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Positive Versus Negative Neuroimaging in Mild Traumatic Brain Injury Outcome: A Meta-Analysis

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ABSTRACT

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Mild Traumatic Brain Injury (mTBI) can be broken into two categories; complicated and uncomplicated. These categories are based on structural imaging scans during the assessment of the injury. If abnormalities appear in the scan, we refer to it as complicated. The present research aims at determining whether there are differences in the neuropsychological deficits in the presences of positive neuroimaging as opposed to negative neuroimaging. This was accomplished with meta-analytic techniques. It was found that neuroimaging does not predict neuropsychological functioning in the chronic state of mTBI.

Keywords: Complicated traumatic brain injury, brain injury outcome, positive imaging

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In the last two decades, there have been hundreds of peer-reviewed articles evaluating the post-acute neuropsychological outcomes of mild traumatic brain injury (mTBI). Some of these have found strong results showing lasting effects, others of which show little if any permanent effects. There are two popular meta-analyses supporting the idea that there are little, if any long term sequelae to mTBI (Binder, Rohling, & Larrabee, 1997; Frencham, Fox, & Maybery, 2005). In examining Binder et al. within their measurement of effect sizes, these researchers reasoned that low effect sizes corresponded to minute changes in neurocognition —findings that could easily be confused with mere testing error within the neuropsychological tests themselves. Binder et al. concluded that because of the low effect sizes in the aggregate studies, a clinician should practice caution before diagnosing a brain injury and that in the long term, there is probably little, if any effect to mild head trauma.

Similarly, Frencham et al. (2005) found a moderate effect size ($g = .32$, $p < .001$). However, upon computing effect sizes in conjunction with those of Binder et al., the effect size diminished ($g = .11$). Binder et al. and Frencham et al. concluded that there were effects in the acute stage that later closely matched control group's performances and that long term effects of mild head injury were mitigated by time since injury.

Moreover, work done by Belanger and colleagues (2005) supports the findings from Frencham et al. and Binder et al. They performed a meta-analysis on the magnitude of impairment from mild traumatic brain injury in relation to other moderating variables such as

time since injury, specific cognitive domain and whether or not the participants were involved in litigation. These researchers found that effect sizes depended upon the moderating variables mentioned above. Regarding time frame, Belanger and colleagues concluded that in the acute stage of injury (<3 months) individuals will experience neuropsychological deficits but that these effects diminish after three months (d = .04; Belanger et al., 2005).

Notwithstanding the conclusions by both Binder et al. and Frencham et al., these works have been challenged by Pertab, James and Bigler (2009) who demonstrated potential methodological flaws in these previous meta-analyses. Pertab and colleagues systematically evaluated aspects such as presence of symptomatic subgroups, mechanisms of injury, time since injury, diagnostic criteria employed, and type of neuropsychological assessment tools used. These investigators found a significant heterogeneity in these areas upon deeper inspection and carried out meta-analysis when more control was used. They concluded that the lower, non-significant effect size report by Binder et al. and Frencham et al. only becomes apparent when overall effect size is considered and that an effect can be found when greater control it utilized (Pertab et al., 2009). Consequently, E. D. Bigler (personal communication), co-author of the Pertab et al. (2009) article, has indicated that he and his colleagues have been informed of a rejoinder to their 2009 study. At the present time, this rejoinder has not yet been published.

Despite any limitation in the current meta-analyses on outcome after mTBI, progress in this field is dependent on large scale studies and on studies that accumulate evidence. From the meta-analysis by Binder et al., (1997) "A large sample is more likely than is a small sample to yield a result that is closer to the population mean" is stated (p. 429). Binder et al. point out that a weakness to their own work is high attrition rate from the articles used in their meta-analyses. They report an attrition rate of about 40% in four of these studies. Obviously, articles with a

higher sample size would shed light on the effect sizes calculated by these meta-analyses and it is clear that there is still some debate in the field regarding long term outcome of head injury.

As an example of a good study with a large sample size, one particular article published in 2009 by Christensen et al. had a sample size of 1,605,216 people with a range of brain injury severity. By use of a risk ratio (RR), these researchers assessed the prevalence and risk of epilepsy following brain injury. Specifically within the mild TBI group, those that had no prior family history of epilepsy had a risk ratio of 2.22 (95% CI 2.07–2.38) meaning they were slightly higher than two times more likely to suffer from epilepsy than normal. Patients in the mild group with a family history of epilepsy had a ratio of (5.75, 4.56–7.27), almost six times the normal rate. In addition, these subjects were tracked far beyond the acute phase of injury with a time line reaching 10 years post injury. In fact, though the risk of epilepsy is highest in the first year after injury, these risks remained high for more than ten years compared to control. This suggests that lasting effects from mTBI can and do occur.

Conducting more large scale studies is not the only problem facing the progression of scientific understanding in mTBI research. Perhaps it is the methods of assessing outcomes that would determine whether negative outcomes are seen in mTBI. For example, neuroimaging techniques can and have greatly aided clinicians in delineating trauma induced brain injury, the magnitude of this damage, and its influence on behavior and cognition (Bigler, 2007; Bigler, 2008). McAllister, Sparling, Flashman, and Saykin (2001) showed how different types of neuroimaging have variable thresholds for detecting structural changes in the brain. In addition to different capacities for detecting changes in the central nervous system (CNS), the many imaging modalities are used for different aspects of neural injury. McAllister et al. states that structural imaging techniques are beneficial for diagnostics and management of TBI while

functional imaging is a strong tool for assessing "pathophysiology, symptom genesis, and mechanisms of recovery." (p. 775). McAllister and colleagues (2001) conclude that imaging is a useful means for detecting and delineating changes in the CNS post injury. Further research is needed to clarify appropriate use of such tools in clinical assessment and whether such tools may assist in clarifying or predicting the sequelae of mTBI.

In sum, the following review of current literature discusses what is known about mTBI outcome, what is known about the use of different neuroimaging techniques as a means of assessing mTBI, and how these techniques might be used to predict neuropsychological outcome.

Review of Literature

Mild Traumatic Brain Injury Defined

The prevalence and magnitude of traumatic brain injury continues to be a public health concern in the United States. In 1999, the National Center for Injury Prevention and Control reported that traumatic brain injury was the leading cause of death among children and young adults in America. Each year, an estimated 1.5 million people have a traumatic brain injury (National Center for Injury Prevention and Control. Traumatic Brain Injury in the United States: A Report to Congress. Atlanta: Centers for Disease Control and Prevention, 1999). Since this report, updated epidemiological research has shown that approximately 1.4 million TBIs occur in the U.S. each year, which included 1.1 million emergency room visits, 235,000 hospitalizations, and 50,000 deaths (Center for Disease Control and Prevention; Langlois, Rutland-Brown, & Wald, 2006). A report in 2008 suggested that an estimated 1.1% of the U.S. population or 3.17 million people were living with long-term TBI-related disability (Zaloshnja, Miller, Langlois, & Selassie, 2008). Corrigan, Selassie, and Orman (2010) found that approximately 43% of TBI

survivors have residual disability one year following injury. Though it is clear that TBI is a public health concern, what's not as clear is what constitutes mild brain injury and what the long term effects are of such injuries.

There has been a long debate in neuropsychology as to what constitutes an mTBI. A majority of clinicians and researchers use the Glasgow Coma Scale (GCS) as a means of classifying different degrees of traumatic brain injury. This scale is based off of three assessment areas; eye opening, motor response, and verbal response. A GCS will be the sum of scores from each individual category with a range from 3-15. Higher scores indicate a less severe injury (Furlow, 2006). Though this rating system has become standard in emergency rooms across the world, there is reason to believe that there are better tools for accurate TBI assessment of whether an mTBI has occurred or not. In 1999, van der Naalt, van Zomeren, Sluiter, and Minderhoud, analyzed GCS compared to post-traumatic amnesia (PTA), another indicator of outcomes after TBI. Upon running a multiple regression on the two classification tools, van der Naalt et al. determined that PTA was a better predictor of neurocognitive outcomes and return to work status even at one year follow up (van der Naalt et al., 1999b). However, PTA is not a standard assessment given in emergency rooms.

Additionally, there are many organizations and authors who have offered definitions for mTBI. Due to the wide range of working definitions, it would benefit the field of mTBI research to promulgate a standard definition for mTBI and clarification on conflicting nomenclature (Bigler, 2008). In 2004, Carroll et al. of the WHO task force conducted a comprehensive review of mTBI literature examining author's definitions of mTBI. In this review, the authors offer a standard operational definition based on definitions from the Mild Traumatic Brain Injury Committee of the Head Injury Interdisciplinary Special Interest Group of the American Congress

of Rehabilitation Medicine and the US Centers for Disease Control and Prevention's mTBI Working Group. It is this definition that will be used in the present study (see Table 1). Specifically, mTBI was defined as a disruption in neuropsychological functioning as a result of a blunt impact, non-penetrating injury to the head from a sudden acceleration, deceleration or rotation of the head, GCS between 13 and 15, PTA less than 24 hours, Loss of Consciousness (LOC) 30 minutes or less (Bigler, 2008; Carroll et al., 2004). The National Academy of Neuropsychology has endorsed this definition of mTBI though they point out that there is still confusion and lack of standardization on how to assess PTA and LOC appropriately (Ruff et al., 2009). In addition to the specifics of diagnosis, some authors maintain that the mechanism of injury behind the injury is just as important to outcome as GCS and PTA (Bigler, 2008).

Table 1. *The WHO Task Force Definition of Mild Traumatic Brain Injury*

1. Confusion/Disorientation
2. LOC ≤ 30 minutes
3. PTA < 24 hours
4. "and/or other transient neurological abnormalities such as focal signs, seizure, and intracranial lesion not requiring surgery"
5. GCS of 13-15 assessed 30 minutes after injury.
6. mTBI manifestations are not due to drugs, alcohol, medications, or other injuries, other pre-existing medical/psychological conditions, or penetrating head injuries.

Note: Operational definition of mTBI as defined by the WHO Collaborating Centre for Neurotrauma Task Force on Mild Traumatic Brain Injury as presented in Carroll et al., 2004. LOC, Loss of Consciousness. PTA, Post-Traumatic Amnesia. GCS, Glasgow Coma Scale score.

Mechanisms of injury. The Center for Disease Prevention and Control (CDC) reports that the four main causes of TBI are falls, motor vehicle accidents (MVA), struck by/against events, and assaults (www.cdc.gov). Figure 1 below was adapted from information from the CDC and Langlois et al. (2006) and summarizes the frequencies of these mechanisms. Why does it matter what the mechanisms of injury are in TBI? Bigler (2008) describes how

mechanism of injury is an important factor when measuring its effects of TBI. For example, a side impact car collision will transfer energy to the brain differently than a tackle on the football field while wearing a helmet (Bigler, 2008). It is important to note that the CDC does not included sports related accidents in their report of TBIs though they do report that approximately 300,000 athletes suffer concussion each year (Moser et al., 2007). In a 2006 report by Langlois et al., authors pointed out that most reports of sports related TBI are only included in epidemiological reports when there was a *reported* loss of consciousness (LOC). However, only 8-19.2% of sports related TBI have a LOC. Adjusting these figures, Langlois and colleagues estimated the number of sports related TBIs to be between 1.6 and 3.8 million annually (Langlois et al., 2006). Obviously sports related accidents contribute to the overall TBI population in the United States.

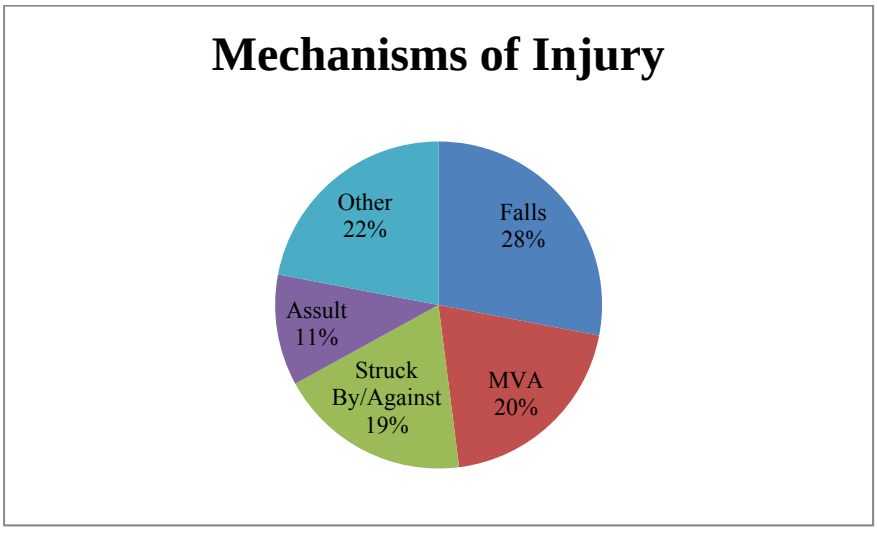

Figure 1: Mechanisms of injury as reported by the CDC. See http://www.cdc.gov/TraumaticInjury/tbi_concussion.html for more information as well as Langlois et al., 2006.

Neuropsychological Testing

Reitan and Wolfson (2000) have shown that neuropsychological testing has been a long used means of illuminating the neuro-behavioral losses people might experience following head trauma of varying degrees. It has become increasingly necessary to use tests that are sensitive to the range of damage. In work done by Reitan and Wolfson, they attempted to distinguish whether groups with varying degrees of head injury differed when evaluated using the Halstead-Reitan Neuropsychological Test Battery (HRB). The HRB looks at 42 variables which are further summarized using the General Neuropsychology Deficit Scale (GNDS). Scores ranging from 0-25 fall in the normal range, 26-40 is considered mild, 41-67 is moderate impairment, and 68 and above is severe. The study reported that compared to control, mild and moderate GNDS scores were significantly worse but that the GNDS scale was successful at isolating individuals with mild head injuries (Reitan & Wolfson, 2000).

Although neuropsychology tests in mTBI have identified cognitive sequelae and differentiated between control groups and mild, moderate, and severe TBI (Hanks et al., 2008; Kashluba, Hanks, Casey, & Millis, 2008) many do not because the tests are not sensitive enough or the data are not examined the right way. For example, Geary, Kraus, Pliskin, and Little (2010) studied memory in mTBI subjects with a verbal learning test consisting of a list of words read several times. The overall results of this test showed no statistical differences between the control and mTBI subjects. However, the researchers point out that the mTBI group did perform statistically worse on the first trial of this test. Thus, the memory and learning the test was trying to elucidate in the mTBI subjects actually covered up the memory construct and mTBI subjects can have deficits not found in validated and frequently used neuropsychological tests (Geary et al., 2010).

In addition, a recent study performed by Vanderploeg, Curtiss, and Belanger, (2005) demonstrated that these inconsistencies in the literature could be a function of how tests were evaluated after testing was completed. The study performed by Vanderploeg et al. used a large sample size (n = 254) of male veterans tested an average of 8 years post injury controlling for source of accident, age, and other confounding variables. These researchers illustrated that when looking at tests as a whole, there appeared to be no long term outcomes to mild traumatic brain injury. These findings support those of Binder et al. (1997) and Frencham et al. (2005). However, these experimenters also used some nontraditional ways of looking deeper into the data. As they looked at complex attention and working memory, the mTBI group had difficulty completing the Paced Auditory Serial Addition Test (PASAT) and exhibited excessive proactive interference (PI). Normally, scores of such tests as the PASAT are only compared among participants who complete the test. In this research, digging deeper revealed that individuals who did not complete the test exhibited left-side visual imperceptions which could be related to a deficit in control and direction of attention resources. The authors found a similar effect when looking at the great amount of PI exhibited during the California Verbal Learning Test (CVLT). Notable is the finding that the individuals not completing such tasks demonstrated an impaired tandem gait. Authors pointed out that this relationship of impaired tandem gait and PI could be related to deficits within the frontal system of the brain. It is important to note, however, that the numbers of people who failed to complete tests and exhibited PI was relatively small (Vanderploeg et al., 2005). Nevertheless, this result could give insight into the function and limitations of neuropsychological testing.

Neuropsychological tests have been useful in the world of sports concussions as well. Research by Echemendia, Putukian, Mackin, Julian, and Shoss (2001) detailed the utility of

neuropsychological tests in determining which athletes were injured and which were ready to return to play. They found that testing was successful at showing significant differences between injured athletes and controls. These authors found that a majority of athletes recovered after a week or at least to a sense that their performance was not altered (Echemendia et al., 2001). In a large prospective study (n = 1631), McCrea et al. (2003) support the findings of Echemendia et al. showing how neuropsychological testing is useful in determining the magnitude of injury and evidence based guidelines for time at which athletes were safe to return to play. Authors demonstrated the usefulness of evaluation on sports where athletes often serve as their own control, an advantage over using control groups that might introduce confounding variables. McCrea et al. concluded that the effects of injury are mitigated by time and that at 90 days, athletes had returned to their baseline (McCrea et al., 2003). This is greatly supported but a meta-analysis by Belanger and Vanderploeg (2005) who assessed the average effect size of cognitive sequelae over 21 sports concussions studies. They determined that the average effect (d = .49) was comparable to the average effect found in non sports related mTBI (d = .54). However, it should be noted that a majority of the studies used in this meta-analysis looked at patients in the acute stage of injury (Belanger & Vanderploeg, 2005). Though a majority of research articles show that most athletes return to baseline by at least 3 months, there is a significant amount of data showing that sustaining a sports concussion leads to an increased risk of future concussions and brain damage (Gaetz, Goodman, &Weinberg, 2000; Iverson, Gaetz, Lovell, & Collins, 2004).

Neuroimaging

Computed Tomography. Computed Tomography (CT) is an imaging modality that, from its advent, has greatly assisted neurological diagnostics (Furlow, 2006). CT is extensively

available, has relatively low cost, and can generate an image of the brain quickly. Unfortunately, in assessment of mTBI, a majority of people show no structural change in their CT (McAllister et al., 2001). Other studies find individuals with mild head injuries have abnormal findings in CT scans 20-35% of the time (Harad & Kerstein, 1992; Schynoll et al., 1993; Shackford et al., 1992; Stein & Ross, 1992 as cited in McAllister et al., 2001). CT imaging is typically used as a day-of-injury assessment tool and has a categorical rating similar to a Glasgow Coma Scale (GCS). However, these scores from brain imaging do not correlate to long term neuropsychological outcomes due to the fact that they are not sensitive enough to detect microscopic changes in the CNS (Furlow, 2006).

Just as important, the lack of sensitivity of CT imaging detecting mild damage could be a function of the type of injury within mTBI. As described before, mild TBI is usually associated with a brief loss of consciousness (LOC) which is referred to as uncomplicated mTBI. When this LOC is brief with the presence of a space occupying lesion however, this is referred to as mild-complicated TBI. Some research has shown that patients with complicated mTBI will perform worse on neuropsychological test than uncomplicated mTBI patients. One such study by Borgaro et al. (2003) found that the presence of a space occupying lesions was predictive of neuropsychological performance and that, in the acute stage, the complicated group was impaired in cognition despite having matched GCS scores with the uncomplicated group (Borgaro et al., 2003). These findings are supported by Lange, Iverson, and Franzen (2009) who also studied patients in the acute stage. The detection of lesions on CT imaging in conjunction with a GCS between 13 and 15 would lead to the assumption that the patient would take longer to recover from the injury if at all (Iverson, 2006; Lange et al., 2009). When evaluating the neuropsychological functioning of persons with complicated mTBI, Kashluba et al. (2008)

demonstrates that mild-complicated TBI parallels that of moderate TBI groups. Because of these findings, failure to find structural change when using CT imaging could be a function of both lack of sensitivity of CT imaging as wells as differences between mild-complicated vs. uncomplicated TBI.

However, the literature on differences between complicated and uncomplicated mTBI do not all agree. Some studies show there to be little, if any, difference between the two. For example, one study found there to be no difference between patients with positive CT scans and those with negative scans on a measure of postconcussional disorder (PCD; McCauley, Boake, Levin, Contan, & Song, 2001) and another found there to be no difference between these groups on neuropsychological status or vocational outcome (Hanlon, Demery, Martinovich, & Kelly, 1999). Hofman et al. (2001) also concluded that the presence of positive imaging after mTBI does not necessarily result in worse neurocognitive outcome and that patients score within the normal range on tests.

Likewise, work by Sadowski-Cron et al. (2006) attempted to find correlations between intra-cranial injuries (ICI) on CT imaging with neurocognitive performance in mTBI patients. Not all patients had an ICI making it difficult to find any relationships between GCS or ICI and cognitive outcomes. Neurocognitive test scans indicated that approximately 51% had marked losses but that there was no difference between patients with or without ICI. This research shows the difficulty of finding significant imaging-outcome relationships using CT. However, the work performed by Sadowski-Cron et al. only used CT day-of-injury imaging. After one year, all patients had returned to work but some had persisting complaints of headaches and tinnitus. These complaints were correlated to ICI which could lead to the assumption that the

presence of ICI on CT scans may be predictive of long term cognitive sequelae in mTBI patients (Sadowski-Cron et al., 2006).

Magnetic Resonance Imaging. A significant amount of research has shown that magnetic resonance imaging (MRI) is more sensitive than CT scanning at detecting CNS changes post TBI (McAllister et al., 2001; Furlow, 2006). A recent study analyzed volumetric changes in the brain across injury severity using MRI. The study found damage severity was related to parenchymal volume loss. The analysis of the volume loss indicated that moderate to severe brain injuries were not significantly different from each other, but together were significantly different from the mild group. The mild group was also significantly different from the control and although the mild group had the smallest volume loss it still contributed to overall volumetric changes (Levine et al., 2008).

Also, Hofman and colleagues (2002) assessed the long term effects of mild traumatic brain injury with MRI, using MRI to calculate a magnetization transfer ratio (MTR) in tissues post injury. The authors found that individuals with mTBI have a reduced MTR along with an increased lesion load, point to an organic cause to mTBI. These MTR findings were seen even in a small sample size (n = 13; Hofman et al., 2002).

In 1987, Levin et al. found correlations between MRI findings and cognitive deficits. A study by Lee et al. (2008) evaluated the difference between CT and MRI in assessing neurocognitive outcomes in mTBI. The researchers compared imaging to neurocognitive tests and found that there were long term effects cognitively for individuals with mTBI as assessed by the California Verbal Learning Test (CVLT). However, no correlation between imaging results and long term outcomes were found. When comparing the use of CT to MRI, CT was successful at detecting parenchymal injuries in 50% of the 36 mTBI subjects but that MRI was 75%

successful. These findings do show that CT and MRI can be used to identify parenchymal changes but that they, according to the authors, are generally not strong enough to find meaningful correlation between damage and neuropsychological changes (Lee et al., 2008).

MRI has shown relationships between brain damage and neuropsychological deficits even in very mild traumatic brain injury. A study performed by Voller et al. (1999) evaluated individuals with mTBI and a GCS of 15 using electroencephalography (EEG) and MRI. They concluded that at an acute stage and 6 weeks post injury, there were neurocognitive deficits in the individuals with damage on MRI scans. Interestingly, none of the patients in the study showed a slowing of processing speed as measured by EEG, even when the MRI showed damage (Voller et al., 1999). One of the elements of brain abnormalities that might be most predictive of deficits is Diffuse Axonal Injury (DAI). One study found that DAI lesion patterns in MRI were predictive of functioning in a range of neuropsychological domains, especially memory and executive functioning (Scheid, Walther, Guthke, Preul, & von Cramon, 2006).

In spite of the previously mentioned studies, not all the literature is in agreement about MRI abnormalities predicting neuropsychological deficits. Recently, Hughes et al. (2004) found MRI abnormalities in 26 of 80 individuals with mTBI. Hughes et al. found a trend of neuropsychological deficits in the individuals with abnormal MRI scans but could not find statistical strength behind the relationship between abnormal MRI and cognitive loss. This is supported by a recent study by Scheid and von Cramon (2010) who retrospectively assessed neuropsychological functioning in individuals with a range of TBI severities. These researchers found there to be no correlation between presence of abnormalities on MRI scans and neuropsychological functioning.

A 2001 study also looked at the correlation between mTBI and neurocognition. This study used MRI and single-photon emission CT (SPECT) to evaluate brain damage. Looking solely at MRI outcomes, 11 of the 18 patients had abnormal scans. This study also found that these patients showed a decrease in cognition and reaction time. Interestingly, there was no statistical significance between patients with abnormal and normal MRI when comparing their neurocognitive tests. Thus, the above findings suggest that MRI is not sensitive enough to detect all damage that affects cognitive performance (Hofman et al., 2001).

Diffusion Tensor Imaging. Diffusion Tensor Imaging (DTI) has become a very useful tool for detailing parenchymal changes in the CNS. DTI is a way of quantifying the cytoarchitecture of brain tissue by analyzing diffusion of water in cells and reconstructing this diffusion to reveal the direction and flow of fiber tracts (Basser, 1995). This reconstruction of white matter is anticipated to greatly help understanding of deficits to white matter tracts in the brain. Catani, M., and de Schotten, M.T. (2008) show that DTI allows for virtual in vivo dissections of these white matter tracts. McAllister and colleagues (2001) postulate that DTI has a higher capacity for detecting minute axonal damage than other forms of imaging. These axonal changes, referred to as Diffuse Axonal Injury (DAI) occur in a majority of mTBI subjects (Belanger, Vanderploeg, Curtiss, & Warden, 2007). Few studies have evaluated the use of DTI to assess mild traumatic brain injury. One DTI parameter, fractional anisotropy (FA), depicts diffusion of water molecules in white matter pathways (Assaf & Pasternak, 2007). A reduction in FA has been associated with specific loss of structural integrity in the brain (Alexander, Lee, Lazar, & Field, 2007; Rutgers et al., 2008).

To illustrate the utility of DTI, recent research by Rutgers et al. (2008) studied the effects on white matter tracts in the brain of patients who have sustained mild traumatic brain injury.

Individuals with mTBI had an average of 9.1 regions of white matter that had decreased in FA and that of these regions, 19.3% of them sustained discontinuity of fiber tracts. Figures 2 and 3 below are images from the original article by Rutgers et al. These images illustrate the separation in the fiber tracts of mTBI patients.

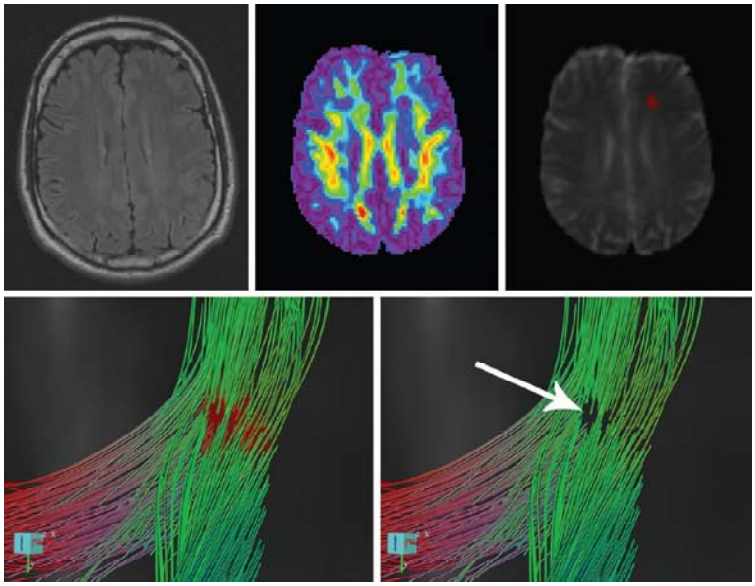

Figure 2: Figure extracted from original article by Rutgers et al. (2008). Image illustrates white matter bundles in Region of Interest (ROI) marked in red. The FLAIR image on the top left doesn't reveal any abnormality while the color coded image in the top middle reveals a reduction in FA. The top right image is a T-2 weighted image with the ROI in red. The bottom pictures are the white matter tracts superimposed on the T-2 image and show the discontinuance of fibers. The bottom right image has the ROI removed. Image used with permission from AJNR.

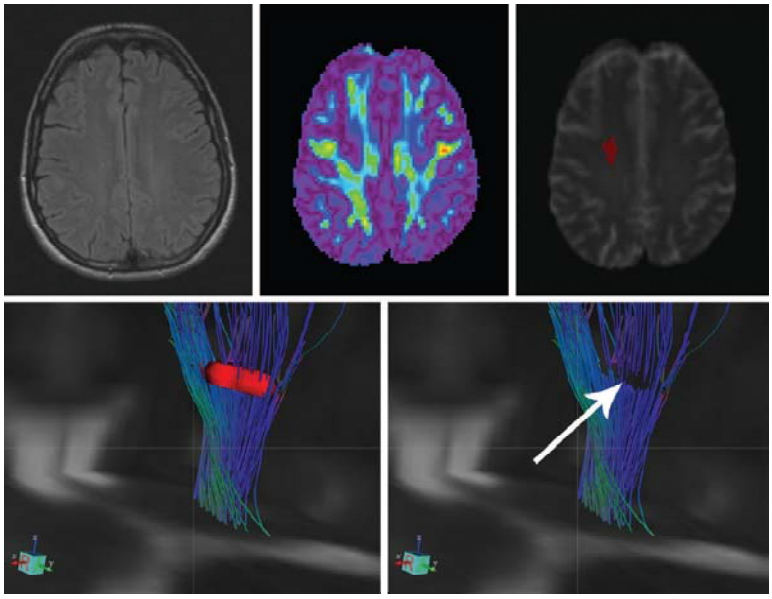

Figure 3: Figure extracted from original article by Rutgers et al. (2008). Image illustrates white matter bundles in Region of Interest (ROI) marked in red. The FLAIR image on the top left doesn't reveal any abnormality while the color coded image in the top middle reveals a reduction in FA. The top right image is a T-2 weighted image with the ROI in red. The bottom pictures are the white matter tracts superimposed on the T-2 image and show the discontinuance of fibers. The bottom right image has the ROI removed. Image used with permission from AJNR.

The work done by Rutgers and colleagues showed that, compared to control groups, mTBI subjects had a significant number of regions in the brain with reduced FA, including the corpus callosum, cingulum and cerebral lobar white matter. There was no difference in the FA changes in patients tested less than three months from injury (subacute) compared to those tested post three months (chronic). This suggests a long term histological change even in mild traumatic brain injury though further work is needed to determine clinical application of such findings.

Similar results were reported by Inglese et al. (2005) who assessed damage to the corpus callosum and internal capsule in individuals in both the chronic and subacute stage of mTBI. Inglese and colleagues found no difference between the control group and patients within 24 hours of injury. The differences become ostensive in the subacute period when compared to

control groups. Inglese et al. postulate that DTI reveals structural changes in areas that were predilection sites for DAI of both subacute and chronic injuries and that this hints that DTI could be used as an early marker and possible prognostic procedure of enduring brain damage. Arfanakis et al. (2002) likewise found that conventional MRI underestimated the extent of axonal injury and that the use to DTI could be used to detect diffuse axonal injury in the acute phase of brain injury and with sharper precision.

The work by Rutgers et al. and Inglese et al. demonstrated a structural change in white matter that cannot be found by more conventional imaging techniques. However, can DTI be used to show neurobehavioral changes in individuals with mTBI in addition to the structural changes? Recent work by Miles et al. (2008) suggests that it can. Miles and colleagues were interested in whether DTI can be used to identify mTBI patients with an increased risk of long term neuropsychological deficits. They found that structural changes in the white matter of the brain predicted executive dysfunction and a decrease in processing speed 6 months post injury (Miles et al., 2008). Although research by Kraus et al. (2007) contradicts cognitive findings in mTBI, their use of DTI also supports the idea that axonal injury occurs across the spectrum of TBI severity.

Additional support for Miles et al. is found in recent work by Niogi et al. (2008a) who used DTI to predict neurocognitive deficits after mTBI. They compared conventional 3T MR imaging to DTI and looked at the difference in cognitive outcomes. These researchers pointed out that in the presence of normal appearing CT or MRI scans, patients are often turned away despite postconcussive complaints. These researchers also found that 10 of 11 patients with normal MRI scans had microstructural damage to white matter tracts on DTI imaging. Further white matter abnormalities correlated with slower reaction time (Niogi et al., 2008a).

Likewise, Niogi et al. (2008b) also conducted a study comparing brain regions of non-injury controls to mTBI patients in areas of the brain associated with memory and attention. They attempted to determine if regions of the brain associated with these functions were the same in an mTBI population. They found that the regions were the same in both groups and that the mTBI group performed worse on tests of memory and attention when experimenters were sure they were testing regions of the brain associated with these functions (Niogi et al., 2008b).

It is of importance to note the advances that have been made with MR imaging. Susceptibility-weighted imaging (SWI) can now detect forms of iron in the brain that once were not detectable. These iron traces come in the forms of ferritin, deoxyhemoglobin, and hemosiderin; hemosiderin being the neuroimaging biomarker for DAI (Haacke, Mittal, Wu, Neelavalli, & Cheng, 2009). As has already been stated, more subtle DAI has shown to not be detectable on convention MR imaging but as MR imaging has advanced, the detection of biomarkers such as hemosiderin have revealed damage previously not seen (Tong et al., 2008). In fact, previous work by Tong et al. (2003) demonstrated the sensitivity of SWI in children with TBI. They showed that SWI detected DAI six times greater than conventional T2 weighted GRE imaging (gradient refocused echo; Tong et al., 2003).

In addition, diffusion weighted imaging (DWI), the technology DTI is based off of, has similar findings to DTI. DWI is very sensitive to diffuse axonal injury. Hou et al. (2007) used this method to compute a measure of the differences in seemingly normal brains and compare these measures. These researchers found that abnormalities seen with DWI were correlated unfavorable outcome in a range of TBI severities (Hou et al., 2007). Galloway, Tong, Ashwal, Oyoyo, and Obenaus, (2008) also found the changes seen with DWI were indicative of long term

effects of the damage. These authors looked at TBI as a whole and found that their measures could correctly predict long term outcomes about 83% of the time.

Finally, it is important to note that higher field strengths have greatly refined detection of neuroimaging abnormalities. One study compared 1.5 tesla (T) to 3.0 T field strength while examining cranial fossas and brain nerves. The results revealed that 3.0T field strength was "considered more conspicuous and less noisy than images at 1.5T" (p. 358), the signal to noise ratio was doubled compared to the 1.5T scans, and more neural parenchyma were detected with the higher field strength (Fischbach, Müller, & Bruhn, 2008). Similar to the Fischbach et al. (2008) article, a previous study by Alexander, Lee, Wu, and Field (2006) examined differences in MRI field strength in DTI. This study pointed out that the signal-to-noise ratio can have an impact on the spatial accuracy and quality of the DTI analysis. These researchers compared DTI analyses from 1.5T and 3.0T MRI and concluded that DTI at 3.0T would result in significantly better measurements (Alexander et al., 2006).

Single-Photon Emission CT. The advent of single-photon emission CT (SPECT), has allowed for the assessment of cerebral metabolism (i.e. hypoperfusion or hyperperfusion). In a review of literature by Davalos and Bennett (2002) the authors evaluated 9 published works assessing the use of SPECT in mTBI diagnostics. They concluded that SPECT was more sensitive to brain damage in mTBI than MRI or CT. The detection of hypoperfusion and hyperperfusion may play an important role in long term cognitive outcomes. The review also found weak relationships between abnormal SPECT and neuropsychological deficits in mTBI (Davalos & Bennett, 2002).

Hofman et al. (2001) assessed MRI and single-photon emission CT and found that the combined use of imaging modalities showed brain injury in 77% of mTBI patients. In this

population, SPECT was abnormal in 11 of 18 patients at 6 months follow up. Further, the patients had atrophy supporting the hypothesis that secondary ischemia injury may be resulting from a hypoperfusion caused by initial injury. Further support came from mTBI patients and animals that had a decline in cerebral autoregulation at follow up. SPECT can be used to assess relationships between long term outcomes and cognitive decline due to atrophy following brain injury (Hofman et al., 2001).

The findings that there are wide spread changes in brain following mTBI is also supported the use of Magnetic Resonance Spectroscopic Imaging (MRSI), a very different technique than SPECT. Research by Govindaraju et al. (2004) found that there were diffuse metabolic changes in the brain following mTBI in patients with normal CT and MRI scans. These differences were measured in the acute phase of injury but found no association between these findings and clinical outcomes at 6 month follow up (Govindaraju et al., 2004). Later work done by Kirov et al. (2007) supported previous findings by Govindaraju et al. Kirov et al. found little difference in the MRSI of mTBI patients compared to controls in the thalamus. Additional research supports the premise that there are metabolic deficits following a range of TBI severities and anatomical locations and that these deficits are associated with cognitive functioning (Babikian et al., 2010, Gasparovic et al., 2009).

In addition, Belanger et al. (2007) found SPECT to be more sensitive than CT and MRI. However, the fact that most of the past research failed to use controls and reported inconsistent findings, more work is needed to elucidate the benefits of SPECT as a prognostic tool in mTBI. It should be noted, however, that SPECT is being used less with the advent of newer techniques for neuroimaging.

Positron Emission Tomography. Positron Emission Tomography (PET) is another means of evaluating metabolic changes in the CNS using glucose or oxygen metabolism. Glucose is typically used, specifically fludeoxyglucose-18F (FDG). As a function is activated in the brain, the region will use more glucose and PET can tract the use of glucose in these regional areas. Research using this modality has actually shown somewhat inconsistent results in mTBI. PET is useful at detecting metabolic abnormalities in mTBI and some studies show correlations between abnormal PET and neuropsychological outcomes (Belanger et al., 2007).

Chen and colleagues (2003) examined PET scans of individuals with persistent cognitive complaints after mild head injury. Comparing patients to controls demonstrated that there were no differences between them in the typically resting state of a PET scan. The two groups differed in PET scan when a spatial working memory test was employed. Results suggest that the post-concussive losses experienced by people might only become ostensive in times of increased cognition (Chen et al., 2003).

Despite the usefulness of PET, it is of importance to note that PET has some significant draw backs. The anatomical resolution of PET is very poor compared to high field strength MRI. It also requires individuals to be exposed to radiopharmaceuticals to generate an image. It is also more expensive and less readily available than MRI or CT technology.

Neuropsychological Outcome in Positive versus Negative Neuroimaging

As mentioned above, the literature is not consistent with regards to whether outcome is worse for complicated mTBI than for uncomplicated. Advances in neuroimaging demonstrate that CT is less sensitive than other imaging modalities and will thus not detect structural changes to the CNS. As previously mentioned, studies have consistently found that individuals with mTBI have abnormal findings in CT scans 20-35% of the time (Harad & Kerstein, 1992;

Schynoll et al., 1993; Shackford et al., 1992; Stein & Ross, 1992 as cited in McAllister et al., 2001). In addition, MRI and more sensitive imaging modalities have consistently been shown to be more sensitive than CT (Hughes et al., 2004; Uchino, Okimura, Tanaka, Saeki, & Yamaura, 2001). Thus, it is difficult to compare neuroimaging results from different imaging modalities. The terms complicated and uncomplicated are typically used to refer to imaging results during the acute stage of injury. For the purpose of the present study, which is more concerned with chronic injury, the terms positive and negative neuroimaging will be used interchangeably with complicated/uncomplicated mTBI. If an imaging scan comes back positive, this means the presence of abnormalities was detected. If the scan was negative, it came back normal.

Several studies have tried to determine if there is a difference in the neuropsychological functioning of people with positive versus negative neuroimaging results. A group of studies has found there to be a significant difference in neurobehavioral and neuropsychological functioning between subjects with positive and negative neuroimaging results (Williams, Levin, & Eisenberg, 1990; van der Naalt, Hew, Zomeren, Sluiter, & Minderhoud, 1999a; Temkin, Machamer, & Dikmen, 2003; Hessen & Nestvold, 2009). However, other studies have resulted in contradictory findings- there is equal outcome or no difference is outcome between patients with abnormal and normal neuroimaging scans (Hanlon, Demery, Martinovich, & Kelly, 1999; Hofman et al., 2001; McCauley et al., 2001; Hughes et al., 2004).

Summary

Imaging modalities such as CT have greatly advanced the initial assessment of brain injury even in very mild cases. However, the literature shows there to be confusion as to whether complicated mTBI is associated with poorer outcomes than uncomplicated mTBI. MRI has proven to be more sensitive and therefore more useful than CT at detecting diffuse injuries

after mild brain injury, especially in the chronic phase of injury. Functional imaging techniques such as PET and SPECT may be superior in detecting deficits associated with mTBI and show promise in assessing long term prognosis of mTBI (Umile, Sandel, Alavi, Terry, & Plotkin, 2002). Of all neuroimaging measures to date, DTI has great promise in determining long term sequelae even in a chronic phase of injury. It seems reasonable to conclude that to better understand mTBI investigations should concentrate on those with definable neuroimaging abnormalities compared to those without such abnormalities. Much of the confusion within mTBI research is likely related to a failure to systematically control for the presence or absence of neuroimaging detected abnormalities.

The present work is designed to analyze the use of different imaging techniques in mild mTBI and how the presence of neuroimaging abnormalities effect outcome. This will be addressed by use of meta-analytic techniques. Meta-analysis is a way to summate data across studies in an objective, quantitative manner. This aggregate method will be used to assess average affect sizes in the two groups of interest – studies of mTBI outcome that also had positive neuroimaging compared to studies of mTBI outcome among individuals with negative neuroimaging.

The rationale for the present study is as follows. The role of brain imaging techniques in the assessment of mild traumatic brain injury have been briefly overviewed including CT, MRI, SPECT, DTI, DWI, and MRSI. Current literature points to the use of newer techniques being more successful at detecting subtle changes in the human brain and in finding relationships to neurobehavioral sequelae following mTBI. Conventional techniques, though more accessible, tend to not be as sensitive as newer modalities such as DTI, SWI, or SPECT. In the areas of neuropsychological testing, overtime the field has worked to refine tests and when used

appropriately, can be sensitive in detecting deficits, even in mild cases of TBI. Studies have shown that complicated mTBI is associated with more neuropsychological sequelae but not all of the literature is in agreement on this matter.

Regardless of advances in testing procedures and imaging techniques, a great debate continues within the field of neuropsychology with regards to persistent deficits following mTBI (Pertab et al., 2009; Greiffenstein, 2009). However, based on the literature, we need ask whether the presence of abnormalities in imaging are associated with more deficits when assessed in the aggregate and is there a difference between complicated and uncomplicated mTBI? Regardless of whether we see differences or not, the results will add to the understanding of testing procedures in neuropsychology in detecting cognitive/neurobehavioral effects of mTBI.

For example, if a meta-analysis reveals that positive mTBI has more neuropsychological deficit than negative mTBI, then perhaps mTBI "complicated" by the presence of neuroimaging abnormalities should be treated differently in rehabilitation settings than the mTBI's with a negative scan.

The directional hypothesis regarding this question (Table 2) is as follows:

Hypothesis- The presence of imaging abnormalities in mTBI will be associated with more post-concussive symptoms, greater neurocognitive and neuropsychological deficits as measured by reported means and standard deviations on tests of memory, attention/concentration, mood/emotion, and executive functioning.

Table 2: *Hypothesis for present study*

Independent Variables	Dependent variable
Presence of Lesions in Neuroimaging	Reported Neuropsychological sequelae
Absence of Lesions in Neuroimaging	

Methods

Studies Selection

Articles for this study were selected from data base searches using the PubMed, EBSCO, and PsychInfo databases. The search terms included: mild traumatic brain injury, mild head injury, mild head trauma, post-concussive syndrome, concussion, closed head injury, mild closed head injury and imaging (neuroimaging, neuroradiology, radiology, and radiologic). Inclusion criteria for articles were based off of researchers' working definition of mild traumatic brain injury (Table 1 above and Figure 4 below). Mild TBI was defined as a Glasgow Coma Scale of 13-15, post traumatic amnesia (PTA) of < 24 hours and a loss of consciousness (LOC) of ≤ 30 minutes (Furlow, 2006; van der Naalt et al., 1999b). Search results were done from January 1, 2003 to December 31, 2009. For the purposes of this paper, long term effects of mild traumatic brain injury were based off of measurement at time periods ≥ 3 months post injury. Because of the significant differences between structural and functional neuroimaging, only structural imaging modalities was used in this study.

Inter-rater Reliability

Regarding inter-rater reliability, data from articles used for the current meta-analysis was extracted by two independent researchers.

Effect Size Calculation

The effect size calculation was performed with standardize information from each article, a necessary step considering clinicians used a wide range of tests to evaluate neuro-behavioral outcomes. Effect size calculation was dependent on the descriptive statistics reported in each article included in the review. The present study extracted data on the control and patient group means and standard deviations on neuropsychological tests. These statistics were then further

used to calculate an effect size for each study. Hedges's g, a standardized mean difference formula, was used to determine effect sizes (see Formula A; Hedges & Olkin, 1985).

$$g = \frac{\overline{X}_1 - \overline{X}_2}{s_p} \qquad \text{(A)}$$

X bar 1 and 2 represent the means for groups being compared. In this study, this was scores from the control group compared to mTBI group. S_p represented the pooled standard deviation for the two groups. In the present study, a majority of the articles used measured more than one neuro-behavioral domain. In this case, there were multiple effect size calculations for each study.

Data Analysis

All analyses was performed with Comprehensive Meta-Analysis 2.0 (Biostat, Englewood, New Jersey). Analyses included effect size calculation, Q-statistic test of heterogeneity, meta-regression, and split groups analysis.

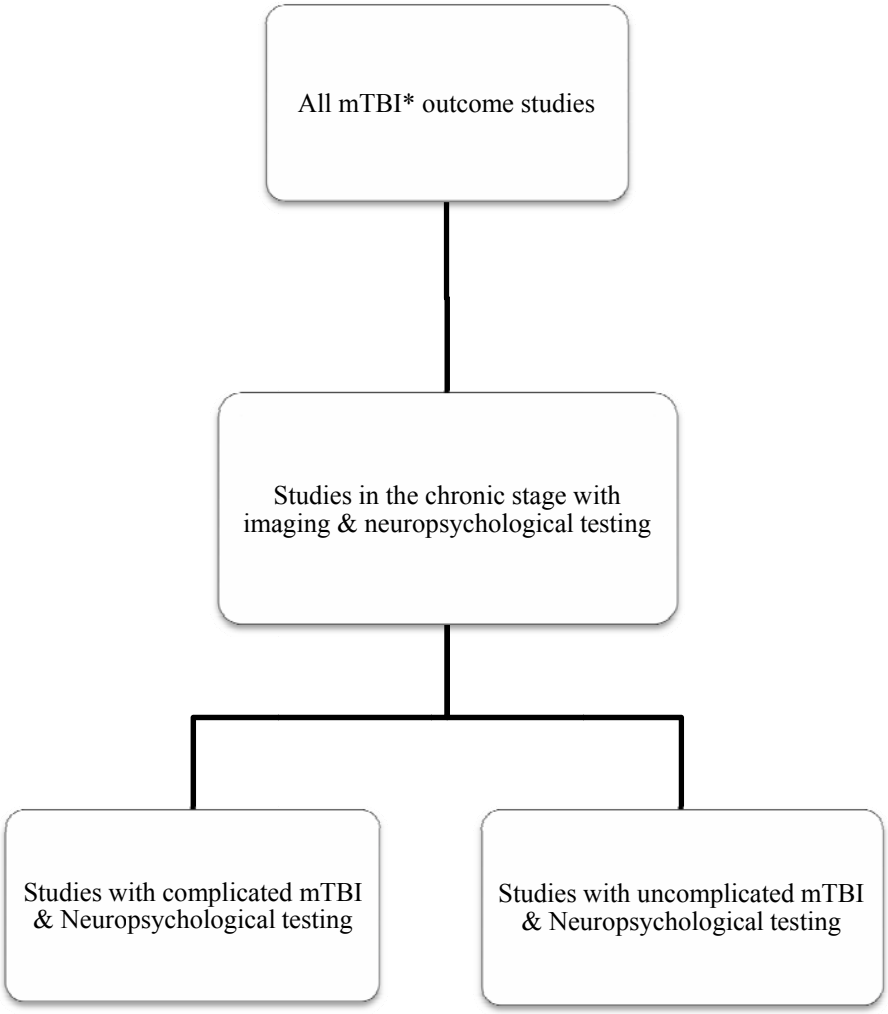

Figure 4: Flowchart showing article selection for meta-analysis, inclusion/exclusion criteria.

* For operational definition of mTBI, see Table 1.

Results

A total of 9 studies were identified that fit the inclusion criteria for this study (table 3). Only the neuropsychological domains of attention, executive functioning, memory, and speed of processing resulted in enough data to be analyzed. Within each of these domains, any particular study may have administered several tests. For example, Chen et al. (2003) had 8 tests of working memory. In order to control for the weight each study contributed to the overall model, summary effect sizes were calculated by domain per study. This results, for example, in one score for Chen et al. (2003) instead of eight. Effect sizes were calculated in this manner and then analyzed again per domain. The results of each domain will be discussed in turn. To determine if there was any difference between positive and negative imaging, two methods of analysis were used. First, a regression was performed with positive/negative imaging as the independent variable and effect size and the dependent variable. Next, studies were groups by positive and negative imaging and a Q-statistic was performed. A Q-statistic is a measure of heterogeneity which would determine if the studies were statistically similar or dissimilar (Borenstein, Hedges, Higgins, & Rothstein, 2009, pp. 105-106).

It is of important note that the original hypothesis included a design where additional variables would have been collected to run a more detailed meta-regression. This was to include variables such as GCS, PTA, LOC, location of lesion, etc. Unfortunately, these variables were not reported with enough consistency across studies to be able to perform such a meta-analysis. Also, the data collected for this study found that a majority of studies either had all positive neuroimaging results or all negative neuroimaging results. Thus, for the present analysis and results, studies were dichotomized at 50% where if the study reported at least 50% of their

sample having positive scans, this was coded as positive. Similarly, if the study reported less than 50% of their sample having positive scans, this was coded as negative.

Table 3: *Characteristics of Source Studies*

Study	mTBI Subjects	Control Subjects	Time Post Injury	Imaging Modality	MOI
Chen, J.K. et al., 2007	9	10	5 months	MRI	Sports
Chen, J.K. et al., 2008	16	16	7.3 months	MRI	Sports
Chen, S.H.A. et al., 2003	5	5	16.6 months	CT & MRI	Fall/blunt object
Fork, et al., 2005	11	17	5-8 months	CT	Not specified
Fujiwara et al., 2008	12	25	12 months	MRI	Mixed (78% MVA)
Ge et al., 2009	21	18	24.6 months*	MRI	Mixed
Kraus et al., 2007	20	18	92.55 months	MRI & DTI	Mixed (85% MVA)
Lee et al., 2008	28	18	12 months	CT & MRI	Mixed (69% MVA)
Miles et al., 2008	12	29	6 months	MRI & DTI	Not specified

Note: * reported time post injury is a median score; MOI, Mechanism of Injury; MVA, motor vehicle accident; MRI, Magnetic Resonance Imaging; CT, Computed Tomography; DTI, Diffusion Tensor Imaging.

For the neuropsychological domain of attention, this meta-analysis revealed that the large effect size was significant ($g = 0.814$, $p = 0.001$; Table 4). Thus, within this domain, mTBI subjects performed statistically worse on neuropsychological tests than the control subjects. However, when comparing the studies reporting positive neuroimaging among subjects to the studies reporting negative neuroimaging, there was no significant difference between groups. As can be seen in Table 5, the Q-statistic test of heterogeneity was insignificant ($p = 0.457$). Thus, the two groups are not significantly heterogeneous. In other words, presence of an abnormality in subject's neuroimaging scans did not predict outcome in the chronic stage of mTBI.

Table 4: *Statistical data for Attention run by random effects model*

Study	Hedges's G	SE*	Variance	Lower Limit	Upper Limit	Z-Value	*p*-Value
Chen,J.K. et al., 2007	0.253	0.255	0.065	-0.247	0.754	0.993	0.321
Fork et al., 2005	0.272	0.189	0.036	-0.098	0.642	1.439	0.150
Kraus et al., 2007	1.870	0.293	0.086	1.296	2.444	6.382	0.000
Miles et al., 2008	0.761	0.201	0.04	0.367	1.154	3.792	0.000
Chen,SHA et al., 2003	0.898	0.484	0.235	-0.051	1.847	1.854	0.064
Ge et al., 2009	0.992	0.334	0.112	0.338	1.647	2.970	0.003
Summary	0.814	0.246	0.06	0.332	1.295	3.313	0.001

Note: *SE = Standard Error

Table 5: *Test of Heterogeneity between positive and negative imaging for Attention*

	Q-value	df (Q)	*P*-value
negative	3.591	2	0.166
positive	21.025	2	0.000
Total within	24.616	4	0.000
Total between	**0.553**	**1**	**0.457**
Overall	25.169	5	0.000

This finding was confirmed with the meta-regression of neuroimaging group. Meta-regression was performed with fixed effect, methods of moments, and unrestricted maximum likelihood models which are presented in Table 6. However, only scatter plots for the fixed effect model is presented here. All three models were insignificant ($p = 0.457$, $p = 0.649$, $p = 0.589$). Thus, within the neuropsychological domain of attention, presence of absence of neuroimaging abnormalities was of little consequence to long term functioning.

Table 6: *Statistical data for regression for neuroimaging in domain of Attention*

	Fixed Effect Regression					
	Point Estimate	SE	Lower Limit	Upper Limit	Z-value	*p*-Value
Slope	0.16711	0.22471	-0.27332	0.60755	0.74368	0.457
Intercept	0.58133	0.18708	0.21466	0.94800	3.10736	0.002
	Mixed Effects Regression (method of moments)					
	Point Estimate	SE	Lower Limit	Upper Limit	Z-value	*p*-Value
Slope	0.24882	0.54666	-0.82262	1.32026	0.45516	0.649
Intercept	0.68407	0.40233	-0.10449	1.47262	1.70026	0.089
	Mixed Effects Regression (unrestricted maximum likelihood)					
	Point Estimate	SE	Lower Limit	Upper Limit	Z-value	*p*-Value
Slope	0.24480	0.45343	-0.64391	1.13351	0.53989	0.589
Intercept	0.67153	0.33877	0.00755	1.33551	1.98225	0.047

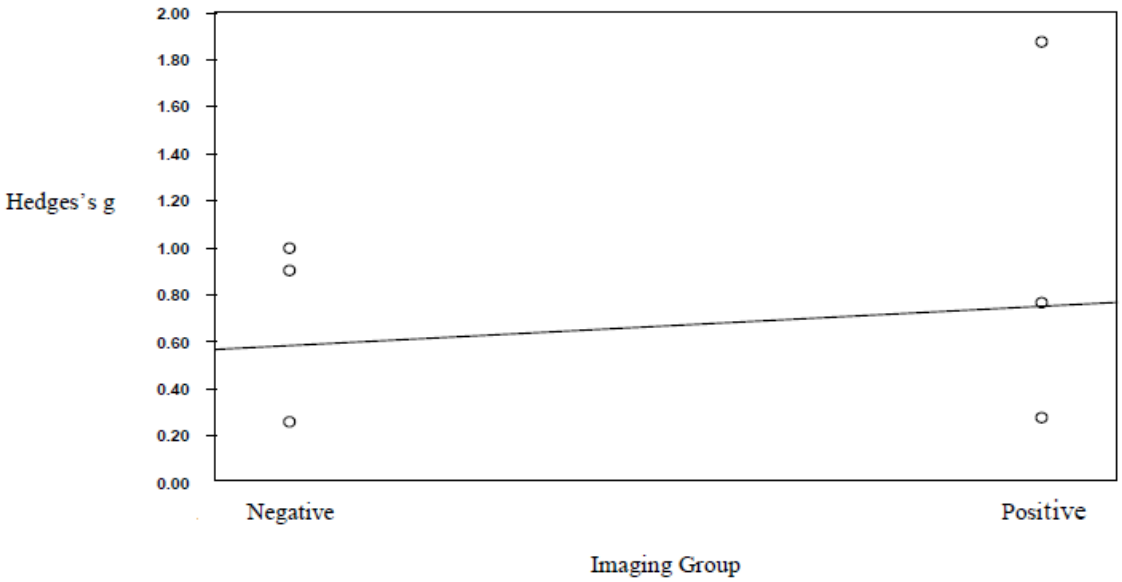

Figure 5: Fixed Effects scatter plot for positive and negative imaging on domain of Attention.

Next, summary effect sizes were calculated for each domain but while grouping studies by imaging. This was done to determine if there were large differences between positive and negative neuroimaging. Table 7 summarizes the results for attention. Note that the effect size for negative imaging was smaller than the effect size for positive imaging. The overall summary shows a significant p-value but when separated out, only studies with positive neuroimaging resulted in a significant summary effect size ($p = 0.012$).

Table 7: *Results for Attention when grouped by neuroimaging*

Study	Neuroimaging	Hedges's G	SE*	Variance	Z-Value	*p*-Value
Chen,J.K. et al., 2007	negative	0.253	0.255	0.065	0.993	0.321
Chen,S.H.A. et al., 2003	negative	0.898	0.484	0.235	1.854	0.064
Ge et al., 2009	negative	0.992	0.334	0.112	2.97	0.003
	Summary for negative	**0.684**	**0.402**	**0.162**	**1.7**	**0.089**
Fork et al., 2005	positive	0.272	0.189	0.036	1.439	0.15
Kraus et al., 2007	positive	1.87	0.293	0.086	6.382	0
Miles et al., 2008	positive	0.761	0.201	0.04	3.792	0
	Summary for positive	**0.933**	**0.37**	**0.137**	**2.521**	**0.012**
	Overall Summary	**0.819**	**0.272**	**0.074**	**3.006**	**0.003**

Note:*SE = Standard Error

For executive functioning, a similar result was observed. The large effects size between mTBI subjects and control was significant ($g = 0.696$, $p = 0.000$; Table 8). Again, however, results show that imaging did not seem to predict outcome. The test of heterogeneity for executive functioning showed that there was no difference between the positive and negative imaging groups ($p = 0.753$; Table 9).

Table 8: *Statistical data for Executive Functioning run by random effects model*

Study	Hedges's G	SE*	Variance	Lower Limit	Upper Limit	Z-Value	*p*-Value
Chen, S.H.A. et al., 2003	0.487	0.288	0.083	-0.077	1.050	1.693	0.090
Fork et al., 2005	0.613	0.172	0.03	0.275	0.951	3.552	0.000
Kraus et al., 2007	1.436	0.314	0.099	0.820	2.052	4.566	0.000
Miles et al., 2008	0.469	0.139	0.019	0.196	0.742	3.365	0.001
Fujiwara et al., 2008	0.947	0.361	0.13	0.240	1.655	2.625	0.009
Ge et al., 2009	0.671	0.303	0.092	0.078	1.264	2.217	0.027
Summary	0.696	0.131	0.017	0.439	0.953	5.311	0.000

Note: *SE = Standard Error

Table 9: *Test of Heterogeneity between positive and negative imaging for Executive Functioning*

	Q-value	df (Q)	*P*-value
negative	0.195	1	0.659
positive	8.655	3	0.034
Total within	8.850	4	0.065
Total between	**0.099**	**1**	**0.753**
Overall	8.949	5	0.111

The Q statistic test of heterogeneity was confirmed with the results in the meta-regression. All three meta-regression models were insignificant (Table 10 and Figure 6). Thus, for the neuropsychological domain of executive functioning, the presence or absence of an abnormality on a patient's neuroimaging scan did not predict function in the chronic stage of mTBI. These results were similar across each neuropsychological domain tested.

Table 10: *Statistical data for regression for neuroimaging in domain of Executive Functioning*

	Fixed Effect Regression					
	Point Estimate	SE	Lower Limit	Upper Limit	Z-value	*p*-Value
Slope	0.07268	0.23058	-0.37926	0.52461	0.31520	0.75261
Intercept	0.57410	0.20844	0.16556	0.98263	2.75422	0.00588

	Mixed Effects Regression (method of moments)					
	Point Estimate	SE	Lower Limit	Upper Limit	Z-value	*p*-Value
Slope	0.18537	0.32369	-0.44905	0.81978	0.57267	0.567
Intercept	0.57609	0.27455	0.03798	1.11419	2.09830	0.036

	Mixed Effects Regression (unrestricted maximum likelihood)					
	Point Estimate	SE	Lower Limit	Upper Limit	Z-value	*p*-Value
Slope	0.13291	0.26778	-0.39193	0.65776	0.49635	0.620
Intercept	0.57505	0.23350	0.11739	1.03270	2.46271	0.014

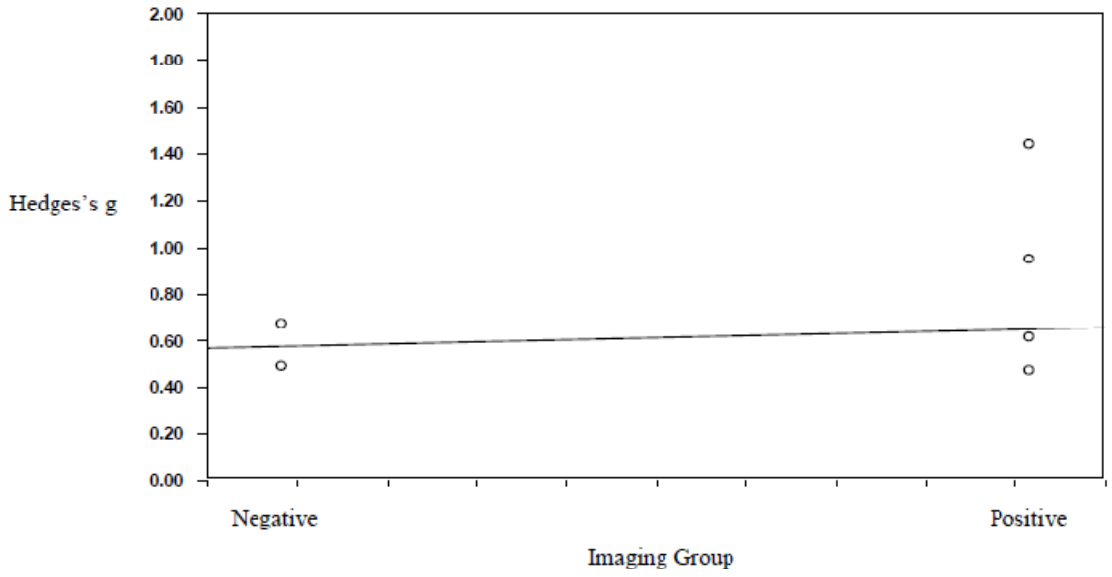

Figure 6: Fixed Effects scatter plot for positive and negative imaging on domain of Executive Functioning.

After initial analysis, summary effect sizes were calculated for each domain but while grouping studies by imaging. This was done to determine if there were large differences between positive and negative neuroimaging. Table 11 summarizes the results for executive functioning. Note that the effect size for negative imaging was only slightly smaller than the effect size for positive imaging but that it was still significant ($g = 0.576$, $p = 0.036$). The overall summary also shows a significant p-value ($p = 0.000$).

Table 11: *Results for Executive Functioning when grouped by neuroimaging*

Study	Neuroimaging	Hedges's G	SE*	Variance	Z-Value	*p*-Value
Chen, S.H.A. et al., 2003	negative	0.487	0.288	0.083	1.693	0.09
Ge et al., 2009	negative	0.671	0.303	0.092	2.217	0.027
	Summary for negative	**0.576**	**0.275**	**0.075**	**2.098**	**0.036**
Fork et al., 2005	positive	0.613	0.172	0.03	3.552	0
Kraus et al., 2007	positive	1.436	0.314	0.099	4.566	0
Miles et al., 2008	positive	0.469	0.139	0.019	3.365	0.001
Fujiwara et al., 2008	positive	0.947	0.361	0.13	2.625	0.009
	Summary for positive	**0.761**	**0.171**	**0.029**	**4.441**	**0**
	Overall Summary	**0.709**	**0.145**	**0.021**	**4.878**	**0**

Note: *SE = Standard Error

Similar findings were seen for the neuropsychological domain of memory. It is important to note that neuropsychological test batteries often test for multiple types of memory. In the present study, memory tests were grouped as a whole. A paucity of data precludes there being analysis for each type of memory tested among the included articles. The overall meta-analysis results for memory are presented in Table 12. Note that the summary effect size was slightly smaller than those of attention and executive functioning but that the effect size for memory was still significant ($g = 0.583$, $p = 0.000$).

Table 12: *Statistical data for Memory run by random effects model*

Study	Hedges's G	SE*	Variance	Lower Limit	Upper Limit	Z-Value	*p*-Value
Chen, J.K. et al., 2007	0.659	0.227	0.051	0.214	1.103	2.904	0.004
Chen, J.K. et al., 2008a	0.168	0.345	0.119	-0.509	0.845	0.487	0.626
Chen, S.H.A. et al., 2003	0.679	0.135	0.018	0.413	0.944	5.009	0.000
Fork et al., 2005	0.475	0.121	0.015	0.238	0.713	3.921	0.000
Ge et al., 2009	0.511	0.320	0.102	-0.116	1.138	1.598	0.110
Kraus et al., 2007	0.649	0.324	0.105	0.015	1.284	2.005	0.045
Lee et al., 2008	1.221	0.460	0.211	0.320	2.121	2.656	0.008
Miles et al., 2008	0.733	0.346	0.12	0.054	1.412	2.117	0.034
Summary	0.583	0.074	0.005	0.438	0.728	7.887	0.000

Note: *SE = Standard Error

It was found that for the domain of memory, neuroimaging did not predict functional outcome. The Q-statistic test of heterogeneity was insignificant with a *p*-value of 0.715 (Table 13). This was again confirmed with meta-regression results where slope on all three models was insignificant (Table 14, Figure 7). Presence of an abnormality on neuroimaging scan did not seem to predict memory functioning in the chronic stage of mTBI.

Table 13: *Test of Heterogeneity between positive and negative imaging for Memory*

	Q-value	df (Q)	*P*-value
negative	2.036	3	0.565
positive	2.879	3	0.411
Total within	4.915	6	0.555
Total between	**0.133**	**1**	**0.715**
Overall	5.048	7	0.654

Beyond initial analysis, summary effect sizes were calculated for each domain but while grouping studies by positive and negative imaging. This was done to determine if there were large differences between positive and negative neuroimaging. Table 15 summarizes the results for memory. Note that both the negative and positive imaging groups maintain significant p-values for this domain and that the effect sizes were relatively similar between positive and negative neuroimaging groups.

Table 14: *Statistical data for regression for neuroimaging in domain of Memory*

	Fixed Effect Regression					
	Point Estimate	SE	Lower Limit	Upper Limit	Z-value	*p*-Value
Slope	-0.05393	0.14794	-0.34389	0.23603	-0.36454	0.715
Intercept	0.61013	0.10421	0.40589	0.81438	5.85489	0.000
	Mixed Effects Regression (method of moments)					
	Point Estimate	SE	Lower Limit	Upper Limit	Z-value	*p*-Value
Slope	-0.05393	0.14794	-0.34389	0.23603	-0.36454	0.715
Intercept	0.61013	0.10421	0.40589	0.81438	5.85489	0.000
	Mixed Effects Regression (unrestricted maximum likelihood)					
	Point Estimate	SE	Lower Limit	Upper Limit	Z-value	*p*-Value
Slope	-0.05393	0.14794	-0.34389	0.23603	-0.36454	0.715
Intercept	0.61013	0.10421	0.40589	0.81438	5.85489	0.000

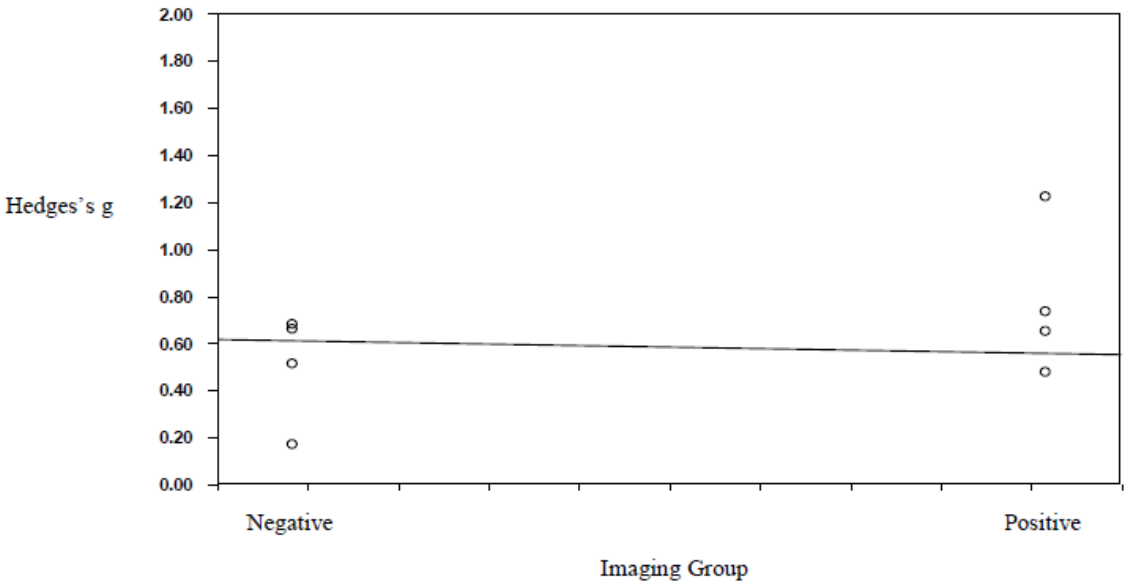

Figure 7: Fixed Effects scatter plot for positive and negative imaging on domain of Memory.

Table 15: *Results for Memory when grouped by neuroimaging*

Study	Neuroimaging	Hedges's G	SE*	Variance	Z-Value	*p*-Value
Chen, J.K. et al., 2007	negative	0.659	0.227	0.051	2.904	0.004
Chen, J.K. et al., 2008a	negative	0.168	0.345	0.119	0.487	0.626
Chen, S.H.A. et al., 2003	negative	0.679	0.135	0.018	5.009	0
Ge et al., 2009	negative	0.511	0.32	0.102	1.598	0.11
	Summary for negative	**0.61**	**0.104**	**0.011**	**5.855**	**0**
Fork et al., 2005	positive	0.475	0.121	0.015	3.921	0
Kraus et al., 2007	positive	0.649	0.324	0.105	2.005	0.045
Lee et al., 2008	positive	1.221	0.46	0.211	2.656	0.008
Miles et al., 2008	positive	0.733	0.346	0.12	2.117	0.034
	Summary for positive	**0.556**	**0.105**	**0.011**	**5.297**	**0**
	Overall Summary	**0.583**	**0.074**	**0.005**	**7.887**	**0**

Note: *SE = standard error

The domain of speed of processing had the greatest paucity of data among the four domains analyzed (Table 16). However, the overall summary still showed a large and significant effect size ($g = 0.979$, $p = 0.002$).

Table 16: *Statistical data for Speed of Processing run by random effects model*

Study	Hedges's G	SE*	Variance	Lower Limit	Upper Limit	Z-Value	*p*-Value
Chen, S.H.A. et al., 2003	0.964	0.306	0.094	0.363	1.564	3.146	0.002
Ge et al., 2009	0.985	0.236	0.056	0.522	1.448	4.173	0.000
Kraus et al., 2007	2.579	0.434	0.189	1.728	3.431	5.938	0.000
Miles et al., 2008	0.333	0.240	0.058	-0.138	0.803	1.387	0.165
Chen, J.K. et al., 2007	0.329	0.314	0.099	-0.286	0.945	1.048	0.295
Summary	0.979	0.320	0.102	0.353	1.606	3.063	0.002

Note: *SE = Standard Error

Results showed that the Q-statistic test of heterogeneity was insignificant thus showing that for the domain of speed of processing, neuroimaging group did not predict functional outcome (Table 17). This was confirmed with the meta-regression (Table 18). Slope for all three models of regression were insignificant.

Table 17: *Test of Heterogeneity between positive and negative imaging for Speed of Processing*

	Q-value	df (Q)	*P*-value
negative	3.143	2	0.208
positive	20.486	1	0.000
Total within	23.629	3	0.000
Total between	**0.037**	**1**	**0.848**
Overall	23.666	4	0.000

Table 18: *Statistical data for regression for neuroimaging in domain of Speed of Processing*

	Fixed Effect Regression					
	Point Estimate	SE	Lower Limit	Upper Limit	Z-value	*p*-Value
Slope	0.05083	0.26452	-0.46761	0.56927	0.19216	0.848
Intercept	0.80766	0.16069	0.49271	1.12260	5.02622	0.000
	Mixed Effects Regression (method of moments)					
	Point Estimate	SE	Lower Limit	Upper Limit	Z-value	*p*-Value
Slope	0.59349	0.77962	-0.93454	2.12153	0.76125	0.447
Intercept	0.76444	0.48588	-0.18788	1.71675	1.57328	0.116
	Mixed Effects Regression (unrestricted maximum likelihood)					
	Point Estimate	SE	Lower Limit	Upper Limit	Z-value	*p*-Value
Slope	0.55268	0.65611	-0.73328	1.83864	0.84236	0.400
Intercept	0.76663	0.40689	-0.03085	1.56411	1.88414	0.060

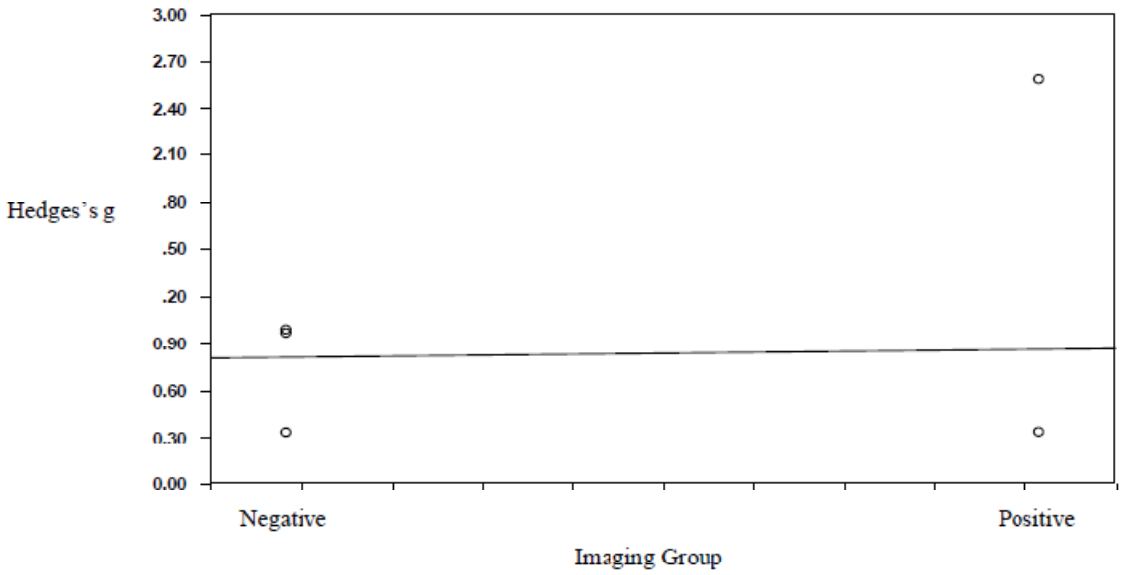

Figure 8: Fixed Effects scatter plot for positive and negative imaging on domain of Speed of Processing.

Also for speed of processing, effect sizes were calculated while grouping studies by imaging. This was done to determine if there were large differences between positive and negative neuroimaging. Table 19 summarizes the results for speed of processing. Note that only the positive imaging groups maintain significant p-values for this domain and that the effect size for positive imaging was almost twice the size as it was for the group with negative neuroimaging.

In conclusion, only the domains of attention, executive functioning, memory, and speed of processing yielded enough data to be analyzed. Across all four domains, large and significant effect sizes were found suggesting that mTBI subjects performed significantly worse on neuropsychological tests than control subjects. For all for domains, the presence of neuroimaging abnormalities failed to be predictive of neuropsychological functioning in the chronic stage of mTBI. This was determined by a Q-statistic test of heterogeneity between

positive and negative neuroimaging groups as well as by meta-regression controlling for neuroimaging status.

Table 19: *Results for Speed of Processing when grouped by neuroimaging*

Study	Neuroimaging	Hedges's G	SE*	Variance	Z-Value	*p*-Value
Chen, S.H.A. et al., 2003	negative	0.964	0.306	0.094	3.146	0.002
Ge et al., 2009	negative	0.985	0.236	0.056	4.173	0
Chen, J.K. et al., 2007	negative	0.329	0.314	0.099	1.048	0.295
	Summary for negative	**0.764**	**0.486**	**0.236**	**1.573**	**0.116**
Kraus et al., 2007	positive	2.579	0.434	0.189	5.938	0
Miles et al., 2008	positive	0.333	0.24	0.058	1.387	0.165
	Summary for positive	**1.358**	**0.61**	**0.372**	**2.227**	**0.026**
	Overall Summary	**0.995**	**0.38**	**0.144**	**2.618**	**0.009**

Note:*SE = Standard Error

Discussion

The present study had two main findings. First, it contradicted previous meta-analyses by providing strong evidence that in the chronic stage of injury, some studies on mTBI subjects indicate significantly worse performance than control subjects on neuropsychological tests of attention, executive functioning, memory, and speed of processing. Second, and more relevant to the hypothesis of this study, it provided evidence through meta-analytic techniques that in the chronic stage of mTBI, neuroimaging abnormalities based on current methods of assessment, do not predict functional outcome in the neuropsychological domains of attention, executive functioning, memory, and speed of processing. Discussion will be provided for both of these two main outcomes followed by a general discussion of limitations to the present meta-analysis and suggestions for future research in this area of neuropsychology.

Contradiction to Previous Meta-Analyses

The present meta-analysis contradicted previous meta-analyses by providing evidence that individuals with chronic stage mTBI perform significantly worse than control subjects on tests of neuropsychological functioning. The first of these two previous studies was conducted by Binder, Rohling, and Larrabee (1997) and included an analysis of 8 studies published from 1986 to 1994. Due to a low effect size, these researchers concluded that clinicians should practice caution before diagnosing a brain injury and that in the long term, there is probably little, if any, consequence to mild head trauma and "… the size of the overall effect was unimpressive and suggestive of clinical nonsignificance." (p. 482).

The second meta-analysis was conducted by Frencham, Fox, and Maybery (2005) but their findings were comparable to that of Binder et al. Frencham et al. found a fairly small but significant effect size ($g = .32$, $p < .001$) but when combining this with the effect size found by Binder and colleagues, the effect size diminished significantly. The most important variable found by Frencham et al. was the time post injury. They concluded that "there was a significant moderating effect of time post-injury on neuropsychological performance, such that the effect of mTBI attenuated over time, and tended towards zero." (p. 345) and that "the effects of mTBI on neuropsychological functioning are small, and in general reduce to levels comparable with non-head injured individuals after the first three months." (p. 348). The meta-analyses mentioned above continue to be widely cited and regarded as evidence of the inconsequential effects of mTBI.

In contrast, Pertab and colleagues (2009) questioned the findings of the studies by Binder et al. and Frencham et al. and critically evaluated the methods used in these two studies. Pertab et al. point out that in the previous meta-analyses significant heterogeneity existed between

studies in the variables of mechanisms of injury, time since injury, diagnostic criteria employed, and type of neuropsychological assessment tools used. Pertab and colleagues, upon examining a small sub-set of neuropsychological measures, found clinically significant lasting effects for individuals with mTBI (Pertab et al., 2009). E. D. Bigler (personal communication), co-author of the Pertab et al. (2009) article, has indicated that he and his colleagues have been informed of a rejoinder to their study. At the present time, this rejoinder has not yet been published.

Even with the findings by Pertab et al. (2009), it would be assumed that a meta-analysis examining long-term neuropsychological effects of mTBI would probably not find very large effect sizes. However, the present study calculated effect sizes by neuropsychological domains and found significant effect sizes ranging from 0.583 to 0.979. These are quite different from the effect size reported by Binder et al. (1997; g=0.07) and Frencham et al. (2003; g=.32). Because this is drastically different from the two previous meta-analyses, caution must be used before accepting these results. To explain these differences the assumptions behind meta-analysis need to be reviewed.

One of the assumptions behind good meta-analyses is the inclusion of all applicable studies. By design, the present study excluded studies that did not have neuroimaging measures. Thus, additional studies assessing the neuropsychological functioning in chronic mTBI were not included in the analysis of effect size for the present study leading to potential bias in the resulting data. For this reason, it is not recommended that the large effect sizes from the results of this study be counted as reliable or representative of the literature. In addition, the studies selected for this meta-analysis may not be reflective of the typical TBI sample. There may have been significant differences in time of assessment post injury, age of the samples, mechanism of injury among the samples, and differing definitions of TBI between studies. These factors create

potential confounds for the results of the present study and will be discussed more fully below. It is also important to consider the fact that all of the subjects from studies in the present meta-analysis received neuroimaging and some of the studies intentionally screened subjects to include a sample with abnormalities. This could significantly push the results toward the direction of clinically significant deficits in the mTBI group. The research questions having to do with the impact of neuroimaging will be addressed next.

Previous Research of Neuroimaging and Functional Outcome

The results of this meta-analysis suggest that neuroimaging does not predict functional outcome in four neuropsychological domains. These findings offer little support to the original hypothesis; if there are abnormalities in the brain imaging scan, this would translate to greater deficit. Some previous research had supported this hypothesis. For example, Williams, Levin, and Eisenberg (1990), tested the neuropsychological functioning of individuals with complicated and uncomplicated closed head injury within 3 months post injury and then measured their neurobehavioral functioning at 6 months post injury. Abnormalities were assessed by radiological examination and were defined as linear or basilar skull fracture, focal brain lesions or depressed skull fractures. These researchers found that the subjects with complicated head injuries, especially those with intracranial lesions, had significantly impaired neurobehavioral functioning (Williams, Levin, & Eisenberg, 1990).

In addition, van der Naalt, Hew, Zomeren, Sluiter, and Minderhoud (1999a) found that individuals with CT abnormalities had worse outcome as measured by the Glasgow Outcome Scale (GOS). Abnormalities in CT were assessed through visual inspection. Overall outcome was related to lesion size, as measured in centimeters, location, and quantity. Lesions found in the frontal and temporal regions were related to worse outcome. These same researchers also

measured outcome after MRI in the chronic stage. Using the Differential Outcome Scale (DOS), they found that focal atrophy and lesions were significantly related to outcome and that significantly fewer individuals with abnormal MRIs were able to return to previous work status (van der Naalt et al., 1999a).

More recent research supports these findings. Temkin, Machamer, and Dikmen (2003) concluded that approximately a third of those with abnormal CT scans had significantly worse outcome even 3 to 5 years post injury. Indeed, these researchers postulated that complicated mTBI seems to have similar functional outcome as moderate TBI (Temkin et al., 2003). Hessen and Nestvold (2009) compared complicated and umcomplicated mTBI subjects 23 years post injury and found that subjects with complicated mTBI's had worse outcome and that these subjects were comparable to subjects with mild post concessional syndrome. It is of important note, however, that these researchers used a slightly different operational definition of complicated mTBI. Complicated mTBI was defined as post-traumatic amnesia >30 minutes and EEG abnormalities within 24 hours of injury (Hessen & Nestvold, 2009). Smits et al. (2008) studied functional outcome in a sample of 312 with mTBI. These researchers found that a majority (63%) had full functional recovery but that post-concussive symptoms persisted in 82% of their sample even 15 months post injury (Smits et al., 2008). Kashluba and colleagues (2008) measured neuropsychological and psychosocial differences between complicated mTBI and moderate TBI and found little difference between these two groups and that at least some degree of impairment persisted for the mTBI group even one year post injury.

In summary, the above studies provide reasonable evidence to suggest that the presence of abnormalities on neuroimaging scans is predictive of worse functional outcome. Several studies support this conclusion despite varying methods of imaging and assessment. It would be

logical to assume that a meta-analysis of outcome and neuroimaging assessment would support this body of research.

Research Related to Current Findings

These earlier findings gave way to the assumption that undertaking a meta-analysis would yield additional evidence that positive neuroimaging data would be significantly associated with worse neuropsychological functioning. Based upon the findings that CT and MRI abnormalities were predictive of functional outcome, it could be assumed that the field is in agreement that positive neuroimaging in mTBI equates to worse outcome. However, the field is not unified and the results of the present meta-analysis seem to better support the body of literature claiming that there is equal, or no difference in outcome between patients with abnormal and normal neuroimaging scans.

For example, Hanlon, Demery, Martinovich, and Kelly (1999) prospectively measured neuropsychological functioning and vocational outcome in 100 mTBI patients with and without CT abnormalities. There was no significant difference in neuropsychological functioning or vocational outcome between these two groups. In a sample of 21 consecutive mTBI patients Hofman et al. (2001) used both MRI and SPECT to predict neuropsychological outcome. In this study, just over half of the subjects had abnormal MRI and SPECT scans and those with positive imaging had signs of brain atrophy in the chronic stage. The neuropsychological testing in this study was fairly comprehensive and included test of memory and learning, attention, speed of processing, visuomotor ability, verbal fluency, and motor functioning. Despite the neurological findings among subjects, there was no significant difference on neuropsychological measures between groups (Hofman et al., 2001).

Likewise, in an attempt to determine risk factors of postconcussional disorder (PCD), another study found that symptoms of PCD were no different statistically between patients with CT abnormalities than those without (McCauley et al., 2001). Hughes et al. (2004) found there to be a significant neuropsychological differences between patient groups with and without MRI abnormalities but these differences disappeared with controlling for age and IQ. There was also no difference in neurobehavioral outcome six months post injury (Hughes et al., 2004).

In summary, the present meta-analysis better supports the above mentioned literature that there is equal, or no difference in outcome based on abnormalities on neuroimaging scans alone. The study by Hanlon et al. (1999) lends the greatest support to this conclusion due to the methods used by these researchers. This study was a prospective design and had a relatively large sample of 100 mTBI patients. The measures used in this study constituted a comprehensive battery of well validated neuropsychological tests. This included two tests of attention, three tests of memory, three languages tests, one test of perception, three tests of executive function, two test of fine motor control, and one test of affect. In addition, this was one of the few studies that also included a psychosocial measure of vocational abilities (Hanlon et al., 1999).

Reasons for Discrepancies

There are numerous reasons for the discrepancies in the literature. Some of these will be discussed more exhaustively below but I will mention some of them here. One of the most important considerations to make is how the neuroimaging abnormality is assessed. Some studies will tests individuals with mTBI in a prospective study design in hospitals or medical school settings. In these situations, abnormalities in the neuroimaging scan are typically determined by a neuroradiologist. Better studies will use two independent radiologists blinded as

to what group- mTBI or control- the neuroimaging scan comes from. This is standard practice and is often seen throughout the literature. This is the means of assessment in some of the studies included in the present meta-analysis. However, there is another way to evaluate neuroimaging scans. In recent years, quantitative neuroimaging assessment has become increasingly used to detect subtle changes in brain states. Considering the extensive training neuroradiologst undergo, it might be assumed that combining data from radiological examination and data from quantitative neuroimaging would be appropriate. In fact, recent studies have demonstrated that comparing the two in more like comparing apples and oranges. Quantitative neuroimaging can help researchers identify damage that cannot normally be seen with the naked eye. Bigler (2001) demonstrates that quantitative analysis of brain scans can reveal twice the normal amount of cerebrospinal fluid in damaged brains that wasn't noticed through visual inspection alone. Turken et al. (2009) used quantitative MRI and DTI to assess subtle brain abnormalities in a male TBI survivor 5 years post injury. This case subject had an initial GCS of 3, was in a coma for two weeks, and post traumatic amnesia for three weeks. Though the patient's initial CT scan revealed an epidural hematoma and a skull fracture, his two year follow u CT and 3 year MRI were reported to be normal. However, when evaluated with quantitative methods, Turken and colleagues found extensive brain abnormalities in this patient. Specifically, they found bilateral cortical thinning, increased gray matter diffusivity, and reduced white matter anisotropy. There were also "extensive abnormalities in the frontal cortices and the underlying white matter." (Turken et al., 2009, Discussion section, para. 1).

In addition to this issue, the studies using radiological assessment do not have a standardized way of assessing brain abnormalities from study to study. Lack of standardization can greatly confound a study and this can be an even bigger problem in meta-analyses that

combine several studies all using different ways to assess neuroimaging abnormalities. The same principle applies to quantitative neuroimaging. Different assessment tools may use varying parameters that may not be tantamount to each other. Also, there are different methods of classifying TBI in CT scans, the most common of which is the Marshall classification methods developed by Marshall and colleagues (1991). The Marshall classification utilizes a rating system based off of "…the status of the mesencephalic cisterns, the degree of midline shift in millimeters, and the presence or absence of one or more surgical masses." (p. 14). Though this is a commonly used method of CT classification, some studies have suggested more detailed methods of CT classification. For example, one study investigated whether assessment could be improved by adding CT characteristics or by partitioning preexisting characteristics into smaller categories (Maas, Hukkelhoven, Marshall, Steyerberg, 2005). This study concluded that discriminative ability was improved by adding more CT characteristics to the analysis. Specifically, assessment sensitivity increases by "adding intraventricular and traumatic subarachnoid hemorrhage and by a more detailed differentiation of mass lesions and basal cisterns." (p. 1178).

Additional significant issues become important to note as the method of detecting brain abnormalities is considered. In detection of more subtle brain abnormalities, it may not be appropriate to combine studies that did not use the same methods for detecting the presence of brain abnormalities in neuroimaging scans. This is just one possible explanation for the discrepancies found in the literature. There are additional reasons for discrepancies. First, sampling error between studies may influence generalizability of one study to the next. Second, heterogeneity between sample characteristics form study to study might influence the results. This includes things such as age of subjects, gender, subject's mechanism of injury,

socioeconomic status, and rehabilitation status. Third, how authors defined traumatic brain injury and brain imaging abnormalities becomes a significant issue. For example, one study may use loss of consciousness to define TBI while the next uses GCS score. One study may use cortical contusions and skull fractures to define abnormalities while the next study uses diffuse axonal injury as their parameter. These issues will be further discusses in relation to the findings of the present study.

Limitations and Considerations

The present study had several limitations that will be enumerated here. These limitations illustrate how susceptible mTBI outcome can be to several factors. In addition to the following limitations, additional considerations and recommendations are given that might help provide more experimental control in future research.

Sample size and power. Although this study does support some of the literature, the present meta-analysis has several limitations that could confound the results. The most obvious limitation is the small number of studies included in the calculation of effect size ($n = 9$). Indeed, when broken down by neuropsychological domain, this number is below nine per domain. Speed of processing only included 5 articles in the effect size calculation. The low number of articles could have a direct impact on the statistical findings of this study. The significant effect sizes between mTBI patients and controls could be the result of sampling error and thus not a true estimate of the population characteristics. The finding that neuroimaging did not predict neuropsychological functioning could be the result of not having enough statistical power in the analysis.

Combining results from dissimilar neuropsychological tests. An additional limitation to the present study, and to any meta-analysis trying to combine neuropsychological test data,

comes from the complication of combining effect size data that might not be appropriate to combine. Each study looking at memory, for example, may have used different types of neuropsychological test of memory. It is not necessarily appropriate to combine results of these tests in meta-analytic form. For instance, typically neuropsychological tests will be standardized from a health comparison group to try to establish what a normal score should be for that test. When comparing more than one test, it cannot always be determine whether the comparisons populations used for standardization were equivalent populations. In addition, different tests within one domain are not necessarily testing the same construct. As pointed out by Guilmette and Rasile (1995), within tests of memory, tests may be looking at paragraph recall, verbal list learning, or paired-association learning. Guilmette and Rasile point out that scores on such tests, though they are scores of memory, are likely looking at different types of memory and were probably "normed" from dissimilar populations and therefore would be inappropriate to equate and combine.

Additional research has demonstrated that validated tests of memory can lead to misdiagnosis of mTBI. Geary, Kraus, Pliskin, and Little (2010) studied memory in mTBI subjects with a verbal learning test consisting of a list of words read several times. The overall results of this test showed no statistical differences between the control and mTBI subjects. However, the researchers point out that the mTBI group did perform statistically worse on the first trial of this test. Thus, the memory and learning the test was trying to elucidate in the mTBI subjects actually covered up the memory construct and mTBI subjects can have deficits not found in validated and frequently used neuropsychological tests (Geary et al., 2010).

Another issue becomes important when it is assumed that neuropsychological tests reveal location of lesions. Neuroimaging has clearly improved our ability to identify lesion location but

before the advent neuroimaging, neuropsychological tests were used to find where damage had occurred. Research by Little et al. (2010) demonstrates how neuropsychological tests may be an inappropriate way to localize brain damage. In their assessment of TBI survivors, Little and colleagues administered test of frontal lobe functioning that revealed significant deficits compared to controls. However, the neuroimaging assessment revealed that the damage associated with these functional deficits occurred in the anterior thalamus and the pathways connecting the anterior thalamus to cortical structures. Before concluding that neuropsychological tests delineate where damage has occurred, caution should be used and neuroimaging should be employed when possible.

Also, several studies have found that neuropsychological tests differ greatly in their sensitivity, or the likelihood of detecting neuropsychological abnormalities (Raskin, Mateer, & Tweeten, 1998; Guilmette & Rasile, 1995). This presents a significant problem with trying to compare or combine results across multiple tests. If, for example, a highly sensitive test results in scores showing significant deficits, it can be assumes that this could result in a large effect size. However, if the same neuropsychological domain is measured with a low sensitivity test and therefore produces a smaller effect size, combining the effect sizes would attenuate and cloud the actual magnitude of the neuropsychological deficit.

This principle can be demonstrated nicely with data from the present study. From the results of this meta-analysis, it was found that speed of processing was the domain with the largest effects size ($g = 0.979$, $p = 0.002$). The domain with the smallest effect size was memory ($g = 0.583$, $p = 0.000$). If the studies for these domains are combined and the summary effect size calculated, the effect size becomes 0.716 (95% CI = .490-.943, $p = 0.000$). It is possible that this washing out is also what explains the lower effect size seen in the memory domain. This

domain consisted of the largest number and studies and the largest number of neuropsychological memory tests. These tests varied in the type of memory being examined and most likely consisted of tests of varying degrees of sensitivity. Similarly, the speed of processing domain, which had the largest effect size among the four domains, could have been high because it had the fewest number of studies and the fewest number of neuropsychological tests. This could have resulted in more homogeneity among neuropsychological tests and thus more sound analysis whereas heterogeneity could cloud the results (Pertab et al., 2009).

Defining neuroimaging abnormalities. The definition of a neuroimaging abnormality also becomes a complication for the present study. Abnormality can have a broad definition depending on many factors. For the purposes of this study, a liberal definition was used for study inclusion. Among the nine source studies, abnormalities included such things as diffuse axonal injury, abnormal signal intensity, gray matter abnormalities, focal cortical contusions, change in gray/white matter volumes, changes in CSF volumes, parenchyma lesions, or changes in fractional anisotropy in DTI studies. The many different types of abnormalities seen in neuroimaging scans are the result of ever changing technology. This is certainly a factor that can influence the results of a meta-analysis of this nature. As discussed in the introduction, neuroimaging modalities differ greatly in their sensitivity and ability to detect subtle changes in the brain after mTBI. An early study demonstrates this idea nicely. Mittl et al. (1994) used MRI to determine the presence of CNS abnormalities in twenty mTBI subject with normal CT scans. The MR scans were assessed by two independent raters that both confirmed abnormal findings of DAI in 30% of the cases (Mittl et al., 1994). Orrison et al. (1994) assessed the difference between CT and MRI in the acute stage of 107 head injury patients. Images were assessed by two independent neuroradiologists. These researchers found that MRI was superior at detecting

contusions, epidural and subdural hematomas, and shear injuries. The sensitivity for MRI was 96.4% and 63.4% for CT (Orrison et al., 1994). In a study 40 children with TBI, Sigmund et al. (2007) used multiple imaging techniques to determine with was more predictive of functional outcome 6 to 12 months post injury. These researchers used CT, T2 weighted MRI, FLAIR, and SWI to assess brain damage in relation to outcome. They found that T2 weighted, FLAIR, and SWI MRI were able to predict functional but that CT could not.

In addition to MRI being more sensitive to parenchymal damage than CT, the advancing technology behind neuroimaging is showing that MRI may not be as sensitive as other modalities, specifically functional neuroimaging. Lewine and colleagues (2007) used MRI, SPECT, and magnetoencephalography (MEG) to try to detect brain abnormalities in subjects reporting consistent postconcussive symptoms. These researchers found that only 4 subjects had abnormal MRIs (presence of atrophy, DAI, or encephalomalacia) while 12 subjects had hypoperfusion on SPECT analysis and 19 subjects showed abnormal dipolar slow wave activity on MEG analysis. The researchers concluded that "The present data indicate that MRI findings… are significantly less likely to be abnormal in these patients than findings from functional methods." (Lewine et al., 2007; p. 149). Despite the differences in imaging modalities, the advances seen in the field of neuroimaging have been extensively studies to determine the relative strength of imaging techniques over time.

Advances in neuroimaging and the detection of brain abnormalities can be attributed to increased field strength and increased ability to detect the blood by-product hemosiderin, which is the bio-marker for diffuse axonal injury (Topal et al., 2008; Bešenski, 2002). Numerous studies have been conducted on differences between different field strengths to show the drastic improvement higher field strengths can have. One such study compared 1.5 tesla (T) to 3.0 T

field strength while examining cranial fossas and brain nerves. This study used three independent raters who assessed the MR images for image quality. The results revealed that 3.0T field strength was "considered more conspicuous and less noisy than images at 1.5T" (p. 358), the signal to noise ratio was doubled compared to the 1.5T scans, and more neural parenchyma were detected with the higher field strength (Fischbach, Müller, & Bruhn, 2008). Also, as was previously mentioned in the introduction, diffusion tensor imaging (DTI) has been successful at detecting minute disruptions in the white matter pathways of the brain (Rutgers et al., 2008). Similar to the Fischbach et al. (2008) article, a previous study by Alexander, Lee, Wu, and Field (2006) examined differences in MRI field strength in DTI. This study points out that the signal-to-noise ratio can have an impact on the spatial accuracy and quality of the DTI analysis. These researchers compared DTI analyses from 1.5T and 3.0T MRI and concluded that DTI at 3.0T will result in significantly better measurements (Alexander et al., 2006). Susceptibility weighted imaging (SWI) has also been found to be more sensitive than conventional MRI. In assessing DAI in a pediatric sample of TBI survivors, Tong et al. (2003) found that SWI found a total of 1,038 hemorrhagic DAI lesions whereas MRI found 162. Significant differences were seen with visual inspection as well as computer analysis. Akiyama et al. (2009) also studied the utility of SWI in detection of microhemmorhages compared to conventional MRI and found the SWI to be more sensitive and better and detecting lesions. In the present study, field strength and imaging parameters were not controlled for because of the several different types of neuroimaging modalities used.

The ever changing technology behind neuroimaging could have confounded the results of this meta-analysis. For example, if there were unseen abnormalities in the patients that were assessed with CT, it would not be appropriate to compare these to the patients that were assessed

with more sensitive neuroimaging. When trying to determine if presence of neuroimaging abnormalities predicts functional outcome, using less sensitive neuroimaging would skew any possible prediction. For future research in this area, it is recommended that meta-analyses restrict inclusion criteria to one type of neuroimaging modalities and a strict operational definition as to what constitutes an abnormality in a scan.

Defining traumatic brain injury. There have been many opinions in neuropsychology as to how to define mild traumatic brain injury. The Glasgow Coma Scale (GCS) has become a standard means of classifying different degrees of traumatic brain injury. This scale is based off of three assessment areas; eye opening, motor response, and verbal response. A GCS score will be the sum of scores from each individual category with a range from 3-15 with higher scores indicating a less severe injury and lower scores, more severe injury (Furlow, 2006). In addition to GCS, post-traumatic amnesia and time of loss of consciousness have also provided useful indices for degree of injury. In 1999, van der Naalt, van Zomeren, Sluiter, and Minderhoud, analyzed GCS compared to PTA using multiple regression and determined that PTA was a better predictor of neurocognitive outcomes and return to work status even at one year follow up (van der Naalt et al., 1999b).

There are many formalized groups and authors who have proposed operational definitions for mTBI, most of which are not in exact agreement and a standard definition is still lacking in the field (Bigler, 2008). Carroll et al. (2004) of the WHO task force conducted a comprehensive review of mTBI literature examining author's definitions of mTBI. In this review, the authors offer a standard operational definition based on definitions from the Mild Traumatic Brain Injury Committee of the Head Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine and the US Centers for Disease Control and

Prevention's MTBI Working Group. It is this definition that was used in the present study (Table 1.). In addition, more studies are using this, or a very similar definition. Specifically, mTBI is defined as a disruption in neuropsychological functioning as a result of a blunt impact, non-penetrating injury to the head from a sudden acceleration, deceleration or rotation of the head, GCS between 13 and 15, PTA less than 24 hours, Loss of Consciousness (LOC) 30 minutes or less (Bigler, 2008; Carroll et al., 2004). Though more studies are endorsing this definition, new research is suggesting that the GCS range might not accurately reflect functional outcomes. When examining functional outcome in mTBI, Kashluba et al. (2008) and Temkin et al., (2003) both concluded that complicated mTBI is more similar to moderate TBI than to other uncomplicated mTBIs. This provides further evidence, along with the previously mentioned findings of van der Naalt et al. (1999b) that the definition used by researchers is not set in stone. In addition, there is debate as to whether a concussion falls under the umbrella of a mild TBI. In a consensus statement about sport concussions, McCrory et al. (2009) stated that "there was acknowledgement that the terms refer to different injury constructs and should not be used interchangeably…" (p. 186). This consensus report gives a definition of concussion that is very different from the definition of mTBI mentioned above. These researchers define concussion without mention of post-traumatic amnesia but do propose that concussion may or may not involve loss of consciousness. They maintain that concussions are a functional disturbance, not a structural one and that a concussion will not have any abnormalities on structural neuroimaging (McCrory et al., 2009). In this sense, concussions might be viewed as analogous to uncomplicated mTBIs but there is no consensus on this point.

One study reviewed 121 studied about mild TBI, mild head injuries, and concussions and the definitions used by these studies. This review found that there are several studies that

separate mTBI and concussion as two distinct constructs but that there are several studies that provide no definition at all and several that view mTBI and concussions as tantamount (Cassidy et al., 2004). For the present study, having inclusion criteria set to include newer articles ranging from 2003 to 2009, and to specify a definition up front, helps control for varying definitions between studies.

Mechanisms of injury. The last limitation to this meta-analysis is concerning the mechanism of injury reported from the studies. As can be seen in Table 3, subjects with different types of mechanisms of injury were included. Of those reporting motor vehicle accidents (MVA), this type of injury represented a majority of the injuries. All of the studies in the present meta-analysis combined subjects so all mechanisms of injury were measured together rather than separate. Research on this topic suggests that the mechanism of injury can greatly influence neuropsychological functioning. Bigler (2007) discusses the fact that evolution has seen a specific range of mechanisms of injury- basic injuries from fights or falls. In today's age, however, we face different types of mechanisms of injury that our brains are not prepared to handle. Motor vehicle accidents and the blast related injuries seen in our returned veterans are thought to have different pathology compared to the more typical mechanisms seen in TBI patients (Bigler, 2007; Elder & Cristian, 2009). Indeed, even within mTBI, the biomechanics of the injury can affect the magnitude of the injury and the functional outcome.

Several studies have detailed how the biomechanics can play an important role in the characteristics of the mTBI. For example, in sport related injuries, concussions are more likely to occur with side or temporal impact than on other areas of the head and within football, helmet to helmet contact is more likely to receive a concussion (Delaney, Puni, & Rouah, 2006). Additional research also found that the likelihood of diffuse axonal injury detected on CT scans

increases 11.0 fold for lateral impact when compared to frontal or oblique impact injuries (Zwahlen, Labler, Trentz, Grätz, & Bachmann, 2007).

All these things considered, studies like these are becoming more important because they reveal just how fragile the human brain can be. Likewise, this fragility is even more impressively demonstrated by Bayly et al. (2005) who demonstrated just how much the human brain is displaced in mild acceleration. In this study, researchers used MRI and high frame rates to record deformation of the brain when it is dropped 2 cm. It was estimated that the acceleration of this task was equivalent to jumping a few inches vertically and landing flat footed or equivalent to 10-15% of acceleration a soccer player experiences when "heading" a ball. The time it took for the head to drop this distances was approximately 40 milliseconds. The researchers found strains effects of 0.02−0.05 during these events wherein a 0.05 strain is approximately equal to a 5% change in the dimension of a local tissue element. They also observed compression in frontal regions of the brain and stretching in posterior regions (Balyly et al., 2005) and similar strain effects are seen in angular head acceleration as well (Sabet, Christoforou, Zatlin, Genin, & Bayly, 2008). Studies like this show that even slight deceleration of the brain can displace tissue. How much more deformation is occurring when the deceleration is happening in MVAs and high impact tackles in football?

In addition, several studies have shown that the speed or rate at which this strain occurs has a direct effect of the damage sustain. Smith, Meaney, and Shull (2003) point out that in normal daily activity, the brain can adapted and easily respond to movements but that when brain movement is rapid, the brain is more stiff and brittle. Thus, rapid movement of brain tissue is more likely to result in DAI (Smith et al., 2003). Research on the strain rate threshold for DAI has been somewhat conflicting with DAI strain thresholds seeming to depend of diameter of the

axons being studied (Smith, Wolf, Lusardi, Lee, & Meaney, 1999). Most of the literature maintains that DAI will occur if the strain rate occurs in less than 50 milliseconds (Smith et al., 1999; Smith et al., 2003).

Gender effect in TBI outcome. In addition to mechanism of injury, some studies have suggested that there is a gender effect among those with concussions. Viano, Casson, and Pellman (2007) studied the biomechanics of concussions among professional football players. They found that, all other variables being equal, the strength of the football player's neck was an independent predictor of the likelihood of concussions. Again, this suggests that males, who tend to have more neck muscle than females, will have less of a chance of sustaining mTBIs. Unfortunately, this cannot be measured in the present meta-analysis. Studies rarely separate mean scores on neuropsychological testing by gender. All means from studies in the present meta-analysis were combined means across gender. In addition, this possible gender effect could also have an effect on neuroimaging results. If women are more likely to experience the concussion, perhaps they are more likely to have complicated, or positive neuroimaging scans.

Though research supports this gender effect, other research suggests that once the head injury has occurred, women seem to have better outcomes. A recent study by Berry et al. (2009) retrospectively examined a data base of 72, 294 TBI patients to determine if there were differences in mortality and complications between men and women. They found that women had a significantly lower risk of mortality and a lower chance of having complications associated with their injury. Interestingly, these researchers also found an age effect for women. It seems that peri-menopausal women (46-55 years old) and postmenopausal women (55+ years old) had a lower mortality rate than their age matched male counterparts where as there was no gender difference between the premenopausal women and their age matched males counterparts (Berry

et al., 2009). Concerning outcome after TBI, Davis et al. (2006) also measured male and female differences while grouping the women by pre- and postmenopausal ages. These researchers found there to be no gender difference in outcome for premenopausal women compared to age match males. However, significantly better outcome was observed in the postmenopausal woman when comparing them to age matched males (Davis et al., 2006).

In short, considering these differences in gender among TBI survivors, it may not be appropriate to average neuropsychological tests across all subjects but may be better to separate averages by gender. Also, age might be an important variable to control for among female TBI survivors.

Rehabilitation status in patients. Another significant limitation to the present study is that none of the articles controlled for rehabilitation status of their TBI samples. Considering all of the studies in this meta-analysis used patients in the chronic stage of mTBI, it is possible that some of these patients had already begun cognitive rehabilitation. If this is not controlled for, scores on certain types of neuropsychological tests may be skewed. For example, a meta-analysis performed by Park and Ingles (2001) found that performance on measures of attention significantly improved after cognitive training. Indeed, more recent research also suggests that various forms of neural rehabilitation seem to improve performance in a wide range of neuropsychological abilities. These include, but are not limited to, auditory memory (Thornton & Carmody, 2008), attention, language and visuospatial training (Rohling, Faust, Beverly, & Demakis, 2009; Park & Ingles, 2001), and executive functioning (Tsaousides & Gordon, 2009). In addition, the efficacy of the different rehabilitation strategies is not always equal (Thornton & Carmody, 2008). Taking these findings into consideration, it is important to only compare samples that are in the same stage of rehabilitation and in the same type of rehabilitation.

Related to the issue of rehabilitation status is the issue as to when the mTBI subjects were tested and scanned in relation to the time post injury. If one group of subjects were tested at 3 months, these might not be comparable to subjects tested at 3 years. As has already been discussed, a case study by Turken et al. (2009) found numerous abnormalities on the neuroimaging scan at initial assessment but that these abnormalities were absent on the patient's CT and MRI scans 2 and 4 years later. In relation to neuropsychological performance, the meta-analysis by Frencham et al. (2005) found that time post injury was the most important prediction of neuropsychological recovery and that the effect of mTBI on functional outcome was mitigated by time post injury.

Future Research

As discussed earlier, the narrow inclusion criteria are likely to have an impact on the results of this meta-analysis. To control for this possible confound, it is recommend that the inclusion criteria be changed to include more articles. The original inclusion criteria for this study dictated included articles published between 2003 and 2010. Extending the criteria back to 2000 or even 1995 would more than likely result in more article the fit the other criteria for this study. The only concern with this change is that technology is much different now than it was in the late 1990's and any change in the findings could be the result of less sensitive neuroimaging techniques.

Next, past research demonstrates that combining effect sizes from different types of neuropsychological tests, or combining effect sizes across neuropsychological domains could cloud the results and lead to a biased summary effect size (Pertab et al., 2009). For future research, it is suggested that effect sizes be calculated across tests or across test shown to have a high between-test correlation and that have been shown to be measuring the same construct.

This would ensure that the calculated effect size was based off of results from tests look at exactly the same cognitive domain. Also, it is recommended that meta-analyses of neuropsychological functioning only combine effect scores within each domain and not across domains. Indeed, a large effect size for one particular domain could be mitigated by a low effect size from a different domain.

In addition, it is recommended that researchers control for significant confounds often ignored in meta-analyses. For example, a recent article by Schmidt (2010) demonstrates that using the wrong kind of meta-analysis techniques can greatly distort the findings. Namely, he compared the difference between random and fixed models of meta-analysis. Schmidt points out that with most research, "some variability is usually left after correcting for artifacts" and that "Only a random effects (RE) meta-analysis model can reveal whether this is the case or not" (p. 239). The difference between a fixed and random model is simple, but if over looked, can have serious consequences to the results. A fixed effects meta-analysis is used when it is assumed that the studies in the analysis can from the same population. In this case, variance is due to the sampling error and not because of real differences between studies.

Since it is rare to have studies from the same population parameter, it is unwise to use a fixed effect model for meta-analysis. Instead, it is safer to use a random effect model. A random effect model test for heterogeneity among included studies to determine if the variance is from the sampling error or other artifacts. It assumes a priori that the studies are not from the same population parameter. Schmidt (2010) shows that from 1987 to 2006, 199 meta-analyses were published within one particular journal. Of the studies that reported the type of model used in their analysis, 79% used a fixed effects model instead of a random effects model. He goes on to illustrate just how big of an impact this can make. In reanalysis of some of these published

meta-analyses, using the random effects model, the author found that the studies underestimated the width of their confidence intervals by an average of 52%. Also, it was found that 90% of these published meta-analyses did not correct for measurement error (Schmidt, 2010). The importance of using the correct methods within meta-analysis cannot be over stated. The results of a meta-analysis that used inappropriate methods leads to biased results that completely defeat the purpose of a meta-analysis.

Lastly, it is recommended that mechanism of injury is either controlled for or that inclusion criteria specify a specific mechanism of injury. Also, considering the evidence that there may be a gender effect with concussions, future studies and meta-analyses would benefit from reporting separate summary scores for males and females.

Conclusions

In conclusion, the results of the present meta-analysis lend some support to some previous findings that presence of abnormalities, based on current methods of assessment, in neuroimaging scans do not predict neuropsychological functioning, though there is conflicting evidence in the literature. This result was found with two types of statistical analysis- meta-regression and the Q-statistic test of heterogeneity. It was also found that individuals with mTBI performed significantly worse on neuropsychological tests than did controls though this could be due to sampling bias and strict inclusion criteria. Several limitations could confound the findings and future research is still needed to control for such things as neuroimaging modality, field strength, mechanism of injury, definition of traumatic brain injury and definition of what constitutes a neuroimaging abnormality. Future meta-analyses would need to control for these variables and should use a random effects model of analysis. In an experimental design, it is recommended that future research control for when assessments and neuroimaging scans are

given in relation to time post injury, patient's rehabilitation status, and neuroimaging assessment methods. It is also recommended that patients be grouped by age, gender, and mechanism of injury. Controlling for all these variables will help elucidate the true impact mTBI has and whether abnormalities neuroimaging can predict neuropsychological functioning in the chronic stage of injury.

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