest approach: In their analysis, this type of procedure brought about more robust r values. A second analysis published recently suggest something similar: In 34 PPCS patients, reaction time in a cognitive task was significantly correlated to the number of damaged white matter tracts as measured by FA (Niogi et al., 2008). Notably, neither of these studies examined more than one MRI marker of TBI, or performed a regression analysis. Future analyses on the predictive power of MRI in PPCS ought to employ systemic white matter damage scores with BOLD patterns and total brain parenchyma loss to assemble a more comprehensive model.

CHAPTER VI

CONCLUSIONS

The initial goal of this study was to examine the relationship between markers of cortical damage and their associated behavioural deficits. This was achieved, albeit in a partial way. We were able to document changes in eye-hand behaviour, self-reported symptoms, and impulse control. Further, we were able to differentiate the two groups based on FA values and BOLD scores. Within our cohort of participants, several significant correlations were made between behavioral and MRI changes in the presence of PPCS. Further, total symptoms could be significantly predicted using just one marker of white damage, and one marker of PPCS-induced plasticity in a BOLD task.

The present results carry much potential in terms of quantifying cortical damage that would otherwise go undetected. In the present analysis, the susceptibility-weighted images were not able to predict group affiliation, meaning that many of these participants could be considered normal with respect to structure based on this single measure. By using a simple visuomotor BOLD task and a DTI pulse sequence, however, group affiliation could be determined with a high degree of certainty. This carries significant weight in terms of return to play/activity guidelines following multiple concussions: If a patient presents with significantly lower FA values in regions of interest, it allows a physician to document why returning to play/activity might jeopardize future cognitive

and motor behavior. Further, the results also have implications for those injured on the job site, and are vying for treatment. Whereas a simple structural MRI might not be sensitive enough to detect changes in cortical function, BOLD and DTI scanning are quite capable. This could potentially be used as qualification criteria for rehabilitation or injury claims in the insurance industry.

Future studies should be conducted in order to combine the BOLD procedure, DTI and total brain parenchyma loss in a predictive model of PPCS. Further refinements could also be made to improve the BOLD task in the hope that a more complex task might be more sensitive to group differences. This will allow greater ecological validity in terms of the BOLD comparison. While future studies must include some subjective measure of self-report symptoms in any analysis, the ImPact should be substituted for a test such as the ANT, or even a task-switching paradigm that might tax executive function to a greater extent.

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