ABSTRACT

Devin Smith
Using fMRI and neuropsychological tests to index brain function and intellectual abilities following a history of multiple concussions
(Under the direction of L. Stephen Miller, Ph.D.)

Concussive injuries occur often in physically trying contact sports such as football and rugby. These injuries can impair neural activity, which in turn negatively effects neurocognitive performance. The purpose of this experiment is to use functional MRI (fMRI) to define and track temporal changes in brain function associated with concussive injuries; assess the positive relationship between fMRI defined brain function and neurocognitive performance using traditional neuropsychological tests; and investigate the relationship between fMRI defined brain function and symptom permanence in athletes with a history of multiple concussions. Based on previous research and the extant literature it is expected that athletes with a history of multiple concussive injuries will show specific patterns of fMRI BOLD response that differentiate them from matched controls. It is also expected that participants with a history of multiple concussions will perform significantly worse on the neuropsychological tasks than matched controls. However, the results indicate no such findings; in fact, there were no significant differences between the experimental group and their control counterparts on the neuropsychological testing, fMRI defined brain activation, response time or accuracy on the fMRI tasks. These results could point to greater neuroplasticity amongst young athletes than was previously thought. It is possible that the tasks used didn’t accurately measure traits that are changed after concussive injuries, or the sample size may not be large enough to show statistically significant differences in behavioral or fMRI data. Finally, it is possible that having two to three concussions is below the threshold at which one can expect to see permanent changes.

INDEX WORDS: Concussive injury, fMRI, fMRI defined brain activation, Neurocognitive performance, RBANS, WTAR, Stroop, OSPAN
USING fMRI AND NEUROPSYCHOLOGICAL TESTS TO INDEX BRAIN FUNCTION AND INTELLECTUAL ABILITIES FOLLOWING A HISTORY OF MULTIPLE CONCUSSIONS

by

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DEDICATION

I would like to dedicate this thesis to my parents, who, with their unconditional love and support, have allowed me all of the opportunities to fulfill my dreams.
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I would like to thank my lab director, Dr. L. Stephen Miller, for taking me on as an undergraduate researcher in his lab almost two years ago and for funding this study. With his constant support and direction, I was able to push through all of the problems that arose during this study. I have now presented this research at an international conference and have written this thesis thanks to him.

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# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACKNOWLEDGEMENTS</td>
<td>v</td>
</tr>
<tr>
<td>LIST OF FIGURES</td>
<td>ix</td>
</tr>
<tr>
<td><strong>CHAPTERS</strong></td>
<td></td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>Background And Significance</td>
<td>1</td>
</tr>
<tr>
<td>Preliminary Studies</td>
<td>6</td>
</tr>
<tr>
<td>Specific Aims</td>
<td>11</td>
</tr>
<tr>
<td>METHODS AND MATERIALS</td>
<td>13</td>
</tr>
<tr>
<td>Participants</td>
<td>13</td>
</tr>
<tr>
<td>Neuropsychological Testing</td>
<td>13</td>
</tr>
<tr>
<td>fMRI</td>
<td>14</td>
</tr>
<tr>
<td>Data Analysis</td>
<td>15</td>
</tr>
<tr>
<td>RESULTS</td>
<td>19</td>
</tr>
<tr>
<td>Participants</td>
<td>19</td>
</tr>
<tr>
<td>Neuropsychological Testing</td>
<td>19</td>
</tr>
<tr>
<td>fMRI behavioral data</td>
<td>20</td>
</tr>
<tr>
<td>fMRI defined brain activation</td>
<td>20</td>
</tr>
<tr>
<td>DISCUSSION</td>
<td>32</td>
</tr>
<tr>
<td>WORKS CITED</td>
<td>35</td>
</tr>
</tbody>
</table>
LIST OF FIGURES

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Block Design of fMRI tasks</td>
<td>18</td>
</tr>
<tr>
<td>2</td>
<td>Average Participant Performance on Neuropsychological Tests by group</td>
<td>23</td>
</tr>
<tr>
<td>3</td>
<td>Average Participant Performance on O-SPAN task by condition and group</td>
<td>24</td>
</tr>
<tr>
<td>4</td>
<td>Average Participant Response Time on O-SPAN task by condition and group</td>
<td>25</td>
</tr>
<tr>
<td>5</td>
<td>Average Participant Performance on STROOP task by condition and group</td>
<td>26</td>
</tr>
<tr>
<td>6</td>
<td>Average Participant Response Time on STROOP task by condition and group</td>
<td>27</td>
</tr>
<tr>
<td>7</td>
<td>fMRI defined brain activation during the O-SPAN task by group</td>
<td>28</td>
</tr>
<tr>
<td>8</td>
<td>fMRI defined brain activation during the Stroop task by group</td>
<td>29</td>
</tr>
<tr>
<td>9</td>
<td>fMRI defined brain activation during the Visual task by group</td>
<td>30</td>
</tr>
<tr>
<td>10</td>
<td>fMRI defined brain activation during the Motor task by group</td>
<td>31</td>
</tr>
</tbody>
</table>
CHAPTER 1
INTRODUCTION

Background and Significance

A concussive head injury can be defined as “a complex pathophysiological process affecting the brain, induced by traumatic biomechanical forces” (Aubry, Cantu, Dvorak et al., 2002). In layman’s terms, it can best be understood as a sudden impact to the head that causes changes in the way that the brain functions. In the existing literature, the terms concussion and mild traumatic brain injury (MTBI) are used interchangeably (Meehan, Bachur, 2009). The ways in which concussive injuries can affect people vary widely; additionally, different people can respond quite dissimilarly to traumatic head injuries. For example, two athletes may sustain similar impact forces, but only one athlete will show signs of a brain injury (Duma, Manoogian, Bussone et al., 2005). This fact presents a major problem for determining how badly someone will be affected by their injury. It is necessary to obtain and compile more data pertaining to these experiences from the athletes so that a better prognosis will be available for future incidents.

Cognitive deficits are normally considered obvious after someone experiences a concussion. However, it is nearly impossible to tell how much someone has been hampered without knowing the level at which they performed at prior to the event. This is especially crucial in athletics when determining at what point someone can return to play - at a time when symptoms have totally resolved. Ideally, participants will have pre-morbid testing results with which to compare against post-concussion functioning. Typically, though, there are no baseline
measures of neurocognitive ability or brain activation prior to an injurious episode. A lack of expectancy and/or thought on behalf of the athletic administration or the players' own feelings of immunity may perpetuate the lack of preparedness. The next best thing to actual pre-morbid results is neuropsychological tests that yield findings which are resistant to traumatic injuries. The injured individual's testimony corroborated by familial accounts can add to the mix to generate a better picture of the person’s intellectual and cognitive abilities pre-concussion.

The ability to monitor the angle and direction of force applied to the head would help tremendously in being able to generate more reliable estimates of post concussive effects. Such measures would allow systematic groupings of different types of concussions (i.e. force to the frontal lobe vs. the occipital lobe) and the length at which specific effects typically linger. Starting in the 1970s the biomechanics of traumatic brain injury have been studied using instrumentation (Moon, Beedle, Kovacic, 1971). Recent strides have been made in gathering this type of data using ingenuity and new technologies. Pellman et al. (2003) used recording from National Football League (NFL) games to monitor head impacts; they recreated the scenarios in the lab using dummies. This allowed the group to measure the expected acceleration, both translational and rotational, of the athletes’ heads during impact. Inspired by this technique, Duma et al. (2005) used a wireless computer system placed within football players’ helmets to measure acceleration, impact - including rotational - forces, and impact sites during practices and games. This recorded data allows a better categorical approach to be taken with regards to concussive blows. Symptoms from each type of concussion based on acceleration, force, and site will be able to be recorded and cataloged for the future prognosis of similar injuries.

Although biomechanical data is a great asset to have, alone it is not enough to detect a head injury. It is necessary to use physical and cognitive symptoms to correctly diagnose a
concussion. There is a plethora of such symptoms that can arise after mild traumatic head injury. For example, a concussive head injury causes a period of abundant release of neurotransmitters and ions in the brain which alters the potential of neuronal membranes; the brain’s glucose metabolism is greatly increased as more energy is needed to correct the abnormal potential (Giza and Hovda, 2001). Soon after this hypermetabolic state, the levels taper off and the brain goes into a metabolic depression (Yoshino, Hovda, Kawamata et al., 1991). The altered state of metabolism prolongs the time in which the concentrations of important neurotransmitters and ions within the brain are awry.

Concussions can also cause impairment of sensory gating, the automatic determination of what sensory stimuli are ignored and accepted (Kumar, Rao, Nair et al., 2005). This can overwhelm the sufferer with too much incoming information causing distress and fatigue. More noticeably, though, this inability to sort out information leads to a perceived distractibility or inability to pay attention to target stimuli (Arciniegas, Olincy, Topkoff et al., 2000). This lack of attention makes it difficult for injured parties to process potentially important information. Additionally, people have reported headaches, dizziness, energy shortages, and decreased memory capability following a mild head injury (Rimel, Giodani, Barth et al., 1981; Levin, Mattis, Ruff et al., 1987). Moreover, Guskiewicz et al. (1996) found that mild head injuries cause a loss of postural stability in sufferers. These symptoms can have quite a dramatic effect on normal everyday functioning, often times requiring a leave of absence from daily activities such as work or school. Typically, symptoms resolve within a matter of days. Guskiewicz et al. (2003) found in one study that it took 3.5 days on average for symptom resolution in collegiate athletes; 87.5 % participants had recovered measurable function within one week. Additionally, McCrea et al. (2003) found that symptoms in concussed collegiate athletes, including cognitive and
balance deficits, resolved on average within 7 days. However, it is not always the case that participants can expect quick recovery.

Concussive injuries can be quite debilitating as the associated symptoms can become chronic. One study found that 62% of subjects reported post-concussive symptoms after 3 months (Ingebrigtsen, Waterloo, Marup-Jensen et al., 1998). In cases where symptoms last longer than three months, the phrase Persistent Post-Concussive Syndrome (PPCS) is used (Bigler, 2008). People with PPCS are plagued for an indefinite amount of time by their concussive injury, being able to do little to nothing about it. Sadly, treatment for a concussion is limited to little more than a rest, wait, and see approach.

Unfortunately, the effects of concussive injuries can be far more sinister than residual acute symptoms. Shortly after a concussion, the injured party may sustain a period of neural vulnerability. If even another minor head injury is experienced while still susceptible, then cerebral swelling and even death can occur (Bowen, 2003). This event is known as second impact syndrome; however, there is disagreement in the literature as to whether this condition actually represents “diffuse cerebral swelling” (McCrory, 2001). Either way, this condition highlights the point that individuals suffering of concussive injuries should be monitored initially after the impact.

Possible death from concussive injuries is only one risk associated with the trauma. Slightly less severe are the mild cognitive impairments (MCI) and significant memory deficits noted in retired football players who sustained three or more concussions. These conditions were five to three times more prevalent, respectively, than in matched controls (Guskiewicz, Marshall, Bailes et al., 2005). In a similar study, Guskiewicz et al. (2007) discovered a positive correlation between the number of past concussions and the likelihood of being diagnosed with clinical
depression. Furthermore, after receiving multiple concussive blows it is possible to develop dementia pugilistica, which can present itself in many ways. Minor effects appear as confusion or ataxia, and can advance to Parkinsonian-like movements, dysarthria, and behavioral changes (Erlanger, Kutner, Barth et al., 1999). This condition is known for having devastated many great boxers. Additionally, obtaining closed head trauma has also been associated with an increased risk of developing Alzheimer’s disease (Plassman, Havlik, Steffens, 2000). The extreme effects of concussions can be startling; they are the driving force behind the rapid growth of interest in concussive injury research, and they call for an understanding of the epidemiology for this type of event.

There are many different scenarios in which concussive injuries can occur. According to Langlois et al., (2004) the situations that yield the highest incidence of concussions are falling events, followed by motor vehicle accidents and then being struck by/against events. Struck by/against events include sports injuries; for example if someone was tackled and struck their head against the ground hard enough to receive a concussion, then they would have been involved in this type of concussive event. Approximately 1.6 to 3.8 million sports related concussions occur per year (Langlois, Rutland-Brown, Wald, 2006). However, many concussive injuries are not even recognized as such by the individual; the confusion may be due to the fact that so many contradictory grading systems exist for this type of trauma. Even still, many of those that are recognized as concussive injuries may not be reported. Those experiencing concussive injury may decide to not admit to or act on their injury because of a restriction placed on normal activities; a student athlete may not tell his coach about his concussion for fear of being benched (McCrea, Hammeke, Olsen et al., 2004). Other times, people may not believe the injury to be significant enough to warrant a visit to the doctor; this is a flawed vision of
concussive injuries probably brought on by a lack of formal education on the subject. Moreover, some cannot afford medical care following a mild traumatic head injury. Because of the horrendous conditions that can develop after a concussion it is absolutely essential that victims of head trauma consult a physician after their experience. Therefore, measures should be developed to obligate sufferers of concussive injuries to seek medical attention at an affordable cost.

Preliminary Studies

Magnetic Resonance Imaging (MRI) has become widely used as a structural imaging method since the first 2-dimensional image produced by Paul Lauterbur in 1973. MRI systems rely on the process of Nuclear Magnetic Resonance (NMR), a protons response to being targeted by a radio frequency pulse, to create a signal that can be read. MRI plays a major role in finding changes to structural integrity following a traumatic event. MRI has been used to show that MTBIs causing loss of consciousness are positively correlated with intracranial abnormalities (Yeates, Taylor, Rusin et al., 2009). Kurča et al. (2006) used MRI to find that participants who experienced a concussion resulting in traumatic lesions differed significantly on performance neuropsychological tests compared to MTBI sufferers without structural damage. This shows that people who experience structural damage may have a different recovery trajectory than those who suffer from an uncomplicated MTBI. While MRI is great for showing faults in structural integrity, it cannot show cerebral abnormalities outside of that realm. Something greater is needed in order to capture changes in brain function in the absence of structural damage.

Functional Magnetic Resonance Imaging, or fMRI, has become quite popular over the years as a means to check for and monitor severity of brain injuries. This is partially due to the fact that it is a noninvasive procedure; furthermore, it may be better able to pick up on subtle
changes in brain functioning than just structural scans alone (Ptito, Chen, Johnston, 2007). FMRI also allows one to follow temporal changes within the brain by scanning at different periods of time; this is especially helpful for tracking symptom resolution following a traumatic head injury. Utilizing the need to replenish oxygen to activated regions of the brain, blood oxygenation level dependent (BOLD) responses allows one to track cerebral blood flow. BOLD fMRI relies on the difference in magnetic properties between oxyhemoglobin and deoxyhemoglobin within the brain. This difference creates a signal, whose strength is correlated with the ratio of the two molecules, which can be picked up by MRI and displayed using various analysis programs. When an area of the brain is activated, it uses oxygen; it is necessary to quickly replenish the oxygen to that area. A rush of blood flows to the area in order to achieve this, thus increasing the ratio between oxyhemoglobin and deoxyhemoglobin; this in turn increases the strength of the signal. It is possible that an increase in BOLD measured activation indicates that the brain has to work harder to complete the same task. Moreover, a greater dispersion of activation could imply the necessitation of recruitment of outside areas to complete tasks. Both possibilities suggest that BOLD contrast has a potential for uncovering altered brain functioning in human subjects. Jantzen et al. (2004) showed this by using fMRI to determine that concussed athletes present greater overall activation than matched controls. Chen et al. (2004) found that concussed athletes present BOLD responses that are different than matched controls. To gauge functional brain activation, it is necessary to instruct subjects to perform some task throughout the scanning process; task specific regions are then activated during the procedure.

Because memory deficits are often associated with concussions, tasks of working memory are sometimes given to measure the severity of the injury. Working memory is put to use when one has to remember and manipulate information while directing attention to and
performing a task. There are many different theories describing the mechanism of working memory; a popular view is the Baddeley and Hitch model of working memory. This model proposes that working memory is made up of a central executive that acts as an attentional control to a phonological loop and visuospatial sketch pad; furthermore, a fourth component, the episodic buffer, was recently added to the model. The phonological loop is suspected of retaining verbal information and supplying a mechanism in which to rehearse it mentally. The visuospatial sketch pad is presumed to be in charge of visual and spatial information. Finally, the episodic buffer plays an intermediary role between the other two slave systems and in processing information into long term memory (Baddeley, 2000). Therefore, deficits in working memory could have a great impact in the sorting and processing of information into long term memory. A large difference in the fMRI defined brain activation on working memory tasks between participants suffering from MTBI and matched controls has been found (McAllister, Saykin, Flashman et al., 1999). Furthermore, Chen et al. (2007) found that those with moderate post-concussive symptoms responded slower to working memory tasks; additionally, those with post-concussive symptoms had less fMRI defined brain activation in task specific regions but greater dispersion of activation than the control group. Various studies have repeatedly implicated certain sections of the brain as regions of interest (ROI) for working memory. These areas include the anterior cingulate cortex, the left prefrontal cortex, the parietal cortex, the left inferior frontal cortex, medial frontal gyrus, precuneus, and cerebellum (Kondo, Morishita, Osaka et al., 2004; Waiter, Deary, Staff et al., 2009; D’Esposito, Postle, Rypma, 2000; O’Hare, Lu, Houston et al., 2008).

The operation span (O-SPAN) has become a popular task used to gauge individuals’ abilities in working memory (Turner, Engle, 1989). This is partially due to its stability and high
reliability in displaying working memory ability (Klein, Fiss, 1999). Recently, the O-SPAN has been automated to allow the task to run without the presence of the experimenter; this version of the O-SPAN has been shown to be reliable and valid (Unsworth, Heitz, Schrock et al., 2005). The transition to automatization makes it easier to run the O-SPAN, especially in instances like in fMRI, in which the experimenter has to be away from the participant. Performance on the O-SPAN task acts as an indicator for how someone will do on the Stroop task, another complex cognitive task (Kane, Engle, 2003). This allows one to assume that some of the same neurocognitive processes are involved for the two tasks.

In 1935, John Stroop performed an experiment which looked at the ability to pick out the names of colors and the colors themselves when there is a discrepancy between the name and color in which it is presented. He found that people responded slower and made greater errors when a discrepancy existed between the name and the physical color of the word. This study has been replicated hundreds of times and has been shown to be reliable. A recent study found that athletes with a history of multiple concussions perform significantly worse on the Stroop Color-Word task, suggesting lasting effects of concussions (Wall, Williams, Cartwright-Hatton et al., 2006). Furthermore, a study from our own laboratory found an increase in activation beyond the regions of interest for subjects participating in a Stroop Color-Word task following brain injury (Mani, Miller, Yanasak et al., 2007a). The anterior cingulate cortex along with the premotor cortex, the postcentral cortex, left putamen, right superior temporal gyrus, the left prefrontal cortex, and the peristriate cortex have been associated with Stroop task performance (Pardo, Pardo, Janer et al., 1990; Cabeza, Nyberg, 2000).

There may also be differences in brain activation for multiply concussed individuals on simpler tasks of motor control and visual perception. Activation changes have been found in
tasks of motor function and retinal photic stimulation following moderate to severe brain injury (Mani, Miller, Yanasak et al., 2007b). In this study, Mani and colleagues found that overall brain activation, but not dispersion, during a simple motor task decreased over time following a concussive injury; alternately, dispersion, but not overall activation levels, decreased over time in a retinal photic stimulation task. Studies using fMRI and positron emission tomography (PET) have shown that the pre-supplementary motor area, the supplementary motor area, the primary motor cortex, sensorimotor cortex, and the basal ganglia are involved in motor control tasks much like the one used in the present study (Hemmelmann, Ungureanu, Hesse et al., 2009; Colebatch, Deiber, Passingham et al., 1991; Roland, Meyer, Shibasaki et al., 1982). The cerebellum has also been implicated in playing a role in executing motor functions (Mancini, Ciccarelli, Manfredonia et al., 2009; Deiber, Ibanez, Honda et al., 1998). Similar studies have found that retinal photic stimulation causes brain activation in the primary visual cortex (Ogawa, Tank, Menon et al., 1992; Kwong, Belliveau, Chesler et al., 1992). It is expected that the same task specific regions of the brain will be activated during the present study’s similar tasks. Imaging data will only solve part of the puzzle; in order to gain the full picture of neurocognitive performance, it is necessary to include neuropsychological testing.

Using various neuropsychological tasks is widely accepted as a legitimate means to determine neurocognitive abilities. This extends to concussive cases where cognitive impairment has taken place (Macciocchi, Barth, Alves et al., 1996; Collins, Scott, Mark et al., 1999). Collins et al. found that subjects with a history of multiple concussive injuries presented with cognitive deficits. Another study found similar results using neuropsychological tests, including the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) in high school
athletes (Moser, Schatz, Jordan, 2005). Gathering neurocognitive data is helpful in piecing together the overall effects of traumatic head injuries.

Specific Aims

The focus of this study was to better understand the effects of concussive head injuries. This experiment employed functional magnetic resonance imaging (fMRI) in order to define changes in brain activation associated with a history of multiple concussive injuries. Also, neuropsychological tasks were used in order to gauge the relationship between neurocognitive ability and fMRI defined brain activation. Finally, the affiliation between fMRI defined brain activation and symptom permanence in subjects with a history of multiple concussions was examined.

Based on research conducted within our own laboratory as well as the existing literature on the subject of concussive injuries our hypotheses are as follows: It was expected that participants suffering from multiple concussions would perform significantly worse on the neuropsychological tests than matched controls. Also, participants with a history of multiple concussions would also present markedly different fMRI BOLD response than control counterparts. Finally, it was anticipated that the experimental group would perform worse on and respond slower to the fMRI tasks.

If concussed athletes' cerebral activation is significantly different than non concussed athletes, then this offers promise for identifying abnormal cerebral functioning. This may also lead to being able to determine after how many concussions the cerebral abnormalities may become permanent. With this knowledge, methods for determining if and when participants should be allowed to return to play can be developed. Furthermore, with a better understanding of the correlation between neurocognitive performance and brain function it will be easier to
gauge the severity of head injuries using neuropsychological tests alone, rather than being coupled with imaging techniques which can be expensive and hard to coordinate. Eventually, neuropsychological tasks may be given on site of the injury to determine how much cognitive decline the individual should expect and for how long. This research will hopefully further shed light on the need for greater study into the field of traumatic brain injuries. Because despite interest in the field growing quickly, there is still so much unknown about this type of injury. In the end, this study will add to the knowledge pertaining to concussions so that better testing and treatment methods may be established.
CHAPTER 2
METHODS AND MATERIALS

Participants

Twenty right-handed male students between the ages of 18 and 23 years old from the University of Georgia were recruited for this study. Ten of these students had no history of concussive injury and made up the control group. The other ten students had a history of multiple concussions with the last concussion being at least six months prior to participation in the study; these students made up the experimental group. Students were recruited from the Club Sports Recreational Athletics Department and through the Research Participant Pool of the Psychology Department, both at the University of Georgia. Participants gave informed consent and completed an MRI screening form to ensure that it would be safe to put them into the magnet. Concussive histories were obtained by self-report through a concussive/demographic questionnaire (See Appendix 1). Participants were limited to those who are physically active for at least thirty minutes on most days. Each participant was scheduled for a single session at a time of convenience. For the control group, two hours of psychological research credit was given for participation in the study as part of a class requirement. There were an abundance of other research studies that students may take part in for credit. This study was completely optional, and participants did not incur any penalties or loss of benefits for refusal to partake.

Neuropsychological Testing

Participants were given Version A of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), which is used to detect and characterize cognitive decline
in adults (Randolph, Tierney, Mohr et al., 1998). This test is made up of twelve subtests in the domains of Immediate Memory, Visuospatial/Constructional, Language, Attention, and Delayed Memory. Next, Participants were asked to complete the Wechsler Test of Adult Reading (WTAR), which is used to estimate pre-morbid intellectual ability (Green, Melo, Christensen et al., 2008). Participants were given a concussion symptom checklist to index current, if any, concussive symptoms.

**fMRI**

FMRI studies were completed using a 16-channel, 3.0 Tesla General Electric (GE) Signa HDx magnetic resonance system during a single scanning session. An 8-channel head coil was attached. There were four fMRI tasks administered ranging from simple motor and visual tasks to complex cognitive tasks; all tasks were created using the program E-Prime 2.0 (Figure 1). For this experiment, the repetition time (TR) was 1.5 seconds, the echo time (TE) was 25 milliseconds, the slice thickness was 4 millimeters, the field of view was 220 millimeters, and 30 slices were taken per volume. The first task that participants were given was a spatial working memory task, O-SPAN. In this task, participants were presented with alternating mathematical equations and letters to solve and remember (O-SPAN condition), respectively; each of these conditions lasted 30 seconds. Subjects were then asked to pick the letters out of a line in the order that they appeared (Response condition); this was followed by a baseline scan and a series of mathematical equations (Math condition) to be solved. Each response, baseline, and math condition lasted 15 seconds, 18 seconds, and 30 seconds respectively. The next task given to the participants was one of response inhibition, a STROOP interference task. This task was broken up into three sections; first, subjects were presented with the names of colors in their respective colors (Congruent condition) and asked to choose what color it was being presented in.
Secondly, a baseline section was prompted followed by a task in which participants were asked to pick the presented physical color of multiple incongruent color name/physical color prompts (Incongruent condition). Both the congruent and incongruent conditions lasted 24 seconds each time, and the baseline condition lasted 12 seconds. The third fMRI task given was a simple passive-response visual perception task. In this retinal photic stimulation, participants were presented with alternating left and right flashing checkerboard patterns separated by a baseline fixation cross. The left and right conditions lasted 30 seconds while the baseline condition lasted 15 seconds each time. The final task was a speeded sequential motor task; in this, the subjects were asked to tap fingers on the right hand followed by a resting period and then finger taps on the left hand. The right, left, and baseline conditions each lasted 15 seconds during this task.

**Data Analysis**

Participants' performances on the neuropsychological tests were analyzed using Microsoft Excel (Microsoft Office Excel 2003 SP3). Within group analysis consisted of calculating group means and standard deviations. Between group results were compared and t-tests were run to check for any significant differences.

Initially, the DICOM images recorded by the magnetic resonance system had to be converted to NIfTI files. Following the conversion, the original structural image for each subject must be brain extracted through the brain extraction tool (BET) on FSL (Smith, Jenkinson, Woolrich et al., 2004; Woolrich, Jbabdi, Patenaude et al., 2009). Performing brain extraction on the structural images allowed an intermediate image to be present when trying to normalize the functional images to the template brain in standard space. FMRI data was processed using the FMRI Expert Analysis Tool (FEAT) tool in FSL. Each stage of analysis for each fMRI task was done separately.
It was necessary to correct for non-sequential image acquisition because images were obtained using an interleaved scan protocol. To compensate for movement during the scans, the Motion Correction FMRIB's Linear Registration Tool (MCFLIRT) was used. The images were normalized and then smoothed using the FEAT tool as well. Finally, prewhitening was performed on the images.

The setup for processing each task followed the same general guidelines with task specific numbers filled in. All 4D data files and their corresponding 3D brain extracted structural images were chosen in each of the tasks’ 1st level analysis. A full model setup for each task was developed using specific explanatory variables and contrasts. Each 1st level analysis was run as a cluster threshold of $z=3.0$ and a cluster significance threshold of $p=.05$. Higher, 2nd and 3rd, level analyses were also run using the FEAT. At the within groups stage of processing, the desired FEAT directories were chosen and appropriate output directories named. FMRIB’s Local Analysis of Mixed Effects (FLAME) 1 was used to run the t-tests at the higher levels as well as an automatic outlier de-weighting. The within groups were run as a cluster threshold of $z=3.0$ and a cluster significance threshold of $p=.05$. The 2nd level for each task was run as a single group average in order to find the groups’ areas and levels of activation. Finally, for the 3rd level processing the same FEAT directories as were used for the within group process were chosen; a combined group appropriate output directory was created for this. The same automatic outlier de-weighting option was picked for this stage as the prior one. Full model setups were designed for the between group analyses; each task had an identical model at this stage. Two explanatory variables (EV) were created. The control group was listed as 1.0 while the experimental was at 0.0 for one EV; they were flipped for the 2nd EV. Two contrasts were made as well. The control group was placed at 1.0 while the experimental was placed at -1.0 for the first contrast; these
were flipped for the second contrast (See Appendix 2). All of the tasks were run at the default cluster threshold of $z= 2.3$ and a cluster significance threshold of $p=.05$.

Specifically for the O-SPAN task, three explicit variables (EV)s were created: O-SPAN condition, Response, and Math condition. Two contrasts were created for this task; the first was the O-SPAN against the baseline, and the second was the O-SPAN condition against the Math condition. The Stroop was made up of 2 EVs, the Congruent and Incongruent conditions. Three contrasts were created for the Stroop: the first was the Congruent against the Incongruent, the second was the Incongruent against the Congruent condition, and the third was the Incongruent condition against the baseline. Both the Motor and Visual tasks had a Left condition EV and a Right condition EV. Both of these tasks used three contrasts: the Left against the baseline, the Right against the baseline, and the Right and Left conditions combined.
Figure 1: Block Design of fMRI tasks

This figure presents the order in which each condition is presented in the four fMRI tasks.
CHAPTER 3
RESULTS

Participants

The average age of participants in the control group was 20.5 years ($s=1.27$), and that of the experimental group was 20.2 years ($s=0.422$). The average number of concussions experienced by the experimental group was 2.9 ($s=0.876$). Three participants had experienced 2 concussions, six had experienced 3 concussions, and 1 participant had obtained 5 concussive injuries. Seventeen of the subjects were members of the University of Georgia Club Sports Recreational Athletics Department; the remaining three subjects were part of the Research Participant Pool of the Psychology Department at the University of Georgia. Four participants from the concussed group presented symptoms of persistent post-concussive syndrome (PPCS). These symptoms included fatigue, sensitivity to light and noise, difficulty concentrating and neck pain.

Neuropsychological Testing

There was a non-significant difference between the two groups’ scaled scores on the WTAR ($p=0.06$) (Fig. 2). The control group’s average was slightly higher than that of the experimental group.

There were no differences on any of the RBANS domains between groups ($p=0.13$, $p=0.19$, $p=0.18$, $p=0.10$, $p=0.07$). The group that, on average, scored higher on the RBANS depended on the subtest. The control group performed somewhat better than their concussed counterparts on the visuospatial/constructional subtest and on the attention subtest. The
experimental group achieved higher average scores than did the control group on the immediate memory, language, and delayed memory subtests (Fig 2).

*fMR behavioral data*

There were non-significant differences between the two groups on accuracy and response time for the O-SPAN task. Behavioral data collected for the O-span task during imaging acquisition indicates that the control group performed better on all three subtasks (O-SPAN condition, Array, and Math Baseline) than did the experimental group (Fig. 3). The time taken to respond for each prompt yielded mixed results for this task; the control group answered quicker, on average, for the O-SPAN condition but slower for the Array and Math Baseline than did the concussed group (Fig 4).

Additionally, there were non-significant differences between the two groups on accuracy and response time for the Stroop task. There was a significant Stroop Effect found in the Experimental group (p=0.024) but not within the Control Group (p=0.17). The Stroop Effect difference between the groups was non-significant (p=0.08). The control group performed better on the congruent condition but worse on the incongruent condition than the experimental group (Fig. 5). The concussed group answered quicker than the control group during the congruent condition, but the results were flipped for the incongruent condition. A Stroop effect occurred in both of the groups, and this effect was more pronounced in the experimental group; the Stroop effect was almost doubled in the concussed group (Fig. 6).

*fMRI defined brain activation*

At the between groups processing level, no significant differences were found for any of the contrasts for any of the tasks.
Both groups showed activation in task specific regions in the O-SPAN task for the O-SPAN condition against the baseline contrast. In the O-SPAN minus baseline contrast, significant activation appeared in the medial frontal gyrus, superior frontal gyrus, paracingulate gyrus, cingulate gyrus, precentral gyrus, inferior parietal lobule, and the precuneus (Fig 7). However, in the O-SPAN minus the Math Baseline condition contrast the control group did not show any activation at all. The experimental group still showed activation in this second contrast. Activation was presented in the cingulate gyrus, the precuneus, the medial frontal gyrus, the superior temporal gyrus, and the superior frontal gyrus.

The appearance of activation in the Stroop task depended on the contrast. In the contrast Incongruent condition minus the Congruent condition, the control group did not yield any activation. The experimental group, however, showed activation in the precuneus, the parietal lobe, the superior, middle, and inferior gyri, the cerebellum, the precentral gyrus, and the occipital lobe in this contrast. In the Incongruent condition against baseline contrast both groups showed activation (Fig. 8). The control group exhibited activation in the medial frontal gyrus, the precentral gyrus, the superior parietal lobule, the precuneus, the inferior parietal lobule, and the cerebellum. The experimental group showed the precuneus, the fusiform gyrus, the inferior parietal lobule, the superior parietal lobule, the inferior frontal gyrus, and the medial frontal gyrus as being activated.

In the visual task, both groups yielded ipsilateral activation relative to which side the flashing checkerboard pattern was presented in. This activation occurred in the lingual gyrus, inferior occipital gyrus, middle occipital gyrus, inferior frontal gyrus, and the superior frontal gyrus (Fig. 9).
Finally, the Motor task for both groups caused greatest brain activation in the cerebellum, pre-central gyrus, and the post-central gyrus (Fig. 10). The Left and Right conditions caused activation in the contralateral hemisphere in the pre-central and post-central gyrus; they presented ipsilateral activation in the cerebellum.
WTAR scores were 117.1 for the control group (CG) and 110.4 for the experimental group (EG) (p=0.06). Immediate memory scores were 101 for the CG and 109 for the EG (p=0.13). Visuospatial/Constructional scores were 113.3 for the CG and 109.3 for the EG (p=0.19). Scores on the language subtest were 96 for the CG and 100.8 for the EG (p=0.18). Attention subtest scores were 106.8 for the CG and 99.2 for the EG (p=0.10). Delayed Memory subtest scores were 97.4 for the CG and 102.6 for the EG (p=0.07).
Average percentage correct in the O-SPAN condition was 91.25% for the CG and 88.13% for the EG (p=0.2). For the Array condition the percentage correct was 91.88% for the CG and 83.75% for the EG (p=0.15). In the Math Baseline condition the percentage correct was 88.75% for the CG and 78.75% for the EG (p=0.07).
The response times for the O-SPAN condition were 2808.84 ms for the CG and 2852.67 ms for the EG (p=0.41). Array condition response times were 1276.09 ms for the CG and 1274.07 ms for the EG (p=0.49). The response times for the Math Baseline were 3031.16 ms for the CG and 3031.08 ms for the EG (p=0.50).
The percentage correct on the Congruent condition was 97.5% for the CG and 93.75% for the EG (p=0.06). The percentage correct on the Incongruent condition was 95.94% for the CG and 94.38% for the EG (p=0.40).
Figure 6: Average Participant Response Time on STROOP task by condition and group

The response times for the Congruent condition were 922.96 ms for the CG and 909.44 ms for the EG (p=0.42). The response times for the Incongruent condition were 991.40 ms for the CG and 1041.25 ms for the EG (p=0.24). The Stroop Effects were 68.44 ms for the CG and 131.81 ms for the EG (p=0.08).
Figure 7: fMRI defined brain activation during the O-SPAN task by group
Contrast: O-SPAN condition against baseline

Above: Control group average activation

Below: Experimental group average activation
Figure 8: fMRI defined brain activation during the Stroop task by group
Contrast: Incongruent condition against baseline

Above: Control group average activation

Below: Experimental group average activation
Figure 9: fMRI defined brain activation during the Visual task by group
Contrast: Right Hemispheric Flashing Checkerboard against baseline

Above: Control group average activation
Below: Experimental group average activation
Figure 10: fMRI defined brain activation during the Motor task by group
Contrast: Right Finger Tapping against baseline

Above: Control group average activation

Below: Experimental group average activation
The data from this study do not support the hypothesis that there are significant fMRI BOLD response differences between the two groups. The data do not indicate that the experimental group performed worse on neuropsychological testing. Finally, the experimental group did not perform worse on nor respond slower to fMRI tasks compared to the control group.

There were slight differences in a couple of the fMRI tasks’ contrasts. In the O-SPAN task, the O-SPAN minus Math Baseline contrast yielded no significant activation within the control group; however, the experimental group had activation in task specific areas. The Stroop task’s Incongruent condition minus Congruent condition contrast yielded similar results. The control group yielded no significant activation while the experimental group had activation in task specific regions. Additionally, within the control group, there was no significant Stroop effect found. This may be because, for the control group, the Incongruent condition was not harder than the Congruent condition to the point that response times between the two conditions would differ. It is possible that these differences indicate that the experimental group does have greater intensity of activation, greater dispersion of activation, and require more time to inhibit themselves than the control group; however, these differences were non-significant, so it is necessary to investigate this difference further by expanding the number of participants recruited.

Except for a single participant, all of the others in the experimental group had obtained two or three concussions. Our relative lack of significant group differences suggests that the
average concussions obtained (2.9) for the experimental group may not be at a threshold at which permanent effects on cognitive abilities and brain activation exist. It may be that athletes can experience three or fewer concussions without having to worry about differences in functional ability; however, it is not a definite finding. Participants with a greater number of concussions should be recruited in order to test this possibility. Until that time, care should still be taken to minimize the number of traumatic head injuries obtained.

It is also possible that the sample group does not accurately represent the general population. This means that young, athletic students with an above average intelligence level may not exhibit the same post-concussive state as someone from a different status. If this is the case, then it is possible that upon testing a wider, more varied group that differences would be found between the control and experimental groups.

While very preliminary, our results suggest that the sample population here may have had greater neuroplasticity than was previously expected. The possibility of being able to completely recover measurable functioning following multiple concussions in these young, physically fit participants warrants further exploration. With the addition of more participants, a more definitive answer as to whether or not the higher level of neuroplasticity exists could be found. In instances in which other injuries are compounded by a concussion, these findings could help direct treatment towards the other injuries.

This study should be continued in the manners previously outlined in order to increase the power of the findings and, therefore, increase the external validity. At that point, more authoritative claims can be made regarding concussive injuries. Currently, there is no specific number of concussions at which people should abandon their previous activities, such as sports, supported by the data. After reviewing the literature, though, it is apparent that people should be
monitored closely and prohibited from resuming normal activities until after most symptoms have resolved. Also supported by this study is the idea that pre-morbid data should be taken prior to beginning high risk activity so as to better monitor injury resolution should something occur. A greater amount of research needs to be completed to better understand concussive injuries.
WORKS CITED


*Neurosurgery, 9*: 221-228.


APPENDIX A

Demographic and Concussive History Questionnaire

1. Are you a right handed male? Yes No
2. How old are you? ________
3. Are you currently enrolled as a student full time at UGA? Yes No
4. Are you physically active for at least 30 minutes on most days? Yes No
5. Are you a member of a collegiate sports team? Yes No
6. Would you consider yourself a student-athlete Yes No
7. Are you feeling well today? Yes No
8. Have you used alcohol in the past 24 hours? Yes No
9. Have you ever experienced a concussion? Yes No

If yes, continue

10. How many concussions have you had?
11. How many of these concussions did you seek professional medical attention for?
12. How many of these concussions caused you to lose consciousness?
13. How many of these concussions caused you to have memory lapse?
14. How long has it been since your last concussion?
Concussion Symptom Checklist: Side 1
## Concussion Symptom Checklist: Side 2

### DURATION

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Briefly</th>
<th>Sometimes</th>
<th>Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Nausea</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Difficulty balancing</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Sleep Disturbances</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Difficulty concentrating</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Feeling “in a fog”</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Feeling “slowed down”</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Sensitive to Light</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Sadness</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Sensitive to Noise</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Nervousness</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

### SEVERITY

<table>
<thead>
<tr>
<th>Not Severe at All</th>
<th>As Severe as Possible</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

48
MRI Participant Screening Form: Side 1

<table>
<thead>
<tr>
<th>Question</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have you had prior surgery or an operation (e.g., arthroscopy, endoscopy, etc.) of any kind?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date of operation:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of surgery:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have you had a prior diagnostic imaging study or examination (MRI, CT, X-ray, etc.)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If yes, please list:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date of imaging study:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of imaging study:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have you experienced any problem related to a previous MRI examination or MR procedure?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If yes, please describe:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have you had an injury to the eye involving a metallic object or fragment (e.g., metallic slivers, shavings, foreign body, etc.)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If yes, please describe:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have you ever been injured by a metallic object or foreign body (e.g., BB, bullet, shrapnel, etc.)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If yes, please describe:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Are you currently taking or have you recently taken any medication or drug?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If yes, please list:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Are you allergic to any medication?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If yes, please list:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you have anemia or any disease(s) that affects your blood, a history of renal (kidney) disease, or seizures?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If yes, please describe:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date of last menstrual period:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post menopausal?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Are you pregnant or experiencing a late menstrual period?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Are you taking oral contraceptives or receiving hormonal treatment?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Are you taking any type of fertility medication or having fertility treatments?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If yes, please describe:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Are you currently breastfeeding?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For female patients:

| Date of last menstrual period:                                            |    |     |

Post menopausal? |    |     |

| Are you pregnant or experiencing a late menstrual period?                 |    |     |
| Are you taking oral contraceptives or receiving hormonal treatment?        |    |     |
| Are you taking any type of fertility medication or having fertility treatments? |    |     |
| If yes, please describe:                                                  |    |     |
| Are you currently breastfeeding?                                           |    |     |
WARNING: Certain implants, devices, or objects may be hazardous to you and/or may interfere with the MR procedure (i.e., MRI, MR angiography, functional MRI, MR spectroscopy). Do not enter the MR system room or MR environment if you have any questions or concerns regarding an implant, device, or object. Consult the MRI Technologist BEFORE entering the MR system room. The MR system magnet is ALWAYS on.

Please indicate if you have any of the following:

- Yes □ No □ Metal cardiac pacemaker
- Yes □ No □ Implanted cardioverter defibrillator (ICD)
- Yes □ No □ Electronic implant or device
- Yes □ No □ Magnetically-activated implant or device
- Yes □ No □ Neurostimulation system
- Yes □ No □ Spinal cord stimulator
- Yes □ No □ Internal electrodes or wires
- Yes □ No □ Bone growth/bone fusion stimulator
- Yes □ No □ Cochlear, otologic, or other ear implant
- Yes □ No □ Insulin or other infusion pump
- Yes □ No □ Implanted drug infusion device
- Yes □ No □ Any type of prosthesis (eye, penis, etc.)
- Yes □ No □ Heart valve prosthesis
- Yes □ No □ Eyelid spring or wire
- Yes □ No □ Artificial or prosthetic limb
- Yes □ No □ Metallic stent, filter, or coil
- Yes □ No □ Shunt (spinal or intraventricular)
- Yes □ No □ Vascular access port and/or catheter
- Yes □ No □ Radiation seeds or implants
- Yes □ No □ Swan-Ganz or thermodilution catheter
- Yes □ No □ Medication patch (Nicotine, Nitroglycerine)
- Yes □ No □ Any metallic fragment or foreign body
- Yes □ No □ Wire mesh implant
- Yes □ No □ Tissue expander (e.g., breast)
- Yes □ No □ Surgical staples, clips, or metallic sutures
- Yes □ No □ Joint replacement (hip, knee, etc.)
- Yes □ No □ Bone/joint pin, screw, nail, wire, plate, etc.
- Yes □ No □ I.U.D., diaphragm, or pessary
- Yes □ No □ Dentures or partial plates
- Yes □ No □ Tattoos or permanent makeup
- Yes □ No □ Body piercing jewelry
- Yes □ No □ Hearing aid

(Removable before entering MR system room)

- Yes □ No □ Other implant
- Yes □ No □ Breathing problem or motion disorder
- Yes □ No □ Claustrophobia

NOTE: You may be advised or required to wear earplugs or other hearing protection during the MR procedure to prevent possible problems or hazards related to acoustic trauma.

I attest that the above information is correct to the best of my knowledge. I read and understand the contents of this form and had the opportunity to ask questions regarding the information on this form and regarding the MR procedure that I am about to undergo.

Signature of Person Completing Form: __________________________ Date: __/__/____

Form Completed By: □ Participant □ Relative □ Nurse

Print name: __________________________ Relationship to Participant: __________________________

Form Information Reviewed By: __________________________ Print name: __________________________

Signature: __________________________

☑ MRI Technologist □ PI

☑ Other

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MRI Participant Screening Form: Side 2
Full model setup of between groups in FEAT tool of FSL