EXECUTIVE FUNCTION DEFICITS IN TRAUMATIC BRAIN INJURY

by

CHARLENE I. LAROUX

A DISSERTATION

Presented to the Department of Human Physiology
and the Graduate School of the University of Oregon
in partial fulfillment of the requirements
for the degree of
Doctor of Philosophy

December 2010

"Executive Function Deficits in Traumatic Brain Injury," a dissertation prepared by Charlene I. LaRoux in partial fulfillment of the requirements for the Doctor of Philosophy degree in the Department of Human Physiology. This dissertation has been approved and accepted by:

_____
Dr. Paul van Donkelaar, Chair of the Examining Committee

_____
Date

Committee in Charge: Dr. Paul van Donkelaar, Chair
Dr. Li-Shan Chou
Dr. Ulrich Mayr
Dr. Marjorie Woollacott

Accepted by:

_____
Dean of the Graduate School

An Abstract of the Dissertation of

Charlene Izumi LaRoux for the degree of Doctor of Philosophy

in the Department of Human Physiology to be taken December 2010

Title: EXECUTIVE FUNCTION DEFICITS IN TRAUMATIC BRAIN INJURY

Approved:_____
Dr. Paul van Donkelaar

The short and long term pathophysiology of traumatic brain injury (TBI) has not been fully elucidated. Individuals recently suffering a mild TBI (mTBI) or having a history of TBI frequently suffer deficits in their ability to maintain and allocate attention within and between tasks. This dissertation examines the influence of mild and chronic TBI on performance of task switching. We employed spatial and numerical task switching paradigms to assess the behavioral deficits in mTBI, and we used an internally generated switching and an externally cued switching task along with functional Magnetic Resonance Imaging (fMRI) to assess the long term deficits in executive function resulting from chronic TBI.

In the first experiment, individuals with mTBI were identified and tested within the first 48 hours of injury and then at a set interval 5, 14, and 28 days post injury. In the second investigation, individuals with chronic TBI were tested at least 12 months after

their most recent injury. Healthy gender, age, and education matched controls were also tested in both studies.

This research demonstrated that mTBI subjects display deficits in switching behavior within 48 hours of injury that failed to resolve a month post-injury; however, these costs did not generalize across the switching task types. Chronic TBI subjects performed internally generated and externally cued switching paradigms with a degree of success equivalent to that of healthy controls but displayed larger amounts of activation and recruited more areas of the brain at lower levels of difficulty and did not increase recruitment in a stepwise fashion at higher levels of difficulty.

Mild TBI causes significant deficits in task switching, but there is specificity in these deficits. Chronic TBI patients performed at a level equivalent to that of controls but displayed different patterns and degree of activation. Taken together, these findings indicate that there may be a specific time frame during which task switching shows behavioral deficits, after which the subject may compensate for these deficits to produce normalized performance.

CURRICULUM VITAE

NAME OF AUTHOR: Charlene I. LaRoux

GRADUATE AND UNDERGRADUATE SCHOOLS ATTENDED:

University of Oregon, Eugene
Portland State University, Portland, Oregon
Lane Community College, Eugene, Oregon

DEGREES AWARDED:

Doctor of Philosophy, Human Physiology, 2010, University of Oregon
Master of Science, Human Physiology, 2006, University of Oregon
Bachelor of Science, Biology, 2002, Portland State University
Associate of Arts Oregon Transfer Degree, 2000, Lane Community College

AREAS OF SPECIAL INTEREST:

Traumatic Brain Injury

PROFESSIONAL EXPERIENCE:

Part-Time Instructor, Lane Community College, Eugene, Oregon, 2009-2010

Graduate Teaching Fellow, Department of Human Physiology, University of Oregon, Eugene, 2003-2010

PUBLICATIONS:

(published under the name Charlene Halterman)

Catena R, Halterman C, van Donkelaar P, Chou L-S. Spatial orientation of attention and obstacle avoidance following mild traumatic brain injury. *Experimental Brain Research*. 2009; 194: 67-77.

Drew, A.S., Langan, J., Halterman, C., Osternig, L.R., Chou, L-S, van Donkelaar P. Attentional disengagement dysfunction following mild traumatic brain injury assessed with the gap saccade task. *Neuroscience Letters.* 2007; 417: 61-5.

DeHaan A, Halterman C, Langan J, Drew A, Osternig L, Chou L-S, van Donkelaar, P. Cancelling planned actions following mild traumatic brain injury. *Neuropsychologia*. 2006; 45: 406-11.

McIntire A, Langan J, Halterman C, Drew A, Osternig L, Chou LS, van Donkelaar P. The influence of mild traumatic brain injury on the temporal distribution of attention. *Exp Brain Res*. 2006; 174: 361-6.

Halterman C, Langan J, Drew T, Rodriguez E, Osternig L, Chou LS, van Donkelaar P. Tracking the Recovery of Visuospatial Attention Deficits in Mild Traumatic Brain Injury. *Brain*. 2006; 129: 559-68.

van Donkelaar P, Langan J, Rodriguez E, Drew A, Halterman C, Osternig L, Chou L-S. Attentional Deficits in Concussion. *Brain Injury.* 2005; 19: 1031-9.

TABLE OF CONTENTS

Chapter		Page
I.	TRAUMATIC BRAIN INJURY ……..	1
	Introduction……	1
	Neurometabolic Cascade of TBI ……...…	1
	Behavioral Deficits Induced by TBI ……..……...	3
	Gait Deficits Associated with TBI ……..……..	3
	Attentional Deficits Associated with TBI …….……	6
	Executive Function Deficits in TBI …….…….	7
	Executive Function in Healthy Controls …….……..	8
	Alterations in Executive Function in TBI …….……	14
	Alterations in Brain Activity Associated with TBI ……..	14
	Fundamentals of Functional Magnetic Resonance Imaging…….	19
	Conclusions …….…….	21
	Knowledge Gap and Hypotheses …….	22
	Hypothesis 1 …….	23
	Hypothesis 2 …….	23
II.	STUDY 1: BEHAVIORAL TASK SWITCHING …….	24
	Introduction …….....	24
	Behavioral Task Switching ……..	24

Chapter Page

Methods …… 27

Participants …… 27

Task …… 28

Data Analysis …… 30

Results ……...…….. 31

Day 1 Results ……..……..….. 31

Recovery of Function Results …… 36

Discussion …… 40

III. STUDY 2: BRAIN ACTIVATION DURING TASK SWITCHING 46

Introduction ……..... 46

Methods ……..…….. 51

Participants …….. 51

Task ……. 51

Behavioral Data Analysis …… 55

fMRI Data Acquisition and Analysis …….. 56

Correlation Analysis …… 60

Results ……..…… 61

Behavioral fMRI Results ……. 61

fMRI Analysis Within-Group Results ……. 63

fMRI Analysis Between-Group Results …….. 64

Region of Interest Analyses ……. 66

Chapter Page

Correlations Within/Between Behavioral Data with fMRI Activation ……..…… 73

Discussion …….. 80

IV. CONCLUSIONS …….. 91

General Discussion …… 91

REFERENCES…….. 93

LIST OF FIGURES

Figure Page

1. Spatial and Numerical Switching Paradigms ……... 30

2. Spatial Task Day 1: Proportional Switch Cost ……. 32

3. Spatial Task Day 1: Proportional Global Cost ……. 33

4. Numbers Task Day 1: Proportional Switch Cost ……. 34

5. Numbers Task Day 1: Proportional Global Cost ……. 35

6. Proportional Switch Cost in Choice Versus Forced Switch Type in the Numbers Versus Spatial Tasks ……. 36

7. Proportional Global Cost in Choice Versus Forced Switch Type ……... 37

8. Switch Cost Versus Switch Rate Across Testing Day ……. 38

9. Spatial and Numbers Task Recovery of Function Across 4 Testing Days ...…… 39

10. Spatial and Numbers Task Recovery of Function Across 4 Testing Days ……... 39

11. Switch Rate Recovery Across Testing Days 2, 5, 14 and 28…….. 40

12. Internally Generated and Externally Cued Switching Paradigms ……. 55

13. Behavioral fMRI: Proportional Switch Cost, Global Cost and Error Rates ……. 62

Figure Page

14. TBI 1b versus rest ……. 65

15. TBI 1c versus rest ……. 66

16. TBI 2a versus rest ……. 67

17. TBI 2b versus rest …… 68

18. TBI 1b>1c …… 69

19. Control 1a versus rest ……... 70

20. Control 1b versus rest ……... 71

21. Control 2a versus rest …… 72

22. Control 2b versus rest …… 73

LIST OF TABLES

Table Page

1. Subject Demographics …… 52
2. Summary of Contrasts Run in FSL …… 60
3. Regions of Activation from Within-Group Analyses …… 74
4. Within and Between Group Analyses …… 75
5. Individual Analysis TBI ……. 75
6. Individual Analysis Control …… 76
7. Within TBI Group Region of Interest Analysis …….. 77
8. Within Control Group Region of Interest Analysis …… 77
9. Between Group Region of Interest Analysis (Control>TBI) …….. 78
10. Between Group Region of Interest Analysis (TBI>Control) …… 78
11. Correlations of fMRI Activation and Behavioral Measures ……. 79
12. Correlations of Error Rates and Proportional Costs ……. 79

CHAPTER I

TRAUMATIC BRAIN INJURY

INTRODUCTION

Traumatic brain injury (TBI) is a pervasive problem in our society. It is estimated that as many as 3 million people per year suffer a TBI. Traumatic brain injuries can range in severity across a broad spectrum from mild to severe (Bailes and Hudson, 2001). The pathophysiology of mild TBI, defined as any transient neurological dysfunction resulting from a biomechanical force (Giza and Hovda, 2001), has not been as thoroughly investigated and thus, has not been clearly elucidated (Kelly et al., 1991).

NEUROMETABOLIC CASCADE OF TBI

Traumatic brain injury leads to a specific process of disruption in the neurometabolism of the patient. Examining the neurophysiological changes associated with TBI may provide us with invaluable insight into the mechanisms that contribute to the cognitive and motor deficits associated with this type of injury.

The neurometabolic process that ensues after a TBI can be roughly broken up into two major stages, where the first stage is a brief period of generalized excitation of the

brain and the second stage is a period of depression in metabolism concomitant with reduced activity. The initial phase of excitation is created by generalized depolarization in axons which leads to an overwhelming release of neurotransmitters such as glutamate into the synapse which in turn leads to major fluxes of ions. Specifically, the potassium efflux, and concomitant calcium influx created by binding of glutamate to NMDA receptors leads to a major shift in the membrane potential that the cell responds to by engaging the sodium-potassium ATPase which pumps potassium back into the cell while moving sodium out of the cell in order to return the membrane potential to resting levels. However, this ATPase activity requires energy, thus forcing the cell to go into a state of hyperglycolysis which leads to increased production of lactate that begins to accumulate in the cell. As the cell attempts to increase ATP production via increased glycolysis, the major influx of calcium previously mentioned has the additional impact of leading to impairment of mitochondrial function, which effectively constrains the ability of the cell to produce adequate energy. These metabolic changes likewise occur during a time where cerebral blood flow is decreased, thus leading to an overall energy crisis of the cell. Further exacerbating these energetic problems, the excess intracellular calcium can lead to enzymatic activation and initiation of apoptosis, neurofilament compaction, and microtubule disassembly which can lead to a build-up of organelles and axonal swelling leading to secondary axotomy (Giza and Hovda, 2001).

The specific timing of neurometabolic changes have been investigated in experimental TBI studies. The initial increase in glutamate release, potassium efflux, and associated increases in metabolic activity (hyperglycolysis) occur on the order of

minutes. Conversely, the significant increases in calcium and decreases in blood flow last on the order of hours and days. Thus, the neurometabolic cascade associated with TBI may have profound impacts on brain function that lead to both acute and chronic effects. Making connections between the timing of neurometabolic events and the degree and duration of behavioral deficits and alterations in brain activation associated with TBI may allow us to further our understanding and develop better techniques for diagnosis, treatment and rehabilitation (Giza and Hovda, 2001).

BEHAVIORAL DEFICITS INDUCED BY TBI

The neurometabolic changes that result from a TBI are thought to underlie many of the behavioral deficits that are typically observed following this injury. Many research studies have examined the clinical/behavioral consequences of TBI, but a large proportion of this research is limited in terms of the depth of understanding of the relationship between these deficits and the underlying causes. More recent studies, including several from the TBI research group at the UO, have examined this relationship in greater detail in the context of gait control, executive function, and spatial attention.

GAIT DEFICITS ASSOCIATED WITH TBI

Research has demonstrated that participation in contact sports can have a significant effect on cognitive function even in the absence of a specific diagnosis with concussion. However, it has likewise been illustrated that such participation in high impact sports may lead to other deficits such as balance dysfunction during gait. Parker

and colleagues (2008) demonstrated that athletes both with and without concussion walked more slowly, swayed more and this sway was faster when compared to non-athletes. Thus, the authors were able to provide data to support the notion that participation in contact sports itself may place individuals at greater risk of gait instability even without clinically significant traumatic brain injury (Parker et al., 2008).

Of further concern when regarding gait stability in concussed individuals is the fact that research has demonstrated significant deficits in gait stability under dual task conditions. Dual task investigations allow a more sensitive assessment of deficits that a particular population may suffer. In general terms, the protocol of a dual task paradigm involves three major conditions. The first could be the execution of a simple task such as walking. The second task could be performing a cognitive task while seated such as spelling words backwards or counting backwards by 3's. The final component to the paradigm is the dual task version where the subject performs the two tasks at the same time. By examining the performance costs in each task during the dual task condition, one can make inferences about the extent to which the processes underlying each task interact with each other. In this sense, dual task paradigms allow the assessment of deficits in allocation of neural resources that facilitate the performance of one or both tasks. Thus, when the researcher observes a larger decrease in performance of the dual task condition relative to simple conditions when comparing a clinical population to a healthy control group, they may infer that the clinical population may be suffering larger competition for resources or a failure to adequately allocate resources to achieve a normal degree of success in performance.

While performing a dual task, concussion patients were shown to walk significantly slower than controls. Furthermore, concussion patients had greater sway and sway velocity relative to healthy controls when attentional resources were taxed during dual task conditions. These deficits in the concussion subjects remained for up to 28 days post-injury, indicating that potential long-term deficits may likewise place concussed individuals at further risk of injury (Parker et al., 2006).

Research has likewise attempted to correlate attentional deficits of concussed subjects as measured by the Attentional Network Test to measures of gait instability. Catena and coworkers (2009) found that deficits in the spatial orientation component of attention immediately following concussive injury correlated with lower obstacle clearance in gait tasks involving obstacle avoidance. This correlation is strengthened by the further observation that concussed individuals made statistically more obstacle contacts relative to controls. Additional analysis indicated that as subjects recovered from concussion over a month post-injury the relationship between leading and trailing foot avoidance during obstacle crossing and the spatial orientation component of attention decreased. Taken together these results demonstrate that mTBI patients suffering from deficits in the spatial orientation component of attention likewise display difficulties in efficiently navigating their environment which places them at greater risk of obstacle contact and thus further gait instability (Catena et al., 2009).

Such findings may have relevance in treatment and intervention post-injury and thus are potentially important considerations when conducting research as well as developing or applying treatments or interventions. If there are underlying differences in

gait parameters of distinct populations due to participation in high-impact sports then it stands to reason that such differences may extend to other variables as well.

ATTENTIONAL DEFICITS ASSOCIATED WITH TBI

Individuals that experience a TBI frequently suffer from attentional deficits as a result of the injury. Specifically, research has illustrated that individuals suffering from a TBI have deficits in their ability to maintain and properly allocate their attention within and between tasks (Ponsford and Kinsella, 1992; Stuss et al., 1989a,b; Felmingham et al., 2004; Spikman et al., 1886; Cicerone, 1996; Chan, 2002; Chan et al., 2003). Our own research has bolstered the evidence for some specific deficits in attention that concussion (or mild TBI) patients suffer. We employed the attention network test (ANT) developed by Fan and colleagues (Fan et al., 2002) that is specifically designed to isolate the alerting, orienting and executive components of attention. According to our results, concussed individuals do not suffer deficits in the alerting component of attention. However, both the orienting and executive components were significantly impaired within 48 hours of injury relative to controls (van Donkelaar et al., 2005). The mTBI patients in our investigation regained normal performance of their orienting of attention within a week of their injury. Conversely, the deficits in the executive component remained throughout the month post-injury testing. These findings support the notion that the regions of the brain most susceptible to mTBI may be those associated with the orienting and executive components of visuospatial attention. Furthermore, the extended period of deficit observed in the executive component may indicate that the degree and

time course for recovery after an mTBI is regionally specific (Halterman et al., 2006) and may indicate deficits that could be associated with chronic traumatic brain injury as well.

EXECUTIVE FUNCTION DEFICITS IN TBI

Interestingly, the executive component of attention has been shown to facilitate the shifting of performance between two tasks constraints. This function of executive attention must therefore engage similar networks of the brain that are involved in deciding whether or not to act. Based upon this assertion, we have also investigated the influence of mTBI on performance of countermanding tasks. Specifically, we employed a countermanding saccade task to probe whether there are any deficits associated with mTBI in controlling the decision to act (DeHaan et al., 2007). In countermanding tasks, the cue to initiate movement is subsequently followed during so-called NO GO trials with a second cue requiring the participant to abort the planning and execution of the response. On the remaining so-called GO trials, no 2nd cue is presented and the participant must execute the response as planned. By manipulating when the 2nd cue arrives relative to the 1st cue, one can gain insight into the timing of the planning process.

Although, mTBI patients and controls displayed markedly longer saccade latencies during the GO trials compared to typical saccadic reaction times without a countermanding contingency, there was no significant difference between these two populations. Moreover, the percentage of NO GO trials that were successfully inhibited increased as the period of time between the 1st and 2nd cues decreased in a manner that was similar in both controls and mTBI patients. It appears that for both control subjects

and mTBI patients, the possibility of encountering an inhibitory stop signal alters the pattern of saccade initiation even if the inhibitory signal does not occur in a particular trial.

Interestingly, subjects with mTBI inappropriately inhibited saccade initiation during 15% of the GO trials. These results indicate that the countermanding component of this task influences individuals with mTBI more significantly than the healthy controls. Some component of the process of saccade generation during a countermanding saccade task causes mTBI subjects to incongruously inhibit their saccade although no stop signal was given. Taken together, this evidence suggests that subjects with mTBI may be particularly susceptible to disruption to their executive function following their injury. In the next section, I will review the literature on the behavioral characteristics of executive function in normal, healthy individuals as well as the underlying patterns of brain activation associated with these behaviors.

EXECUTIVE FUNCTION IN HEALTHY CONTROLS

Executive function is an essential factor in the capacity to resolve conflict, use relevant information and ignore irrelevant information, and efficiently switch between tasks requiring unique sets of responses or behaviors for their performance (Fan et al., 2002). Although there are many ways to examine or manipulate executive function, task switching paradigms are among the most commonly employed.

In general terms, the organization of a task-switching paradigm follows a three prong approach. In the first two versions of the task, the subject is taught two sets of

rules, or two unique ways of responding to the same set of stimuli. In the third version of the task the subject is required to switch back and forth in a set fashion between the two ways of responding to the stimuli (e.g. internally generated random sequence, externally cued random sequence or internally generated fixed sequence). This three-fold sequence of tasks allows the researcher to examine baseline reaction times under the two simple conditions relative to each other, as well as in comparison to the reaction times generated during the task-switching version.

Additionally, within the task-switching version, the investigator may further tease apart the nuance of task-switching costs by examining the difference in reaction time between trials where the subject was actually generating a switch from one response rule to the other (switch cost) relative to those trials where the subject was continuing to respond with the same rule but still in the overall context of switching (global cost).

Due to the focused and specific nature of task-switching paradigms, they have proven to be quite a sensitive evaluation of executive function in healthy individuals as well as an assessment tool of executive function deficits associated with various clinical populations. In healthy normal individuals the reaction times on the switching task are invariably larger than on the two simple versions of the task. Additionally, healthy subjects tend to have the longest reaction times on the trials where they are actually executing switches (switch cost), whereas the reaction times associated with employing the same rule as they did on the previous trial (global cost) tend to be intermediate between the baseline reaction times & the switch reaction times.

Investigations of healthy subjects performance across a variety of switching tasks has demonstrated that the dorsal medial frontal cortex (MFC) plays a significant role in decision making and action selection. Furthermore the pre-supplementary motor area (pre-SMA) has been implicated in the changing or initiation of a new task that requires the execution of a distinct manner of responding (Rushworth et al., 2007). Anterior cingulate cortex has likewise been implicated in performance of switching tasks due to its hypothesized role in configuring the priorities associated with performance of the new task (Hyafil et al., 2009).

Task-switching studies have also examined patterns of brain activation associated with specific types of switching in healthy individuals such as internally generated switches and externally cued switches. The results of these types of investigations have demonstrated that the two tasks lead to unique patterns of activation. Namely, the use of a cued task-switching paradigm leads to activation in the left precentral sulcus, inferior frontal sulcus (inferior frontal junction) and the pre-SMA. It has been proposed that these regions are specific to the activity of preparing for a particular task (Forstmann et al., 2005). Conversely, neuroimaging in an internally generated switching task that follows a set sequence of switches lead to activation of anterior medial prefrontal cortex and the left frontopolar cortex (Forstmann et al., 2005; Luks et al. 2002; Brass and von Cramon 2003, 2004). Thus, one could expect that these regions would play an essential role in the performance of task switching. The question remains whether one could expect similar patterns of responding in individuals with a history of TBI.

Some insight into this question may be gained by examining brain activation patterns in elderly individuals performing task switching tasks as the elderly in many ways demonstrate cognitive and attentional deficits similar to those observed with TBI. In an event-related potential (ERP) study performed by De Sanctis and colleagues (De Sanctis et al., 2009), elderly participants were split into high-performing (HP elderly) and low-performing (LP elderly) groups based upon task-switching ability. The HP elderly group displayed a unique pattern and intensity of activation in the brain associated with task-switching. The prefrontal regions of HP elderly had significantly larger and more differentiated patterns of activity relative to both healthy young adults and LP elderly. Thus, it may be that HP elderly were able to preserve executive function capacity by further recruitment and larger amplitude activations within the regions of the prefrontal cortex. These types of studies in healthy individuals and the elderly may provide invaluable insight into the patterns of behavioral deficits and alterations in brain activation that we may expect to see in individuals with a history of TBI.

An additional aspect of switch processing that has been investigated previously is the source of the cues used to switch – that is, whether they are provided externally by the experimenter or internally by the participant. These studies have indicated that switch costs are greater when the switch is externally dictated compared to voluntarily generated (Mayr and Bell, 2006) suggesting that 'random' generation of switching during the voluntary task is dictated in part by external influences such as stimulus presentation order and the costs associated with performance of this task may be due to specific strategies that subjects employ to mitigate these influences.

Traditional task switching paradigms commonly use spatial stimuli that are less convenient for examining stimulus repetitions, whereas employing non-spatial stimuli allows investigators to probe the influence of these stimulus repetitions in a more efficient manner. These non-spatial task switching paradigms examine the processing associated with the stimulus-response relation. Mayr and Bell (2006) demonstrated that switch costs were substantially smaller in magnitude for a non-spatial switch task using numbers compared to the traditional spatial switch paradigm. This suggests that processing during the spatial switching task may involve greater influence from 'bottom-up' factors created by the stimuli themselves, thus influencing the behavior of the subject as well as requiring more careful control of the strategies to reduce these exogenous influences in order to maximize successful performance of the tasks.

This investigation by Mayr and Bell (2006) may be particularly informative to our own research on TBI because of the specific interpretations that this prior research proposed. Specifically, Mayr and Bell made two particularly important observations, the first being that under the voluntary switching condition the subjects were more likely to switch when the stimulus itself changed relative to when it remained the same. The second observation was that those individuals with a selectively slower no-switch response showed less perseveration, which is the tendency to find it easier to respond in the same fashion as the previous trial relative to switching the response to a new rule, and thus these individuals' show less stimulus-driven effects on their performance of the task. The authors submit that this pattern of performance is a specific strategy adopted by participants that allows them to respond to each trial discretely with minimal influence of

preceding trials. These observations and interpretations may inform our own predictions about TBI performance on this type of task switching.

Finally, the neural substrate underlying the switch mode has also been investigated. Rushworth et al., (2002) developed two forms of task-set-switching paradigms to elucidate the regions of the brain involved in switching task sets. The first, response-switching (RS) paradigm, required the subject to switch between two alternative sets of rules to respond to identical stimulus sets. The second paradigm, visual-switching (VS), required the subject to switch between two rules regarding selection of a specific component of the stimulus to which to respond, thus subjects were forced to select and alternately ignore competing elements of the stimuli. This investigation demonstrated that switching during the RS paradigm induced brain activation of the rostral cingulate zone, caudal cingulate zone, as well as the presupplementary motor area (pre-SMA). Taken together these regions collectively represent the medial frontal area. Conversely, switching during the VS task caused recruitment of only one distinct medial frontal area, on the border between the pre-SMA and SMA. This investigation went one step further and applied repetitive transcranial magnetic stimulation (rTMS) to assess the role of the medial frontal cortex in task switching. The results demonstrated that in fact the pre-SMA is essential for task switching during the RS paradigm but only during the time of the switch itself. However, no significant effect was shown with stimulation of the border between pre-SMA & SMA during the VS task. Thus, the medial frontal cortex appears to play a prominent role in task switching when the responses rather than the visual stimuli are the focus of the switch.

ALTERATIONS IN EXECUTIVE FUNCTION IN TBI

There are very few detailed studies of executive dysfunction in TBI. There is one study which used a task-switching task to probe executive dysfunction in severe TBI (Azouvi et al., 2004) and these authors found that these patients have slower response times and greater switch costs than controls. However, if these individuals are given predictable advanced knowledge about the upcoming task and an external cue, they are able to take advantage of the additional time to prepare ahead for the task switch. This raises the question as to whether chronic TBI patients may still show deficits associated with performance of this type of executive function task.

One implication of these slower response times in patients with severe TBI should be that they would also show less perseveration as did subjects in the Mayr and Bell study (2006). However, it is important to acknowledge that the slowed reaction times in the TBI patients is likely not a chosen strategy so much as a deficit or limitation in the behavioral capacity post-injury. Based on this interpretation, one could expect to see slowed reaction times and increased perseveration going hand-in-hand as two outcomes of the injury itself and impacts on the performance of task switching in TBI. Regardless of which interpretation one favors, it seems clear that task switching paradigms may be powerful tools to probe the executive dysfunctions associated with TBI.

ALTERATIONS IN BRAIN ACTIVITY ASSOCIATED WITH TBI

When reviewing the current research on TBI that employed MRI technology, the vast majority of the 350 articles that come up in the search are actually looking primarily

at the physiological and anatomical damage and disruption associated with TBI. When adding another search parameter of executive function the results drop to a paltry 12 articles. The majority of studies employing MRI technology in conjunction with assessments of executive function within the TBI population are not relying on fMRI. Instead, most studies are using specific types of MRI scans to examine anatomical damage and/or physiological disruption associated with TBI and then correlating these findings with various neuropsychological assessments. Furthermore, these neuropsychological evaluations tend to be clinically oriented assessments of executive function as opposed to the more specific information one may glean from a paradigm such as task switching. Nonetheless, the most interesting and relevant results of these investigations are summarized below.

Bergeson and colleagues (2004) correlated both clinical and quantitative assessments of atrophy within specific regions of the brains of TBI patients with a battery of cognitive assessments. The use of MRI was specifically to examine and assess the degree of atrophy, whereas all neuropsychological testing was performed outside of the scanner. The results of this investigation demonstrated that atrophy rating in the TBI population was significantly greater than that of controls. Furthermore, the clinical atrophy rating, which was a semi-quantitative assessment that allowed examination of atrophy within specific regions of the brain, correlated with the ventricle-to-brain ratio which was a more global but quantitative measure of atrophy. Additionally, the higher clinical ratings of atrophy within frontal and temporal brain regions correlated with both

memory and executive function deficits as assessed in the battery of exams within the TBI population.

Other investigations have likewise made efforts to correlate measures of anatomical integrity with neuropsychological deficits as assessed with behavioral exams. For instance, research conducted by Kraus and colleagues (2007) employed diffusion tensor imaging (DTI) to assess axonal integrity of chronic TBI patients while correlating these assessments with performance on cognitive examinations that included measures of executive function, attention and memory. The research found that the fractional anisotropy (FA), which is a measure of white matter integrity, was decreased in all regions of interest for chronic TBI patients that had suffered either a moderate or severe injury based upon the duration of loss of consciousness greater than 30 minutes or if the Glasgow Coma Scale (GCS) was less than 13. It is important to mention that the GCS is a scale used to assess the responsiveness of a patient that has suffered brain trauma. The scale is out of 15, where large scores (13-15) imply mild TBI, moderate TBI falls in the range of 9-12, and severe TBI scores ranks between 3 and 8.

Interestingly, the Kraus study also found decreased FA in mild TBI, but in fewer of the regions that they explored relative to the moderate to severe TBI group. The researchers likewise correlated the total number of regions with reduced FA scores in TBI groups relative to healthy controls, with the cognitive measures previously mentioned. This comparison showed a negative correlation between total number of regions with reduced FA scores (where larger numbers implied poorer white matter

integrity) and cognitive domain measurements, thus demonstrating that larger white matter disruption is a predictor for cognitive deficits (Kraus et al., 2007).

As mentioned above, relatively few investigations have probed the changes in brain activation generated by mTBI. The few studies that have examined mTBI primarily focused on the specific deficits of working memory. This research has demonstrated that mTBI patients performing working memory tasks engage significantly more areas beyond those typically recruited by control subjects on the same task. Furthermore, mTBI subjects tend to display maximal activation even during small working memory load conditions (Chen et al., 2004, 2007; Christodoulou et al., 2001; McAllister et al., 1999, 2001, 2006; Perlstein et al., 2004). Alterations in brain activation have also been observed in mTBI subjects performing tasks that probe a variety of functions including cognitive control (Scheibel et al., 2007; Soeda et al., 2005), memory retrieval (Levine et al., 2002), and sensorimotor coordination tasks (Jantzen et al., 2004; Lotze et al., 2006) One of the few studies employing fMRI and measures of executive function within the TBI population was conducted by Scheibel and colleagues (2009). This investigation used fMRI to examine the commonly reported phenomenon of more extensive cognitive-control related brain activation following TBI, in order to determine how these increases may be influenced by TBI severity. The study employed a stimulus response compatibility task where subjects were required to respond to presentation of a set of arrows all pointed in the same direction either by making a compatible response with a button press indicating the direction that the arrows pointed, or with an incompatible response with a button press that indicated the direction opposite to which the arrows

pointed. The TBI subjects were separated into mild, moderate or severe TBI groups based upon their respective GCS scores.

Interestingly, this study demonstrated that individuals with GCS scores lower than 8 produced increased, diffuse activation during performance of the task and these areas of increased activation included structures thought to mediate cognitive control as well as visual attention. The results further demonstrated that midline structures such as the cingulate gyrus and thalamus showed the greatest increases in activation which the authors explained by citing their vulnerability to damage caused by TBI. The final result of this investigation was that higher activation was associated with better performance on the task and the larger the degree of increase in activation relative to controls varied with severity. The researchers concluded from this study that the pattern of increased activation in TBI patients may assist performance of cognitive tasks and may thus be compensatory in nature (Scheibel et al., 2009).

Despite the existence of a number of interesting studies correlating physiological disruption or anatomical damage to executive function deficits, there is clearly a paucity of TBI research that specifically examines the pattern of brain activation associated with performance of executive function tasks within this population. Thus, it was the aim of the current research to fill this specific gap in the literature and further elucidate the relationship between known and previously discussed pathophysiological processes that occur within the brain of TBI patients with specific executive deficits.

FUNDAMENTALS OF FUNCTIONAL MAGNETIC RESONANCE IMAGING

The theory behind fMRI is that the powerful magnetic field of the scanner aligns the nuclear spins within atoms and molecules placed at the center of this homogenous field. Additionally, there is an inherent difference in the response to the magnetic field of oxygenated and deoxygenated blood that allows one to pinpoint regions of the brain with increased deoxygenated blood. Thus, fMRI investigations rely upon the assumption that brain areas involved in the performance of a task will be subject to increased blood flow with an increase in delivery of oxygenated hemoglobin that is coupled directly to the neuronal activity and thus metabolic needs of that region of neuronal tissue. The term that describes these changes in stimulated tissues response to the magnetic field is referred to as the blood-oxygenation-level dependent effect or BOLD effect (Brown and Semelka, 2003).

There has been a significant amount of controversy surrounding the explanation that links neuronal activity to the BOLD effect. Specifically, the discussion has focused on the cellular mechanism that allows active neurons to receive increased cerebral blood flow, thus facilitating delivery of resources such as oxygen and glucose to compensate for the higher energetic costs of associated with activity. One hypothesis that provides a possible explanation of the cellular mechanism is known as the astrocyte-neuron lactate shuttle. Although this hypothesis is not the only one proposed, and is not universally accepted, a brief description of the hypothesis seems appropriate to elucidate why this is such a central issue in the use of fMRI to examine brain activation associated with performance of cognitive tasks.

The physiological processes described by the astrocyte-neuron lactate shuttle hypothesis, explained in as brief and simplified fashion as possible, is initiated by the release of neurotransmitter at the synapse which leads to an uptake of this neurotransmitter into the astrocytes surrounding the neurons. The neurotransmitter is co-transported into the neuron with sodium ions thus setting up a concentration gradient within the astrocyte that must be 'reset' to baseline levels via activation of a Na^+/K^+ ATPase which in and of itself requires ATP. This increased use of glucose within the astrocyte increases the rate of glycolysis within the cytoplasm of the astrocyte and sets up an increased import of glucose from the vasculature. Concomitant with the increase in glycolysis is an increased production of lactate which is literally 'shuttled' or transported from the astrocyte into the neuron thus providing a source of energy to the neuron via conversion of lactate to pyruvate which may then enter the mitochondria within the neuron leading to increased ATP production (Tsacopoulos and Magistretti, 1996).

The proposed connection between this series of metabolic steps and increased cerebral blood flow is that the release of the neurotransmitter glutamate actually elicits two major responses. The first response to glutamate release at the synapse is the uptake by the astrocyte as discussed. The second response to glutamate release is a receptor-mediated stimulation of nitrous oxide formation in neurons and/or astrocytes that has the physiological impact of increasing cerebral blood flow in the region by causing vasodilation (Magistretti and Pellerin, 1999). This is the most clearly delineated explanation that I have come across that not only explains the cellular mechanism of neuronal activity that leads to increased CBF, but likewise helps justify the use of fMRI

to investigate changes in brain activation associated with performance of a cognitive or motor task while in the scanner.

CONCLUSIONS

It is clear that TBI is a common type of injury in our society that can be costly to treat and may lead to long lasting difficulties for those that sustain this type of trauma. The damage associated with TBI is created by a specific set of physiological processes described by the neurometabolic cascade. The physiological damage and disruption causes clear deficits in a myriad of behavioral measures including but not limited to gait, attention, memory and executive function. The behavioral changes can be underlain by alterations in the structure, function and activation of the brain itself. Researchers may examine these alterations in detail by using motor and/or cognitive paradigms that involve specific behaviors controlled or influenced by regions of the brain susceptible to TBI and likewise by employing fMRI while the subject performs these types of tasks.

With this understanding of the background behind TBI, this dissertation set out to examine the executive function deficits created by this form of injury. To achieve this end, two studies were performed. The first study used a behavioral task switching paradigm in acute mild TBI (mTBI) to elucidate specific executive function deficits that are observable within the first 48 hours of injury when compared to controls and likewise to examine if and how these deficits resolve within a month of injury again relative to controls. The additional aim of this first investigation was to determine the degree to

which any deficits in task switching behavior generalize between modalities of the switching paradigm.

The second study aimed to further probe the long term (chronic) effects of this type of TBI on executive function. The study employed fMRI while subjects performed two types of task switching in an effort to probe for any long term deficits in executive function associated with TBI. The goal of this study differed from the first because instead of examining any generalized deficits across different forms of a task switching paradigm, this investigation used two related forms of task switching specifically to probe for deficits in top down control that TBI subjects may suffer relative to healthy controls.

KNOWLEDGE GAP AND HYPOTHESIS

This dissertation seeks to fill the knowledge gap pertaining to the influence of mild and chronic TBI on executive function as probed with a task-switching protocol. Specifically, it is poorly understood what influence mTBI has on performance of voluntary compared to forced switching tasks and whether these differences generalize across variations in switching protocol. Furthermore, the neural mechanisms underlying the executive dysfunction associated with TBI have yet to be clearly elucidated. It is the goal of this research to further investigate the alterations in brain activation in task-switching associated with mild and chronic TBI.

HYPOTHESIS 1

Mild TBI subjects will show greater switch costs than controls in both a choice and forced switching task. However, their greater tendency to perseverate in the choice switching paradigm will lead to a relatively smaller increase in switch costs in this version of the task.

HYPOTHESIS 2

Individuals with chronic TBI will display significant differences in blood oxygen level dependent (BOLD) signal during performance of task switching paradigms in the fMRI scanner. Specifically, chronic TBI subjects will show an increase in both the level and extent of activation in areas typically engaged in task switching paradigms. Individuals with chronic TBI will show an increase in recruitment of supplementary regions of the brain to compensate for deficits inherent in their performance, or to maintain performance at levels similar to an uninjured subject.

CHAPTER II

STUDY 1: BEHAVIORAL TASK SWITCHING

INTRODUCTION

Behavioral Task Switching

Through research and clinical work it has been well established that TBI sufferers often experience a wide array of deficits associated with their injury. One particular deficit in the TBI population that has received a good deal of focus is that of attention. Research has demonstrated that TBI patients frequently have difficulty maintaining and properly allocating attentional resources within and between tasks. (Ponsford and Kinsella, 1992; Stuss et al., 1989a,b; Felmingham et al., 2004; Spikman et al., 1986; Cicerone, 1996; Chan, 2002; Chan et al., 2003). In fact, our own research has shown that even mild TBI sufferers experience deficits in attention when we administered the attention network test (ANT) developed by Fan and colleagues (Fan et al., 2002). The results of this earlier study showed that mTBI patients suffer deficits in both the orienting and executive components of attention when tested within 48 hours of injury relative to controls (van Donkelaar et al., 2005). Furthermore, the deficits in the executive component remained throughout the month post-injury testing. These findings provided the groundwork for the current investigation because it raised the question as to whether

the regions of the brain associated with the orienting and executive components of visuospatial attention are particularly susceptible to TBI.

Executive attention is involved in the process of shifting performance between two tasks constraints, and likewise is involved in the decision whether or not to act. We have examined this issue previously using a countermanding saccade task (DeHaan et al., 2007). During such a task, the subjects were presented with a visual cue telling them to initiate their eye movement, and on a certain proportion of trials, referred to as NO GO trials, they would then be presented with a second auditory cue indicating that they must abort the planning and execution of the response. On the remaining so-called GO trials, no 2nd cue is presented and the participant must execute the response as planned. The goal of administering this type of task was to probe whether there were any deficits associated with mTBI in controlling the decision to act (DeHaan et al., 2007). By manipulating when the 2nd cue arrives relative to the 1st cue, one can gain insight into the timing of the planning process.

Although mTBI patients and controls displayed markedly longer saccade latencies during the GO trials compared to typical saccadic reaction times without a countermanding contingency, there was no significant difference between these two populations. Moreover, the percentage of NO GO trials that were successfully inhibited increased as the period of time between the 1st and 2nd cues increased in a manner that was similar in both controls and mTBI patients. The most interesting and insightful result of this study was that subjects with mTBI inappropriately inhibited saccade initiation during 15% of the GO trials. These results indicate that the countermanding component

of this task influences individuals with mTBI more significantly than the healthy controls. Some component of the process of saccade generation during a countermanding saccade task causes mTBI subjects to incongruously inhibit their saccade although no stop signal was given.

The body of research on the TBI population to date indicates that the executive function networks of the brain may be particularly prone to damage or disruption. Since task-switching paradigms are particularly effective at probing executive function, it seems logical to employ such a task as a more sensitive and in depth investigation of the executive attention deficits in TBI relative to healthy controls. In an effort to predict the outcome of such research within the TBI population, it is useful to begin with a brief review of task switching results in healthy individuals.

Research involving healthy control subjects indicates that the costs associated with switching between two tasks are greater when the switch is externally dictated by a set sequence of switches relative to a task where the subject voluntarily generates switches between the tasks (Mayr and Bell, 2006). Additionally this prior research on healthy controls has demonstrated that switch costs were substantially smaller in magnitude for a non-spatial switch task using numbers compared to the traditional spatial switch paradigm. This suggests that processing during the spatial switching task may involve greater influence from ‘bottom-up’ factors created by the stimuli themselves, thus influencing the behavior of the subject as well as requiring more careful control of the strategies to reduce these exogenous influences in order to maximize successful

performance of the tasks. Thus, it seems that these tasks may be powerful tools to probe the executive dysfunctions associated with TBI.

In the first study, task switching deficits following mTBI were examined using both a forced and voluntary (or choice) switching paradigm. In addition, in an effort to better understand whether switching deficits generalize, we examined the performance using both a spatial and non-spatial (numbers) version of the switching task. It was hypothesized that mTBI subjects would display larger switch costs than controls under both the choice and forced switching conditions. Additionally, it was predicted that because of this increased switch cost that mTBI subjects would tend to show decreased switch rates when given the opportunity to dictate their own rate and pattern of switching in the choice switching paradigm.

METHODS

Participants

Sixteen participants with mTBI were identified from within the University of Oregon population. Subjects were tested within 48 hours of injury and 5, 14, 30 days post-injury. All mTBI participants were identified as having mTBI by a certified athletic trainer and/or attending medical doctors from within the university intercollegiate athletic program or student health center. The causes of injury included impacts to the head during a participation in a sporting event, or accidental falls or collisions. Severity of all injuries was categorized in accordance with the definitions developed by the American Academy of Neurology (1997). Only individuals with concussion grade of I and II were

permitted to participate in this study. A grade I designation was assigned to an mTBI participant if they were disoriented as to time and place for <15 minutes. Individuals were designated with a grade II ranking if they remained disoriented for >15 minutes. However, grade III designations, characterized by a loss of consciousness for any period of time were not allowed to participate. Likewise, any individual that suffered a prior mTBI within the 6 months prior to this most recent injury were not permitted to participate. In addition, 13 control participants matched for age, gender, education level and sports participation were also tested at the same time intervals. All participants signed an informed consent form prior to participating in the study and the local university human subject's compliance committee approved the experimental protocol.

Task

The behavioral paradigm consisted of a number switching and a spatial switching task (Figure 1). In the number switching task, a single digit between 1 and 9, excluding the number 5 was presented within a white square frame measuring 3.2 cm x 3.2 cm at the center of the computer screen. In the magnitude version of this task, the subject was instructed to indicate with an appropriate button press whether the number was greater than or less than 5. These responses were mapped onto the number pad of the keyboard as 7 if the number was greater than 5 and 4 if the digit was less than 5. The number stayed on the screen until the correct response was made and then was replaced 100ms after the response by the subsequent number. By contrast, in the parity version of this number switching task, the subject was presented with the same type of number stimuli

but was instructed to indicate whether the number was odd or even by pressing the "+" or "-" respectively. By contrast in the "spatial" version of the task, the subject was presented with a vertically oriented rectangle 10.3cm x 3.3cm, within which a red dot 1 cm in diameter appeared either at the top or bottom. In the "congruent" condition the subject was instructed to indicate whether the dot was at the top or bottom of the rectangle by pressing the 7 or 4 respectively. In the "incongruent" condition the subject was required to press the "+" if the dot appeared at the top, whereas they pressed the "-" button if the dot appeared on the bottom. Thus, for each paradigm the subject learned 2 sets of rules to respond to the same stimuli, and the responses for each set of rules was mapped onto 2 unique keys (4 keys total for the two conditions).

For each paradigm above, the subjects completed the "simple" version in which only one task constraint was followed as well as the "switching" version in which the task constraints were alternated across trials. For example, in the spatial switch trials, subjects were required to switch from congruent to incongruent responses at the appropriately cued time within a sequence of trials. The switching occurred under two contingencies. In the first, called the "forced" switching paradigm, the subjects were required to switch from one mode of responding to the other every 2nd trial (Figure 1). In the second, called the "choice" switching paradigm, the subjects were instructed to switch on their own every few trials without an external prompt with the caveat that they switched on average approximately every 2nd trial.

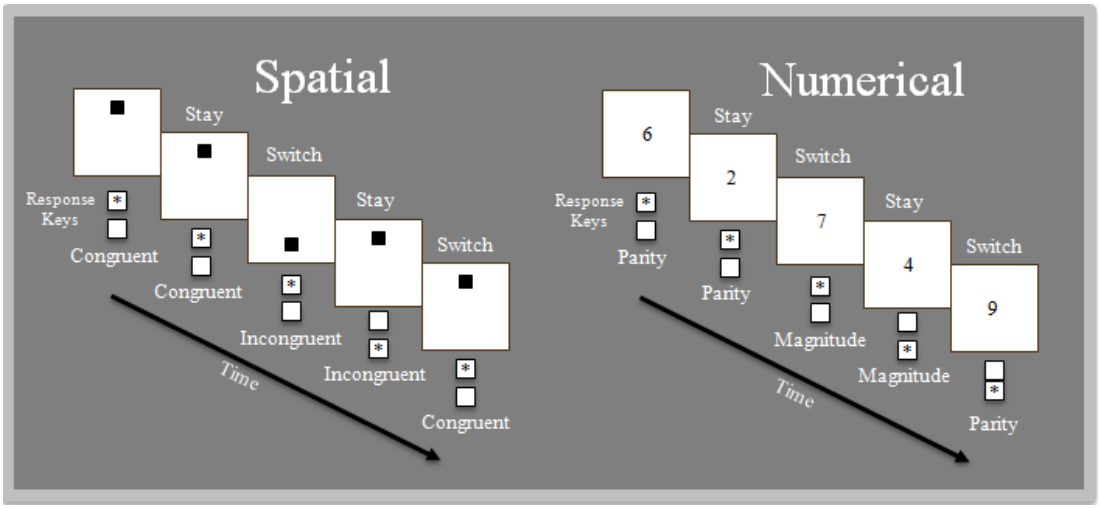

Fig 1. Spatial and Numerical Switching Paradigms Participants were presented with a stimulus that was either spatial or numerical. The subjects learned two sets of rules indicating how to respond to the stimuli and then alternated back and forth between the rules in either a set sequence every two trials or in a self-selected pattern of switches (choice).

Data Analysis

The primary behavioral dependent variable of interest was the task-switching cost on accurate trials calculated as the difference in reaction time between switch and repeat trials. Reaction times were calculated as the time from onset of the stimulus to the time when the subject pressed one of the potential response keys. To determine the relative cost of performing the switching tasks, we calculated both the proportional global cost for each group by dividing the mean reaction times during repeat trials by the mean reaction time for the baseline simple trials (and multiplying by 100), and the proportional switch cost for each group by dividing the mean reaction times during switch trials by the mean reaction time for the baseline simple trials (and multiplying by 100). Error rate was

designated as the percentage of trials within a condition where the subject responded incorrectly by pressing the wrong response key. We omitted from the reaction time analysis trials where errors were made, trials immediately following errors, and where reaction times were greater than 5000ms. To capture the initial effects of the injury as well as the subsequent recovery of function, we performed separate statistical analysis of the data for the results from the 1st day in isolation and from all the days combined. Specifically, for the data from the 1st day, mixed model analyses of variance (ANOVAs) were performed with 2 within-subject factors (task type: number versus spatial task; and switch contingency: forced versus choice) and 1 between-subjects factor (group: participants with mTBI versus matched controls). For the data across all 4 testing days an additional within-subject factor was included (testing day: 2, 5, 14, & 28). Significant main effects or interactions were further examined using post-hoc Tukey's tests.

RESULTS

Day 1 Results

Combined analysis of performance on the spatial and numerical switch tasks under the forced and choice conditions showed these measures were influenced by mTBI within 48 hours of the injury. In particular, on the 1st testing day mTBI participant reaction times were markedly slower during switch trials relative to controls within the spatial version of the task, but not in the numerical version of the task. This result held true for both the forced and voluntary conditions. These effects were captured in the proportional switch costs which were significantly larger in the mTBI group

(F[1,104]=26.221, p<0.00001) (Figures 2 and 4) and for the spatial version of the task (F[1, 104]=12.555, p=.00059) (Figure 6) but were not dependent on whether the switches were performed under the forced or voluntary conditions (F[1,104]=1.6520, p=.20154). Figure 2 shows the proportional switch cost for each group in the spatial version of the task for the forced and choice conditions and Figure 4 shows that analogous data for the numbers version of the task. The interaction between group and switch task type was significant (F[1,104]=10.883, p=.00133) and post-hoc Tukey's tests revealed that this was due to the difference between the mTBI and control groups in the spatial switching but not in the numerical switching task.

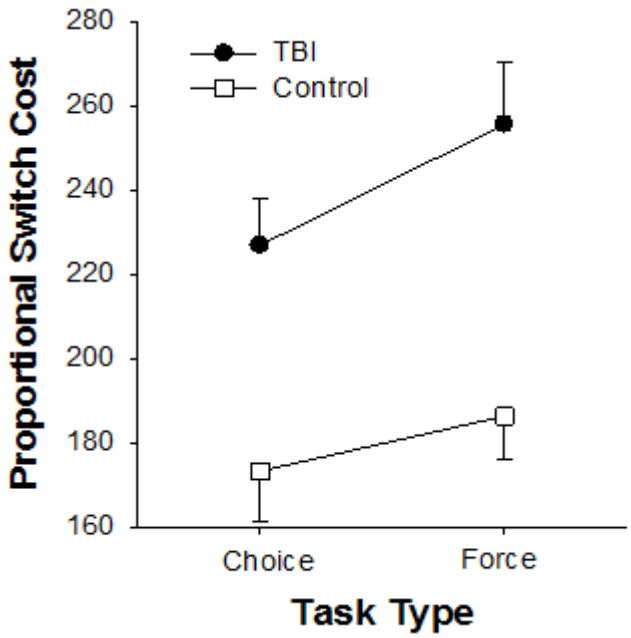

Fig 2. Spatial Task Day 1: Proportional Switch Cost. TBI subjects displayed significantly larger proportional switch costs relative to controls in both the choice and forced versions of the task when tested within the first 48 hours of injury. *Error bars*, intersubject standard error.

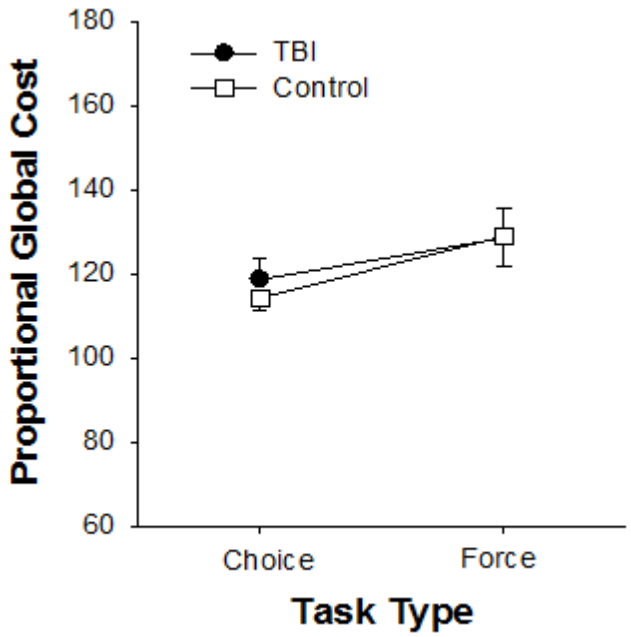

Fig 3. Spatial Task Day 1: Proportional Global Cost. TBI and control subjects showed no significant differences in the global costs associated with performance of the task switching paradigm regardless of choice or forced switching condition. *Error bars*, intersubject standard error.

In contrast to the effects of mTBI on proportional switch costs, Figures 3 and 5 show that proportional global costs were similar across groups (F[1,104]=.05693, p=.81188) and showed no interaction between group and switch task type (F=[1,104]=.00048, p=.98255). Interestingly, Figure 7 demonstrates that there was an interaction of switch task type and condition for this measure (F[1,104]=11.615, p=.00093), indicating that proportional global costs in both groups of participants were differentially affected across the two task types (spatial versus numbers) according to the switching condition (choice versus forced). Specifically, proportional global costs were smaller in the context of choice switching during the spatial task relative to the numbers task. Conversely, proportional global costs were smaller in the context of forced switching during the numbers task relative to spatial task (Figure 7). Finally, analysis of error rates revealed no

significant main effects or interactions. Thus, overall mTBI caused a marked increase in switch costs in the spatial version of the task that was similar for both the forced and voluntary conditions, but did not lead to a disproportionate increase in either error rates or the global cost of switching.

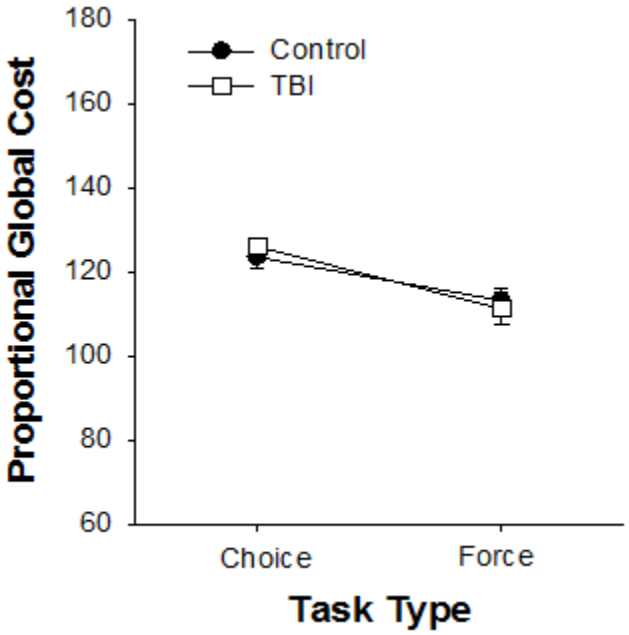

Fig 4. Numbers Task Day 1: Proportional Switch Cost. TBI and control subjects showed no significant differences in the proportional switch cost associated with performing the switch task regardless of choice or forced switching condition. *Error bars*, intersubject standard error.

We next examined the relation between switch cost and switch rate in the voluntary switch task. Recall that participants were free to switch on their own every few trials in this condition. Our question was whether switch rate was related in a systematic manner to the associated switch cost. Initial analysis of the switch rate data revealed that it was similar across groups ($F[1,104]=.65$, $p=.424$) and across the switch task type ($F[1,104]=.036$, $p=.85$). Figure 8A shows a scatter plot of switch costs relative to switch

rate for each individual mTBI and control participant in both the spatial and numbers version of the task on the first day of testing. Linear regression analysis revealed that the relationship between switch cost and rate was significant in the participants with mTBI ($r^2 = 0.1991$, $p=0.0135$), but not in the controls ($r^2 = 0.0961$, $p = 0.1404$).

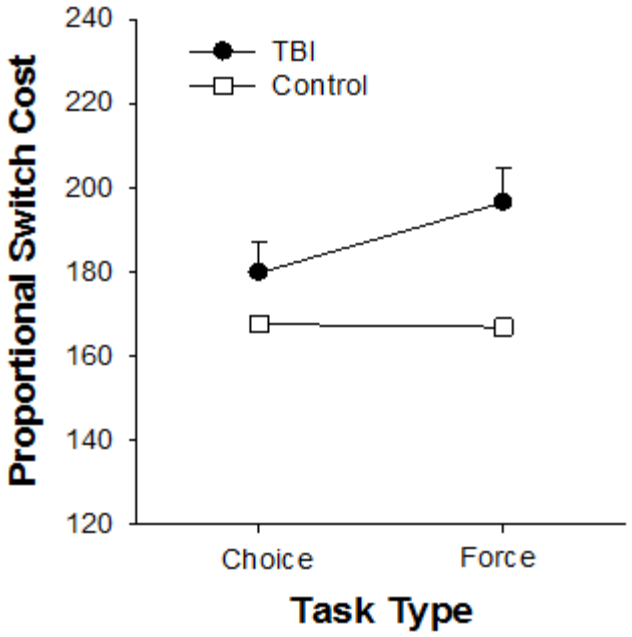

Fig 5. Numbers Task Day 1: Proportional Global Cost. TBI and control subjects showed no significant differences in the proportional global cost associated with performing the switch task regardless of choice or forced switching condition. *Error bars*, intersubject standard error.

Thus, there was a weak, but significant linear relation between switch cost and switch rate in the participants with mTBI: those who switched less frequently also tended to have larger switch costs. By contrast, this relationship did not reach significance in the control participants.

Recovery of Function Results

Having demonstrated that participants with mTBI had significantly larger proportional switch costs in the spatial task immediately after their injury, we next examined the extent to which this deficit normalized during the 1-month post-injury period. Statistical analysis revealed significant effects of group ($F[1,414]=148.81$, $p<.0001$), switching task type ($F[1,414]=57.24$, $p<.0001$), and day ($F[3,414]=12.968$, $p<.0001$).

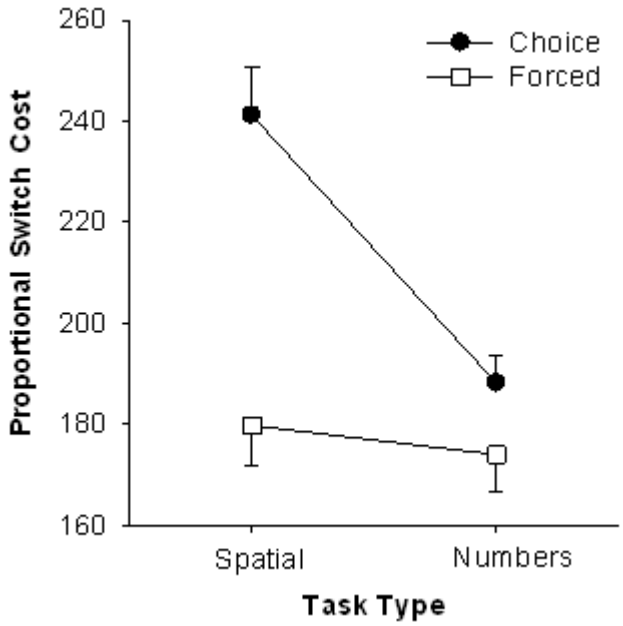

Fig 6. Proportional Switch Cost in Choice Versus Forced Switch Type in the Numbers Versus Spatial Tasks: Collapsing all subjects' data according to switch type for the spatial and numbers tasks shows a significant increase in proportional switch cost for choice on the spatial task, but not on the numbers and no affect of forced switching across either task type. *Error bars*, intersubject standard error.

Importantly, there was no significant group x day interaction ($F[3,414]=1.0854$, $p=.35504$). These combined effects are captured in Figure 9 which displays the marked group differences across days for the spatial (Figure 9A), but not the numerical version of the task (Figure 9B). It is clear from the figure that both groups improved their

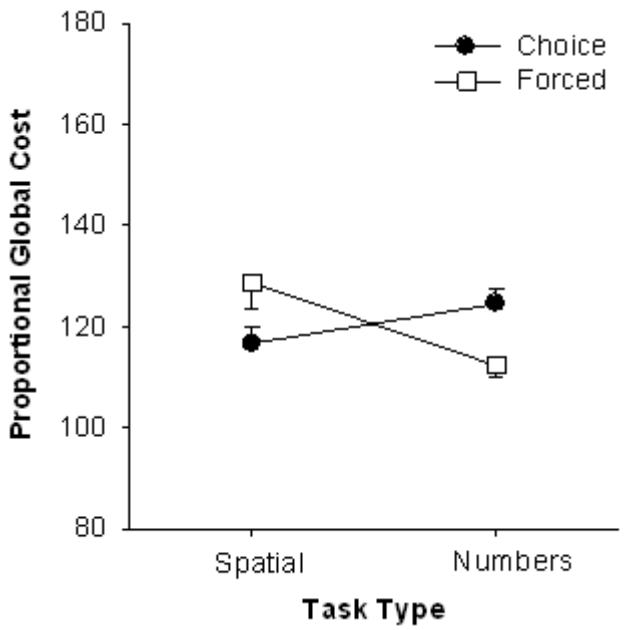

Fig 7. Proportional Global Cost in Choice Versus Forced Switch Type
Collapsing all subjects' data according to switch type for the spatial and numbers tasks shows a larger increase in global cost of choice type on numbers relative to spatial, and the opposite pattern where global cost was lower in forced for the numbers task relative to spatial. *Error bars*, intersubject standard error.

performance on both versions of the task, but the group differences that were apparent in the spatial task remained even after 1 month of recovery.

In contrast to the effect on proportional switch cost, analysis of the proportional global cost data revealed no significant effects of group ($F[1,414]=.17$, $p=.68$). There was however a similar improvement in this variable across days ($F[3,414]=14.2$, $p<.0001$) (Figure 10A & B). In addition, as with the data from the first day, there was a significant interaction between switch task type and condition ($F[1,414]=29.023$, $p=.0001$).

Finally, we examined the relationship between switch rate and switch cost when the tasks were performed under voluntary switching conditions. In addition, to these

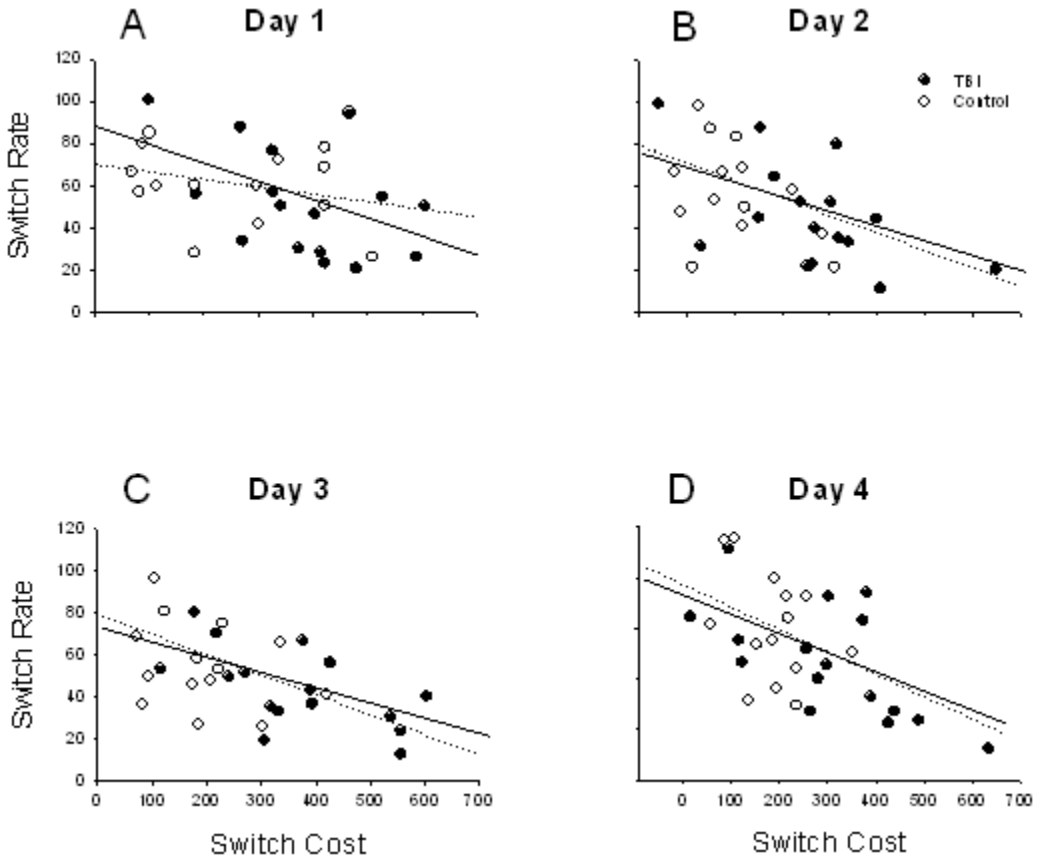

Fig 8. Switch Cost Versus Switch Rate Across Testing Day. Each graph depicts the switch rate plotted as a function of switch cost for every TBI subject and control.

effects for proportional switch cost, we also examined the extent of recovery in switch rate and the relation between switch rate and cost for the voluntary condition (Figure 8B, C & D). Interestingly, there was a significant group effect for switch rate across the 4 testing days ($F[1,200]=6.9922$, $p=.00884$) with controls switching more often than participants with mTBI (Figure 11). Recall that this group difference was not apparent on the 1st day of testing. Linear regression analyses across each day for each participant

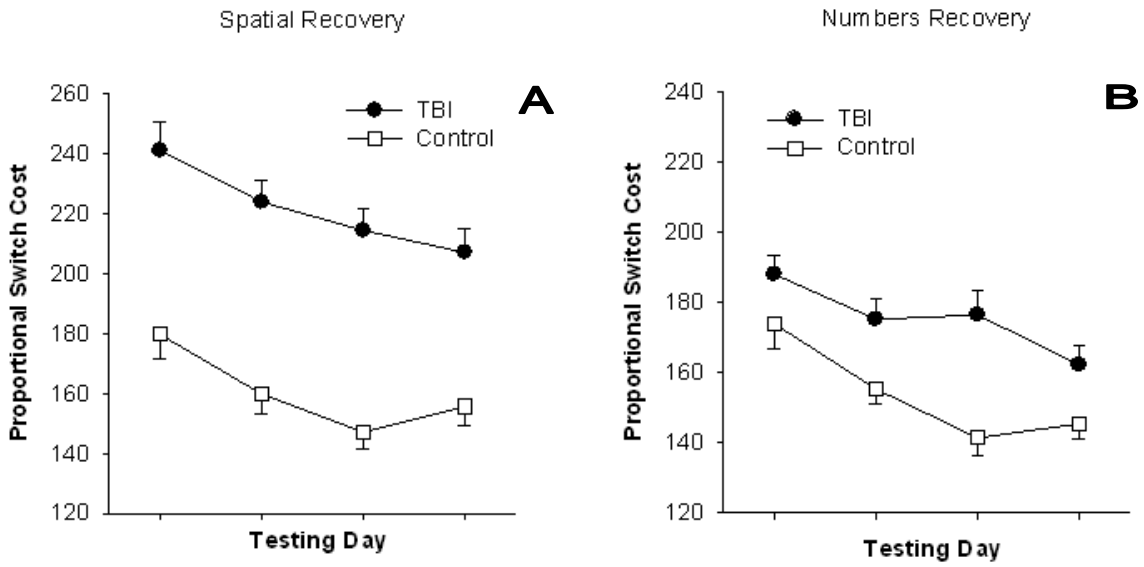

Fig 9. Spatial and Numbers Task Recovery of Function Across 4 Testing Days. Significant differences in proportional switch cost remain in TBI patients relative to controls on the spatial task but not on the numbers task on day 2, 5, 14 and 28. *Error bars*, intersubject standard error.

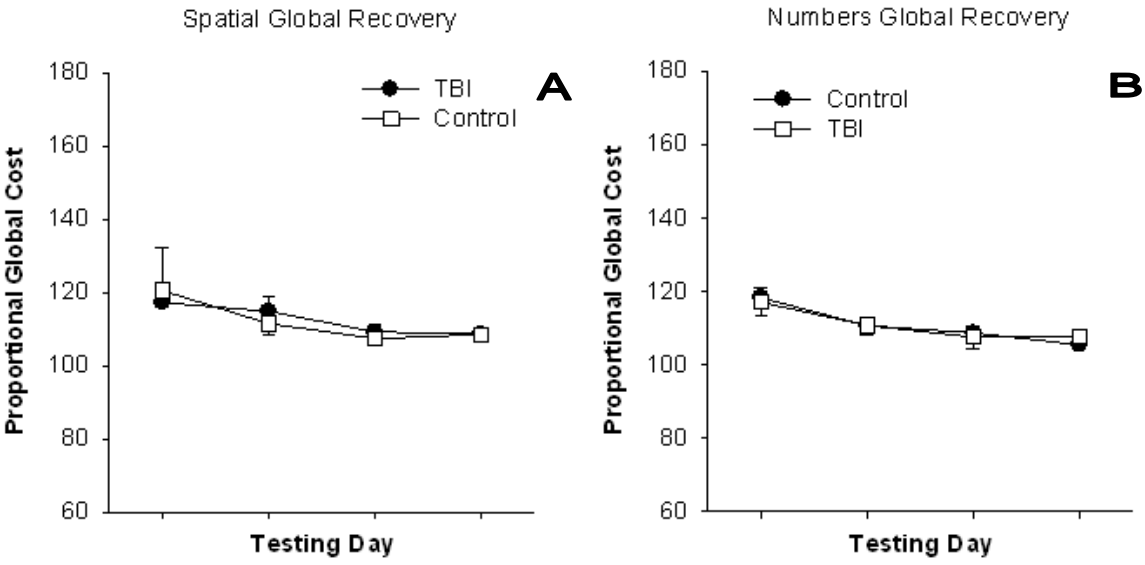

Fig 10. Spatial and Numbers Task Recovery of Function Across 4 Testing Days. No significant difference was found in the proportional global cost for either numbers or spatial task on testing day 2, 5, 14 or 28. *Error bars*, intersubject standard error.

group (Figure 8) revealed that the significant correlation between switch rate and switch cost apparent on the first day for the mTBI subjects was maintained throughout the month of testing (Day 5: $r^2 = 0.2278$, $p = 0.0077$; Day 14: $r^2 = 0.3410$, $p = .0007$; Day 28: $r^2=0.3155$, $p=0.0012$). Furthermore, significant correlations between switch rate and switch cost appeared in the control group on the third and fourth testing days (Day 14: $r^2=0.2346$, $p=0.0165$; Day 28: $r^2=0.2683$, $p=0.0095$).

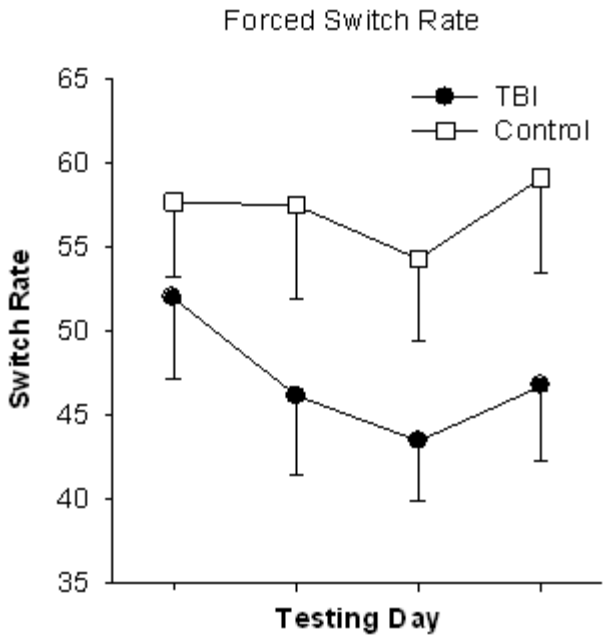

Fig 11. Switch Rate Recovery Across Testing Days 2, 5, 14 and 28. A significant difference was found between switch rate of TBI and controls only when data from 4 testing days was taken together, despite there being no significant difference between data points on any given day. *Error bars*, intersubject standard error.

DISCUSSION

In the present experiment, we examined the executive function deficits induced by mTBI using a task-switching paradigm. We hypothesized that mTBI subjects would show

greater switch costs than controls in both the choice and forced switching tasks. However, their greater tendency to perseverate in the voluntary switching paradigm would lead to a relatively smaller increase in switch costs in this version of the task. Our results showed that participants with mTBI had significantly larger proportional switch costs than controls in both the forced and choice versions of the paradigm. By contrast, global switch costs were similar in both groups regardless of switch type. These deficits in switching did not generalize between the two switching tasks indicating that the deficit observed in mTBI subjects is specifically related to difficulty in the process of spatial switching but not switching during the numbers task. In addition, the switch cost differences between participants with mTBI and controls for the spatial switch task were maintained throughout the 1-month testing period.

Finally, there was a tendency for the mTBI participants to perseverate in the choice switching paradigm and this was related to consistently larger switch costs than controls. However, there was no evidence that the switch costs were smaller in magnitude in the choice compared to forced versions of the task. Taken together, the results indicate that spatial task-switching effectively probes the executive dysfunction associated with mTBI and suggests that the brain regions involved in executive function may be particularly susceptible to damage or disruption from this type of head injury.

We have previously demonstrated that participants with mTBI have small but pervasive deficits in the spatial distribution of attention as probed by the Attentional Network Test (ANT (van Donkelaar et al., 2005; Halterman et al., 2006). In particular, although mTBI did not affect the alerting component of attention, both the orienting and

executive components were substantially modulated by the injury. Furthermore, the results indicate that these dissociable attentional networks are subject to differing rates of recovery. Specifically, the deficits observed in the ability to orient attention resolved within the first week post-injury, whereas the executive component deficits were still present 30 days post-injury. In addition, we have observed similar subtle, but systematic, deficits in the ability to disengage attention (Drew et al., 2007), distribute attention across time (McIntire et al., 2006), and countermand saccadic eye movements (DeHaan et al., 2007). Although the deficits we have observed in these tasks are significant, they are nevertheless, quite subtle. This may be due to the automaticity inherent in the experimental tasks themselves (e.g., Botvinick et al., 1999). By contrast, task-switching requires active, top-down regulation to facilitate successful performance and therefore, is a more sensitive probe of executive dysfunction after mTBI as can be observed by the larger differences in performance between patients and controls in the present study. Analogous task switching deficits have been observed previously in severe closed-head injury (CHI) patients (Schmitter-Edgecombe and Langill, 2006), and the current results extend this finding to more mild forms of head injury.

Given the marked differences in performance between the participants with mTBI and controls, we can ask what implications this has with respect to the network of brain areas that contribute to the processing underlying task switching, Recent brain imaging, lesion, and TMS studies have demonstrated that a number of medio-frontal sites play a key role in task switching performance. Rushworth and colleagues (2001) showed that the medial frontal cortex (MFC) is transiently activated when a subject switches between

the two stimulus-response mappings in a task-switching task. This activation denotes the processing associated specifically with the local costs of switching itself, not the global costs of being in the context of task switching. This same group has demonstrated that lesions within the cingulate cortex indirectly contribute to task switching deficits due to its normal function related to attention to action and voluntarily initiated action (Rushworth et al., 2003, 2005). In addition to medio-frontal areas, the lateral prefrontal cortex also appears to contribute to task switching performance. Mayr and colleagues (2006) demonstrated that individuals with left prefrontal lesions had increased reaction times during switching, analogous to our mTBI patients in the current study.

Finally, recent experiments by Niogi and colleagues (2008) using diffusion tensor imaging have demonstrated a relation between the structural integrity of different white matter tracts and deficits in the executive component of attention as measured with the ANT in participants with mTBI. They found that the fractional anisotropy scores in the left anterior corona radiata (ACR) were lower (indicating reduced integrity of the white matter) in those participants with mTBI who had larger deficits in executive attention. The ACR runs adjacent to and makes connections with the anterior cingulate gyrus. Taken together, this evidence suggests that regions within the lateral prefrontal cortex and medial frontal cortex may play a critical role in performance of task-switching and therefore may likewise by particularly susceptible to damage caused by mTBI (Niogi et al., 2008).

Finally our evidence demonstrates that participants with mTBI had significantly larger switch costs than controls in the spatial version of the task, but performed no

differently than controls in the numerical version. Why might this be the case? It is possible that this difference is related to the deficits in spatial attention that we have previously demonstrated in this population. Our prior investigation employing the attention network test demonstrated that mTBI subjects specifically showed deficits in the orienting of spatial attention (Halterman et al., 2006). Thus, it is possible that this deficit in spatial attention compounded with the challenge of task switching between spatially congruent and incongruent responses was sufficient to tease apart specific deficits within the mTBI population.

Individuals suffering from recent mTBI display an increased cost of switching between spatial tasks within the first 48 hours of injury relative to healthy matched controls, and this increased switch cost is maintained throughout a 1 month post-injury testing phase. Conversely, there is no significant difference in reaction times of mTBI and control subjects while performing a task when no switching is required – the so-called global cost. Furthermore, it is clear that mTBI subjects had a tendency to have lower switch rates and larger switch costs, but these subjects form a continuum with controls where high functioning mTBI participants looked similar to controls on the lower end of the spectrum. However, these results did not continue throughout the month of testing post-injury, indicating that this aspect of switching may be subject to greater recovery than the overall cost of switching itself.

In conclusion, this study has demonstrated that mTBI causes significant deficits in the ability to perform spatial task switching, but this deficit does not generalize to a numbers switching paradigm. Furthermore, the lack of resolution of the spatial switching

deficits one month post-injury would indicate that this type of deficit could continue to pose difficulties for a subject in everyday tasks. Thus, this may be a factor to consider in decisions regarding return to play in sports where spatial attention could be taxed significantly. Additionally, these results would likewise suggest the utility of employing spatial task switching paradigms in intervention or training protocols for mTBI patients with the hope that specific targeting of a known deficit will aid the rate and degree of recovery.

CHAPTER III

STUDY 2: BRAIN ACTIVATION DURING TASK SWITCHING

INTRODUCTION

Individuals suffering from TBI often experience a widely varied spectrum of associated deficits. In particular it has been noted that TBI patients suffer from attentional deficits that make it difficult for them to maintain and properly allocate these resources within and between tasks. (Ponsford and Kinsella, 1992; Stuss et al., 1989a,b; Felmingham et al., 2004; Spikman et al., 1986; Cicerone, 1996; Chan, 2002; Chan et al., 2003). This observation is bolstered by our own research that uncovered deficits in attention by employing the attention network test (ANT) developed by Fan and colleagues (Fan et al., 2002). The most noteworthy results of this prior investigation were that mTBI patients suffer deficits in both the orienting and executive components of attention when tested within 48 hours of injury relative to controls (van Donkelaar et al., 2005). Of further interest was the fact that the deficits in the executive component remained throughout the month post-injury testing. Moreover, the results of the first study in this dissertation directly demonstrated using a task-switching paradigm that

participants with mTBI have a marked executive function deficit which last at least a month post-injury. These findings provided the groundwork for the current investigation because it raised the question as to whether the extended period of deficit observed in executive function may indicate that the degree and time course for recovery after a TBI is regionally specific (Halterman et al., 2006) and may indicate deficits that could be associated with chronic traumatic brain injury.

Executive function is an essential factor in the capacity to resolve conflict, use relevant information and ignore irrelevant information, and efficiently switch between tasks requiring unique sets of responses or behaviors for their performance (Fan et al., 2002). Although there are many ways to examine or manipulate executive function, task switching paradigms are among the most commonly employed because such tasks allow the investigator to tease apart any deficits in performance of the task that a population may suffer relative to a healthy control group and further these deficits may be further linked to problems in executive function due to its critical role in successful performance of the task.

Prior studies of healthy individuals performing switching tasks have identified the dorsal medial frontal cortex (MFC), pre-supplementary motor area (pre-SMA) and anterior cingulate regions of the brain as being involved in the process of performing task-switching paradigms. The MFC has been proposed as playing a role in decision making and action selection, whereas pre-SMA may be involved in the changing or initiation of a new task that requires the execution of a distinct manner of responding (Rushworth et al., 2007). Finally, the anterior cingulate cortex is hypothesized to play a

role in configuring the priorities associated with performance of the new task (Hyafil et al., 2009). Thus, one may expect to find activations in these regions of the brain across a spectrum of task switching paradigms.

Conversely, it is worth noting that not all task-switching paradigms are organized and executed in the same fashion and thus may involve unique patterns of brain activation associated with specific types of switching. Prior investigations have likewise examined performance of unique forms of task switching such as internally generated switches and externally cued switches in healthy control populations. The results of these types of investigations have demonstrated that the two tasks lead to unique patterns of activation. A cued task-switching paradigm leads to activation in the left precentral sulcus, inferior frontal sulcus (inferior frontal junction) and the pre-SMA. It has been proposed that these regions are specific to the activity of preparing for a particular task (Forstmann et al., 2005). Conversely, neuroimaging studies examining internally generated switching tasks that follow a set sequence of switches demonstrate activation of anterior medial prefrontal cortex and the left frontopolar cortex (Forstmann et al., 2005; Luks et al., 2002; Brass and von Cramon 2003, 2004). Thus, one could expect that these regions would play an essential role in the performance of task switching. The question remains whether one could expect similar patterns of activation in individuals with a history of TBI.

One may gain some insight into the possible impacts of TBI on task switching by observing how other clinical populations are affected. Specifically, one study examined the brain activation patterns in elderly individuals performing task switching tasks.

Although there are distinct differences between these two clinical populations, the elderly in many ways demonstrate cognitive and attentional deficits similar to those observed with TBI. In an event-related potential (ERP) study performed by De Sanctis and colleagues (De Sanctis et al., 2009), elderly participants were split into high-performing (HP elderly) and low-performing (LP elderly) groups based upon task-switching ability. The HP elderly group displayed a unique pattern and intensity of activation in the brain associated with task-switching. The prefrontal regions of HP elderly had significantly larger and more differentiated patterns of activity relative to both healthy young adults and LP elderly. Thus, it may be that HP elderly were able to preserve executive function capacity by further recruitment and larger amplitude activations within the regions of the prefrontal cortex.

In accordance with these results, one may expect to find that TBI patients tested using a task switching paradigm may either fall into a category similar to the LP elderly where clear deficits in task-switching are observed, or conversely may display no deficits in behavioral performance similar to the HP elderly group. If TBI patients show no significant differences in performance of task switching relative to healthy controls, it may require recruitment of brain regions in a unique pattern and/or an extended degree of brain activation relative to controls, in order to facilitate this 'normal' performance of the task.

Finally, research involving individuals with severe TBI has demonstrated that this population has slower response times and greater switch costs than healthy controls (Azouvi et al., 2004). However, if these individuals are given predictable advanced

knowledge about the upcoming task and an external cue, they are able to take advantage of the additional time to prepare ahead for the task switch. This raises the question as to whether chronic TBI patients may still show deficits associated with performance of this type of executive function task. Specifically, it may be that chronic TBI patients will actually perform better on an externally cued task switching paradigm relative to an internally generated switching paradigm.

Based upon the results of our prior research it is clear that mTBI subjects have difficulty in the spatial orientation of attention and likewise spatial task switching. It remains to be seen to what extent the switching deficit of TBI subjects will impair performance of an internally and externally controlled task switching paradigm. In the second study, spatial task switching deficits in patients with chronic TBI were examined using both an internally generated and externally cued switching paradigm. It is clear that the state of our environment influences our behavior and furthermore that TBI subjects can have difficulty integrating certain aspects of their environment. During performance of an internally generated predictable sequence of task switching the individual would need to generate additional internal, memory-based action to maintain the task-set. By contrast, an externally cued task switching paradigm reduces the need for this endogenous control because the cue itself aids the retrieval of the relevant task set or goal (Forstmann et al., 2005). Thus, the performance of internally generated task switching may require additional processing resources in TBI subjects in order to successfully integrate internal and external information.

It was hypothesized that chronic TBI subjects would display larger switch costs than controls under both the internally generated and externally cued switching conditions. Additionally, it was predicted that because of this increased switch cost that chronic TBI subjects would tend to show different patterns of brain activation associated with performance of the two tasks and would show greater deficits in performance in the internally generated task relative to the externally cued task.

METHODS

Participants

Ten participants with chronic TBI (Table 1) were identified from within and outside the University of Oregon population. Subjects were recruited for the study if they had a history of 1 or more concussions with their most recent injury being a minimum of 12 months prior to the date of testing. All TBI participants' history of TBI was based upon previous medical records. At the time of testing all TBI subjects had complaints of ongoing symptoms (e.g., headaches, difficulty concentrating, attentional deficits, etc). Ten matched control subjects were identified based upon gender, age and level of education. All participants signed an informed consent form prior to participating in the study and the local university human subject's compliance committee approved the experimental protocol.

Task

The behavioral paradigm consisted of an internally generated switching and an externally cued switching task (Figure 12) performed while in the MRI scanner at the Lewis Center

for Neuroimaging. In both tasks an array of 4 vertically oriented rectangles appeared, with each rectangle occupying the corner of an imaginary square. In each array, three of

Table 1. TBI Subject Demographics. Summary of demographics for TBI subjects. Controls were gender, age and education matched.

Subject	Age	Injuries	Time Post
1	48	2	> 4 years
2	45	4	> 4 years
3	22	2	> 2 years
4	23	6	> 2 years
5	34	10	> 3 years
6	21	4	> 3 years
7	41	2	> 1 years
8	32	1	> 15 years
9	24	2	> 2 years
10	22	3	> 1 years

the rectangles were green and one rectangle was red. In both conditions of the task the subject would be required to identify the spatial location of the red rectangle.

In the internally generated switching task, three conditions were included. All three conditions began with the presentation of a central fixation crosshair for 17 seconds, followed by the presentation of the 4 rectangles of the stimulus with the central fixation crosshair remaining in the center. The stimuli would remain on screen until the subject pressed the correct response button. The first condition consisted of the congruent task in which the subject was required to indicate via a button press the side (left or right) that the red rectangle appeared on. The congruent response would indicate a left button

press if the red rectangle appeared on the left or a right button press if the red rectangle appeared on the right. The subject did not need to register whether the red rectangle was on the top or the bottom of a given side. There was a total of 5 blocks in this task, with 20 trials per block, and a 17 second break separating the blocks where only the central fixation crosshair was visible.

The second condition consisted of the incongruent task where the subject was required to indicate via button press the 'opposite' side (left or right) that the red rectangle appeared on. The incongruent response would require a left button press if the red rectangle appeared on the right or a right button press if the red rectangle appeared on the left. There was a total of 5 blocks in this task, with 20 trials per block.

The final condition of the internally generated switching task was the switching condition. During this condition the subject was instructed to generate an internally guided switch every two trials, beginning with two congruent responses then alternating to two incongruent responses. There was a total of 10 blocks of 20 trials each for this condition, and a 17 second break separating the blocks where only the central fixation crosshair was visible (Figure 12A).

Similarly, the externally cued switching task was comprised of three separate conditions. The task consisted of the same vertically oriented rectangles with 3 green and one red, where the goal was to indicate the side that the red rectangle appeared on in a congruent or incongruent manner, however in this series of conditions the central fixation crosshair was replaced with specific shapes coding for a specific type of response. In the first condition, the shapes were circles and squares alternately presented and both shapes

indicated that a congruent response was necessary. The condition once again consisted of 5 blocks with 20 trials each, and a 17 second break separating the blocks where only the central fixation crosshair was visible.

The second condition of the externally cued switching task consisted of the four rectangles surrounding a triangle that was alternately right-side up or upside-down, and indicated that an incongruent response was necessary. This condition contained 5 blocks of 20 trials each, and a 17 second break separating the blocks where only the central fixation crosshair was visible.

The third and final condition of the externally cued switching task was the switching condition where the stimuli were administered in a random order alternating between circles, and squares (indicating congruent responses were to be executed) and right-side up, and upside down triangles (indicating incongruent responses were to be executed) in a random fashion. On any continuous sequence of congruent trials the circles and squares were applied in an alternating fashion, as was true of the right-side up or upside-down triangles. Furthermore, during each block the subject was prompted to perform equal numbers of congruent and incongruent responses. This condition consisted of 10 blocks with 20 trials each, and a 17 second break separating the blocks where only the central fixation crosshair was visible (Figure 12B).

The administration of these tasks to the subject in the MRI scanner was applied in a pseudo-randomized fashion where the subject completed the three conditions of the internally generated switching task in a random fashion, and the three conditions the externally cued switching task in a random fashion.

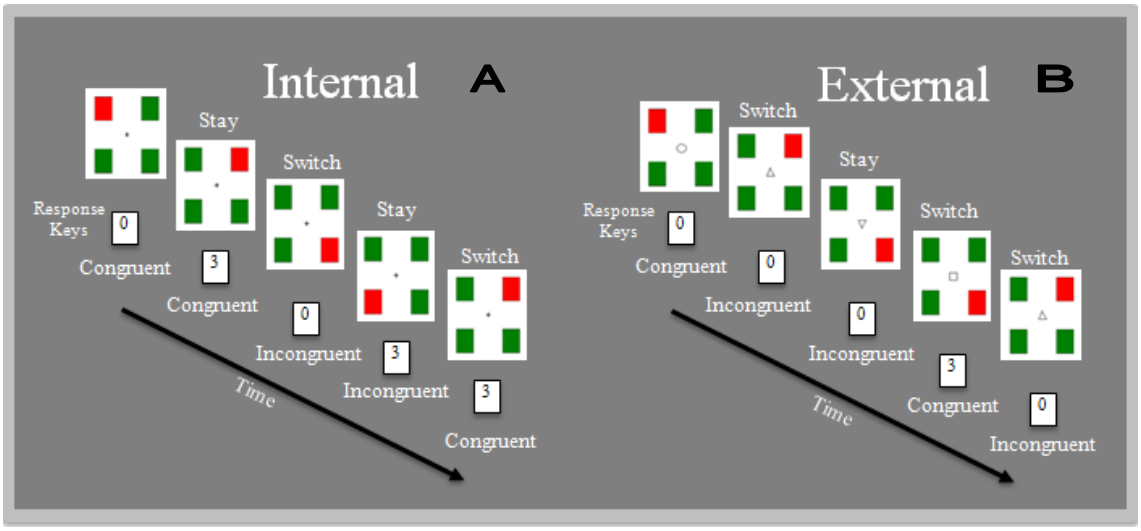

Fig 12. Internally Generated and Externally Cued Switching Paradigms Participants were presented with a stimulus containing 3 green and one red rectangle. The subjects' task was to determine the side (right or left) where the unique red rectangle appeared and respond via button press (right or left represented by numbers 3 and 0 respectively) in either a congruent or incongruent fashion.

Behavioral Data Analysis

The primary behavioral dependant variable of interest was the task-switching cost on accurate trials calculated as the difference in reaction time between switch and repeat trials. Reaction times were calculated as the time from onset of the stimulus to the time when the subject pressed one of the two potential response keys. To determine the relative cost of performing the switching tasks, we calculated both the proportional global cost for each group by dividing the mean reaction times during repeat trials by the mean reaction time for the baseline simple trials (multiplied by 100), and the proportional switch cost for each group by dividing the mean reaction times during switch trials by the mean reaction time for the baseline simple trials (multiplied by 100). Error rate was

designated as the percentage of trials within a condition where the subject responded incorrectly by pressing the wrong response key. We omitted from the reaction time analysis trials in which errors were made, trials immediately following errors, and trials with reaction times greater than 5000ms.

The statistical analysis for this study examined 1 within-subjects factor (task type: internally generated versus externally cued) and 1 between-subjects factor (groups: participants with TBI versus matched controls). For the dependent variables within-subjects effect of task type and the between-subjects effects for groups and their interactions will be investigated.

fMRI Data Acquisition and Analysis

During the internally generated and externally cued switching paradigms described above the underlying pattern of brain activation was examined using fMRI. For this purpose whole-brain functional scans were collected using a gradient-echo T2*-weighted sequence. The functional scans had the following parameter settings: TR/TE – 2000ms/30ms; flip angle – 80º; 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. For each simple condition of the internally generated or externally cued tasks, there were five blocks consisting of 20 trials, interleaved with short periods of rest (17 seconds) allowing the

scan to last approximately 3-5 minutes. For the switching condition of the internally generated or externally cued tasks, there were 10 blocks consisting of 20 trials, interleaved with short periods of rest (17 seconds) allowing the scan to last approximately 5-8 minutes. In addition, a whole brain anatomical scan was collected using a T1-weighted MPRAGE sequence. The anatomical scans had the following parameter settings; TR/TE – 2530ms/30ms; flip angle – 7º; FOV – 256mm; voxel size – 1.3 x 1.3 x 1mm. Together, the functional and anatomical scans took approximately 40 minutes. In addition, prior to the fMRI session the participant performed the task in a mock scanner until comfortable with the task and setup. This setup mimics all aspects of the real scanning session (target presentation, lying horizontal, etc) in order to acclimatize the participant to the scanner environment.

Image analysis was performed using FSL software using both a whole brain and region of interest (ROI) approach. The functional scans were realigned to the first scan acquired to correct for head movements and co-registered with the T1 weighted anatomical image normalized to MNI space. The same normalization was applied to the functional images with reslicing resulting in a 4x4x4mm resolution. These normalized scans were subsequently smoothed with an 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 the different stimulus-response contingencies within each run as predictor variables and rest as a null variable. For the whole brain analysis, the Z statistic images were created

comprising the entire scanned volume using a threshold for clusters of Z>2.3 and a standard corrected cluster significance of p=.05.

For the ROI analysis, we used the Harvard-Oxford cortical structure probabilistic atlas utility in FSL to select eight areas within the brain. The utility allowed masks to be created that were then applied to the functional scans as in the whole brain analysis (i.e., threshold for clusters of Z>2.3 and a standard corrected cluster significance of p=.05) to produce Z statistic images that were restricted to the specific ROI. The eight ROIs that were selected included the bilateral superior frontal gyrus, middle frontal gyrus, inferior frontal gyrus pars triangularis, inferior frontal gyrus pars opercularis, superior parietal lobule, supramarginal gyrus anterior division, supramarginal gyrus posterior division, and the angular gyrus. The selection of these regions aimed to capture activation within regions of the brain involved in performance of task switching (Cutini et al. 2008, Ruge, Muller and Braver 2010, Brown, Vilis and Everling 2008, Nagel et al., 2008).

For both the whole brain and ROI analyses each individual subject's data was analyzed separately and then compiled into within-group analyses for the two tasks (internally generated and externally cued switching). Within these group analyses we examined the mean brain activation for the simple conditions (congruent or incongruent, with or without cues) as well as the mean for the switching condition of each task. The results from these analyses provided insight into the activation patterns within each group associated with each condition. The results from the within group analyses for each condition were then submitted to between-group analyses. The goal here was to directly

contrast the patterns of activation observed in each condition across the TBI and control groups.

Thus, to summarize, for the fMRI analyses we determined the significant activations associated with each condition relative to rest within each subject group (TBI and control). We also determined the significant activations associated with each condition between each group (TBI>controls and Controls>TBI). For the whole brain analysis, these contrasts were performed for the entire volume of brain tissue, whereas for the ROI analysis, the contrasts were restricted to the areas outlined above.

The between-group contrasts aimed to identify brain regions that were more activated in controls relative to TBI, and vice versa, brain regions more activated in TBI than controls. This is an important set of contrasts because our hypothesis states that we expect not only a different degree of activation in TBI, but likewise an increased recruitment of supplementary areas in the TBI group relative to controls.

This is a subtle but important component to the study because our hypothesis implies that a TBI subject performing the task at a lesser or equal degree of success may display smaller brain activations in regions of the brain susceptible to injury, but may actually increase recruitment and activation in new areas of the brain to enhance their performance of the task. This hypothesis applies specifically to chronic TBI patients that are relatively removed from the time of injury, because time post-injury allows for the possibility of significant plasticity or adaptation to compensate for deficits in behavior (Table 2 bottom).

Table 2. Summary of Contrasts Run in FSL. Where 1a refers to the internally-generated congruent task, 1b is the internally-generated incongruent task, 1c is the internally generated sequence switching, 2a is the externally-cued congruent task, 2b is the externally-cued incongruent task and 2c is the externally cued switching task.

Within-Groups Analyses			
Task 1 internal	1a TBI 1a Control	1b TBI 1b Control	1c TBI 1c Control
Task 2 external	2a TBI 2a Control	2b TBI 2b Control	2c TBI 2c Control
Between-Group Comparisons			
Task 1 internal	1a TBI>control 2a Control >TBI	1b TBI>Control 2b Control>TBI	1c TBI>Control 1c Control>TBI
Task 2 external	2a TBI>Control 2a Control>TBI	2b TBI>Control 2b Control>TBI	2c TBI>Control 2c Control>TBI

Correlation Analysis

To examine whether there was any relationship between the behavioral and brain activation variables, linear correlation analyses were performed within each subject group. These analyses examined whether proportional switch cost, proportional global cost, and error rate were related to the total number of activated voxels in each task condition.

RESULTS

Behavioral fMRI Results

Figure 13 shows the behavioral results from the task performance while the participants were in the scanner. The results of the proportional switch cost analysis demonstrated no significant main effect of group ($F[1,36]=1.3713$, $p=.24929$), and no interaction between group and task ($F[1,36]=.12058$, $p=.73043$). However, there was a main effect of task ($F=[1,36]=8.5323$, p-.00599), demonstrating that both TBI and control subjects were slower in their switching responses on the externally cued switching paradigm relative to the internally generated switching paradigm (Figure 13A).

The results of the proportional global cost analysis likewise showed no significant main effect of group ($F[1,36]=1.1879$, $p=.28299$), nor any group by task interaction ($F[1,36]=.01990$, $p=.88860$). However, similar to the proportional switch cost, there was a highly significant main effect of task ($F[1,36]=18.727$, $p=.00011$) indicating that both groups were significantly slower in performing repetitions of the same task in the context of the externally cued switching task relative to an internally generated switching task (Figure 13B).

Finally, there was no significant difference in performance of the switching tasks with regard to error rates of the two groups. There was no main effect of group ($F[1,36]=1.4879$, $p=.23048$), or task ($F[1,36]=.00515$, $p=.94320$), and no interaction of group by task ($F[1,36]=.00515$, $p=.94320$) (Figure 13C).

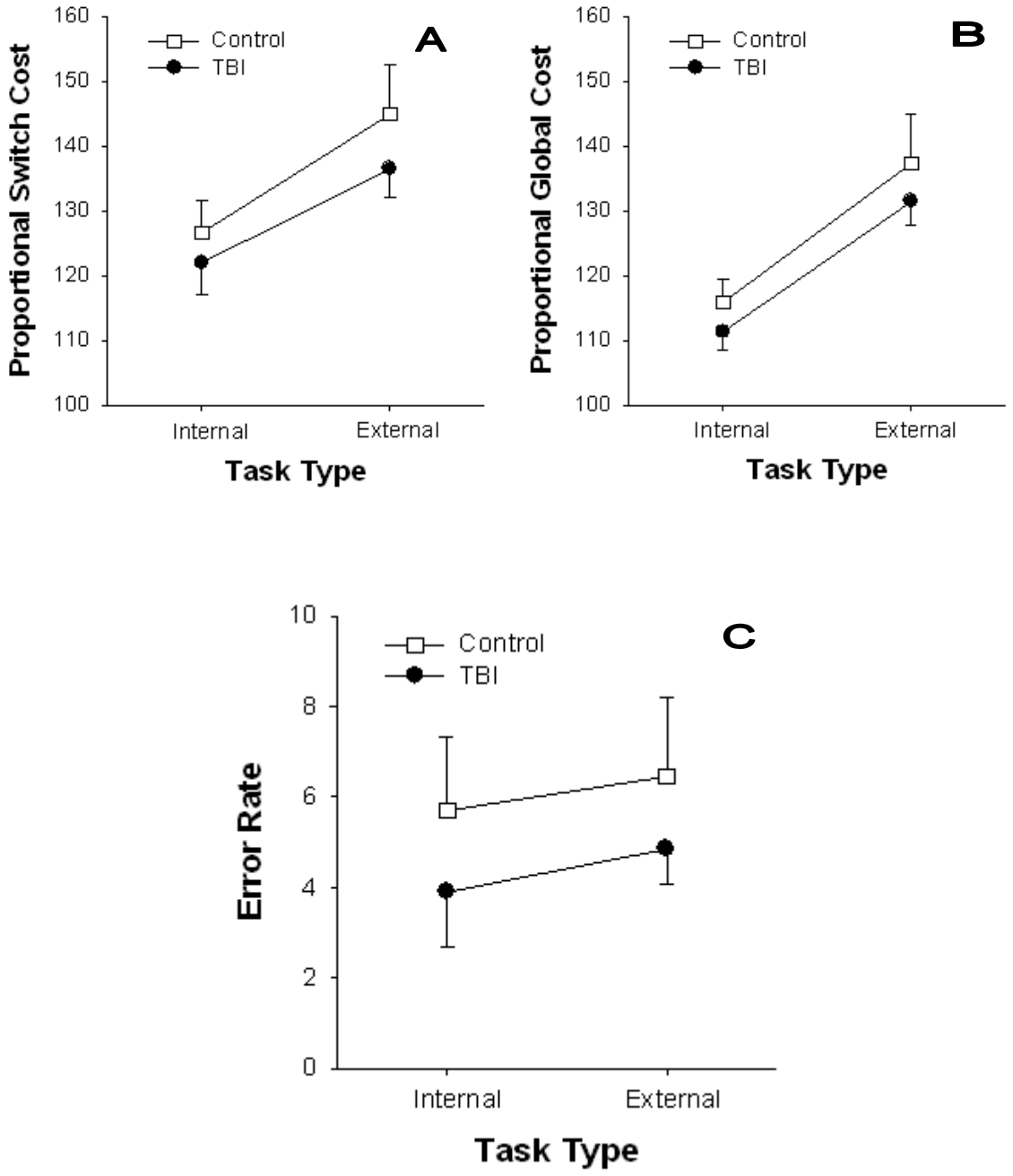

Fig 13. Behavioral fMRI: Proportional Switch Cost, Global Cost and Error Rates. No significant group differences were found in the behavioral data of TBI and controls in these analyses. Significant task effects (internal vs. external) were observed for both proportional switch and global costs. *Error bars*, intersubject standard error.

fMRI Analysis Within-Group Results

The overall pattern of activation in the within-group analyses illustrated that TBI subjects showed more activation across many of the conditions relative to controls, and the specific regions of activation associated with each condition often differed between TBI and controls. Recall that the 6 different conditions are as follows: simple congruent internally generated task -1a; simple incongruent internally generated task - 1b; internally generated switching task - 1c; simple congruent externally-cued task - 2a; simple incongruent externally-cued task - 2b; and the externally-cued switching task - 2c. The regions of significant activation for each condition relative to rest are summarized in Table 3.

Somewhat surprisingly, there were several conditions in which there was no significant within-group activation at conventional levels of significance ($p>.05$). For the TBI group this included conditions 1a and 2c and for the controls it included conditions 1c and 2c. This is most likely due to variability across the small number of subjects in each group and the relative complexity of the tasks. Indeed, some of the individual TBI and Control subjects displayed robust activations in the conditions in which no significant within-group activations were observed (see Tables 5 and 6). By contrast, the lack of significant activations did not appear to be due to any inherent errors in the analysis procedures themselves – subsequent control scans in a small number of subjects performing a simple manual motor task revealed robust sensorimotor area activations using the same analysis procedures. Despite these limitations in the data, there was still some significant activation in the remaining conditions which are displayed in Figures

14-21 and summarized in Table 3. In condition 1b, the TBI group showed significant activation across a broad swath of sensorimotor areas that included the visual, parietal, sensory and motor cortices as well as the medial frontal gyrus (Figure 14). In condition 1c, TBI subjects showed significant activation in the precentral gyrus, postcentral gyrus, inferior frontal gyrus and superior frontal gyrus (Figure 15). For the externally-cued task, TBI subjects activated the middle occipital gyrus and inferior occipital gyrus in task 2a (Figure 16) and the middle occipital gyrus and the medial frontal gyrus in task 2b (Figure 17). We likewise compared the degree of activation between the conditions. However, only one of these contrasts was significant. When we compared the degree of brain activation in TBI performing task 1b relative to the activation during performance of task 1c there was a significant difference in the degree of brain activation (Figure 18).

Conversely, when performing condition 1a the control group showed significant activation in the postcentral gyrus (Figure 19). In condition 1b, significant activation was observed in the medial frontal gyrus (Figure 20). In the externally-cued conditions, control subjects activated the postcentral gyrus in condition 2a (Figure 21), and the fusiform gyrus, precentral gyrus, and precuneus in condition 2b (Figure 22).

fMRI Analyses Between-Group Results

The results of the between-group analysis demonstrated that for this set of tasks there was no significant difference between the groups (Table 4, right side). The results of the individual analysis for each subject (tables 5 and 6) demonstrate that there was significant activation for many subjects under many conditions. However, the large

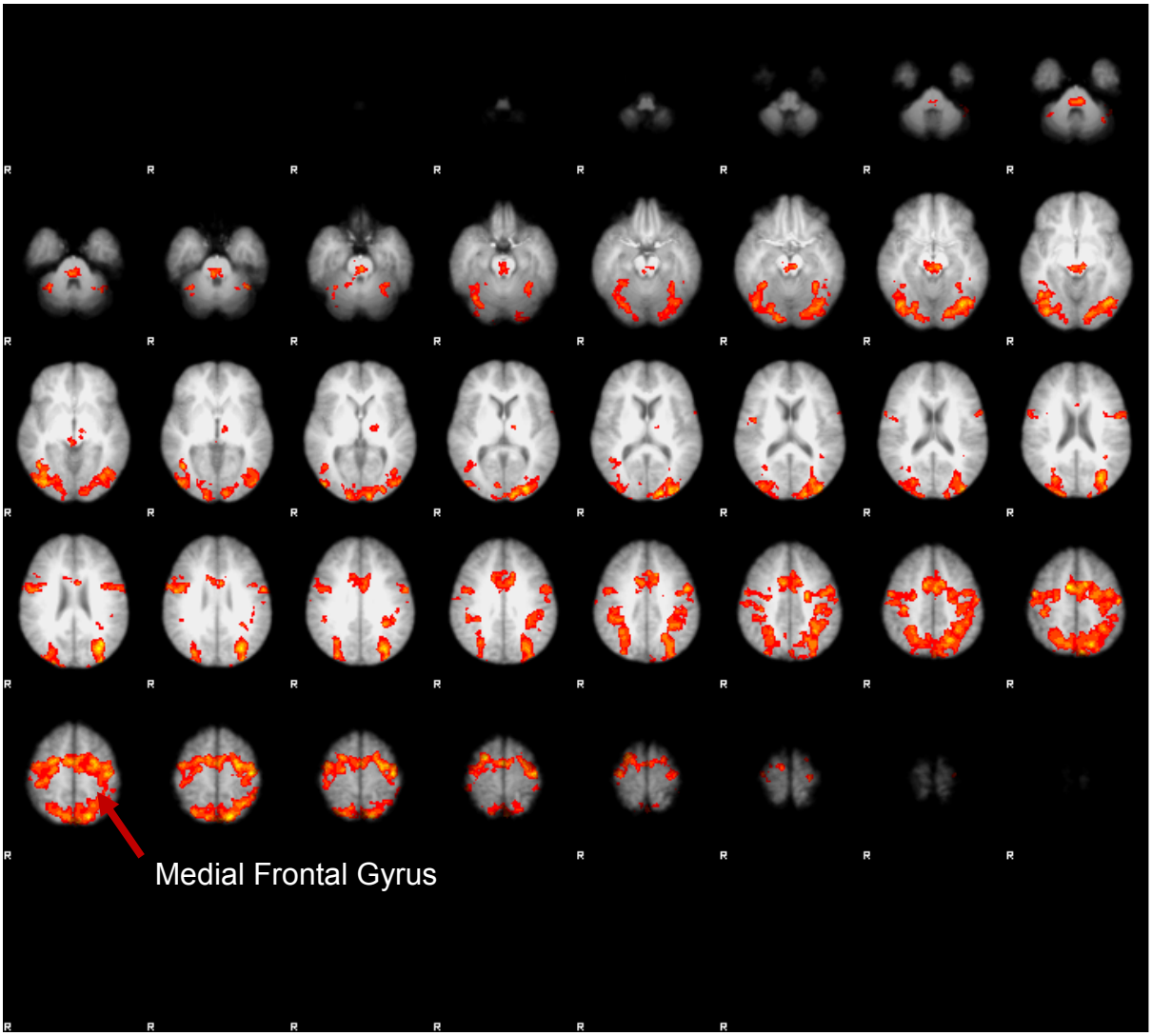

Fig 14. TBI 1b versus rest shows the contrast of brain activation associated with performance of task 1b minus brain activation associated with the rest condition

degree of variability within both groups across the various conditions ultimately made the results statistically insignificant.

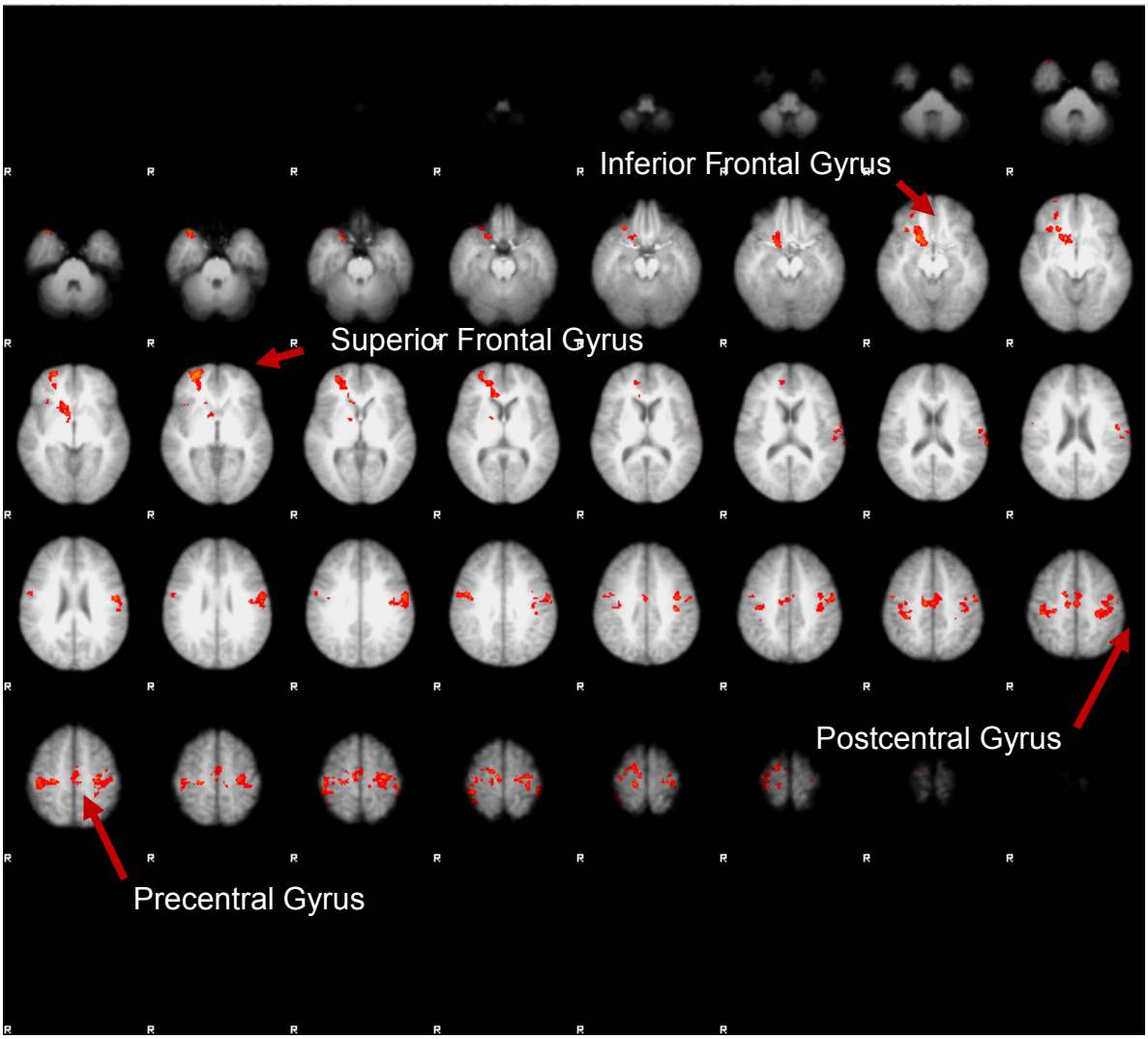

Fig 15. TBI 1c versus rest shows the contrast of brain activation associated with performance of task 1c minus brain activation associated with the rest condition

Region of Interest Analyses

The region of interest analyses within groups yielded significant results on only a handful of conditions (Tables 7 and 8). These regions of interest analyses yielded

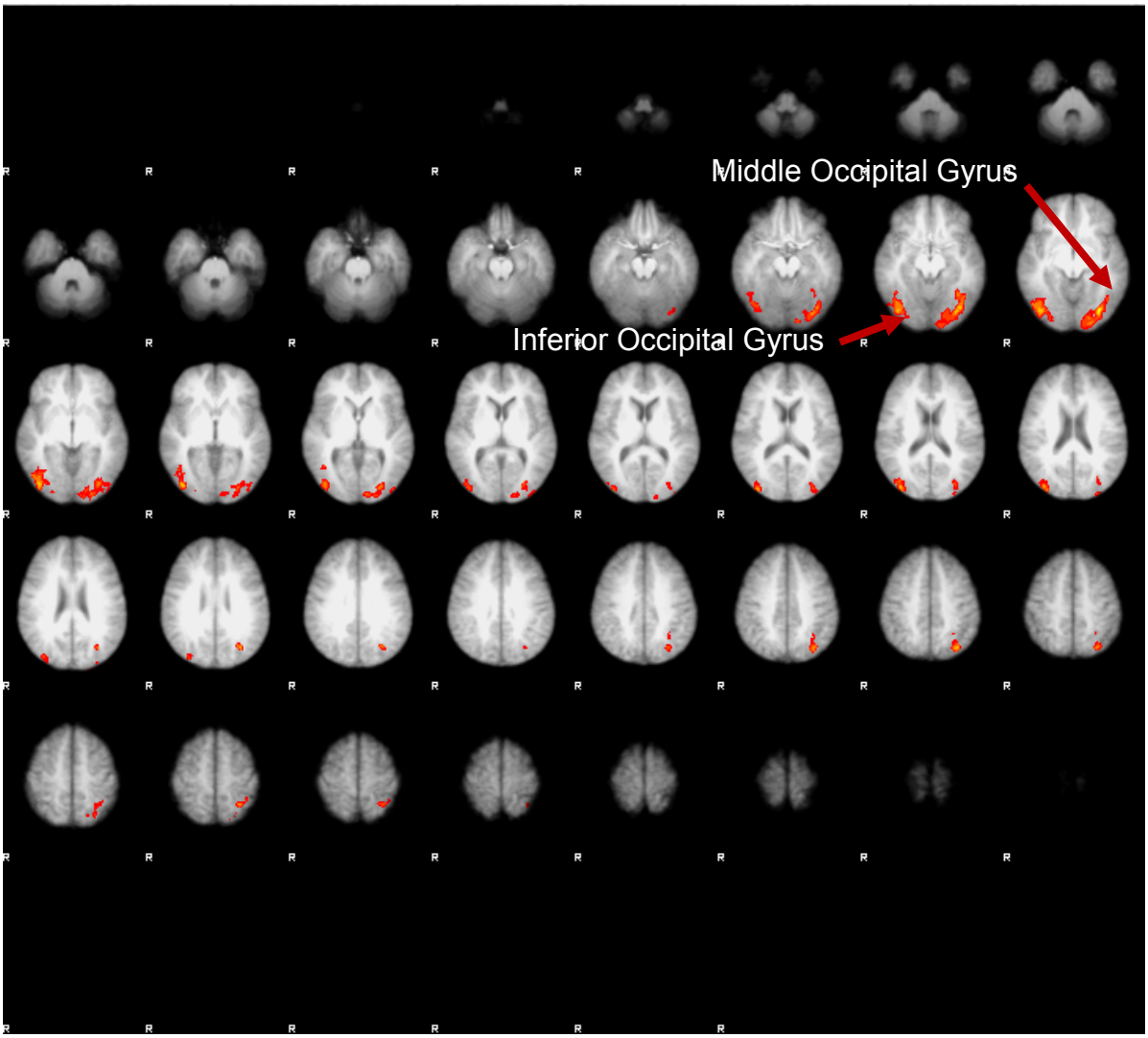

Fig 16. TBI 2a versus rest shows the contrast of brain activation associated with performance of task 2a minus brain activation associated with the rest condition

significant results within the TBI group for tasks 1b, 1c, 2a and 2b that differed slightly from the whole brain analysis previously discussed. Specifically, during task 1b the TBI groups showed significant activation in the superior frontal gyrus, middle frontal gyrus, inferior frontal gyrus pars opercularis, superior parietal lobule, both anterior and posterior

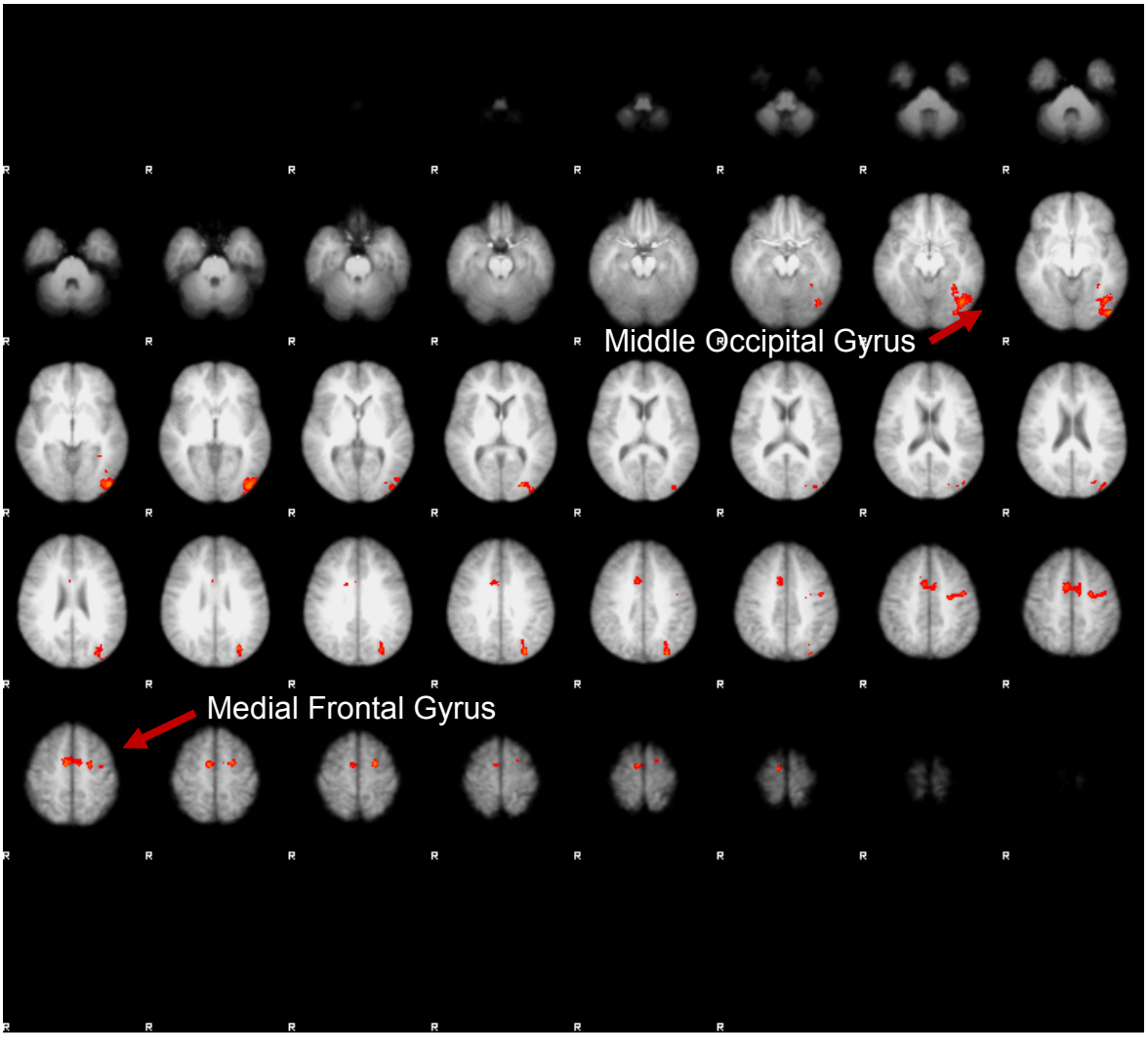

Fig 17. TBI 2b versus rest shows the contrast of brain activation associated with performance of task 2b minus brain activation associated with the rest condition

divisions of the supramarginal gyrus and the angular gyrus none of which were identified in the whole brain analysis. Furthermore, in the 1c condition, the region of interest analysis for the TBI group yielded significant activation within the superior parietal lobule. In condition 2a, there was activation found within the superior frontal gyrus,

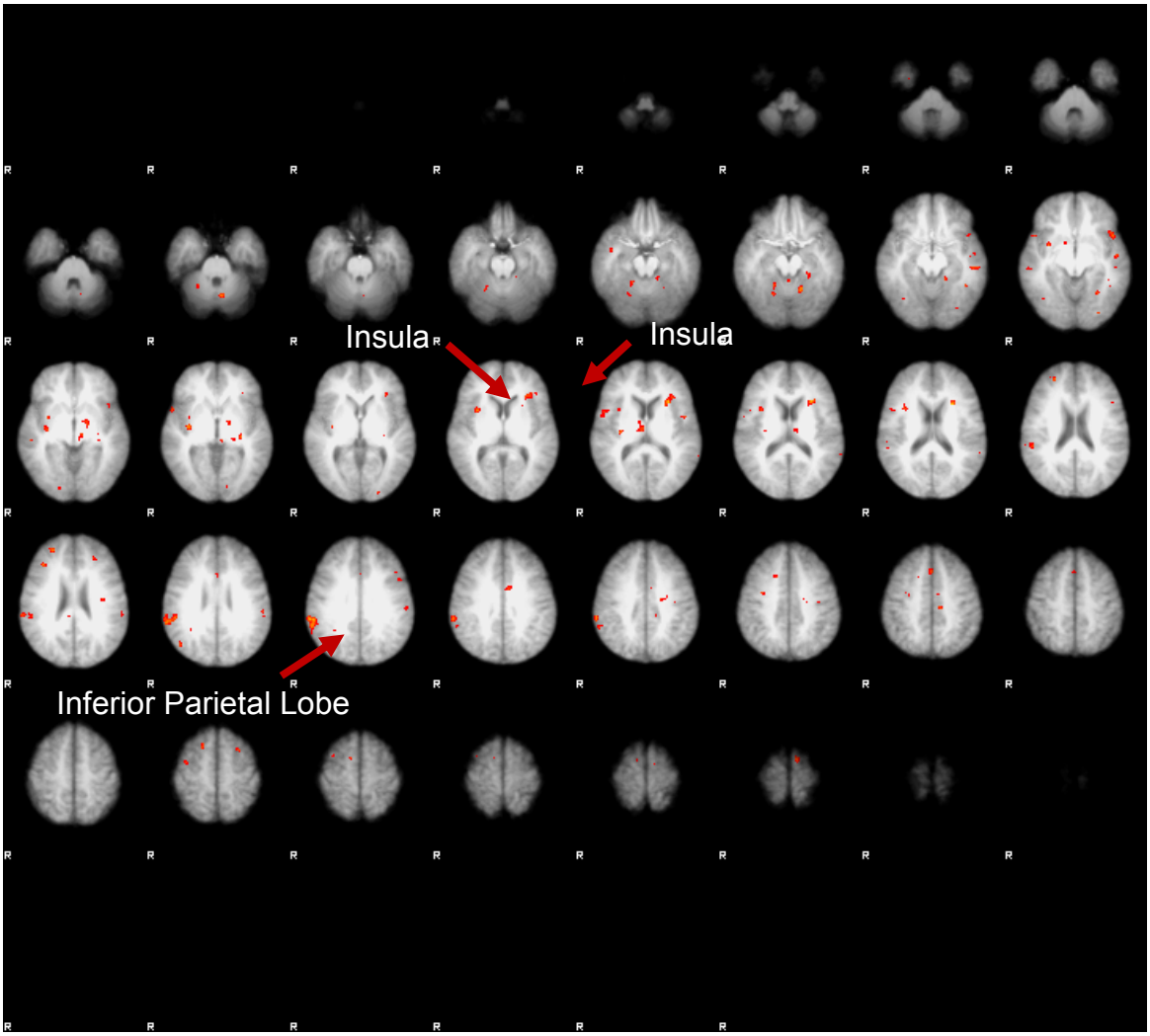

Fig 18. TBI 1b>1c shows the contrast of brain activation associated with performance

middle frontal gyrus and superior parietal lobule within the TBI group. Finally, the task 2b region of interest analysis within the TBI group demonstrated significant activation within the superior frontal gyrus, middle frontal gyrus and the inferior frontal gyrus pars opercularis. Each of these results of the region of interest analysis of task 1b minus brain activation associated with performance of task 1c within the TBI group yielded activations that were not apparent in the previous whole brain assessments.

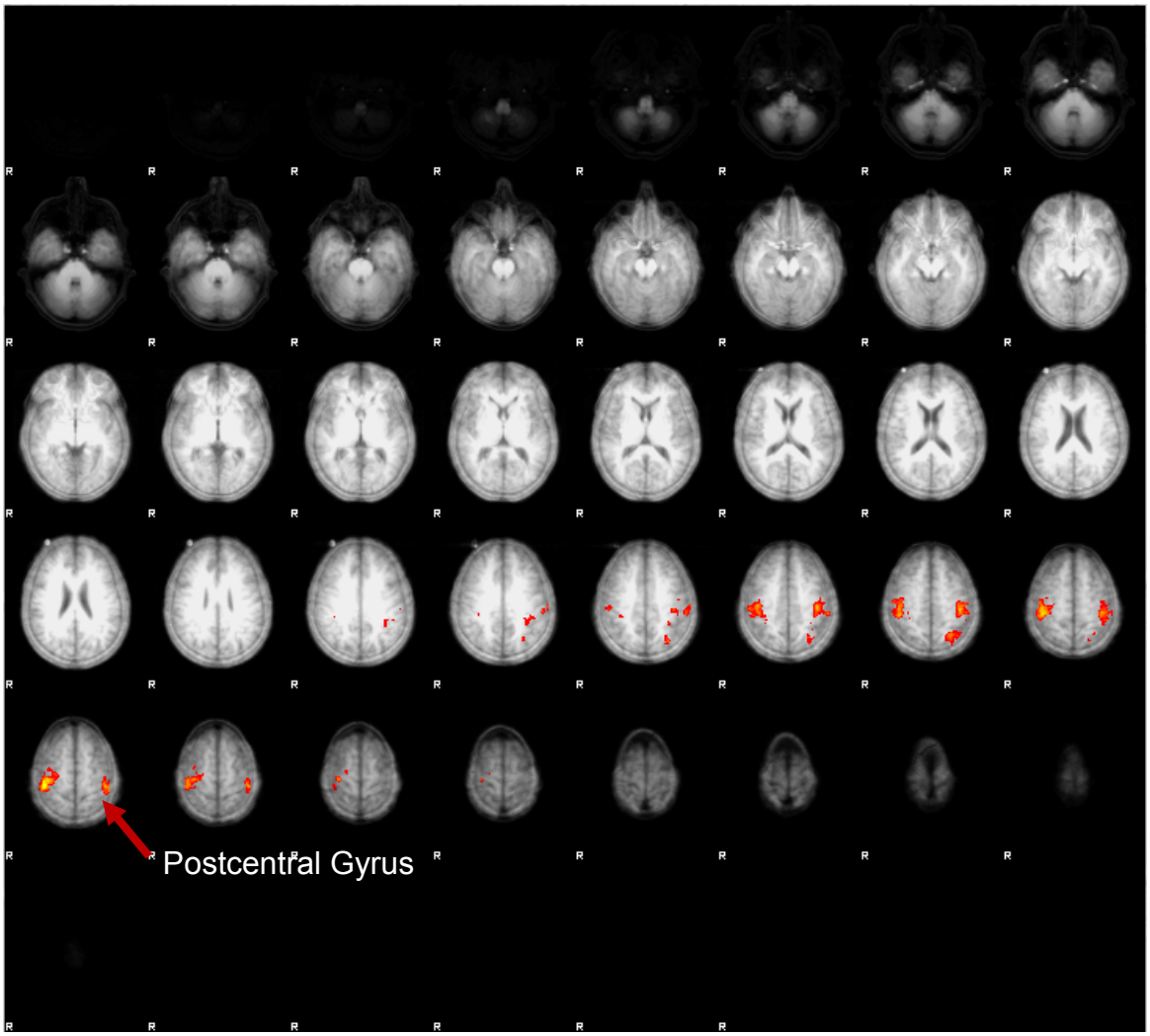

Fig 19. Control 1a versus rest shows the contrast of brain activation associated with performance of task 1a minus brain activation associated with the rest condition.

By contrast the within group region of interest analysis of the controls yielded significant activation within the superior parietal lobule and the angular gyrus. Similar to the results of the within group region of interest analysis of the TBI group, the patterns of activation revealed within the control group were unique relative to the previous whole brain analysis. Despite additional regions of activation uncovered during the within group

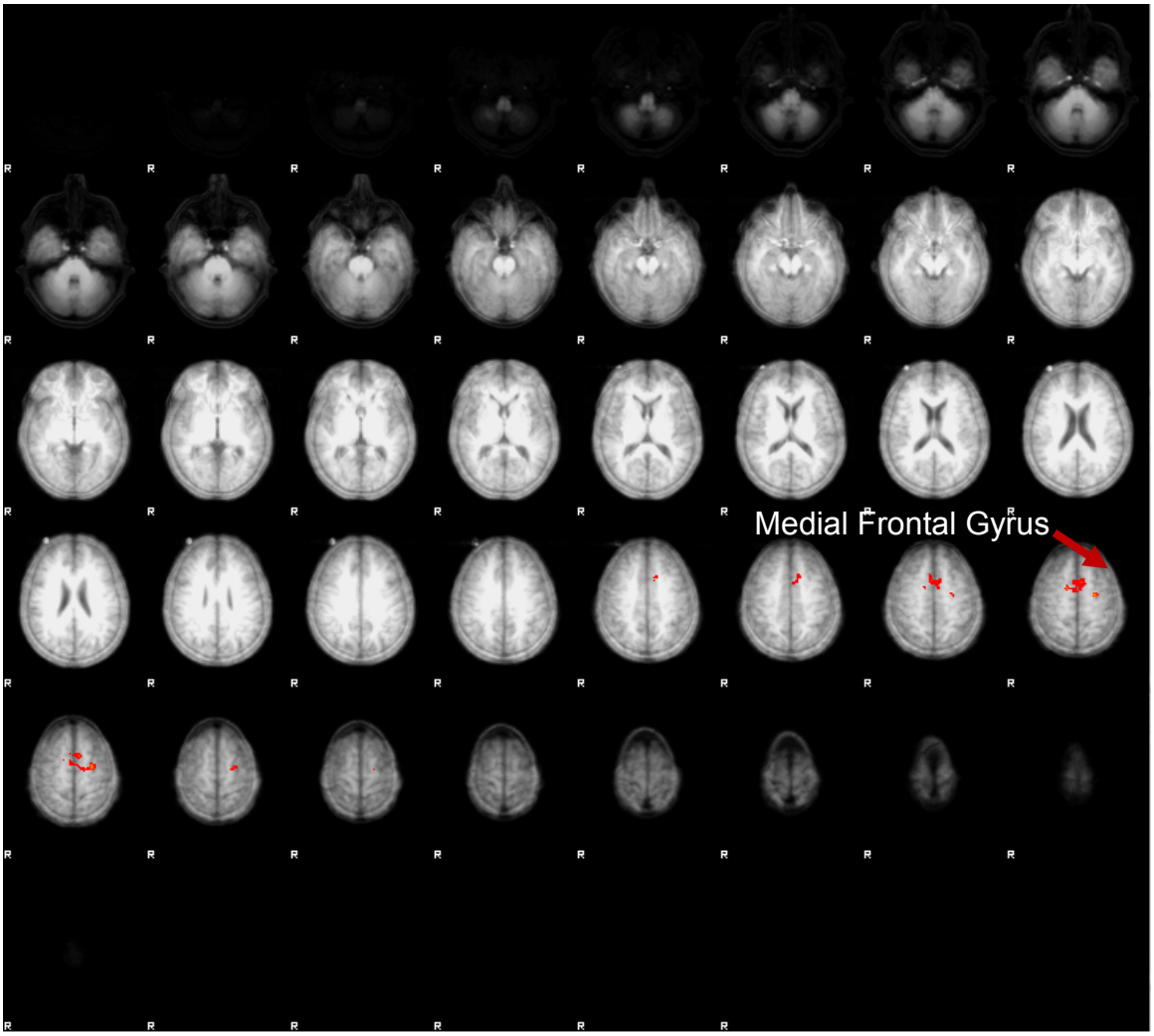

Fig 20. Control 1b versus rest shows the contrast of brain activation associated with performance of task 1b minus brain activation associated with the rest condition

region of interest analysis, the activation during performance of task 1a in the superior parietal lobule as well as the anterior division of the supramarginal gyrus. The control group likewise showed significant activation within task 1b in the anterior division of the supramarginal gyrus. During performance of task 2a, the control subjects showed

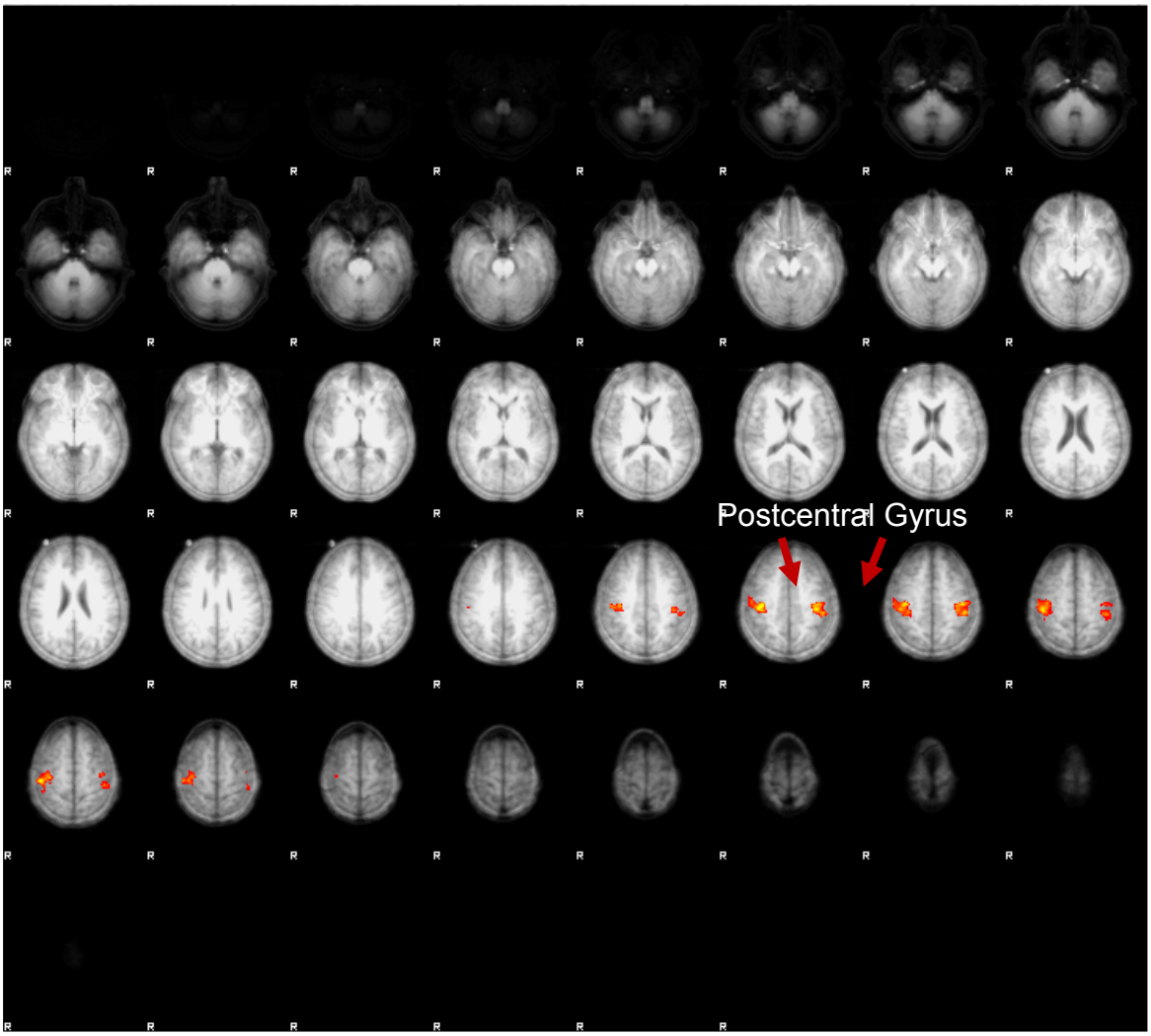

Fig 21. Control 2a versus rest shows the contrast of brain activation associated with performance of task 2a minus brain activation associated with the rest condition

significant activation in the superior parietal lobule and anterior division of the supramarginal gyrus. Finally, during task 2b control subjects showed significant between-group region of interest analysis showed no significant activations when directly comparing the TBI and control groups (Tables 9 and 10).

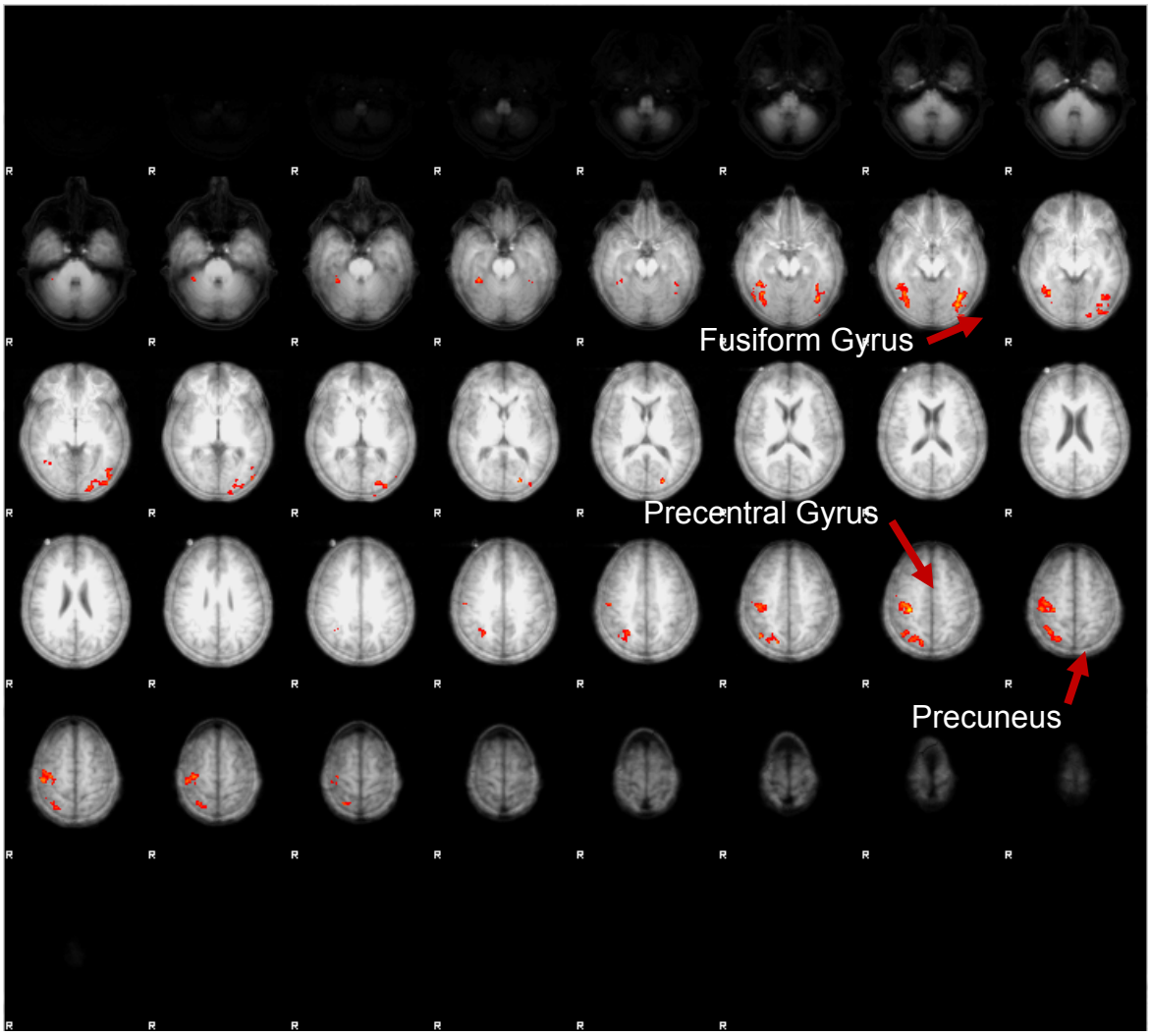

Fig 22. Control 2b versus rest shows the contrast of brain activation associated with performance of task 2b minus brain activation associated with the rest condition

Correlations Within/Between Behavioral Data with fMRI Activation

The correlation assessments between the brain activation data and the behavioral measures indicated that there were several significant correlations in the control subjects that were not evident in the TBI group, and one significant correlation in the TBI

Table 3. Regions of Activation from within-group analyses
Regions of significant activation across the spectrum of tasks are shown with the Talaraich coordinates, corresponding Brodmann's area and anatomical location as well as the total number of contiguous voxels.

TBI						
Task	Talaraich Coordinates					
	X	Y	Z	Brodmann's Area	Anatomical Location	Number of Voxels
1b	-2	-45	32	BA 9	Medial Frontal Gyrus	27404
1c	26	-19	55	BA 6	Precentral Gyrus	1838
	-42	-18	45	BA 3	Postcentral Gyrus	1602
	21	16	-20	BA 47	Inferior Frontal Gyrus	733
	24	49	-1	BA 10	Superior Frontal Gyrus	512
2a	-29	-80	4	BA 18	Middle Occipital Gyrus	2254
	41	-76	-4	BA 19	Inferior Occipital Gyrus	1264
2b	-38	-77	1	BA 19	Middle Occipital Gyrus	1182
	-6	0	55	BA 6	Medial Frontal Gyrus	876
Control						
Task	Talaraich Coordinates					
	X	Y	Z	Brodmann's Area	Anatomical Location	Number of Voxels
1a	38	-25	50	BA 3	Postcentral Gyrus	979
1b	-6	1	50	BA 6	Medial Frontal Gyrus	400
2a	39	-22	50	BA 3	Postcentral Gyrus	793
	-38	-25	50	BA 3	Postcentral Gyrus	544
2b	-32	-74	-8	BA 19	Fusiform Gyrus	643
	37	-22	50	BA 4	Precentral Gyrus	552
	26	-59	50	BA 7	Precuneus	469

Table 4. Within and Between Group Analysis
Shows the total number of activated voxels in the within-group analyses for both subject groups and each condition in columns 2 and 3, as well as the between-groups analyses in columns 4 and 5.

	Within Group Analysis		Between Group Analysis	
Task	TBI Only	Control Only	Control > TBI	TBI > Control
1a	0	1957	0	0
1b	28373	400	0	0
1c	4685	0	0	0
2a	3518	1337	0	0
2b	2058	2081	0	0
2c	0	0	0	0

Table 5. Individual Analysis TBI
Displays the total number of activated voxels found within each individual TBI subject across the six conditions.

	TBI					
Subject	1a	1b	1c	2a	2b	2c
1	52	527	1687	42	0	0
2	28	5810	5982	42	98	183
3	0	4779	0	1030	11210	5838
4	3994	179	554	220	252	0
5	2974	3900	5201	1667	0	0
6	101	389	65	0	26	0
7	145	1143	0	4152	966	1978
8	0	0	1082	0	32	450
9	4314	3333	0	3048	3184	56
10	4075	6989	10056	10034	5949	7314

group that was not observed in the control group (Table 11). Specifically, when we correlated the number of activated voxels in task 1c (internally generated switching) with the error rate there was a positive correlation in the control subjects but not in the TBI subjects. Additionally, the correlation of the number of activated voxels in task 2b (cued congruent) with the error rates showed a positive correlation in the controls. Finally, the control subjects performing task 2c (cued switching) had a positive correlation between

the number of activated voxels and the error rate. The result of these correlations demonstrates that within the control group in tasks 1c, 2b and 2c those subjects prone to making more errors likewise were more likely to show an increased amount of activation within the brain as measured by the number of activated voxels. The one significant correlation in the TBI group occurred during the externally cued switching task 2c where there was a negative correlation between error rate and proportional switch cost (Table 12). This result indicates that for this condition, TBI subjects prone to make more errors tended to have a lower proportional switch cost, whereas TBI subjects with lower error rates tended to have higher proportional switch costs.

Table 6. Individual Analysis Control
Displays the total number of activated voxels found within each individual control subject across the six conditions.

	Control					
Subject	1a	1b	1c	2a	2b	2c
1	118	76	0	0	481	0
2	150	543	1631	7646	924	0
3	6653	953	556	145	427	0
4	0	0	70	409	0	5106
5	26	0	43	615	1149	188
6	2399	2853	278	235	638	0
7	3442	4398	2586	2189	1669	347
8	1278	1549	4513	7772	1797	3247
9	3048	2200	6953	808	10058	133255
10	592	2671	0	4217	5522	31

Table 7. Within TBI Group Region of Interest Analysis
Shows the number of activated voxels found within the TBI group across the six conditions within each specific region of interest.

	Task Type					
Regions of Interest	1a	1b	1c	2a	2b	2c
Superior Frontal Gyrus	0	3317	0	350	240	0
Middle Frontal Gyrus	0	2761	0	293	238	0
Inferior Frontal Gyrus pars triangularis	0	0	0	0	0	0
Inferior Frontal Gyrus pars opercularis	0	753	0	0	202	0
Superior Parietal Lobule	0	4482	246	231	0	0
Supramarginal Gyrus anterior division	0	2356	0	0	0	0
Supramarginal Gyrus posterior division	0	2183	0	0	0	0
Angular Gyrus	0	2004	0	0	0	0

Table 8. Within Control Group Region of Interest Analysis
Shows the number of activated voxels found within the control group across the six conditions within each specific region of interest.

	Task Type					
Regions of Interest	1a	1b	1c	2a	2b	2c
Superior Frontal Gyrus	0	0	0	0	0	0
Middle Frontal Gyrus	0	0	0	0	0	0
Inferior Frontal Gyrus pars triangularis	0	0	0	0	0	0
Inferior Frontal Gyrus pars opercularis	0	0	0	0	0	0
Superior Parietal Lobule	875	0	0	406	731	0
Supramarginal Gyrus (anterior)	851	163	0	317	0	0
Supramarginal Gyrus posterior	305	0	0	0	0	0
Angular Gyrus	0	0	0	0	310	0

Table 9. Between Group Region of Interest Analysis (Control>TBI)
Shows the total number of activated voxels found within each region of interest where control activation is greater than TBI.

	Task Type					
Regions of Interest	1a	1b	1c	2a	2b	2c
Superior Frontal Gyrus	0	0	0	0	0	0
Middle Frontal Gyrus	0	0	0	0	0	0
Inferior Frontal Gyrus pars triangularis	0	0	0	0	0	0
Inferior Frontal Gyrus pars opercularis	0	0	0	0	0	0
Superior Parietal Lobule	0	0	0	0	0	0
Supramarginal Gyrus (anterior)	0	0	0	0	0	0
Supramarginal Gyrus posterior	0	0	0	0	0	0
Angular Gyrus	0	0	0	0	0	0

Table 10. Between Group Region of Interest Analysis (TBI>Control)
Shows the total number of activated voxels found within each region of interest where TBI activation is greater than controls.

	Task Type					
Regions of Interest	1a	1b	1c	2a	2b	2c
Superior Frontal Gyrus	0	0	0	0	0	0
Middle Frontal Gyrus	0	0	0	0	0	0
Inferior Frontal Gyrus pars triangularis	0	0	0	0	0	0
Inferior Frontal Gyrus pars opercularis	0	0	0	0	0	0
Superior Parietal Lobule	0	0	0	0	0	0
Supramarginal Gyrus (anterior)	0	0	0	0	0	0
Supramarginal Gyrus posterior	0	0	0	0	0	0
Angular Gyrus	0	0	0	0	0	0

Table 11. Correlations of fMRI Activation and Behavioral Measures
Demonstrates the series of correlations performed to examine the relationship between performance of the task switching task (RT – reaction time, ER – error rates) and the level or degree of activation within the brain (voxels - number of activated voxels) across the conditions.

Correlations Performed	TBI		Control	
	r^2 Value	P value	r^2 Value	P value
Task 1a voxels x Task 1a RT	0.2907	0.1078	0.0017	0.9110
Task 1a voxels x Task 1a ER	0.0004	0.9582	0.2289	0.1619
Task 1b voxels x Task 1b RT	0.0886	0.4035	0.2713	0.1226
Task 1b voxels x Task 1b ER	0.2895	0.1086	0.0475	0.5451
Task 1c voxels x Task 1c PGC	0.0663	0.4726	0.0409	0.5753
Task 1c voxels x Task 1c PSC	0.2979	0.1026	0.0248	0.6640
Task 1c voxels x Task 1c ER	0.3840	0.0560	0.4216	0.0422*
Task 2a voxels x Task 2a RT	0.0561	0.5102	0.2431	0.1476
Task 2a voxels x Task 2a ER	0.0472	0.5464	0.0810	0.4255
Task 2b voxels x Task 2b RT	0.0150	0.7358	0.0229	0.6766
Task 2b voxels x Task 2b ER	0.2445	0.1462	0.7127	0.0021*
Task 2c voxels x Task 2c PGC	0.0000	0.9904	0.0025	0.8903
Task 2c voxels x Task 2c PSC	0.0020	0.9019	0.0101	0.7821
Task 2c voxels x Task 2c ER	0.0132	0.7518	0.6602	0.0043*

*Significant at p-value <0.05,

Table 12. Correlations of Error Rates and Proportional Costs
Table 12 Demonstrates the series of correlations performed to examine the relationship between performance of the task switching task (PGC – proportional global cost, PSC – proportional switch cost) and the error rates (ER) across the switching conditions.

Correlations Performed	TBI		Control	
	r^2 Value	P value	r^2 Value	P value
Task 1c ER x Task 1c PGC	0.1241	0.3181	0.0151	0.7353
Task 1c ER x Task 1c PSC	0.3123	0.0931	0.0005	0.9515
Task 2c ER x Task 2c PGC	0.3000	0.1012	0.0193	0.7017
Task 2c ER x Task 2c PSC	0.4345	0.0381*	0.0001	0.9838

*Significant at p-value <0.05,

DISCUSSION

We hypothesized that individuals with chronic TBI would display significant differences in brain activation during performance of task-switching paradigms relative to controls during performance of the same task. Specifically, we predicted that chronic TBI subjects would show an increase in both the level and extent of brain activation in areas typically engaged in task-switching paradigms relative to controls. We predicted that these differences would reflect behavioral differences in task performance similar to those observed in the first study. The results showed that chronic TBI and control subjects did not display differences in their behavioral output while performing internally generated switching in a set sequence and externally cued switching. However, there was evidence from this study that the proportional switch costs for externally cued switches were greater than those observed for internally generated switches. Additionally, it appears that despite the lack of major behavioral output differences between the two groups, there may have been subtle differences in the pattern and degree of activation within the brain during performance of these switching paradigms in the within group analyses; however, when we performed between group analyses no differences in the degree of brain activation was found. This lack of between group differences could be due to one or more of the following shortcomings in the study: i) lack of power due to an insufficient number of subject; ii) heterogeneity across the TBI subjects due to the variability in the length of time since injury, and the number and severity of those injuries; and iii) lack of sensitivity of the task-switching paradigm.

The equivalent behavioral performance in the two subject groups contradicts the findings of the first study. This may be the case because despite the fact that the TBI participants in the fMRI study suffered from chronic symptoms (e.g. headache, difficulty concentrating, attentional problems, etc) as the result of 1-10 mild to moderate TBIs from 1-15 years prior, they were otherwise very high functioning. This contrasts with the mTBI subjects from the 1st study who were assessed during the 1st month post-injury. The different behavioral effects in the two studies imply that there is a critical time period during which task switching behavior is maximally disrupted, after which the brain presumably compensates as needed to allow normalized performance.

The current fMRI results are partially consistent with prior findings where mTBI subjects were able to perform at an equal level with healthy controls and yet still displayed differences in brain activation. Specifically, McAllister et al., (2001) employed a set of working memory tasks that incremented from easy to difficult in a stepwise fashion in a study comparing mTBI patients within a month of injury relative to healthy control subjects. The results of that study indicated that although there was no significant difference in performance across the tasks and levels of difficulty, there were differences in brain activity. In particular, patients with mTBI showed the greatest increases in activation during the moderate working memory load conditions, but did not display major increases in activation at the higher working memory load. Conversely, control subjects brain activity ramped up progressively in step with each increase in the working memory difficulty. This result points to a difference in the allocation of working memory resources associated with performance of the task in mTBI patients relative to healthy

controls. Thus, one may propose that the analogous findings in the present study where no behavioral differences are observed despite the unique configuration of brain regions being activated may be due to differences in the pattern of allocation of resources themselves.

The pattern of brain activation during performance of these switching tasks corresponds to the findings from a variety of executive function and task switching research. Activation within the inferior frontal gyrus (IFG) has been suggested to play a role in inhibition of responses, particularly in go/no-go saccade tasks (Chikazoe, 2010). This is of some potential interest because our own investigations of go/no-go saccade tasks in TBI indicate that these subjects erroneously inhibit responses on some 15% of go trials (DeHaan et al., 2007). This may indicate that the network leading to inhibition is heavily relied upon by TBI subjects in the performance of this type of saccade task. In the present study, IFG activation in the TBI group was specifically associated with performance of the internally generated switching task 1c. Thus, one could theorize that inhibition would be necessary to stop oneself from executing the inappropriate response to a given stimuli, as well as inhibiting the previously used response rule when performing switches.

However, there are two concerns with justifying the role of IFG activation found in TBI while performing these task-switching paradigms. The first concern is simply that the go/no-go saccade task is very different from either of the task-switching paradigms employed in this study. There is no direct equivalent within the task switching paradigms of the explicit no-go signal employed in the saccade task. Thus, one may be skeptical that

the IFG area is actually performing inhibition activity in this task series. The second concern is that IFG activation has been implicated in a wide variety of tasks including but not limited to attention, intention, cognitive choices, awareness and visual perception (Chikazoe, 2010). Researchers have thus proposed that the IFG region may be involved in many tasks requiring engagement of awareness or establishment of a task-set system. This more general interpretation may better inform the role of this region in the performance of task switching.

Additional evidence for the possible role of IFG activation can likewise be extracted from an fMRI study comparing interference resolution in young and older adults. A study performed by Zhu and colleagues (Zhu et al., 2010) where subjects performed an arrow flanker task that required focus on the central informative arrow while ignoring the irrelevant flanker arrows. This study indicated that older adults have greater difficulty inhibiting irrelevant components of stimuli and this deficiency correlated with decreased activation in the IFG. This may inform the interpretation of the results from the current investigation because the TBI subjects were activating IFG as an apparent supplementary region that did not appear to be significantly activated in healthy controls. Thus, the fact that behaviorally TBI and controls perform these tasks equivalently may be due to an additional recruitment of IFG to inhibit inappropriate responses, ignore irrelevant information, or maintain awareness and rehearsal of the relevant task-set.

An investigation by Aron and colleagues examined the performance of task-switching paradigms in healthy control subjects and individuals with specific damage to

the inferior frontal gyrus pars opercularis (Aron et al., 2004). The results of this study demonstrated that the pars opercularis region of the inferior frontal gyrus plays a role in the inhibition of responses and/or task-sets in performance of task switching. This interpretation correlates well with the result of the current study where within the ROI analyses the pars opercularis region of the IFG was activated in TBI subjects during both the tasks 1b and 2b (internally generated incongruent responses and externally cued incongruent responses respectively). In both of these tasks, the TBI subjects activated the pars opercularis region of the IFG in order to successfully inhibit inappropriate responses to the stimuli.

The precentral gyrus was activated in task 1c within TBI and task 2b within the control group. The challenge of interpreting the activation within this region, is reconciling this result with those found in previous studies. Research has implicated this region as being involved in a network associated with task switching (Dove et al., 2000) This interpretation sounds reasonable except for the fact that in the current investigation the precentral gyrus was activated in the internally generated switching task (1c) for TBI, but in the externally cued simple incongruent response condition (2b) for controls. However, another study conducted by Sylvester and colleagues demonstrated that the precentral gyrus is essential in the process of inhibiting incorrect prepotent responses and also in selection of the correct response (Sylvester et al., 2003). Thus, within the current investigation, one can assume that prepotent incorrect responses would need to be inhibited during switching conditions as well as in the incongruent response conditions. Therefore, the precentral gyrus activity of the TBI and control groups may be related

primarily to inhibition of the inappropriate response and selection of the appropriate response from two alternative choices.

Activity in the superior frontal gyrus was found in a study by Cutini and colleagues (Cutini et al., 2008) in which subjects were required to switch response types in accordance with two simple visual stimuli using two alternative button responses ‘m’ or ‘n’. In one scenario the stimuli alternated at random between a ‘+’ or a ‘-‘, and these stimuli could be colored green or red. When the stimuli were red, the subjects used the button ‘n’ to respond to the ‘-‘ stimuli and the ‘m’ button to respond to the ‘+’ stimuli. When the stimuli were green this rule reversed and subjects responded to the ‘-‘ stimuli by pressing the ‘m’ button, and responded to the ‘+’ stimuli by pressing the ‘n’ button. The activity within the superior frontal gyrus was found to be associated explicitly with the process of switching between the tasks. This finding helps bolster the role of the SFG activity found in both the whole brain and ROI analyses within our own investigation in the process of task switching. Thus, the role of SFG in performance of the task 1c where subjects were executing internally generated switches is likely related to the process of switching itself.

Activation of the precuneus has been observed in tasks with increased demands on attentional resources including detection of stimuli, stimulus features or the process of shifting attention (Barber and Carter, 2005). Additionally, the precuneus has been implicated in the process of stimulus-response (S-R) mapping. Specifically, studies have shown that the precuneus is significantly activated when S-R mapping is switched as occurs in the current series of task-switching paradigms (Barber and Carter, 2005;

Brown, Vilis and Everling, 2007). The reason we observe precuneus activity in controls during the externally cued incongruent response task 2b may be related to both the process of detecting relevant stimulus features, such as the cue and the location of the red rectangle, as well as the S-R mapping because the subject must likewise integrate the cue information to make an incongruent response.

The fusiform gyrus has been referred to as a visual association cortex due to its function in relaying visual information across a spectrum of stimuli types including verbal and nonverbal stimuli (Bitan et al., 2006). Indeed, the fusiform face area (FFA) has been suggested to be specifically involved in the memory and recall of visual face stimuli (Kanwisher et al., 2006). How can activation in this area be related to the processes underlying task performance in condition 2b in control subjects in the current study? A recent study by Johnson and colleagues (2007) sheds some light on this issue. These authors demonstrated that the FFA is activated when subjects are asked to explicitly think about just-presented visual stimuli. To the extent that such reflective thought contributes to the ability to accurately suppress prepotent responses and generate incongruent responses, one might expect the FFA to become activated (Johnson et al., 2007).

The activation in the occipital areas (medial and inferior occipital gyri) was only observed in the TBI subjects in conditions 2a and 2b. Such aberrant activation in occipital areas has been reported previously in executive function tasks in patients with schizophrenia (Wilmsmeier et al., 2010). As with other compensatory activations, it appears likely that the occipital activity apparent in patient populations like those with

schizophrenia and TBI reflects an attempt by the brain to accommodate task performance with neural circuits that are not normally engaged in the behavior.

The left middle frontal gyrus has been linked to the process of top-down control of task-set. Specifically, this means that activity within the left MFG was required for modulation of endogenous control of task-set (Aron et al., 2004). The MFG region has also been implicated in the process of general task preparation (Gratton et al., 2009). Based on these findings it is not surprising to observe MFG activation in both the TBI and control subjects during task 1b where subjects were performing internally generated incongruent responses. This task would certainly fall under the category of endogenous control, and likewise would be predictable from trial to trial thus allowing for the possibility of general task preparation. However, based upon the results of these prior investigations, the identification of MFG activity in the current study in TBI patients during the performance of task 2b where subjects were using external cues to create incongruent responses is surprising, particularly if MFG is involved primarily in top-down control. It is possible that since the task involves only incongruent responses, that the MFG activation is a reflection of task preparation. On the other hand it is conceivable that the TBI subjects themselves adopted a different strategy for performance of this task by simply ignoring the cue once it had been established that all the stimuli were incongruent. This would effectively cause the externally cued task to be more similar to the internally generated one.

Further evidence in TBI subjects for recruitment of brain areas involved in inhibition processes comes from the activation of the supramarginal gyrus (SMG) during

task 1b. It has been noted in previous fMRI investigations employing go/nogo tasks that SMG is one of multiple regions activated specifically during the nogo trials and thus is consistent with the interpretation of the role of this region in inhibition of responses (Brown, Vilis and Everling 2007). However, other researchers have proposed that SMG may be involved in responses to novel events or during performance of tasks requiring retrieval and/or updating of task rules from working memory (Perianez et al., 2004) which seems to correspond to a functional role in task-switching paradigms. Regardless of whether one favors the explanation that SMG is involved in inhibition or updating of task rules, both explanations provide insight as to why TBI subjects actively recruited this region within the 1b task to facilitate their performance. Additionally, activation within this region was observed in the control group under tasks 1a (simple internally generated congruent task) as well as 2a (simple externally cued congruent task). Thus, it seems most logical to interpret this activation as being indicative of retrieval of task rules from working memory.

Finally, we showed that variations in the accuracy of task switching performance in the control subjects were positively correlated with the extent of activation across the whole brain – subjects who made more errors during the switching conditions also tended to activate more of the brain relative to subjects who made fewer errors. This correlation was not observed in the TBI subjects.

In summary, the results of this study indicate that although there are no significant differences in behavioral output of the internally and externally generated switching tasks between TBI and controls, there are significant differences in the pattern and degree of

activation in the within group analyses. These differences were not very robust, however, and when direct group comparisons were made, no significant activations were found. These results could be attributed to several interacting factors. The chronic TBI subjects had a history of at least one, but as many as ten traumatic brain injuries. These injuries also occurred anywhere from one year to as much as fifteen years prior to testing. These two factors alone create a diverse range of severity of impact from multiple TBIs and time post injury where recovery or compensation could have occurred. It is also important to note that the age at the time of injury was also not accounted for. Prior investigations by Senathi-Raja and colleagues (Senathi-Raja, Ponsford, and Schonberger, 2010) have demonstrated that age at the time of injury may influence the severity of cognitive deficits suffered. Specifically, this investigation demonstrated that subjects who were older at the time of injury likewise displayed poorer performance across a variety of cognitive measures even after accounting for normal age-related declines. Thus, it is conceivable that our subjects' age range at the time of injury, from 19 to 44, may also have contributed to the lack of significant results. Finally, the lack of significant differences in brain activation could be due to the relatively low number of participants and the inherent variability with which they approached the task.

Nevertheless, the current results are consistent with previous findings from TBI groups where the subjects require increased recruitment of resources at lower levels of difficulty in order to maintain the same level of behavioral output as healthy controls. Additionally, the majority of brain regions activated in the TBI group seem to play a role in inhibition, establishment of task set, or detection and resolution of conflict.

Conversely, some of the most interesting patterns of brain activation in controls are likely related to attentional shifts and stimulus-response mapping. These different patterns of activity in controls and TBI subjects support the initial hypothesis that TBI subjects would display larger degrees of activation and would recruit more supplemental areas of the brain to aid performance of the switching tasks.

CHAPTER IV

CONCLUSIONS

GENERAL DISCUSSION

The goals of this dissertation were two-fold. The first goal was to examine the influence of mild TBI on performance of task-switching and whether these impacts generalize across different forms of this task. The second goal was to examine the neural mechanisms underlying executive dysfunction in chronic TBI. These aims were achieved to varying degrees in the conduction of this investigation. We were able to determine that individuals suffering from recent mTBI display deficits in switching behavior within 48 hours of injury that failed to resolve completely even a month post-injury. We likewise were able to demonstrate that these costs in switching did not generalize from a spatial to a numbers task, thus there is some specificity in the deficits of switching behavior within the mTBI population.

Further, we determined that chronic TBI were able to perform internally generated and externally cued switching paradigms with an equivalent degree of success as healthy controls. However, despite the similarities in performance, the TBI group did display a subtle but unique pattern of activity within the brain associated with this performance. Specifically, TBI subjects appeared to increase brain activation at lower

levels of difficulty, but did not continue to increase recruitment at higher levels in a stepwise fashion. This suggest that the TBI subjects themselves have learned to cope with their deficits in such a way that allows them to be high-functioning and thus not display deficits in performance relative to controls.

Conversely, it may be a situation where the tasks themselves simply were not sensitive enough to thoroughly probe the differences in performance of these chronic TBI patients. It is also important to note that the TBI subjects were significantly removed from the dates of their various injuries. Thus, there may have been significant physical as well as behavioral changes that occurred in order to attain normal functionality post-injury.

Future studies should be conducted in order to examine whether the differences in chronic TBI and healthy controls may likewise include behavioral deficits that were simply not captured within the current investigation due to lack of sensitivity within the paradigms employed. I would suggest including higher degrees of difficulty in the internally generated task which elicited more significant differences in brain activation between the two groups. One may hope that administration of a more difficult task would not only show different patterns of brain activation, but would likewise cause any distinctions in the behavioral output to become more readily apparent.

REFERENCES

American Academy of Neurology, Practice parameter: the management of concussion in sports. Report of the Quality Standards Committee. *Neurology* 1997; 48: 581-5.

Azouvi P, Couillet J, Leclercq M, Martin Y, Asloun S, Rousseaux M. Divided attention and mental effort after severe traumatic brain injury. *Neuropsychologia* 2004; 42:1260-68.

Bailes J, Hudson V. Classification of sport-related head trauma: a spectrum of mild to severe injury. *J Athl Train* 2001; 36: 236-43.

Barber A, and Carter C. Cognitive control involved in overcoming prepotent response tendencies and switching between tasks. *Cerebral Cortex*. 2005; 14: 866-912.

Bergeson A, Lundin R, Parkinson R, Tate D, Victoroff J, Hopkins R, Bigler E. Clinical rating of cortical atrophy and cognitive correlates following traumatic brain injury. *The Clinical Neuropsychologist* 2004; 18: 509-20.

Bitan T, Booth J, Choy J, Burman D, Gitelman D, Mesulam M. Shifts of effective connectivity within a language network during rhyming and spelling. *J Neurosci*. 2005; 25: 5397-403.

Brass M, von Cramon. The role of the frontal cortex in task preparation. *Cerebral Cortex* 2002; 1047: 908-14.

Brass M, von Cramon. Decomposing components of task preparation with functional magnetic resonance imaging. *Journal of Cognitive Neuroscience* 2004; 16: 609-20.

Brown M, Vilis T, Everling S. Isolation of saccade inhibition processes: Rapid event-related fMRI of saccades and nogo trials. *NeuroImage* 2008; 39: 793-804.

Brown M, Semelka R. MRI basic principles and applications 3rd edition. 2003. John Wiley and sons, Inc. Hoboken, New Jersey.

Botvinick M, Nystrom L, Fissel K, Carter C, Cohen J. Conflict monitoring versus selection-for-action in anterior cingulate cortex. *Nature* 1999; 402: 179-91.

Casey B, Davidson C, Hara Y, Thomas K, Martinez A, Galvan A, Halperin J, Rodriguez-Aranda C, Tottenham N. Early development of subcortical regions involved in non-cued attention switching. *Developmental Science*. 2004; 7: 534-42.

Catena R, van Donkelaar P, Halterman C, Chou LS. Spatial orientation of attention and obstacle avoidance following concussion. *Exp Brain Res*. 2000; 194: 67-77.

Chan R. Attentional deficits in patients with persisting postconcussive complaints: a general deficit or specific component deficit? *J Clin Exp Neuropsychol*. 2002; 24: 1081-93.

Chan R, Hoosain R, Lee T, Fan Y, Fong D. Are there sub-types of attentional deficits in patients with persisting post-concussive symptoms? A cluster analytical study. Brain Inj. 2003; 17: 131-48.

Chen J, Johnston K, Frey S, Petrides M, Worsley K, Ptito A. Functional abnormalities in symptomatic concussed athletes: an fMRI study. *Neuroimage*. 2004; 22: 68-82.

Chen J, Johnston K, Collie A, McCrory P, Ptito A. A validation of the post concussion symptom scale in the assessment of complex concussion using cognitive testing and functional MRI. *J Neurol Neurosurg Psychiatry*. 2007; 78: 1231-38.

Chikazoe J. Localizing performance of go/no-go tasks to prefrontal cortical subregions. *Curr Opin Psychiatry* 2010; 23: 267-72.

Christodoulou C, DeLuca J, Ricker J, Madigan N, Bly B, Lange G, Kalnin A, Liu W, Steffener J, Diamond B, Ni A. Functional magnetic resonance imaging of working memory impairment after traumatic brain injury. *J Neurol Neurosurg Psychiatry*. 2001; 71: 161-68.

Cicerone K. Attention deficits and dual task demands after mild traumatic brain injury. *Brain Inj*. 1996; 10: 79-89.

Cutini S, Scatturin P, Menon E, Bisiacchi P, Gamberini L, Zorzi M, Dell'Acqua R. Selective activation of the superior frontal gyrus in task-switching: An event-related fNIRS study. *NeuroImage*. 2008; 42: 945-55.

DeHaan A, Halterman C, Langan J, Drew A, Osternig L, Chou L-S, van Donkelaar P. Canceling planned actions following mild traumatic brain injury. *Neuropsychologia* 2006; 45: 406-11.

De Sanctis P, Gomez-Ramirez M, Sehatpour P, Wylie G, Foxe J. Preserved executive function in high-performing elderly is driven by large-scale recruitment of prefrontal cortical mechanisms. *Hum Brain Mapp* 2009; 30: 4198-214.

Dove A, Pollmann S, Schubert T, Wiggins C, von Cramon D. Prefrontal cortex activation in task switching: an event-related fMRI study. *Cognitive Brain Research*. 2000; 9: 103-9.

Drew A, Langan J, Halterman C, Osternig L, Chou L-S, van Donkelaar P. Attentional disengagement dysfunction following mTBI assessed with the gap saccade task. *Neuroscience Letter* 2007; 417: 61-5.

Fan J, McCandliss B, Sommer T, Raz A, Posner M. Testing the efficiency and independence of attentional networks. *J Cogn Neurosci* 2002; 14: 340-7.

Felmingham K, Baguely I, Green A. Effects of diffuse axonal injury on speed of information processing following severe traumatic brain injury. *Neuropsychology* 2004; 18: 564-71.

Forstmann B, Brass M, Koch I, von Cramon Y. Internally generated and directly cued task sets: an investigation with fMRI. *Neuropsychologia* 2005; 43: 943-52.

Giza C, Hovda, D. The neurometabolic cascade of concussion. *J Athl Train* 2001: 36: 228-35.

Gratton G, Wee E, Rykhlevkaia E, Leaver E, Fabiana M. Does white matter matter? Spatio-temporal dynamics of task switching in aging. Journal of Cognitive Neuroscience. 2008; 21: 1380-95.

Halterman C, Langan J, Dreq A, Rodriguez E, Osternig L, Chou L-S, van Donkelaar P. Tracking the recovery of visuospatial attention deficits in mild traumatic brain injury. Brain 2006; 129: 747-53.

Hyafil A, Summerfield C, Koechlin E. Two mechanisms for task switching in the prefrontal cortex. 2009; 29: 5135-42.

Jantzen K, Anderson B, Steinberg F, Scott Kelso J. A prospective functional MR imaging study of mild traumatic brain injury in college football players. *AJNR Am J Neuroradiol*. 2004; 25: 738-45.

Johnson M, Mitchell K, Raye C, D'Esposito M, Johnson M. A brief thought can modulate activity in extrastriate visual areas: Top-down effects of refreshing just-seen visual stimuli. *Neuroimage*. 2007; 37: 290-9.

Kanwisher N, Yovel G. The fusiform face area: a cortical region specialized for the perception of faces. *Philos Trans R Soc Lond B Biol Sci*. 2008; 361: 2109-28.

Kelly J, Nichols J, Filley C, Lillehei K, Ruinstein D, Kleinschmidt-DeMasters B. Cocnussion in sports. Guidelines for prevention of catastrophic outcome. *JAMA* 1991; 27: 2867-9.

Kraus M, Susmaras T, Caughlin B, Walker C, Sweeney J, Little D. White matter integrity and cognition in chronic traumatic brain injury: a diffusion tensor imaging study. 2007; 130: 2508-19.

Levine B, Cabeza R, McIntosh A, Black S, Grady C, Stuss D. Functional reorganization of memory after traumatic brain injury: a study with H(2)(15) positron emission tomography. *J Neurol Neurosurg Psychiatry*. 2002; 73: 173-81.

Lotze M, Grodd W, Rodden F, Gut E, Schonle P, Kardatski B, Cohen L. Neuroimaging patterns associated with motor control in traumatic brain injury. *Neurorehabil Neural Repair*. 2006; 20: 14-23.

Luks T, Simpson G, Feiwell R, Miller W. Evidence for anterior cingulated cortex involvement in monitoring preparatory attentional set. *NeuroImage* 2002; 17: 792-802.

Mayr U, Bell T. On how to be unpredictable. *Psychological Science* 2006; 17: 774-80.

Magistretti P, Pellerin L. Cellular mechanisms of brain energy metabolism and their relevance to functional brain imaging. *Phil Trans. R. Soc. Lond. B*. 1999; 354: 1155-63.

McAllister T, Sparling M, Flashman L, Guerin S, Mamourian A, Saykin A. Differential working memory load effects after mild traumatic brain injury. *NeuroImage* 2001; 14: 1004-12.

McIntire A, Langan J, Halterman C, Dreq A, Ostenig L, Chou L-S, van Donkelaar P. The influence of mild traumatic brain injury on the temporal distribution of attention. *Experimental Brain Research* 2006; 174: 361-6.

McNab F, Leroux G, Strand F, Thorell L, Bergman S, Klingberg T. Common and unique components of inhibition and working memory: an fMRI, within-subject investigation. *Neuropschologia* 2008; 46: 2668-82.

Nagel M, Sprenger A, Hohagen F, Binkofski F, Lencer R. Cortical mechanisms of retinal and extraretinal smooth pursuit eye movements to different target velocities. *Neuroimage*. 2008; 41: 483-92.

Niogi S, Mukherjee P, Ghajar J, Johnson C, Kolster R, Lee H, Suh M, Simmerman R, Manley G, McClandiss B. Structural dissociation of attentional control and memory in adults with and without mild traumatic brain injury. *Brain* 2008; 131: 3209-21.

Parker T, Osternig L, van Donkelaar P, Chou LS. Gait stability following concussion. *Med Sci Sports Exerc*. 2006; 38: 1032-40.

Parker T, Osternig L, van Donkelaar P, Chou LS. Balance control during gait in athletes and non-athletes following concussion. *Med Eng Phys* 2008; 30: 959-67.

Perianez J, Maestu F, Barcelo F, Fernandez A, Amo C, Alonso T. Spatiotemporal brain dynamics during preparatory set shifting: MEG evidence. *NeuroImage*. 2004; 21: 687-95.

Perlstein W, Cole M, Demery J, Seignourel P, Dixit N, Larson M, Briggs R. Parametric manipulation of working memory load in traumatic brain injury: behavioral and neural correlates. *J Int Neuropsychol Soc*. 2004; 10: 724-41.

Pessoa L, Rossi A, Japee S, Desimone R, Ungerleider LG. Attentional control during the transient updating of cue information. *Brain Research* 2009; 1247: 149-58.

Ponsford J. Kinsella G. Attentional deficits following closed-head injury. *J Clin Exp Neuropsychol*. 1992; 14: 822-38.

Ruge H, Muller S, Braver T. Anticipating the consequences of action: An fMRI study of intention-based task preparation. *Psychophysiology*. 2010; 47: 1019-27.

Rushworth M, Hadland K, Paus T, Sipila K. Role of the human medial frontal cortex in task switching: a combined fMRI & TMS study. *J Neurophysiol*. 2001; 87: 2577-92.

Rushworth M, Hadland K, Gaffan D, Passingham R. The effect of cingulate cortex lesions on task switching and working memory. *J Cogn Neurosci* 2003; 15: 338-53.

Rushworth M, Passingham R, Nobre A. Components of attentional set-switching. *Exp Psychol*. 2005; 52: 83-98.

Rushworth M, Buckley M, Behrens T, Walton M, Bannerman D. Functional organization of the medial frontal cortex. *Current Opinion in Neurobiology*. 2007; 17: 1-8.

Senathi-Raja D, Ponsford J, Schonberger M. Impact of age on long-term cognitive function after traumatic brain injury. *Neuropsychology*, 2010; 24: 336-44.

Scheibel R, Newsome M, Steinberg J, Pearson D, Rauch R, Mao H, Troyanskaya M, Sharma R, Levin H. Altered brain activation during cognitive control in patients with moderate to severe traumatic brain injury. *Neurorehabil Neural Repair* 2007; 21: 36-45.

Scheibel R, Newsome M, Troyanskaya M, Steinberg J, Goldstein F, Mao H, Levin H. Effects of severity of traumatic brain injury and brain reserve on cognitive-control related brain activation. *Journal of Neurotrauma* 2008; 26: 1447-61.

Schmitter-Edgecombe M, Langill M. Costs of predictable switch between simple cognitive tasks following severe closed-head injury. *Neuropsychology* 2006; 20: 675-84.

Soeda A, Nakashima T, Okumura A, Kuwata K, Shinoda J, Iwama T. *Neuroradiology*. 2005; 47: 501-6.

Spikman J, van Zomeren A, Deelman B. Deficits of attention after closed-head injury: slowness only? *J Clin Exp Neuropscyhol*, 1996; 18: 755-67.

Stuss D, Stethem L, Hugenholtz H, Picton T, Pivik J, Richard M. Reaction time after head injury: fatigue, divided and focused attention and consistency of performance. *J Neurol Neurosurg Psychiatry* 1989a; 52: 742-48

Stuss D, Stethem L, Picton T, Leech E, Pekchat G. Traumatic brain injury, aging and reaction time. *Can JNeurol Sci* 1989b; 16: 161-7.

Sylvester C, Wager T, Lacey S, Hernandez L, Nichols T, Smith E, Jonides J. Switching attention and resolving interference: fMRI measures of executive functions. *Neuropsychologia*. 2003; 41: 357-70.

Tsacopoulous M, Magistretti P. Metabolic coupling between glia and neurons. *The Journal of Neuroscience*. 1996; 16: 877-85.

van Donkelaar P, Langan J, Rodriguez E, Drew A, Halterman C, Osternig L, Chou L-S. Attentional deficits in concussion. *Brain Inj* 2005; 19: 1031-9.

Wilmsmeier A, Ohrmann P, Suslow T, Siegmund A, Koelkebeck K, Rothermundt M, Kugel H, Arolt V, Bauer J, Pedersen A. Neural correlates of set-shifting: decomposing executive functions in schizophrenia. *J Psychiatry Neurosci*. 2010; 35: 321-9.

Zhu D, Zacks R, Slade J. Brain activation during interference rslution in young and older adults: an fMRI study. *NeuroImage* 2010; 50: 810-7.