Neuropsychological Sequela of Mild Traumatic Brain Injury: A Contemporary Meta-Analytic Review

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NEUROPSYCHOLOGICAL SEQUELA OF MILD TRAUMATIC BRAIN INJURY: A CONTEMPORARY META-ANALYTIC REVIEW

by

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ABSTRACT
NEUROPSYCHOLOGICAL SEQUELA OF MILD TRAUMATIC BRAIN INJURY:
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Mild traumatic brain injuries (MTBIs) result in a constellation of non-specific physical, cognitive, and psychological symptoms. There is significant variability in neurocognitive recovery after MTBI, ranging from a few days to a few months, and others who fail to make complete recovery. A broad literature has attempted to elucidate what individual differences explain this variability. The present study sought to build upon previous meta-analyses, which systematically aggregated and examine relevant literature, by including a more heterogenous population and utilizing contemporary meta-analytic techniques. Three online databases (PsychINFO, PubMed, MedLine) were searched for pertinent studies. Separate random-effects Analogue-to-ANOVA were utilized to examine the overall neurocognitive effects of MTBI across time points, stratified by age, psychological comorbidity, populations of interest (athletes, general medical referrals, Veterans, litigants), and whether performance validity tests (PVT) were utilized. Subsequent analyses utilized meta-regressive techniques to simultaneously examine the variables of interest. After article review, 109 studies were retained for analysis (N_{MTBI} = 5919, $N_{Control}$ = 8318). Analogue-to-ANOVA analyses revealed a medium-large overall neurocognitive effect size in the first 24 hours post-injury (d = .64) that decreased to a small effect size over the first 90 days (d = .24). Driven by a higher number of Veteran and litigant samples, the effect size increased in the post-acute period (> 90 days; d = .39). Veteran samples were observed to have significantly larger effect sizes than other populations considered. Meta-regressive analyses found that, across heterogenous populations, time since injury (TSI) was predictive of overall cognitive function only prior to 90 days post-injury, but not in the post-acute period. Psychological functioning was the most important predictor of cognitive functioning after MTBI (β = .47), over and above TSI, population, demographic variables, injury parameters, age, or PVT. This study is consistent with the growing research suggesting that psychological functioning largely explains MTBI recovery and suggests that assessment of emotional well-being and psychological functioning should be part of routine clinical care for the management of MTBI.

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Neuropsychological Sequela of Mild Traumatic Brain Injury: A Contemporary Meta-Analytic Review

A traumatic brain injury (TBI), generally, occurs when brain functioning is disrupted or brain pathology arises due to an external force (Menon, Schwab, Wright, & Maas, 2010). Researchers and clinicians typically classify TBI by severity (e.g., mild, moderate, severe). Seventy to ninety percent of all medically treated TBIs are mild in nature (Cassidy et al., 2004). Mild traumatic brain injury (MTBI), or concussion, is extremely common, affecting as many as 42 million people annually and 12 percent of all individuals during their lifetime (Cassidy et al., 2004).

MTBI may result in a constellation of non-specific physical, cognitive, and psychological symptoms (McCrea, 2008). For most individuals, these symptoms resolve in fewer than three months (Carroll et al., 2004). However, for reasons not completely understood, a small, yet significant number of individuals continue to experience distressing symptoms years after an injury. Furthermore, the relationship between these chronic, self-reported symptoms and neuropsychological outcomes are poorly understood. The cognitive sequela that arise post-MTBI appear to differ across time for different patient populations. Thus, it is critically important to consider how biological, psychological, and/or social factors impact recovery.

Defining MTBI

Until recently, there was no universally accepted definition of MTBI. The lack of a sound operational definition for diagnosis has resulted in considerable discrepancies in the MTBI literature (Cassidy et al., 2004). In addition, standard imaging techniques, such

as MRIs and CT scans, do not detect "uncomplicated" MTBIs (i.e., a MTBI that does not result in cranial fracture or intracranial bleed) and therefore have low diagnostic utility. More sophisticated imaging techniques, such as Diffusion Tensor Imaging (DTI) can detect group-level differences between concussed and non-concussed individuals (e.g., Ivanov et al., 2017); however, these imaging techniques are not yet sensitive enough for routine clinical application (Asken, DeKosky, Clugston, Jaffee, & Bauer, 2017 Jaffee, & Bauer, 2017). At present, the same holds true for other biomarkers, such as cerebral spinal fluid and bloodwork (Lewis et al., 2017; c.f., Nitta et al., 2019).

The diagnosis of MTBI is made on the basis that a transient disruption of cognitive functioning that occurred due to a direct or indirect impact to the head. The American Congress of Rehabilitation Medicine (ACRM) and the World Health Organization (WHO) Task Force (Carroll et al., 2004) provide two well-accepted MTBI definitions. Both the ACRM and WHO Task Force define MTBI as an acute disruption of brain functioning due to trauma that manifests as one or more of the following (1) loss of consciousness (LOC) less than 30 minutes, (2) altered mental state (e.g., dazed, disoriented, or confused), (3) pre- or post-traumatic amnesia less than 24 hours, and (4) a Glasgow Coma Scale score between 13-15 after 30 minutes (see Table 1 for complete diagnostic criteria). Uniquely, relative to earlier diagnostic criteria, these classification systems do *not* require the presence of LOC. The main difference between the two classification systems, the ACRM allows for any alteration of mental state (e.g., feeling dazed) at the time of the accident, whereas the WHO Task Force definition specifies "confusion and disorientation." While both definitions exclude patients with more severe injuries, critics emphasize that TBI severity should be conceptualized as a continuum

(Roozenbeek, Maas, & Menon, 2013). Nonetheless, these definitions operationalize MTBI, which certainly facilitates more reliable clinical judgement and improves research.

Table 1.
Definitions of Mild Traumatic Brain Injury and Concussion from Different Agencies

ACRM (1993)	A patient with mild traumatic brain injury is a person who has had a traumatically induced physiological disruption of brain function, as manifested by at least one of the following: 1. Any period of loss of consciousness; 2. Any loss of memory for events immediately before or after the accident; 3. Any alteration in mental state at the time of the accident (e.g., feeling dazed, disoriented or confused); and 4. Focal deficits that may or may not be transient; but where the severity of the injury does not exceed the following: • Loss of consciousness for approximately thirty minutes or less; • After 30 minutes an initial GCS of 13-15 • Past-traumatic amnesia not greater than 24 hours
WHO Task Force (2004)	MTBI is an acute brain injury resulting from mechanical energy to the head from external physical forces. Operational criteria for clinical identification include: (i) 1 or more of the following: confusion or disorientation, loss of consciousness for 30 minutes or less, post-traumatic amnesia for less than 24 hours, and/or other transient neurological abnormalities such as focal signs, seizure, and intracranial lesion not requiring surgery; (ii) GCS score of 13-15 after 30 minutes post-injury or later upon presentation for healthcare. These manifestations of MTBI must not be due to drugs, alcohol, medications, caused by other injuries or treatment for other injuries (e.g., systemic injuries, facial injuries or intubation), caused by other problems (e.g., physiological trauma, language barrier or coexisting medical conditions) or caused by penetrating craniocerebral injury
International Conference of Concussion in Sport (2013)	Concussion is a brain injury and is defined as a complex pathophysiological process affecting the brain, induced by biomechanical forces. Several common features that incorporate clinical, pathologic, and biomechanical injury constructs that may be utilized in defining the nature of a concussive head injury include:

International Conference of Concussion in Sport (2013) Continued	1. Concussion may be caused by a direct blow to the head, face, neck, or elsewhere on the body with an "impulsive" force transmitted to the head. 2. Concussion typically results in the rapid onset of short-lived impairment of neurological function that resolves spontaneously. However, in some cases, symptoms and signs may evolve over a number of minutes to hours 3. Concussion may result in neuropathologic changes, but the acute clinical symptoms largely reflect a functional disturbance rather than a structural injury, and as such, no abnormality is seen on standard structural neuroimaging studies. 4. Concussion results in a graded set of clinical symptoms that may or may not involve loss of consciousness. Resolution of the clinical and cognitive symptoms typically follows a sequential course. However, it is important to note that in some cases, symptoms may be prolonged.

Note. ACRM = American College of Rehabilitation Medicine; WHO = World Health Organization; GCS = Glascow Coma Scale

Although the terms MTBI and concussion are often used interchangeably, some argue that sports-related concussion (SRC) is not synonymous with MTBI, but rather reflects a subset of mild head traumas (McCrory et al., 2013). In a Consensus Paper from the 4th International Conference on Concussion of Sport, concussion was defined as, "a complex pathophysiological process affecting the brain, induced by biomechanical forces" (McCory et al., 2013, pp. 555). The paper also clarifies that a concussion may be the result of a blow or forces transmitted to head that results in acute neurologic dysfunction (LOC may or may not occur). In principle, there is significant overlap between how concussion and MTBI are defined (Table 1); they are considered synonymous and analyzed together in the present study.

Prevalence and Significance

The failure to develop an agreed upon diagnostic criterion for MTBI until early 2000 made determining the "true" prevalence rate challenging. The Center for Disease Control examined Emergency Department records across the United States from 2002-2006 and estimated that 1.7 million individuals are medically treated or fatally injured due to TBI each year (Faul, Xu, Marlena, & Coronado, 2010). In a later report to Congress (Frieden, Houry, & Baldwin, 2015), it was acknowledged that the previous estimate of 1.7 million individuals was likely low as it did not account for individuals who were treated in non-hospital settings, individuals who did not receive treatment, or Veterans who were treated at Veteran Affairs (VA) medical centers. One meta-analysis attempted to quantify MTBI prevalence rates by examining the prevalence rate from all published studies (Cassidy et al., 2004). The authors found pervasive heterogeneity in methodology across studies. For example, MTBI was variably defined, if at all, by authors. Due to the extent of the methodological variability between studies, the authors expressed hesitation in providing a single incidence rate. Nonetheless, based on the available data, Cassidy and colleagues estimated the incidence rate to be between 100 to 300 per 100,000 adults. Much like the CDC, the authors acknowledged that this estimate is likely an underestimate as a majority of MTBIs are not medically treated. It was estimated that the likely incidence rate approaches 600 per 100,000 adults.

Athletes are also susceptible to TBI and the CDC estimated that 300,000 athletes in the United States sustain a concussion annually (Thunnan, Branche, & Sniezek, 1998), or 1.64 per 100 athlete-seasons across all sports (Powell & Barber-Foss, 1999). However, this may be a gross underestimate as almost half of all SRC go unreported (McCrea,

Hammeke, Olsen, Leo, & Guskiewicz, 2004). This is especially problematic as resuming physical activities, especially participating in contact sports, prior to symptom resolution, may increase risk of sustaining another brain injury (Guskiewicz et al., 2003).

Military personnel are also particularly vulnerable to TBIs. In fact, MTBI are so pervasive for active duty members it is considered the hallmark injury of recent military conflicts. As the mortality of soldiers have decreased over time, the prevalence of TBIs in this population has increased. From October 1, 2001, the start of Operation Enduring Freedom (OEF), to the end of 2011, 235,046 service members (4.2%) were diagnosed with a TBI (The CDC, NIH, DoD, and VA Leadership Panel, 2013). In 2011, alone, 33,149 military personnel were diagnosed with a TBI. During the same 10-year period, 7.7% of *all* services sought at VAs were from OEF and Operation Iraqi Freedom (OIF) personnel for TBI-related conditions. Similar to other MTBI estimates, these numbers may underestimate the true number of TBIs as many MTBIs are likely not recognized or reported in combat theater.

Traumatic brain injury clearly represents a major public health issue. The economic cost of TBI is disproportionately larger than other injuries (Ma, Chan, & Carruthers, 2014; Max, MacKenzie, & Rice, 1991), with the estimated cost of treatment approaching $13.1 billion per year and an additional $64 billion are estimated to be lost due to indirect costs (e.g., inability to work, disability) (Rutland-Brown, Langlois, Thomas, & Xi, 2006). Furthermore, 3.32 million individuals (1.1% of total population) are living with long-term disability due to TBI (Zaloshnja, Miller, Langlois, & Selassie, 2008 & Selassie, 2008). Even though more than 70% of TBIs are considered “mild” in severity (CDC, 2010; Cassidy et al., 2004), in some individuals, these injuries can still

result in permanent or long-term problems that negatively impact one's ability to function (e.g., see Alves, Macciocchi, & Barth, 1993; Englander, Hall, Stimpson, & Chaffin, 1992).

Epidemiology and Mechanism of injury

Previously, motor vehicle accidents (MVAs) were the primary mechanism for TBIs (Cassidy et al., 2004). However, as driving policies and vehicles are becoming safer, the overall number of MVAs are decreasing, thus leading to a reduction in MVA-related TBIs (Roozenbeek et al., 2013). Simultaneously, as the population grows older and life expectancy increases, the number of TBIs related to falls are increasing. In fact, an estimated 35.2% of all emergency department visits, hospitalizations, and deaths are fall-related (vs. 17.3% for MVAs; CDC, 2010). Older adults over the age of 75 now have the second highest incidence rate of TBIs, second only to younger adults, aged 15-19 (Faul et al., 2010). Altogether, the median age of TBIs is now shifting to an older age (Roozenbeek et al., 2013).

After a physical trauma, neurologic dysfunction may arise from either contact (blunt trauma) or inertial forces (acceleration/deceleration). The primary biophysical mechanisms of an MTBI arises from inertial forces (acceleration/deceleration) that is transferred to the brain (Meaney & Smith, 2011). Early efforts to understand the relationship between these forces and brain dysfunction focused on linear acceleration and deceleration (Meaney & Smith, 2011). Animal models showed a positive correlation with the initial increase of pressure in the brain and acceleration forces, which predicted neurologic dysfunction. However, understanding of the mechanisms of a TBI has shifted

to understand that the rotational forces exerted on the brain may be the predominant mechanism of injury (Gennarelli et al., 1982; Unterharnscheidt & Higgins, 1969). During rotational acceleration/deceleration, neuronal axons can tear or shear away from the cell body (Smith, Meaney, & Shull, 2003). The axonal tearing and shearing results in diffuse axonal injury (DAI), and DAI severity is associated with poorer neurological outcomes. In fact, if the head and neck are immobilized such that rotational forces cannot be applied, it is more difficult to produce unconsciousness from a physical trauma (Meaney & Smith, 2011).

Symptom Recovery

Unlike moderate and severe TBI, the non-specific constellation of cognitive, physical, and emotional symptoms the arise post-MTBI are not reliably predicted by injury parameters (e.g., loss of consciousness, post-traumatic amnesia) (McCrea, 2008). Clinicians and researchers track recovery post-MTBI through self-report of post-concussive symptoms (PCS). Common self-reported PCS include, but are not limited to, headaches, dizziness, cognitive slowing, difficulty concentrating, light and noise sensitivity, fatigue, drowsiness, and memory difficulties. Important to recognize, many MTBI symptoms are non-specific and may be difficult to distinguish from common experiences and/or symptoms associated with other mental health conditions (e.g., Post-Traumatic Stress Disorder) (American Psychiatric Association, 2013). For instance, as many as 75.7% of healthy volunteers reported experiencing PCS in the past two-weeks (e.g., headaches) despite the absence of a head injury (Iverson & Lange, 2003). Furthermore, there is evidence that certain populations, such as athletes, tend to underreport symptomology (McCrea, 2008), whereas other populations, such as

individuals involved in litigation, tend to over report symptomology (Feinstein, Ouchterlony, Somerville, & Jardine, 2001). Thus, there is need for more objective measures with high sensitivity and specificity to MTBI symptoms, which is crucial for accurate diagnosis and to monitor symptom recovery of MTBI.

Given their relative objectivity and sensitivity to MTBI, neuropsychological measures are regularly utilized during a clinical evaluation to diagnose and monitor symptom recovery post-MTBI (McCrea, 2008). For example, in longitudinal study following 1,631 NCAA athletes, McCrea and colleagues found that a group of concussed athletes were reportedly asymptomatic based on self-report after two days, yet, continued to show impairment on balance and neuropsychological testing seven days post-injury (McCrea et al., 2005). Thus, the authors advocated that neuropsychological assessment is vital in detecting the subtle, residual effects of sustaining an MTBI, even in the absence of reported symptoms. In fact, a meta-analysis found that, in non-litigant samples, neurocognitive measures were sensitive to detecting the acute cognitive effects of a MTBI in nearly all cognitive domains (Belanger, Curtiss, Demery, Lebowitz, & Vanderploeg, 2005).

Possible Modifiers of Cognitive Recovery after MTBI

There is considerable variability regarding the cognitive effects of sustaining an MTBI. For example, some researchers have documented a small overall effect size (d = .11) at 1-month post-MTBI (Ponsford, Willmott, et al., 2000), whereas others have reported a moderate-large effect size (d = .64) for a similarly aged sample over the same time period (Voller et al., 1999). Likewise, some studies, particularly those investigating

athletes, show a non-significant effect size after approximately seven days (McCrea et al., 2003), whereas other studies document that that the neurocognitive effects do not resolve until three or more months (e.g., Kwok, Lee, Leung, & Poon, 2008). The discrepant findings between studies (i.e., between-study heterogeneity) may be due to one of any number of factors that appear to contribute to the individual differences seen in cognitive recovery. A review of primary potential effect modifiers is outlined below.

Population. The course of neuropsychological recovery post-MTBI drastically differs depending on the "population" (i.e., athlete, Veteran, general-medical referral, litigant) investigated. Numerous studies have demonstrated that cognitive effects of MTBI in athletes are largely resolved in about one week (Belanger & Vanderploeg, 2005; Macciocchi, Barth, Alves, Rimel, & Jane, 1996; McCrea et al., 2003; McCrea, Kelly, Randolph, Cisler, & Berger, 2002). On the other hand, individuals who are prospectively recruited from emergency departments and medical clinics (i.e., general medical referrals, GMR) may take one to three months before neuropsychological symptoms resolve. For instance, many studies have reported significant effect size differences at least one month after MTBI (Dikmen, Machamer, & Temkin, 2017; McAllister et al., 2001; c.f., Gentilini et al., 1985). Similarly, some studies have shown significant effect sizes three months after the initial injury (Belanger, Curtiss, et al., 2005; Gentilini, Nichelli, & Schoenhuber, 1989; c.f., Ponsford, Willmont, et al., 2000). There are many likely reasons for the discrepancy in cognitive recovery between athletes and the general population that sustains an MTBI. First, athletes tend to be younger and healthier (i.e., high school and college) and have high motivation to return to play (McCrea, 2008). Furthermore, the mechanism of injury may differ for athletes and the general population. For instance, the

most common reason for an MTBI to be medically treated is due to a fall or MVA (Faul et al., 2010). The acceleration/deceleration forces associated with these events may be inherently different from SRC.

As previously noted, MTBI is a significant concern in military populations. Despite MTBI being the "hallmark" injury of OEF/OIF, there are unique challenges associated with studying MTBI in this population. Traumatic brain injury is often overlooked in favor of treating and triaging more obvious physical injuries such as wounds or traumatic amputations (Belanger, Scott, Scholten, Curtiss, & Vanderploeg, 2005) and details related to injury parameters or post-injury recovery are infrequently documented (Belanger, Uomoto, & Vanderploeg, 2009). Alteration of consciousness may go unnoticed in theater, or may be confused with the emotional reaction or adrenaline rush likely to accompany traumatic military experiences (Belanger et al., 2009). Finally, from a pragmatic standpoint, neuropsychological evaluations are unlikely to be conducted in combat theater (Dolan et al., 2012). Nevertheless, one study investigating the acute effects of an MTBI found that Veterans with MTBI who were assessed in the first 24 hours performed significantly worse (large effect size) compared to a normative sample of non-concussed Veterans on a brief cognitive screener (McCrea et al., 2014). It is unclear when residual cognitive symptoms resolved because follow-up testing was not conducted in the study. Thus, it is unclear if these acute cognitive symptoms resolve in a few days, like athletes, or over the course of several months, similar to non-athletic civilians.

Most of the research investigating how active service members and Veterans function post-injury have been conducted months and years after TBI. However,

ascertaining the neurocognitive effects of MTBI in this population is difficult because of several factors. Some research suggests, there is little-to-no long-term cognitive effects in Veterans post-deployment who suffer an MTBI when other comorbidities are absent (Combs et al., 2015; Nelson et al., 2012; Vasterling et al., 2012; Verfaellie, Lafleche, Spiro, & Bousquet, 2014). However, there is compelling evidence to suggest a potential negative neurocognitive effect of comorbid mental health conditions and MTBI. For example, Veterans with co-morbid mental-health disorders performed significantly worse on neurocognitive assessments compared to Veteran controls (Nelson et al., 2012) or Veterans who sustained an MTBI with no mental health comorbidities (Combs et al., 2015; Verfaellie et al., 2014). Salient secondary gain issues in VA settings may also complicate cognitive recovery in Veterans due to the limited nature of VA healthcare post-deployment. Absent of a service-connected disability, Veterans in the US are granted only five years of VA healthcare post-deployment ("Returning Service Members (OEF/OIF/OND) - Health Benefits," 2014). Thus, there are clear incentives for Veterans to report symptomology of MTBI as early as possible (Rona et al., 2012), and there is an incentive to suppress performances when completing neurocognitive measures. Illustrating the latter, as many as 58% of a sample referred for a TBI evaluation in the VA system failed a performance validity test (PVT), which is a type of test designed to assess for sub-optimal test engagement or purposeful performance suppression (Armistead-Jehle, 2010).

Importantly, insufficient effort and issues with secondary gain are not limited to Veterans who experience an MTBI but are also a confounding issue with civilians who are involved in the litigation process related to their TBI (e.g., individuals involved in a

motor vehicle accident and claiming disability). Members of the "litigant" population tend to experience greater subjective symptoms (Feinstein et al., 2001) and perform worse on measures of neurocognitive functioning. In fact, a meta-analysis found that the cognitive effects of MTBI for individuals in this group *worsen* over time, rather than resolve (Belanger, Curtiss, et al., 2005). In a large sample of individuals involved in litigation for MTBI, 40% failed an established PVT (Flaro, Green, & Robertson, 2007 2007). In fact, the failure rate of the litigation group with MTBI was 23 times higher than a group with high motivation to perform well and twice as large as the rate observed in samples with more severe TBI. There is clear evidence that poor effort during the forensic evaluation accounts for much of the variance in cognitive testing (Green, Rohling, Lees-Haley, & Allen, 2001). It seems that individuals with potential secondary gain issues may follow a different trajectory of cognitive recovery due to factors not related to the injury, such as insufficient effort and symptom exaggeration. Thus, the true nature of their cognitive recovery is unknown.

Age. A significant portion of the MTBI literature investigates high school and college athletes. Fewer empirical studies focus on children and older adults. This discrepancy is notable given that children aged 0-4 years have the highest rate of ED visits due to TBI and adults aged 75 and older have the highest rate of hospitalizations and death due to TBI (Faul et al., 2010). This section will summarize research findings specific to these age groups to make clear that age has the potential to impact recovery.

Studies on the acute cognitive effects of MTBI in pediatric samples are limited, in part because there are unique challenges associated with diagnosing MTBI in young children. For example, because language skills are not fully developed, it is difficult to

assess symptoms post-injury (Anderson, Catroppa, Morse, Haritou, & Rosenfeld, 2001). Nevertheless, one prospective study found that children aged 6-18 years had marginally lower (but not significantly lower) scores on a brief cognitive screener compared to controls with orthopedic injuries when evaluated acutely in an ED (Grubenhoff, Kirkwood, Gao, Deakyne, & Wathen, 2010). In another study, children who presented to an ED performed below children with orthopedic injuries on measures of psychomotor speed and reaction time (Brooks, Khan, Daya, Mikrogianakis, & Barlow, 2014). The patient groups did not perform differently on measures of memory, attention, and executive functioning.

Consistent with the adult literature, there is variability and conflicting findings regarding long-term outcomes for children who sustain MTBI. While some researchers report no long-term sequela associated with pediatric MTBI (e.g., Ponsford et al., 1999), others express concerns regarding the possibility of long-term sequala (e.g., Anderson et al., 2001). In fact, a systematic review of 40 articles published between 1970 to 1995 regarding MTBI in children and adolescents categorized 13 articles suggesting poor outcomes, 18 with null findings, and 9 that were uncertain regarding cognitive, academic, and psychosocial outcomes (Satz et al., 1997). Importantly, after reviewing *only* methodologically strong studies, the authors posited that there are few adverse or long-term effects.

Consistent with the adult literature, children and adolescents' pre-existing conditions and psychological comorbidities likely impact MTBI recovery. A longitudinal study conducted by researchers at UCLA found that, compared to controls with orthopedic injuries, the only predictors of cognitive impairment 1- and 12-months post-

injury were parental education level, pre-injury behavioral issues, academic achievement, and pre-injury learning disorders (Babikian, McArthur, & Asarnow, 2013). Additionally, research has documented that children who continue to experience behavioral issues for extended periods of time post-MTBI are more likely to have had a previous head injury, learning difficulties, pre-injury emotional and behavioral problems, psychiatric problems, and/or additional neurological issues (Ponsford et al., 1999). In an additional study, children who sustained an MTBI and had pre-morbid attentional difficulties had poorer neuropsychological outcomes relative to children who sustained an orthopedic injury (Studer et al., 2014). Taken together, while it appears that children and adolescents demonstrate acute cognitive impairments post-MTBI that largely resolve during the course of a month, pre-existing factors may delay full recovery.

Consistent with child and adolescent literature, the research regarding cognitive outcomes for older adults who sustain an MTBI is mixed. There are a number of studies that have identified adverse cognitive outcomes for older adults who sustain MTBI (e.g., de la Plata et al., 2008; Goleburn & Golden, 2001; Rapoport & Feinstein, 2000). Conversely, there are numerous studies suggesting that there are no adverse long-term outcomes for older adults who sustain an MTBI (e.g., Feinstein et al., 2001; Mosenthal et al., 2004; Rapoport et al., 2008). At closer inspection, the adverse cognitive effects may be a result of secondary factors, such as pain, or psychological distress. For example, there is evidence that older adults who sustain an MTBI perform worse than same-aged controls on measures of neuropsychological functioning than non-injured controls, but not worse than individuals who sustained orthopedic injuries (Kinsella, Olver, Ong, Gruen, & Hammersley, 2014) Thus, the injury characteristics (e.g., pain, medication,

altered sleep cycle) may account for the worse cognitive functioning, rather than the MTBI, itself. In addition to injury characteristics, older adults who sustain an MTBI were found to have higher rates of depression and anxiety symptoms relative to healthy controls (Goldstein, Levin, Goldman, Clark, & Altonen, 2001), which places older adults at a higher risk for adverse cognitive outcomes (Dotson, Resnick, & Zonderman, 2008b) .

Psychological Comorbidities, Pre-Injury Disposition, and Post-Concussive Symptomatology. Even in the absence of a head injury, psychological distress and mental health disorders are associated with worse neurocognitive functioning (e.g., Dotson et al., 2008b; Gualtieri, Johnson, & Benedict, 2006; Snyder, 2013). Thus, it is unsurprising that the presence of a comorbid psychological disorder may prolong or complicate neuropsychological recovery from an MTBI (Combs et al., 2015; Nelson et al., 2012; Verfaellie et al., 2014). However, many additional factors, such as personality features and coping mechanisms, even in the absence of a comorbid mental health diagnosis, can extend or be the direct cause of continued symptomatology in patients who sustain an MTBI. For example, pre-injury somatization, anxiety sensitivity (i.e., anxiety-related somatic symptoms), alexithymia (i.e., difficulty understanding and describing emotions), and depressive personality traits, have all been found to predict duration of post-concussive symptomology (Nelson, Tarima, et al., 2016; Wood, O'Hagan, Williams, McCabe, & Chadwick, 2014; Yuen, Tsai, Lin, Yang, & Huang, 2016) Interestingly, even in healthy, non-concussed research participants, self-reported symptoms consistent with PCS align with maladaptive personality constructs. Specifically, students who reported higher “PCS” reported more negative, depressive, anxious, dependent, sadistic, somatic, and borderline traits (Garden, Sullivan, & Lange, 2010).

The relationship between PCS symptomatology and neurocognitive functioning is less clear, however, as some studies found an association between neurocognitive dysfunction and prolonged PCS (Collie, Makdissi, Maruff, Bennell, & McCrory, 2006; Iverson, Gaetz, Lovell, & Collins, 2004; Sterr, Herron, Hayward, & Montaldi, 2006), and others have not (Chan, 2001). Stulemeijer and colleagues (2007) examined the direct link between pre-injury factors, PCS, and neuropsychological functioning longitudinally by recruiting patients from an ED and conducting evaluations 6 months post-MTBI (Stulemeijer, Vos, Bleijenberg, & van der Werf, 2007). Participants were dichotomized into groups based on cognitive complaints. Interestingly, while the high-cognitive complaint group did have worse pre-injury and post-injury psychological and emotional well-being, there were no differences in neuropsychological performance between groups. Thus, a clear connection between pre- and post-injury psychological functioning, reported PCS, and neuropsychological performance was not established. In contrast, another study found that worse cognitive functioning was predicted by greater cognitive complaints, PCS, and affective factors (depression, anxiety, and neuroticism) in individuals with MTBI (Clarke, Genat, & Anderson, 2012). The discrepant findings may be a result of the latter authors' decision to exclude a significant portion of their sample (27%) due to insufficient effort. Thus, the association between poor neurocognitive functioning and PCS and affective symptoms in Clark and colleagues' (2012) study may be an artifact of not considering whether the examinees were adequately engaged with testing. Thus, the link between PCS and neurocognitive functioning remains somewhat unclear.

Secondary Gain and Insufficient Effort. Secondary gain issues, insufficient effort, or exaggerated symptom reporting may confound interpretation of neurocognitive performance during standard clinical evaluations, medicolegal forensic assessments, and research protocols. As previously noted, Veterans may perceive an incentive to exaggerate symptom complaints or suppress cognitive performance to increase the probability of receiving service-connected disability (Hoge, Goldberg, & Castro, 2009; Rona et al., 2012). Similarly, the dramatic costs associated with healthcare and rehabilitation services may increase the likelihood that an examinee may put forth insufficient effort during assessments (Bigler, 2008). Indeed, this is documented, with as many as 58% of Veterans putting forth sub-optimal effort (Armistead-Jehle, 2010) and much of the variability (as much as 50%) in cognitive performance being explained by insufficient effort (e.g., Armistead-Jehle, 2010; Green et al., 2001; Nelson et al., 2010). As expected, individuals who fail PVTs perform poorer on cognitive testing than individuals who pass PVT, even after sustaining an MTBI (e.g., Jak et al., 2015; Stulemeijer et al., 2007).

It is important to recognize that insufficient effort and PVT failure during neuropsychological evaluations are not limited to individuals with potential for secondary gain. PVT failure also frequently occurs in individuals experiencing emotional distress. For example, in a sample of patients with MTBI who were recruited from an ED and evaluated six months post-MTBI, 27% of the sample failed a PVT (Stulemeijer et al., 2007). Those who failed a PVT did worse on almost all neuropsychological measures. Though, PVT failure was not associated with involvement in litigation, it was associated with higher emotional distress, greater negative affectivity (i.e., tendency to experience

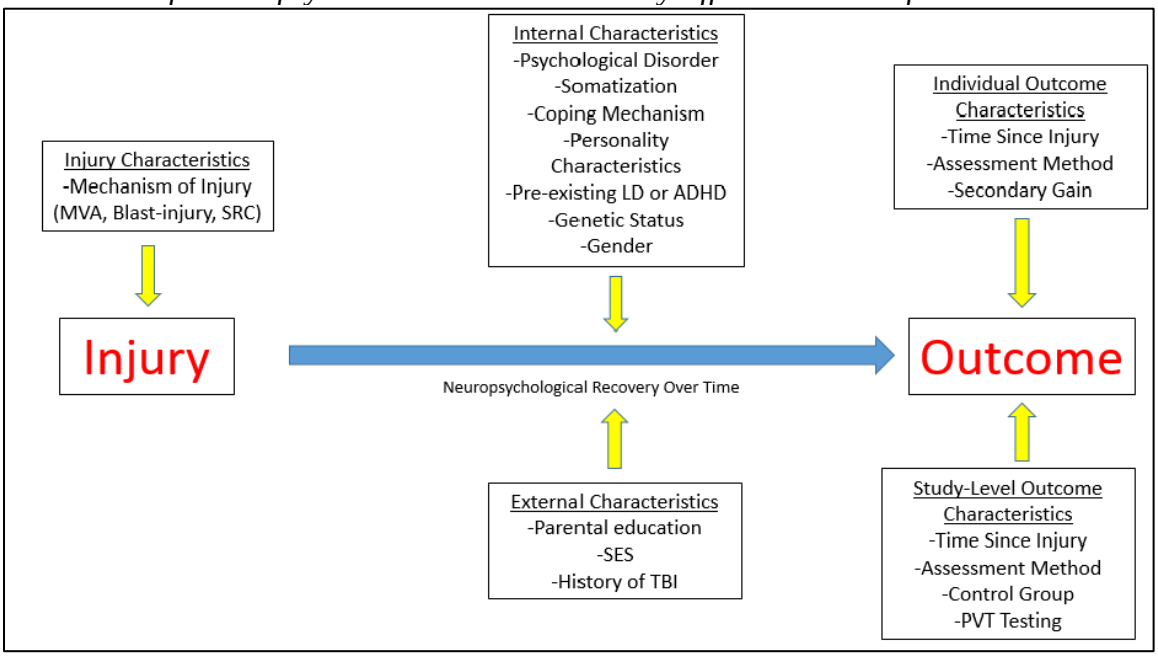
distress), lower education, failing to return to work, and fatigue. Similarly, in a large sample of OIF/OEF Veterans who sought treatment for an MTBI, 30% of the sample failed at least one PVT (Jak et al., 2015). In addition, 74% and 85% of the individuals in the group that failed at least one PVT carried a clinical diagnosis of depression and/or PTSD, respectively. The prevalence of these disorders occurred at a significantly higher incidence rate relative to the group that passed all PVTs. Consistent with these general findings, individuals with a history of a mental health issues are four times more likely to fail one or more PVTs during an MTBI evaluation (Donders & Boonstra, 2007).

In summary, issues unrelated to MTBI injury parameters can lead to poor effort during neuropsychological assessment and suppressed cognitive performance. Thus, it is crucial for clinicians to consider the possibility of insufficient effort when quantifying neurocognitive symptoms associated with MTBI and subsequent recovery.

Summary of Effect Modifiers. There are a multitude of factors that can potentially affect the neuropsychological recovery from an MTBI: population, age, psychological comorbidities, performance invalidity, to name a few. Yet, almost none of these issues are mutually exclusive. For instance, psychological comorbidities are not only found in Veterans, but can also be found in civilians. Performance invalidity is not limited to individuals involved in litigation. Athletes, who are typically motivated to return to play, may have maladaptive coping mechanisms or depressive personality characteristics that may increase the likelihood of prolonged cognitive recovery. None of these individual differences occur in isolation, but rather are complexly interwoven into multifaceted biopsychosocial mechanisms that can affect recovery (see Figure 1). Thus, it is extremely challenging to conduct empirical studies evaluating the intersection of these

individual differences. Rather, quantitative reviews of a multitude of studies may elucidate the unique contributions these individual differences make to cognitive recovery after sustaining an MTBI.

Figure 1.
Illustration of the Biopsychosocial Factors that May Affect Outcome After MTBI



Note: MVA = Motor Vehicle Accident; SRC = Sports-Related Concussion; LD = Learning Disorder; ADHD = Attention Deficit/Hyperactivity Disorder; TBI = Traumatic Brain Injury

MTBI Meta-Analytic Reviews

There is an emerging literature examining how individual differences might affect cognitive recovery after an MTBI, though there are discrepancies in these findings. Thus, there is a critical need for comprehensive quantitative analysis to integrate available research to elucidate the neuropsychological effects of sustaining an MTBI across broad populations. In brief, meta-analyses critically integrate and analyze the results of multiple

studies. Data from multiple studies are aggregated, "averaging" effect sizes reported in relevant studies. Relative to a single study, a meta-analytic review has increased power to detect a "true" effect if one exists (Bartolucci & Hillegass, 2010; Cohn & Becker, 2003). Furthermore, by pooling the results of multiple studies, meta-analyses often include a more heterogeneous pool of participants than a single study, which increases the generalizability of estimated effects (Bartolucci & Hillegass, 2010; Borenstein, Hedges, Higgins, & Rothstein, 2009). Several meta-analyses have been conducted examining the neuropsychological effects of sustaining an MTBI (See Table 2). While this body of literature has dramatically improved our understanding of MTBI, several notable methodological issues are present across studies and will be expanded upon below.

Binder, Rohling, and Larrabee (1997) conducted the first meta-analytic review to investigate the neuropsychological impact of MTBI. The review included 11 studies that examined mild head trauma (MHT; N_{MHT} = 314; $N_{Controls}$ = 308). All the studies were conducted at least 3 months post-injury and a small and non-significant overall effect size (i.e., estimated effect size of all cognitive constructs combined) was reported (Cohen's *d (d)* = .12; Hedge's *g (g)*= .07), suggesting no significant, negative cognitive effects of MTBI after three months. The researchers also examined whether MTBI might affect specific neuropsychological constructs and concluded that attention is mildly impacted (*d* = .20; *g* = .17) after 3 months or more. While this meta-analytic review is seminal in nature, there are some notable limitations that should be recognized. First, the number of included studies was relatively small (k = 11) and a single study contributed nearly half (51%) of the patients with MHT. In addition, considerable between-study statistical

Table 2.
Summary of All Known Meta-Analyses Examining Neuropsychological Effects of MTBI

First Author	Year	Population of Interest	Total K	Sub-group Comparison	*k*	*d*
Binder	1997	Mixed	11	-	11	0.12*
Frencham[a]	2005	Mixed	17	Acute (< 3 months)	12	0.33*
				Post-Acute (> 3 months)	5	0.28
				Total	17	0.32*
Belanger	2005a	Clinical/ medical referrals	39	Litigation-based sample < 90 days	2	0.52*
				Litigation-based sample ≥ 90 days	6	0.78*
				Clinic-based sample < 90 days	-	-
				Clinic-based sample ≥ 90 days	11	0.74*
				Unselected sample < 90 days	23	0.63*
				Unselected sample ≥ 90 days	8	0.04
Belanger	2005b	Athletes	21	Within 24 hours: Self as control	5	0.44*
				Within 24 hours: Non-concussed control group	10	0.97*
				1-7 days: Self as control	11	-0.08
				1-7 days: Non-concussed control group	11	0.43*
				7+ days: Self as control	5	-0.65
				7+ days: Non-concussed control group	6	0.22*
Pertab	2009	Mixed	18	> 3 months	18	-0.09
Rohling	2011	Re-analysis of: Binder (1997) Frenchman (2005) Pertab (2009)	48	< 7 days	16	0.39*
				8-30 days	12	0.32*
				31-92 days	4	0.14
				> 93 days	16	0.17
				All time points	48	0.28*
Konigs	2012	Mixed	21	< 6 months - FSIQ	3	0.08
				> 6 months - FSIQ	2	-0.07
				< 6 months - PIQ	4	0.12
				> 6 months - PIQ	3	-0.05

				< 6 months - VIQ	3	-0.26
				> 6 months VIQ	2	-0.36
Green	2013	Mixed	13	Studies with AAN Methodology Rated I or II	7	.52*
				Studies with AAN Methodology Rated III or IV	5	.38*
Dougan	2014a	Athletes	91	Aggregate across all comparison groups	40	0.54*
				Compared to baseline and control group	9	0.41*
				Independent Control Group	7	0.59*
				Pre-Injury Baseline Injury	24	0.55*
Dougan	2014b	Athletes	31	Grade 1 or 2 Concussion	2	0.23*
				Grade 3 Concussion	12	0.63*

Note. All effect sizes were converted to the same scale with positive effect sizes indicating worse outcomes; d = Cohens' d; k = number of included studies; FSIQ = Full Scale IQ; PIQ = Perceptual IQ; VIQ = Verbal IQ; Effect sizes with asterisks indicate that the authors found the effect size to be significantly greater than zero
Many of the included studies made other sub-group comparisons that were not listed
[a] Frenchman reported Hedge's *g*, not Cohen's *d*.

heterogeneity was present, as evidenced by an extreme range of observed effect sizes (*d* ranged from -.41 to .82) and large standard deviations (SD_d = .17; SD_g = .18). Significantly, excessive between-study heterogeneity can impede ability to draw accurate conclusions (Greco, Zangrillo, Biondi-Zoccai, & Landoni, 2013; Greenland, 1987). Furthermore, this heterogeneity suggests the possibility that effect modifiers, or covariates, are likely to be contributing to variability between studies.

Approximately 10 years later, Frenchman, Fox, and Mayberry (2005) updated Binder and colleagues' (1997) meta-analysis by including seventeen additional studies. It was determined that MTBI has a small negative overall effect on neurocognitive functioning (*g* = .32). This study also considered whether time since injury moderated

changes in neurocognitive functioning. A moderate effect size (g = .33) was observed during the acute stages of recovery (< 3 months) and there was a small, non-significant effect size in the post-acute stage (g = .11). To analyze the effect of time, the researchers performed a subgroup comparison, stratifying the studies by the covariate, time (acute versus post-acute). Two separate estimates of effect size, one for acute MTBI and one for post-acute, were computed. Although this approach is common in systematic reviews, the method of conducting multiple sub-group comparisons increases the risk of Type I errors (Cafri, Kromrey, & Brannick, 2010; Wang, Lagakos, Ware, Hunter, & Drazen, 2007).

Published the same year as Frenchman and colleagues' (2005) meta-analytic review, Belanger and colleagues also examined the effects of time, as well as other possible moderators, on neurocognitive outcomes post-MTBI (Belanger, Curtiss, et al., 2005). Thirty-nine articles published between 1970 and 2004 were identified that examined the neurocognitive effects of sustaining an MTBI in a medical-seeking population (i.e., non-athletes). The authors reported a medium overall effect size (d = .54), with small to medium effect sizes across nearly all cognitive domains. To explore the potential influence of additional moderators, sub-group analyses were conducted by stratifying neurocognitive domains by time post-injury (< 90 days, ≥ 90 days) and sample characteristics (litigation-based samples, clinic-based studies, unselected sample studies). These analyses showed that, generally, for the non-litigant studies, the effect sizes failed to reach significance after 90 days, whereas the effect sizes for the litigant-based studies tended to increase over time. While the researchers' decision to stratify the sample by post-injury time intervals and sample selection shed invaluable insight into the differences in recovery across different populations, the Q statistic (a measure of

between-study heterogeneity) still reached significance across most of these sub-group analyses, suggesting not all meaningful moderators were explored. Furthermore, the process of stratification meaningfully depleted the number of studies included in each sub-group analysis. For example, only two studies included a litigation-based sample in the acute recovery period, which calls into question the precision of the observed effect size.

Belanger and Vanderploeg (2005) conducted an additional meta-analytic review analyzing the effects of MTBI on athletes. A medium effect size was observed across all cognitive domains (d = .49). They also investigated the moderating effect of time by performing three subgroup analyses during the acute period of recovery (within 24 hours, 1-7 days, and beyond 7 days). Unlike the medical-seeking population from the previous analysis, the neurocognitive effects of MTBI resolved in nearly all domains after seven days for the athlete populations included in this study. In addition, likely due to a practice effect, studies that utilized a pre-post comparison design resulted in effect sizes nearly half as large as the effect sizes derived from studies using a non-concussed control group. Notably, again, these sub-group analyses resulted in a smaller number of studies included in each analysis and the Q statistic remained significant, suggesting the influence of additional moderators.

Several additional meta-analytic studies have examined the neuropsychological effects of sustaining an MTBI in various populations (Green, 2013; Konigs, de Kieviet, & Oosterlaan, 2012; Pertab, James, & Bigler, 2009; Rohling et al., 2011). Generally, researchers have found that cognitive residuals resolve in less than three months post-injury. However, various moderator variables (e.g., litigation status, study methodology)

result in different effect size estimates. Despite attempts to explore these moderator variables, significant between-study heterogeneity generally remains, even when multiple subgroup comparisons are made (e.g., Belanger, Curtiss, et al., 2005). Thus, the field would benefit from an updated analysis that further explores moderator variables and attempts to control for between-study heterogeneity.

Meta-Regression

Meta-analytic methodologies are continuing to evolve and may be useful in addressing some of the issues previously described. Specifically, meta-regression analysis (Stanley & Jarrell, 1989) can control between-study heterogeneity, systematically test the significance of effect modifiers, or covariates, and quantify their effect on the effect size estimator. This method would address several limitations associated with prior meta-analytic reviews of MTBI, such as the significant between-study heterogeneity and the decrease in k due to multiple sub-group comparisons.

Similar to meta-analytic reviews, meta-regression has increased power to detect small effect sizes and yields results that are more likely to generalize than findings from a single study. The clear advantage of meta-regression is the ability to control for significant between-study heterogeneity. This is done by investigating whether covariates meaningfully impact effect size differences in regression models. Thus, researchers can simultaneously consider the effect of the covariates on neurocognitive recovery without having to conduct subgroup comparisons. As an example, a meta-analysis examining the relative risk of contracting tuberculosis (TB) after inoculation with a BCG vaccine included 13 studies and identified that the risk ratio of contracting TB was 0.65 (Colditz et al., 1994). Considerable heterogeneity was present among the studies and risk ratios

varied from .20 to 1.56 ($Q(12) = 152.23$, $p < .0001$). It was hypothesized that the vaccine would be more effective in colder climates because individuals living farther away from the equator would have a weaker, natural immunity to TB. A meta-regression was conducted to further explore this issue with latitude identified and added as a covariate to the model (Berkey, Hoaglin, Mosteller, & Colditz, 1995). Latitude was a significant covariate with the risk ratio of contracting TB with a BCG vaccine decreasing in effectiveness as distance from the equator increased. Remarkably, latitude accounted for 79% of the between-study heterogeneity. Meta-regression methods are also useful in examining the magnitude a study characteristic has on an effect size. For example, a meta-regression was conducted to examine the dose-response effect of prophylactic aspirin and secondary stroke prevention (Johnson et al., 1999). The authors investigated if the relative risk of secondary stroke was altered with different doses of aspirin in a single analysis, rather than performing multiple subgroup analyses based on dose-size. The authors found that a flat (i.e., linear) dose-response curve in stroke prevention suggests that all doses of aspirin in the model similarly prevented subsequent strokes.

To date, only one study has examined the neurocognitive effects of MTBI utilizing meta-regression to address issues associated with between-study heterogeneity (Dougan, Horswill, & Geffen, 2014). Overall, Dougan and colleagues' analyses (k = 91) identified a small to moderate decrease in neuropsychological functioning ($d = .40$), moderate to large increase in self-reported symptoms ($d = .66$), and a small effect in balance disturbance ($d = .11$) was associated with concussion.[1] Meta-regression analyses

[1] The study reported negative effect sizes to represent greater dysfunction. However, the direction of the effect sizes were reversed to remain consistent with the direction of the effect sizes reported in the previous studies. As such, the direction of the beta values for the reported regression were also reversed.

were conducted separately to control for time since injury, age, and education. The first regression analysis showed that the overall dysfunction associated with a concussion decreased over time (β = -.06), which suggests that a moderate to large effect of concussion would be observed in the first 24 hours but would decrease to a small to moderate effect after 10 days. This analysis, however, did not account for all the between-study heterogeneity and the *Q* statistic remained significant. Negative relationships between the neuropsychological effects of concussion and age (β = -.11) and education (β = -.20) were additionally reported. After controlling for these variables, the between-study heterogeneity reported in these two analyses (i.e., Cochran's *Q*) was no longer significant. While this study is the first of its kind to use a meta-regression to better explain changes in neuropsychological functioning after MTBI, only a SRC literature was analyzed. Thus, our understanding of the neuropsychological effects of sustaining an MTBI would further improve if a more inclusive meta-regression were conducted that included a broader literature and considered additional moderator variables.

Present Study

MTBI is a significant public health crisis, affecting millions of individuals in the US each year (Faul et al., 2010). There is considerable variability in presentation and duration of the cognitive, physical, and emotional symptoms that occur post-MTBI. Furthermore, there are cognitive, psychological, emotional, and demographic factors that potentially influence the extent of dysfunction and the duration of recovery (e.g., Fann, Uomoto, & Katon, 2001; Goleburn & Golden, 2001). Given the range of individual differences that could potentially affect MTBI recovery, a well-conducted quantitative

analysis of a broad literature would be of great value to clinicians and researchers. While several meta-analyses have been conducted examining the cognitive effects of MTBI (see Table 2), these studies have some notable methodological limitations (e.g., between-study heterogeneity, decreased power due to multiple sub-group comparisons). Meta-analytic regression addresses some of these limitations and may be useful in understanding how individual differences affect cognitive recovery after an MTBI.

A comprehensive, updated meta-analytic review was conducted that incorporated the largest number of published studies pertaining to MTBI, to date. Furthermore, this research utilized meta-regression techniques to control between-study heterogeneity and systematically test the direct influence of effect modifiers. The information garnered from these analyses has the potential to inform clinical care by establishing patient prognosis based on a host of individual differences.

Primary Aims

Aim 1: Conduct an updated meta-analysis examining the neuropsychological effects of sustaining an MTBI across heterogeneous populations.

A significant body of literature makes clear that the acute neurocognitive effects of a single MTBI largely diminish three months post-injury (e.g., Belanger, Curtiss, et al., 2005). Yet, several factors may contribute to documented variability in recovery. Thus, a primary aim of this study is to conduct an updated meta-analysis to elucidate how effect modifiers (e.g., population, age, psychological comorbidities, and performance invalidity) may affect MTBI recovery.

Hypothesis 1: *Consistent with the previous literature, a medium overall effect is expected in the acute period post-MTBI that will fail to reach significance after three months.*

Hypothesis 2: *It is expected that (a) effect sizes will differ across the different "populations;" (b) effect sizes will not differ for the different age groups (c) effect sizes will differ for individuals with psychological comorbidities (d) effect sizes will differ for studies where effort testing is implemented*

Hypothesis 3: *Despite stratifying by these different effect modifiers and performing multiple sub-group analyses, it is hypothesized that between-study heterogeneity will still exist.*

Aim 2: To conduct a meta-regression to control for potential between-study heterogeneity and quantify the effect of covariates has on the neuropsychological functioning post-MTBI.

Previous meta-analyses have documented that between-study heterogeneity is evident despite efforts to control for this variability via multiple sub-group comparisons. Thus, a meta-regression will be useful to examine the neurocognitive effects of sustaining an MTBI while controlling for this potential variability. Additionally, it will allow for the systematic testing of each effect modifier to determine if specific covariates affect estimated effect sizes. If so, the meta-regression will quantify the extent that each covariate affects the estimated effect size.

Consistent with Hypothesis 2, it is hypothesized that time since injury, psychological comorbidities/psychological functioning, and the utilization of PVTs will affect the estimated effect sizes of neuropsychological dysfunction post-MTBI. However, as outlined in the sections above, the unique between-study differences in findings across populations may be a result of the intersection of external (e.g., secondary gain) and internal factors (e.g., psychological comorbidities/psychological functioning). Thus, once the unique variance of time since injury, psychological comorbidity, and PVT testing are controlled, group membership (i.e., population) may not be an important predictor of MTBI outcome.

Hypothesis 4: *When entered into a meta-regression, time since injury, psychological comorbidities, and PVT testing will be significant covariates. Effect sizes are expected to decrease over time but increase in the presence of psychological comorbidities and increase if PVTs are not implemented. Whereas, population and age will not reach significance.*

Methods

Institutional Review and Best Practice Guidelines

The present study did not require direct intervention or interaction with human subjects, nor was personal, private information identifiable during the systematic review process. Therefore, this study was exempt from institutional review **(**Electronic Code of Federal Regulations, 2018; Part 46 – Protection of Human Subjects**)**. In accordance with best-practice guidelines, the study was prepared in accordance with the PRISMA statement guidelines (Moher, Liberati, Tetzlaff, & Altman, 2009). Search criteria, selection criteria, and proposed analyses were pre-registered on a publicly available, online database (PROSPERO Registration Number: CRD42018099719).

Literature Search and Inclusion Criteria

Consistent with previous meta-analyses (e.g., Belanger, Curtiss, et al., 2005; Dougan et al., 2014), the internet databases PsychINFO, Medline, and PUBMED were utilized to identify relevant studies. To maximize the number of pertinent articles and decrease the number of non-relevant studies, key terms were entered into the databases as follows: ("Mild Traumatic Brain Injury" OR "MTBI" OR "Concussion" OR "Mild Head Injury") AND (Neuropsycholog* OR Assess* OR Evaluat* OR Cogniti*)[2]. Furthermore, to ensure pertinent articles were not overlooked, the reference from prior MTBI meta-analyses were also reviewed. The initial literature search was conducted November 2017.

[2] The asterisk (*) at the end of the truncated search term allows for the simultaneous search of multiple iterations of the word. For example, neuropsych* searchers for neuropsychology and neuropsychological.

Table 3.
Inclusionary and Exclusionary Criteria for Article Selection

Inclusionary Criteria:
• Published in English • Involved human research subjects • MTBI or concussion was clearly defined and consistent with the ACRM, WHO Task Force, or International conference on Concussion in Sports criteria • Included if the neuropsychological performance of an MTBI group is compared to pre-injury self, non-concussed control group, or orthopedic injury or pain control group • Included if the study utilized standardized and validated neurocognitive measures (e.g., Lezak, 1995; Strauss, Sherman, & Spreen, 2006) to assess cognitive functioning
Exclusionary Criteria:
• Insufficient information to calculate effect sizes • Average age of participants is not provided • Sample size of each group is less than 10 • Case study • Non-empirical study • Meta-analysis • Systematic review • Intervention study • Participant recruitment based on neuropsychological normality or impairment • If average time since injury is not reported or if average time since injury of the study participants is greater than three years • If sample includes subjects with complicated (e.g., intracranial hemorrhage, skull fracture) TBI

Briefly, empirical studies were included if an MTBI occurred and well-validated neuropsychological assessments were utilized to document cognitive functioning within three years from the initial injury. Articles were excluded if there was insufficient information to calculate or estimate effect sizes (See Table 3 for full inclusionary and exclusionary criteria). Additionally, if data for all cognitive outcome measures were not reported, the study was excluded. That is, studies were excluded if the authors only provided data for the significant, but not the non-significant findings. If assessments took place across multiple timepoints and the authors did not report the data from *all time*

points, the study was retained so long as all data were provided for at least one time point.

Data Extraction and Evaluation of Inter-rater Reliability

Three supervised graduate students (DM, MN, KR) conducted an initial screening by reviewing titles and abstracts of articles obtained from the initial online search for inclusionary/exclusionary criteria. To increase inter-rater reliability, a training session was conducted to establish systematic and consistent screening and reviewing of article titles and abstracts (See Appendix A for flowsheet outlining the approach to abstract coding). A subset of articles were double-coded to establish inter-rater reliability. Of the 492 articles (8.2%) that were double-coded, inter-rater reliability was strong (*kappa* = .887). Discrepancies and uncertainty in article coding were resolved via a consensus conference among the reviewers and a licensed psychologist (JH).

After initial review of the articles, the full text documents were further screened for inclusion/exclusion criteria. This process was completed by the primary investigator (DM). The same reviewers and licensed psychologist took part in data extraction, effect size calculation, and identification of moderator variables once an article was identified as meeting full inclusionary/exclusionary criteria. All extracted data utilized for effect size calculations were double coded for accuracy by supervised research assistants.

Variables of Interest

While this study was inherently exploratory in nature, all variables of interests were selected *a priori* and listed with the open-access systematic review registry, PROSPERO. This was done to reduce potential bias and prevent *p*-hacking (i.e.,

conducting multiple analyses until statistical significance was found). Variables of interested are detailed below.

Cognitive Outcome Measures. Consistent with previous meta-analyses (Belanger, Curtiss, et al., 2005; Belanger & Vanderploeg, 2005; Dougan et al., 2014; Frencham et al., 2005; Rohling et al., 2011), tests were grouped in a manner that is consistent with neuropsychological literature (Lezak, 1995; Strauss, Sherman, & Spreen, 2006). Nine outcomes based on cognitive domains were created: (1) general ability/IQ; (2) orientation; (3) language abilities/academic achievement; (4) attention/working memory; (5) processing speed; (6) executive functioning; (7) immediate memory; (8) delayed memory; (9) fine motor movement. The effect sizes of all cognitive outcome measures were also aggregated via arithmetic mean to create a single, "Overall" effect size to represent the total cognitive sequalae of sustaining an MTBI.

Diverging from the precedent of most other MTBI meta-analyses (c.f., Pertab et al., 2009), only validated neurocognitive assessments frequently used in clinical practice that measured the cognitive domains outlined above were selected for analysis . This was done to increase the internal consistency within cognitive domains. In addition, this ensures that a lack of between-group differences in cognitive recovery does not reflect experimental test construction and unknown psychometric properties. For example, in an imaging study conducted 37 days post-injury, performance differences were not observed between patients medically referred for treatment of MTBI and a control group for a working memory task used during neuroimaging; however, in the same study significant differences were found in a well-established task of attention and working memory (McAllister et al., 2011). A measure was considered "validated" if (1) the measure is

referenced by well-established sources of psychological assessment (Lezak, 1995; Strauss et al., 2006); or (2) if relevant validity studies have been published in referred journals. If a study included both validated and non-validated assessment measures, the study was retained and only the validated measures were included in the analysis.

Moderator Variables. This study sought to determine if effect modifiers, or covariates, affect cognitive recovery from MTBI. Specifically, the primary covariates of interest are: time post-MTBI, population (e.g., athletes, Veterans, general medical referrals, litigants), age, psychological comorbidities, and if the study used PVTs to exclude non-credible performance. Given that Aim 1 analyses utilize categorical variables, continuous moderator variables were also coded categorically for these analyses (See Appendix B for the data code sheet for additional information).

Time since Injury. For pair-wise comparisons (Aim 1), time since injury was coded categorically into five discreet time strata: 1) ≤ 24 hours; 2) 1-8 days; 3) 9-30 days; 4) 31-90 days; and 5) > 90 days. These timepoints were selected for consistency with documented neurometabolic and neurophysiological recovery periods post-MTBI (Giza & Hovda, 2001), and with the assessment intervals commonly used within the empirical literature. The mean time since injury was coded as a continuous variable for meta-regression analyses (Aim 2).

It is common that studies report outcomes for multiple time points when the study participants are followed longitudinally. However, inclusion of multiple time points from a single study in a given analysis biases the overall calculation of the observed effect size as that study is given more weight than other studies with a single time point. It is uncertain, however, how multiple timepoints were handled in previous MTBI meta-

analyses. To our best knowledge, previous studies created a single outcome by averaging these timepoints together. However, important variability regarding cognitive recovery is potentially lost by this method. For example, if a study found a large effect size (d = 1.00) in the first 24 hours after an injury and a small, non-significant effect size one year after the injury (d = .01), the mathematic average would give the potentially erroneous conclusion that a medium effect size (d = .50) was found after 6 months. To prevent studies with multiple outcomes from unduly biasing the overall results, only a single time point per time strata was utilized in each analysis

In an effort to reduce bias and preserve important variability, an arithmetic average across timepoints was not utilized. For Aim 1, multiple timepoints were analyzed separately based on their respective time stratum (i.e., ≤ 24 hours, 1-8 days, 9-30 days, 31-90 days, and > 90 days). However, if a study reported multiple outcomes that fell within a given time strata, the furthest timepoint with (presumably) the smallest effect size was selected for analysis. For example, Kontos and colleagues (2016) reported outcomes for three time points within the "9-30 day" window (14 days, 21 days, and 28 days). Therefore, the data from the furthest time point (28 days) was retained for pairwise analyses.

For Aim 2, time since injury was analyzed as a continuous variable. Therefore, multiple time points could not be analyzed separately. To avoid the issues involved with averaging multiple time points as done by other studies, only the furthest time point was retained for analysis. For example, Nelson and colleagues (2016) reported outcomes for four time points post-injury: < 24 hours, 8 days, 15 days, and 45 days. Only the data from 45 days post-injury was retained for analysis. The rationale for selecting the furthest time

point was two-fold: (1) in the very acute stages of MTBI, the extent of cognitive dysfunction appears to be similar across populations (McCrea et al., 2014) and (2) a primary objective of this project is to determine moderating factors of cognitive recovery post-MTBI, and not necessarily the acute effects of sustaining an MTBI.

Population. For both the pair-wise analysis and the meta-regression, population were coded as a categorical variable (Athlete, General Medical Referral, Veteran, and Litigant). While we acknowledge the inherent medicolegal nature of neuropsychological assessments with Veterans, any Veteran sample was coded as "Veteran" even if the sample consisted of individuals involved in a compensation/disability evaluation. Even if it represented a minority of the participants, a study was coded as "litigant" if it included any participants who were involved in litigation or seeking compensation for their injury.

Age. The average age of the study sample was coded in two ways: categorically (children, high school and college, adult, older adults; Aim 1) and as the mean age of the sample (Aim 2). Study samples with an average age of 0-13 years of age were coded as "children," samples with a mean age between 14-22 were coded as "high school and college," samples with a mean age between 23-64 were coded as "adults," and samples with an a mean age of 65+ were coded as "older adults."

Psychological Comorbidity and Functioning. Similar to age, psychological comorbidities were coded both categorically (Aim 1) and continuously (Aim 2). If the entire sample had the presence of a psychological comorbidity, it was coded as "100% psychological comorbidity," whereas, if the study explicitly excluded study subjects with psychological comorbidities, it was coded as "0% comorbidity." Any sample percentage in between the two was be coded as "mixed." If the study did not specifically state that

psychological comorbidities were assessed or screened, the study was conservatively labelled as "mixed."

If questionnaires assessing emotional well-being and personality were reported, the effect sizes of mood disturbance relative to the control group were calculated in the same manner as the cognitive constructs (see Effect Size Calculation for methodology). Initially, psychological functioning was stratified into separate psychological constructs (depression, anxiety, PTSD, SUD, somatization, internalizing behaviors, externalizing behaviors). While there may be different effects across various psychological constructs a single "Overall" psychological functioning variable was created to increase power and conciseness. This variable was intended to capture the overall extent of psychological distress experienced by the MTBI samples relative to the controls, and it was created via arithmetic mean of the effect sizes across psychological constructs and is the primary moderator variable of psychological functioning for meta-regression analyses (Aim 2).

Performance Validity Testing and Effort. Studies that utilized embedded and/or freestanding PVTs to identify and exclude study participants with sub-optimal task engagement were coded categorically (effort screened; effort not screened).

Secondary Moderator Analyses. Much like simple linear regression, there must be a sufficient ratio of covariates to data points to include multiple moderator variables in an analysis. That is, it is recommended that there be at least 10 studies included in a meta-regression analysis for every covariate (Borenstein et al., 2009). As a result, this can limit the number of covariates considered. The following additional moderators were coded for supplemental, exploratory analyses.

Post-Concussive Symptomology: The presence of post-concussive symptomology (PCS) was coded in a continuous manner. An effect size of PCS symptomatology was calculated when questionnaires were given to both the MTBI and control groups (See Effect Size Calculations for methodology).

Control group. The control group implemented by researchers may affect the observed outcomes (Belanger & Vanderploeg, 2005; Dougan et al., 2014). Some studies attempt to control for extraneous variables such as pain or psychological distress when assessing the cognitive sequelae of an MTBI. These studies tend to lead to a more conservative effect size estimate than studies that utilize healthy, non-injured participants as controls. Therefore, the type of control group (non-injured control, pre-injury baseline, non-injured control & pre-injured baseline, orthopedic injury, trauma, chronic pain) was documented.

Injury Parameters. If provided by the author, the percentage of individuals who experienced LOC, post-traumatic amnesia, and/or a prior MTBI were also coded.

Demographics. Given that demographic factors such as race (Shafi et al., 2007), sex (Bazarian, Blyth, Mookerjee, He, & McDermott, 2010), and education (Dougan et al., 2014) may affect cognitive recovery, pertinent demographic information was also recorded when available.

Effect Size Calculations

As most data from MTBI neuropsychological outcomes studies are continuous, all dependent variables were converted into the effect size, Cohen's *d*, as is convention for

studies in this field[3] (Belanger, Curtiss, et al., 2005; Belanger & Vanderploeg, 2005; Binder et al., 1997; Dougan et al., 2014; Konigs et al., 2012; Pertab et al., 2009; Rohling et al., 2011; c.f., Frencham et al., 2005). If another effect size were provided (e.g., Pearson correlation, *r*), it was converted into Cohen's *d* following standardized processes (Lipsey & Wilson, 2000). Likewise, in the absence of group means or calculated effect sizes, the inferential statistics reported by the authors may also be used to estimate the effect size (Lipsey & Wilson, 2000).

Effect sizes were calculated in accordance with well-established methods outlined by Lipsey and Wilson (2000). Effect size calculation differed based on the study design utilized by the authors, which fell into one of three categories: 1) two independent groups 2) repeated measures design and; 3) independent groups with repeated measures.

Independent Groups, Post-Test Only. The standardized mean difference between two independent groups was calculated based on the following equation:

$$d = \frac{M_{Control} - M_{TBI}}{SD_{Pooled}} \quad (1)$$

Where the SD_{pooled} is the pooled standard deviation and was calculated as:

$$SD_{pooled} = \sqrt{\frac{(n_1-1)SD_1^2+(n_2-1)SD_2^2}{n_1+n_2-2}} \quad (2)$$

The standard error of the effect size estimate (SE_d) was calculated as:

[3] While most meta-analyses in this field utilize Cohen's *d*, there are some criticisms of this methodology as Cohen's *d* is a biased effect size estimate (Lakens, 2013). Rather, some researchers report Hedges *g* as it attempts to correct for bias (e.g., Frenchman et al., 2005). However, when sample sizes are large ($n > 20$) the difference between the two effect sizes are negligible (Lakens, 2013). Given that we expect a large *k* with large sample sizes, we expect there to be no meaningful differences between Cohen's *d* and Hedges *g*.

$$SE_d = \sqrt{\left(\frac{n_1+n_2}{n_1\,n_2}\right) + \frac{d^2}{2(n_1+n_2)}} \quad (3)$$

Repeated Measures (Same Sample) Design. In this dependent-sample design, the post-injury scores of the participants are compared to their own pre-injury baseline scores, resulting in a standardized change score (compared to a standardized difference scores produced from the other designs). The formula for the standardized change is calculated as follows:

$$d_{RM} = \frac{M_{diff}}{\sqrt{SD_1^2+SD_2^2-2r(SD_1^2+SD_2^2)}}\, x\, \sqrt{2(1-r)} \quad (4)$$

where M_{diff} is the mean difference in scores between time 1 and time 2, and *r* is the correlation between time 1 and time 2. The standard error of d_{RM} is calculated by the following equation:

$$SE_{d_{RM}} = \sqrt{\left(\frac{1}{n} + \frac{d^2}{2n}\right) 2(1-r)} \quad (5)$$

Notably, these formulas require both the average *change scores* as well as the correlation between the two time points, both of which are rarely provided by the authors. When correlations are not provided, it is recommended to estimate the correlation from similar studies (Borenstein et al., 2009). However, studies where such information are provided (i.e., test-retest reliability, reliable change studies) typically sample from a healthy, non-injured pool of participants (c.f., Nelson, LaRoche, et al., 2016). Thus, those correlations are unlikely to resemble the true correlation in testing outcomes in an MTBI sample where the scores are expected to change across time.

Other formulas that do not require average change scores or correlations have been proposed (Becker, 1988; Morris & DeShon, 2002). These formulas utilize either the pre-injury standard deviation (Becker, 1988) or pool the standard deviations from both time points (Morris & DeShon, 2002). However, these methodologies have been found to result in larger estimated effect sizes (Belanger & Vanderploeg, 2005; Dougan et al., 2014) and are susceptible to maturation and practice effects. Finally, most studies utilizing this design involved athletes; it is rare that baseline testing is obtained in non-athlete populations. Thus, to ensure consistence in study designs across all populations, the formula proposed by Lipsey and Wilson (2000), which requires the correlation between the two time-points, was utilized. Notably, this methodological decision resulted in the exclusion of most of the repeated measures study designs.

Independent Groups with Repeated Measures. Likely the most robust experimental design, the pre-post design with independent groups accounts for any potential practice effects from repeated testing. The effect size is calculated by subtracting the standardized difference of the control group from the standardized difference of the injured sample via the following equation:

$$d = \frac{(M_{Control\,T2} - M_{Control\,T1}) - (M_{MTBI\,T2} - M_{MTBI\,T1})}{SD_{Pooled\,T2}} \quad (6)$$

where $SD_{Pooled\,T2}$ is calculated the same manner as Equation (2); that is, the standard deviation is pooled from the MTBI and control group post-injury outcomes. The SE_d for the independent group with repeated measures design is calculated the same way as Equation (3) where the post-injury sample sizes are used.

Outlier Analysis

Publication bias, the non-random exclusion or absence of studies, can lead to outlying study effects. One source of publication bias is the small-study effect (Greco et al., 2013). The small-study effect occurs when smaller studies tend to systematically have different effect sizes than larger studies. This may be due to differences in methodology where smaller studies are less methodologically sound than larger, well-funded studies; or, due to a file-drawer effect, where smaller studies with null findings are less likely to be published (Greco et al., 2013). Due to the smaller sample size of these studies, there is greater variability which can lead to an inflation in reported effect sizes compared to larger studies (Sterne, Gavaghan, & Egger, 2000; Sterne, Egger, & Smith, 2008).

To assess for publication bias, a funnel plot was constructed and visually inspected (Bartolucci & Hillegass, 2010). A formal test of asymmetry in the funnel plot was conducted via Egger's Regression Intercept (Egger, Smith, Schneider, & Minder, 1997), which uses linear regression to measure the degree of bias seen from the small study effect. As asymmetry increases, the intercept of the line deviates from 0. This test determines if the intercept is significantly different from 0.

To determine the extent that the file-drawer effect may be problematic, a Fail Safe File Drawer analysis (Rosenthal, 1979) was also calculated. This analysis calculates the number of unpublished studies necessary to offset the obtained effect size estimate. If a relatively small number of studies are needed to offset the obtained effect size, there is likely a file-drawer effect. However, if many studies are needed to offset the potential results, then a file-drawer effect is less likely.

Data Analysis

Effect sizes were derived from each study with an Excel program developed by the primary investigator (DM). This program incorporated the methodological calculations outlined by Lipsey and Wilson (2000) and is freely available to the public (https://www.marquette.edu/psychology/frl-neuropsychology-and-personality-lab.php). The pairwise and meta-regression analyses were conducted utilizing Comprehensive Meta-Analysis Version 3 software (Borenstein, Hedges, Higgins, & Rothstein, 2016).

Individual effect sizes from each study were aggregated and weighted based on the following equation:

$$d = \frac{\sum w_i d_i}{\sum w_i} \quad (7)$$

where d_i is the effect size estimate of a particular study and w_i is the weighted variance. The way in which w_i is calculated depends on whether a fixed-effect or a random-effect is being calculated.

Previously published MTBI meta-analytic studies conducted fixed-effect analyses. A fixed-effect meta-analysis assumes that there is one true effect size and the various studies included in the analysis are estimating that effect size. It assumes that the included studies are a random sample of a relevant distribution of effects, and that the calculated effect size is an estimate of the mean effect of said distribution. Furthermore, all factors that could potentially influence the effect size are the same across all study populations (Borenstein et al., 2009). Thus, the only source of error observed when calculating the overall weighted effect size is the random error found within studies. In

contrast, the current study conducted random-effects analyses. A random-effects model assumes that the true effect size varies from study to study (Borenstein et al., 2009). The studies included in the meta-analysis are assumed to be a random sample from a relevant distributions of true effects, rather than a distribution of a single effect, as in the case of fixed-effects. Thus, there are two sources of error: the within-study error and between-study error.

All prior MTBI meta-analyses conducted fixed-effect analysis (e.g., Dougan et al., 2014). However, the purpose of the present study is to determine the extent that moderator variables (i.e., population, age, psychological comorbidities, PVT performance) affect cognitive recovery after sustaining an MTBI. It was hypothesized that some of these modifiers would influence the overall effect of an MTBI. It would be illogical, therefore, to conduct a fixed-effect meta-analysis given that we do not assume there is one "true" effect size associated with MTBI. Thus, a random-effects meta-analysis was selected as the primary analytical method. The rest of this section elaborates upon methodological issues that are specific to each Aim.

Aim 1. An updated meta-analysis examining the neuropsychological effects of sustaining an MTBI across heterogeneous populations was conducted. Consistent with the approach utilized in prior MTBI meta-analyses, multiple sub-group comparisons were conducted. A random-effects analogue-to-ANOVA was conducted to examine differences in observed effect sizes across cognitive domains (e.g., processing speed, immediate memory, executive functioning), populations (athletes, general medical referrals, Veterans, litigants), ages (children, high school and college, adults, older adults), the presence of psychological comorbidity (none, mixed, 100%), and if effort was

systematically evaluated. Multiple comparisons were made to determine if the estimated effect size is significant in the acute phases (≤ 24 hours,1-8 days), sub-acute phases (9-30 days, 31-90 days) and the post-acute phase (> 90 days) after sustaining an MTBI. For the sake of parsimony and to reduce Type I errors, all moderator analyses were conducted utilizing the Overall cognitive functioning variable.

To assess for between-study heterogeneity, or a wide distribution of observed effect sizes not due to chance, Cochran's *Q* was calculated. Cochran's *Q*, which follows a Chi square distribution is calculated as follows:

$$Q = \sum w_i(d_{i\_}\bar{d})^2 \quad (8)$$

where $\bar{d}$ is the mean calculated effect size and d_i is the effect size of the *i*th study. A smaller *Q* statistic suggests a lack of heterogeneity (Bartolucci & Hillegass, 2010) whereas a larger *Q* statistic suggests that the variability in observed effect sizes cannot be explained by random sampling error, alone. Notably, some researchers posit that due to differences in methodology and the demographic composition of various studies, heterogeneity is inevitable (Higgins, Thompson, Deeks, & Altman, 2003). Thus, another index for heterogeneity is I^2, which measures the impact of the heterogeneity on meta-analytic results, rather than attempting to detect it as Cochran's *Q* does. This variable, which ranges from 0-100, provides an estimate of the variability that remains unexplained after the analysis. I^2 was calculated as follows:

$$I^2 = \left(\frac{Q-df}{Q}\right) * 100 \quad (9)$$

where higher values of I^2 indicates more variability in effect size estimates due to heterogeneity, rather than random, sampling error.

Aim 2. A random-effects meta-regression was conducted, which was modelled as follows:

$$y_i = \beta_0 + \beta_1 x_{1j} + \beta_2 x_{2j} + \cdots \beta_i x_{ij} + \varepsilon_j + \eta \quad (10)$$

Where y_i is the effect size for the *i*th study and β_0, the Y intercept, is the estimated overall effect size when the covariates are not considered (Berkey et al., 1995). The covariates, β_i, have the value x_{ij} for each study, j. The error terms, ε_j represents the imprecision of estimating the effect size for each study, j (i.e., sampling error). ε_j ~ N(0, σ_j^2) where σ_j^2 is the within-study variance and used to estimate ε_j. The between-study variability for the *j*th study is η_j. η_j ~ N(0, τ^2) where τ^2 is the is the true effect size across studies and used to estimate between-study variable. Therefore, in a random-effect analysis, the observed effect size has the following distribution: y_i ~ N($X_j\beta, \tau^2 + \sigma_j^2$).

Based on methodology of similar meta-regressive studies (Etnier, Nowell, Landers, & Sibley, 2006; Lee, Hermens, Porter, & Redoblado-Hodge, 2012), each effect modifier was modeled, separately, with mean time since injury as a covariate. That is, population, average age of sample, the effect size of psychological and personality questionnaires, and PVT testing were modeled separately after controlling for the mean time since injury. Significant of covariates was determined via Knapp-Hartung instead of a Z-test as the Knapp-Hartung is more conservative, yet more accurate when using random-effects analyses (Knapp & Hartung, 2003). Significant covariates were then

entered into a meta-regression simultaneously. To further examine neurocognitive recovery curves over time, linear and non-linear (quadratic) models were also conducted.

The variability explained by each predictor was calculated. Much like the coefficient of determination in simple linear regression (i.e., R^2), this metric was calculated by finding the ratio of the variance explained by the covariate and the total variance. However, the covariates are study-level covariates, thus only providing a measure of the between-study variability. Thus, to provide a better metric, the R^2 will reflect a ratio of the "true" variability (i.e., between- and within-study variability) (Borenstein et al., 2009), τ^2:

$$R^2 = \frac{\tau^2_{Explained}}{\tau^2_{Total}} \quad (9)$$

Power Analysis

A priori power analyses were conducted with R statistical packages (R Core Team, 2014) using a script (Quintana, 2016) that utilizes the formulas for random-effects meta-analytic power analyses outlined by Valentine, Pigott, and Rothstein (2010). Based on previous meta-analyses, large between-study heterogeneity was assumed for the power analyses. Table 4 displays the combination of different number of studies (k) and average number of MTBI and control participants needed to detect a small effect size (*d* = .20) with at least 80% power.

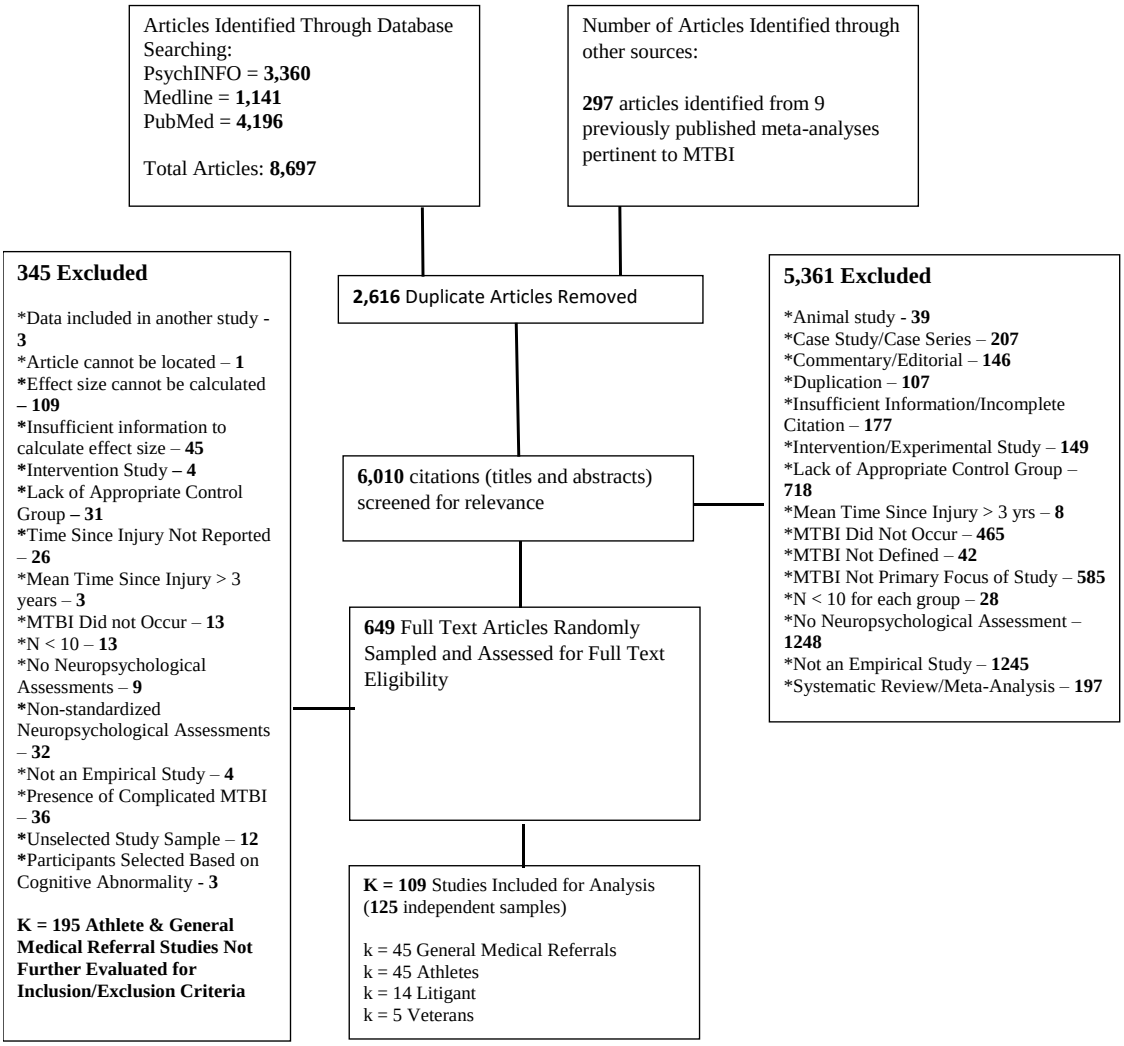
Table 4
Power Analysis Displayed Minimum Number of Effects and Participants Needed to Attain Sufficient Power to Detect a Small Effect Size

Number of Effects	Average n Per Group	Power
30	55	0.82
35	45	0.80
40	40	0.81
45	40	0.84
50	35	0.84
55	30	0.82
60	30	0.85
65	25	0.81
70	25	0.84
75	25	0.84
80	20	0.81
85	20	0.83
90	20	0.85
95	20	0.86
100	20	0.88

Results

The initial article search across databases (PsychINFO, PubMed, MedLine) identified 8,697 studies for potential inclusion. Another 297 articles were identified from previously published meta-analyses (38 of which were unique and not duplicates with the primary literature search). After duplicates were removed, 6,010 titles and abstracts were screened for potential inclusion. Of these articles, 5,361 were excluded, leaving 649 articles whose full text was reviewed for possible inclusion (Figure 2).

Figure 2.
Flow of Meta-analysis Search and Application Inclusion Criteria



Despite careful cultivation of search terms and stringent inclusionary and exclusionary criteria, the recent explosion in the MTBI literature resulted in a much larger pool of potential studies than anticipated. For example, the final sample of studies aggregated across all sources was nearly six times larger than the largest MTBI meta-analysis published to date (1,243 vs. 6,010; Dougan et al., 2014). Similarly, there were 200 more papers whose full text was reviewed for inclusionary criteria compared to the largest previous meta-analysis (420 vs. 649). In order to limit the scope of the project, while maintaining an ability to evaluate primary aims and maintain adequate power, the decision was made to randomly select studies for detailed review until a pre-determined number (k = 45) of studies for each population sub-group met inclusionary criteria. Articles were selected based on population (rather than other moderator variables of interest) as a primary aim of the study was to discern moderator variables the explain the well-established differences in cognitive recovery across various populations (e.g., athlete vs. GMR; GMR vs. litigants). The decision to randomly sample articles to review was made after consultation with a meta-analytic expert who advised on study methodology (Jackson, 2018, personal communication, May 17, 2018). While this methodology is novel, it is defensible as a random effects meta-analysis assumes that the effects included in the analyses are a random distribution among the true population effect. Therefore, by randomly selecting articles for inclusion, we maintain the randomness of the distribution among the true population effect[4]. As such, 45 articles met full inclusionary criteria for the athlete and general medical referral (GMR) groups. However, only 14 studies with individuals involved in litigation and 5 studies with Veterans met full criteria. In total,

[4] This methodology deviated from the analyses that were initially proposed and registered with PROSPERO

109 studies met full criteria for inclusion in analyses. Fifteen studies provided data for multiple, independent samples, yielding a total of 125 independent samples included in the analyses (N_{MTBI} = 5,919, $N_{Control}$ = 8,318). Across all studies, sub-groups, and time points, 747 outcomes were extracted for analysis. Table 5 displays the characteristics of the included studies.

Outlier Analysis and Publication Bias

Extreme Scores. The distribution of all 747 effect sizes from all 125 samples were analyzed for outlying data points. Any effect size more than 3 standard deviations from the mean of all observed effect sizes (-1.97, 2.81) were considered outliers (Dougan et al., 2014; Hedges & Olkin, 1985; Lipsey & Wilson, 2000). Eight effects were identified as outliers, originating from three studies (McCauley et al., 2014; Moser, Schatz, & Jordan, 2005; Roebuck-Spencer et al., 2012). One outlier was in the negative direction (*d* = -2.05 7 days after injury; Moser et al., 2005) and the remaining seven were in the positive direction (*d* ranged 3.69 to 11.48, 2 days and 404 days post-injury; Roebuck-Spencer et al., 2012; McCauley et al., 2014). The data from McCauley (2014) were not true marginal means, but rather means after adjusting for age, sex, and perceived stress. In Moser (2005) only a single effect, measuring language, was found to be an outlying effect. In the study completed by Roebuck-Spencer (2012), the study was an independent sample with repeated measures. The effect sizes were extreme, in part, because the control group showed significant improvement with repeated testing, whereas the MTBI groups showed significant declines. Rather than excluding these studies, the effect sizes were reduced to the next major cluster of non-outlying effect sizes (Lipsey & Wilson, 2000).

Table 5.
Characteristics of Included Studies

	Sample Information					Demographic Information			Injury Parameters						
Sample	**Country**	**Population**	**n MTBI**	**n Control**	**Control Group**	**Age**	**Mean Education**	**% Female**	**% Previous MTBI**	**% LOC**	**% PTA**	**Psych Comorbidity**	**PVTs**	**TSI (days)**	**d**
McCrea (2003)	USA	Athlete	94	56	NIC	20.04	14.78	0	43.2	0	0	Mixed	No	7 90	0.016 0.035
Pontifex (2009)	USA	Athlete	30	36	NIC	19.9	14.2	23	100	53	50	Mixed	No	1044	0.2
Elbin (2012)	USA	Athlete	14	14	NIC				100			Mixed	No	278.7	0.168
Gardner (2010)	Australia	Athlete	34	39	NIC	23	13.36	0	100			0	No	560.1	0.227
Singh (2014)	USA	Athlete	25	25	NIC	21.16	13.44	0				0	No	270.6	0.088
Moser (2002)	USA	Athlete	13	13	NIC	16.36		21				Mixed	No	7.5	0.377
Mrazik (2016)	Canada	Athlete	63	31	NIC & PIB	21.8	14.2	0				Mixed	No	10	-0.457
Guskiewicz (1997)	USA	Athlete	11	11	NIC	18.6		27.7	0	54.5	18.18	Mixed	No	1	0.444
Tsushima (2013)	USA	Athlete	26	25	NIC	15.42	9.23		0			Mixed	No	6.8	0.207
Koehl (2016)	USA	Athlete	29	25	NIC	14.41	8.1	20.7	31	44.8	44.8	0	No	53.79	0.853
Hammeke (2013)	USA	Athlete	12	12	NIC	16.5				40	8.8	Mixed	Yes	0.54 49	0.28 0.023
Sim (2008)	USA	Athlete	14	14	NIC & PIB	15.5		21.42	42.86	14.28	28.57	Mixed	No	6.3	0.817
Sikoglu (2015)	USA	Athlete	14	13	NIC	20.1		35.71	57.14	0		0	no	76.45	0.629
Moser (2005)	USA	Athlete	25	82	NIC	15.8	10.5		40			Mixed	No	7	-0.087
McCrea (1998)	USA	Athlete	33	568	NIC			0		0	0	Mixed	No	0.01	1.1
Hutchison (2011)	Canada	Athlete	36	18	OI	19.78		67	36			0	No	3	0.189
Moore (2017)	Canada	Athlete	14	16	NIC	23.36	17.29	0	100	0	28.57	0	No	819	0.186
Baillargeon (2012)g	Canada	Athlete	15	15	NIC	23.4	16.1	0				0	No	189	0.147
Baillargeon (2012)f	Canada	Athlete	17	17	NIC	14.8	8.8	0				0	No	174	0.151
Baillargeon (2012)e	Canada	Athlete	16	16	NIC	11	4.9	0				0	No	177	-0.199
Kontos (2016)b	USA	Athlete	22	10*	NIC	16.5		45				0	No	7 28	1.339 1.044
Kontos (2016)a	USA	Athlete	15	10*	NIC	16.45		47				0	No	7 28	1.658 1.352
Schatz & Sandel (2013)b	USA	Athlete	37	37	NIC			14	92			0	Yes	3	0.111
Schatz & Sandel (2013)a	USA	Athlete	81	81	NIC			33	92			0	Yes	3	0.631
Broglio (2016)	USA	Athlete	24	21	NIC	16.3		54.16	0	0	0	Mixed	No	6.2 26.2 79.5	0.443 0.374 0.134
Bruce (2003)	USA	Athlete	19	19	NIC	20.1		0	52.63	21.05	68.42	Mixed	No	0.0833 7	0.405 0.193
Pica (2007)	USA	Athlete	72	84	NIC	16.21	11.09	0	45.9			Mixed	No	1 6 45	0.239 0.141 0.007
Miller (2003)	USA	Athlete	60	62	NIC	16.56		0		10		Mixed	No	1 6 50	-0.023 0.015 0.063

Table 5 continued.
Characteristics of Included Studies

	Sample Information					Demographic Information			Injury Parameters						
Sample	**Country**	**Population**	**n MTBI**	**n Control**	**Control Group**	**Age**	**Mean Education**	**% Female**	**% Previous MTBI**	**% LOC**	**% PTA**	**Psych Comorbidity**	**PVTs**	**TSI (days)**	**d**
Sim (2006)	USA	Athlete	14	14	NIC & PIB	15.6		0.4	40			Mixed	No	6.3	0.924
McCrea (2002)	USA	Athlete	91	1189	NIC	17.52				15.6	16.48	Mixed	No	0.0104	1.029
Stueland (2001)	USA	Athlete	14	12	NIC			0				0	Yes	4.5	0.394
Gardner (2012)	Australia	Athlete	46	41	NIC	24.2	13.89	0				Mixed	Yes	1.935	0.371
Virji-Babul (2013)	Canada	Athlete	12	10	NIC	15.5		16.66				Mixed	No	35.66	0.683
Field (2003)m	USA	Athlete	35	18	NIC	19.85		4	53			Mixed	No	1 7	1.035 -0.054
Field (2003)l	USA	Athlete	19	20	NIC	15.2		0	53			Mixed	No	1 7	1.137 0.911
Register-Mihalik (2013)	USA	Athlete	132	38	NIC & PIB	18.59	0	34.85				Mixed	No	2.36	0.409
Sasaki (2014)	Canada	Athlete	16	18	NIC	21.68		38	38.23			Mixed	No	95	0.009
Macciocchi (1996)	USA	Athlete	183	48	NIC			0		4.8		0	No	1 5 10	0.479 0.382 0.467
Terry (2012)	United States	Athlete	20	20	NIC	20.3	14.3	0	100	22	44.4	0	No	588	0.363
Collie (2006)b	Australia	Athlete	36	42*	NIC	23.3		0		19.4	36.1	Mixed	No	3.5	-0.018
Collie (2006)a	Australia	Athlete	25	42*	NIC	22.3		0		32	36	Mixed	No	2.2	0.169
Gosselin (2007)	Canada	Athlete	10	11	NIC	24.3	14.7	30	100	20	40	0	No	132	0.413
Schatz (2005)	USA	Athlete	72	66	NIC	16.5	20.8	10.4		99		Mixed	Yes	3	1.108
Nelson (2016)	USA	Athlete	165	166	NIC & PIB	17.46		16.4				Mixed	Yes	0.7954 8 15 45	0.527 0.169 0.073 0.035
Guskiewicz (2001)	US	Athlete	36	36	NIC & PIB	19.5	13	31		19	31	Mixed	No	1 5 1	0.542 0.345 0.267
Chin (2016)	USA	Athlete	166	164	NIC & PIB	17.47	11	16.3				Mixed	No	8 15 45	0.011 -0.005 -0.08
Forbes (2016)	US	Athlete	105	105	NIC	15.9	10	100				Mixed	No	813	0.016
Fischer (2016)	USA	GMR	11	12	NIC	33	14.09	27	36	54.5		Mixed	No	0.246	1.061
Nash (2014)	France	GMR	89	70	OI	35.4		22.5				Mixed	No	360	-0.185
Shores (2008)	Australia	GMR	79	86	OI	31.5	11.4	24				Mixed	Yes	0.261	1.089
Mayer (2015)	USA	GMR	15	15	NIC	13.47	6.87	13.3		66.6		0	No	15.33	0.439
Barwood (2013)	Australia	GMR	16	16	NIC	38.25	12.875	37.5	0	87.5	37.5	0	No	348.75	-0.298
Dall'Acqua (2017)	Switzerland	GMR	49	49	NIC	34.9	12.6	63.2	0			0	Yes	5.28 360	0.358 0.183
Mayer (2014)	USA	GMR	30	30	NIC	27.83	13	46.67				Mixed	Yes	15	0.246
Saluja (2015)	Canada	GMR	15	15	NIC	15		53.3	20			Mixed	No	39.3	0.456

Table 5 continued.
Characteristics of Included Studies

	Sample Information					Demographic Information			Injury Parameters						
Sample	**Country**	**Population**	**n MTBI**	**n Control**	**Control Group**	**Age**	**Mean Education**	**% Female**	**% Previous MTBI**	**% LOC**	**% PTA**	**Psych Comorbidity**	**PVTs**	**TSI (days)**	**d**
Raz (2011)	USA	GMR	28	18	NIC	35.6		32				0	No	558.9	0.895
Macciocchi (2013)	USA	GMR	53	64	OI	26.91	11.89	11.3	0			Mixed	No	48	0.163
Xiong (2014)	China	GMR	25	25	NIC	32.5	12.84	36	0			Mixed	No	32.07	0.538
Studer (2015)	Germany	GMR	36	27	OI	11		54.3	31.4	36.1	52.8	Mixed	No	120	-0.05
Sheedy (2009)	Australia	GMR	100	100	OI	33.64	13.19	22				Mixed	No	0.579	0.539
Goldstein (2001)	USA	GMR	18	14	NIC	62.3						Mixed	No	24.99	0.365
Cicerone (1997)	USA	GMR	50	40	NIC	34.6	14.8					Mixed	Yes	396	0.605
De Monte (2005)	Australia	GMR	112	32	OI	25.35	12.53	20.5	59			0	No	0.353	0.334
Borgaro (2003)	USA	GMR	14	14	NIC	46.1	11.8	30				Mixed	No	15.6	1.207
Meyers (2004)	USA	GMR	57	32	CP	36.93	12.63	24.56				Mixed	Yes	227.7	0.576
Hess (2003)	USA	GMR	33	33	OI	37.2	11	21				Mixed	no	33.4	0.655
Shee (2016)	USA	GMR	91	86	NIC	33.7	14.3	938.5				Mixed	No	39.5	0.208
Chen (2012)	Taiwan	GMR	20	18	NIC	36.6	15	50	0			0	No	16.9	0.211
Harman-Smith (2013)	Australia	GMR	84	95	OI	34.8	13.3	54				0	Yes	168.7	0.191
Levin (1987)	USA	GMR	57	56	NIC	23.22	12.38	39				0	No	7 30	0.979 0.405
McNally (2013)d	USA	GMR	112	44.5*	OI	11.83		33		0		Mixed	No	10.5	-0.061
McNally (2013)c	USA	GMR	74	44.5*	OI	12.15		23		100		Mixed	No	10.5	-0.145
Subotic (2017)b	Canada	GMR	17	9*	NIC	42.7	14.9	53	47			Mixed	No	8.5	1.059
Subotic (2017)a	Canada	GMR	28	9*	NIC	46.1	16.4	82	50			Mixed	No	8.5	1.086
Bohen (1995)b	Netherlands	GMR	11	5.5*	NIC	27.4	5.1	45.45				0	No	687	-0.434
Bohen (1995)a	Netherlands	GMR	11	5.5*	NIC	27.2	4.6	45.45				0	No	678	0.456
Sroufe (2010)	USA	GMR	28	45	OI	13.5		43	19	25	29	0	Yes	1 7 31.5	-0.012 0.052 0.212
Lange (2015)b	Canada	GMR	52	18*	OI	34.1	15.3	21.2	0	94.2	100	Mixed	Yes	46.8	0.091
Lange (2015)a	Canada	GMR	20	18*	OI	34.1	14.4	45	0	90	100	Mixed	Yes	46.7	0.048
Acreman (2014)	Canada	GMR	41	39	CP	38.63	13.8	31.7				Mixed	Yes	30	-0.818
Bergloff (1995)	USA	GMR	15	15	NIC	28	13.23	53.33				Mixed	No	358.5	0.612
Sheedy (2006)	Australia	GMR	100	100	OI	33.62	13.22	31	44.8	72.4		Mixed	No	0.725	0.497
Schmidt (2017)	USA	GMR	14	14	NIC	20.2	12.9					Mixed	No	11	0.22
Bodzy (2011)	USA	GMR	62	82	NIC	10.83		46.66				0	No	2	0.167
Mayer (2011)	USA	GMR	27	26	NIC	27.15	13.22	57.7	0	0	0	0	Yes	11.32	0.166
De Monte (2005)h	Australia	GMR	50	18	OI	26.86	12.79	100				0	No	0.3246	1.039
De Monte (2005)i	Australia	GMR	14	8	OI	24.42	12.47	0				0	No	0.3342	0.569
Padre (2009)	Canada	GMR	37	79	NIC	26.7	13.14	35.14		81.08	100	0	No	4.4 93	0.389 0.25
Diwakar (2015)	USA	GMR	25	25	NIC	32.7	14.7	16		64	96	0	Yes	954	0.507
Van Beek (2015)	Belgium	GMR	20	20	NIC	10.8		35	0			0	No	12.85 201	0.995 0.346

Table 5 continued.
Characteristics of Included Studies

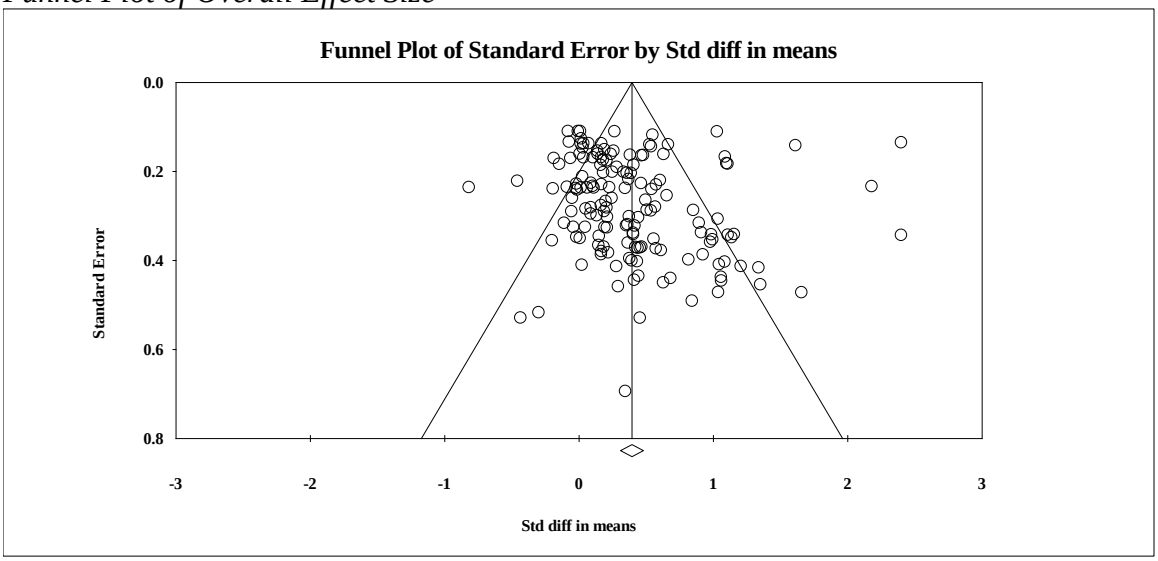
	Sample Information					Demographic Information			Injury Parameters						
Sample	**Country**	**Population**	**n MTBI**	**n Control**	**Control Group**	**Age**	**Mean Education**	**% Female**	**% Previous MTBI**	**% LOC**	**% PTA**	**Psych Comorbidity**	**PVTs**	**TSI (days)**	**d**
Keightley (2014)	Canada	GMR	15	15	NIC	14.47	0	53.33	20			0	No	41.13	0.422
Gulbrandsen (1984)	Norway	GMR	56	56	NIC	11.33		32.14	0			0	No	180	0.283
McKinlay (2002)	New Zealand	GMR	86	613	NIC	4.87		42.47	0			Mixed	No	30	0.18
Leh (2017)	Canada	GMR	15	13	NIC	30.7	12.4	60	0	0	0	0	No	126	0.435
Studer (2014)h	Switzerland	GMR	23	13	OI	11.05	6	100	27.5	35	50	0	No	30 120	-0.017 0.166
Studer (2014)i	Switzerland	GMR	17	25	OI	11.05	6	0	27.5	35	50	0	No	30 120	-0.109 -0.041
Van Beer (2015)	Belguim	GMR	20	20	NIC	10.8		35	0			0	No	12.85	0.417
Dikmen (2017)	USA	Litigant	120	130	TC	28	12.4					Mixed	No	30 360	0.017 -0.073
Hattori (2009)	USA	Litigant	15	15	NIC	45	16	80				0	No	858	0.574
Lange (2014)	Canada	Litigant	43	36	OI	30.4	14.6	23.3	0	93	0	Mixed	Yes	46.1	0.091
McAuley (2014)	USA	Litigant	73	65	OI	19.1	10.5	27.4		78.1		Mixed	No	2.5208	2.18+
Hattori (2009)	USA	Litigant	15	15	NIC	45	16	80				Mixed	No	858	0.574
Leininger (1990)d	USA	Litigant	22	11.5*	NIC	30.7	13.5	55		0		Mixed	No	183	0.467
Leininger (1990)c	USA	Litigant	31	11.5*	NIC	32.9	13.7	60		58.4		Mixed	No	252	0.558
Curtis (2012)	USA	Litigant	71	133	CP	42.5	12.6	36.6		60.3	33.333	Mixed	Yes	780	0.03
Richards (2000)g	Canada	Litigant	20	20	NIC	26.85	14.1	50	0	77		0	No	720	0.986
Richards (2000)j	Canada	Litigant	20	20	NIC	69.1	12.7	50	0	55		0	No	954	1.11
Zakzanis (2011)	Canada	Litigant	20	54	NIC	39	13.1	50				0	Yes	748.3	1.156
Mathias (2004)	Australia	Litigant	40	40	NIC	32.4	12.4	20		80		Mixed	Yes	26.3	0.464
Raskin (1997)n	USA	Litigant	10	10	TC	41.8	14.2	100				1	No	427.2	0.293
Raskin (1997)o	USA	Litigant	10	10	NIC	40.4	13.2	100				Mixed	No	746.7	0.843
Ponsford (2011)	Australia	Litigant	90	80	OI	34.98	13.58	26		92.5	96.7	Mixed	No	7 90	0.259 0.139
Nelson (2017)	USA	Litigant	94	80	OI	29.11		39.4	35.1			Mixed	Yes	1.62 14.6 43.8	0.027 -0.192 0.103
Haran (2016)	United States	Veteran	440	88	NIC	28.8		0				Mixed	No	3.06	0.55
Roebuck-Spencer (2012)b	USA	Veteran	197	200*	NIC	25.9		6.23		20.7	4.6	Mixed	No	402	4.203+
Roebuck-Spencer (2012)a	USA	Veteran	305	200*	NIC	26		7.61		31.5	9.1	Mixed	No	404	11.482+
Sorg (2014)	USA	Veteran	30	15	NIC	30.7	13.3	13	73	60	0	0	Yes	1080	0.353
Ivins (2015)	USA	Veteran	56	773	NIC	26.9		0		53.5	62.5	Mixed	Yes	23	0.666
McCrea (2014)	USA	Veteran	63	554	NIC	26.65		0		54.7	29.4	Mixed	No	1	1.613

Notes: LOC = Loss of Consciousness; PTA = Post-traumatic Amnesia; PVTs = Performance Validity Tests; TSI = Time Since Injury in days; NIC = Non-Injured Control; NIC & PIB = Non-Injured Control and Pre-Injury Baseline; TC = Trauma Control; OI = Orthopedic Injury; CP = Chronic Pain; GMR = General Medical Referral; *=outlying effect size prior to trimming; + = control group was split in half and distributed among both independent samples

a = independent sample with PCS; b = independent sample without PCS; c = independent sample with LOC; d = independent sample with no LOC; e = independent sample with children; f = independent sample of high school/college students; g = independent sample of adults; h = independent sample of females; i = independent sample of males; j = independent sample of older adults; l = independent sample of high school students; m – independent sample of college students; n = independent sample of individuals who sustained traumas; o = independent sample of individuals who did not sustain trauma

Publication Bias. Given the lack of independence in studies with multiple outcome measures (i.e., memory, processing speed, executive functioning), all analyses assessing publication bias were conducted using the overall cognitive dysfunction outcome measure. A Fail-Safe N analysis across all time points revealed that 5,254 missing studies with a null effect are needed to bring the observed effect size to a non-significant value (i.e., $p < .05$). Visual inspection of a funnel plot reveals a general symmetry of observed effects across the overall observed effect (Figure 3), suggesting no evidence of publication bias. Similarly, a formal test of asymmetry, Egger's regression intercept found a non-significant intercept ($\beta_0 = 0.556$, $t(150) = 1.17$, $p = 0.24$), which suggests no evidence of publication bias.

Figure 3.
Funnel Plot of Overall Effect Size



Aim 1: Pair-Wise Meta-Analytic Findings

Cognitive Functioning Over Time. Table 6 shows the results of the random-effects meta-analysis, which displays the observed effects size for each cognitive domain

stratified by time. This analysis does not control for potential effect modifiers (i.e., population, psychological comorbidity, PVTs). For this analysis, the time points are assumed to be independent of one another. While each study only contributes one study per time strata, there is an inherent violation of independence and perfect correlation (r = 1.00) is assumed when comparing the effects between time strata (e.g., 24 hours vs > 90 days). As such, the standard errors within a time point stratum may be erroneously small, resulting in an increase in potential Type I errors when estimating the effect size within each time strata. Conversely, assuming a perfect correlation across time points results in an inflation of the standard error when comparing between-time strata, resulting in an increase in potential Type II errors.

In general, medium to large effect sizes were evident in acute stages post-MTBI, which decreased over time. Contrary to expectation, effect sizes tended to increase again after 90 days post-MTBI. *Consistent with Hypothesis 1, medium overall effect sizes were evident in the acute periods post-MTBI (≤24 hours, 1-8 days). In contrast to expectation, the overall effect size remained significant, even after 3 months.* More detailed analyses across each cognitive domain are outlined below.

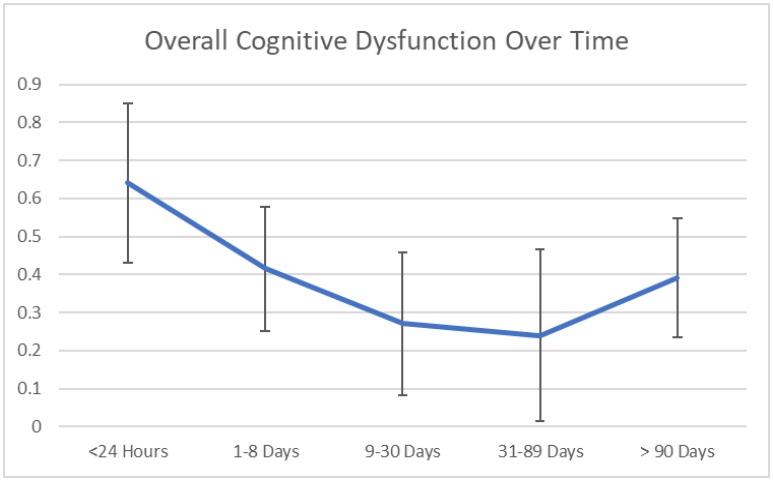
Overall Cognitive Dysfunction. The analogue-to-ANOVA failed to reach significance (*Q Between*(4) = 8.907, *p* = .063) suggesting there were no differences in observed effect sizes over time. Consistent with previous meta-analyses, a medium-to-large effect size (*d* = .641) was observed when assessing overall cognitive functioning during the first 24 hours after sustaining an MTBI. A medium-small effect size is observed 1-8 days post-MTBI (*d* = .415) and small, but significant effect sizes is observed until 90 days post-MTBI (*d* range .271-.240). Contrary to the previous research,

Table 6
Cognitive Dysfunction Post-MTBI Stratified by Time

	≤ 24 Hours				1-8 Days				9-30 Days				31-89 Days				≥ 90 Days				
	k	d	95% CI	Q	k	d	95% CI	Q	k	d	95% CI	Q	k	d	95% CI	Q	k	d	95% CI	Q	Q between
Orientation	11	0.887*	0.617-1.158	49.989*	2	0.252	-0.326-0.83	1.55	1	0.996	-0.09-2.082	0.00	3	0.143	-0.395-0.68	10.36*	2	0.584	-0.15-1.319	0.00	8.579
General Ability/IQ	5	1.296*	0.759-1.833	161.07*	7	0.232	-0.239-0.703	9.98	13	0.167	-0.185-0.52	25.683*	12	0.28	-0.092-0.651	25.68*	18	0.641*	0.327-0.956	23.17*	15.038*
Language/Achievement	1	0.201	-0.311-0.712	0.00	1	-1.071*	-1.69 - -0.452	0.00	6	0.203	-0.036-0.442	7.20	4	0.121	-0.192-0.435	1.86	9	0.249*	0.053-0.445	14.63	16.188*
Attn/Working Memory	12	0.52*	0.33-0.711	30.3*	18	0.348*	0.188-0.508	29.8*	18	0.191*	0.016-0.366	44.76*	13	0.054	-0.144-0.251	12.53	28	0.27*	0.128-0.413	72.74*	12.838*
Processing Speed	14	0.605*	0.38-0.829	29.87*	30	0.472*	0.319-0.625	121.96*	18	0.203*	0-0.406	69.93*	13	0.26*	0.024-0.496	21.7*	30	0.274*	0.112-0.436	89.93*	10.667*
Executive Function	8	0.259	-0.015-0.533	15.1*	16	0.254*	0.073-0.434	30.54*	16	0.198	-0.005-0.401	68.56*	13	0.205	-0.02-0.431	23.69*	30	0.201*	0.046-0.356	67.32*	0.326
Immediate Memory	17	0.628*	0.405-0.851	128.85*	14	0.334*	0.085-0.584	75.89*	8	0.275	-0.061-0.61	5.52	10	0.3	-0.003-0.604	9.84	26	0.274*	0.076-0.472	45.22*	6.608
Delayed Memory	17	0.723*	0.504-0.942	137.94*	27	0.425*	0.25-0.6	127.45*	15	0.367*	0.12-0.615	36.2*	15	0.369*	0.131-0.607	28.08*	26	0.332*	0.138-0.526	33.89	8.289
Visuospatial Skills					4	0.379	-0.113-0.87	18.49*	6	0.238	-0.159-0.635	15.73*	8	0.312	-0.032-0.655	31.78*	10	0.345*	0.035-0.654	17.1*	0.245
Fine Motor Mvmt	2	0.786	0.291-1.281	0.64	2	0.459	0.056-0.862	1.23	3	0.078	-0.185-0.341	4.33	3	0.446	0.073-0.819	1.65	7	0.293	0.108-0.478	5.66	7.608
Overall	22	0.641*	0.432-0.85	116.55*	36	0.415*	0.251-0.578	139.592*	29	0.271*	0.083-0.459	90.407*	20	0.24*	0.015-0.464	22.00	45	0.391*	0.235-0.546	337.426*	8.907

Note . IQ = Intelligence Quotient; Attn = Attention; Mvmt = Movement
Values that are bolded and have an * indicate values with p < .05; Significance levels were not futher stratified

Figure 4.
Overall Cognitive Dysfunction Over Time



the effect size increases from small to medium-small after 90 days (d = .391). This finding likely reflects the fact that most of the studies with litigant and Veteran samples were assessed at this time point (see Population analyses). Significant between-study heterogeneity was observed for all time points except the 31-89 day time strata.

Orientation. A large effect size (d = .887) in orientation was observed in the first 24 hours post-MTBI. Effect sizes across the other time strata were non-significant, likely due to the small number of studies. Nevertheless, observed effect sizes in these time strata ranged from small to large (d range = .252-.996). The analogue-to-ANOVA failed to reach significance (Q *Between*(4) = 8.579, p = .073), suggesting no significant differences in observed effect sizes over time. Significant between-study heterogeneity was evident in the ≤ 24 hour and 31-89 day time strata.

General Ability and Intelligence. There were significant differences in observed effects across time points (Q *Between*(4) = 15.04, p = .005). A very large effect size was observed in the first 24-hours post-MTBI. Small, non-significant effect sizes (d range .280-.167) were observed in the 1-8 day, 9-30 day, and 31-89 day time strata, all of which were significantly smaller than the effect size observed ≤ 24 hours post-MTBI (all p's < .05). Mirroring the results of analysis of overall cognitive dysfunction, a non-significant increase in the effect size from small to medium-large was observed after 90 days (d = .641; Z = 1.46, p = .15). The effect size observed after 90 days remained significantly smaller than the initial effect size observed at 24 hours (Z = 2.060, p = .04). Significant between-study heterogeneity was observed in all time strata except the 1-8 day time strata.

Language and Academic Achievement. The analogue-to-ANOVA was significant (*Q Between*(4) = 16.188, $p < .01$) suggesting differences in observed effect sizes over time. A small, non-significant effect size was observed in the first 24 hours, post-MTBI ($d = .201$). After 1-8 days, the effect size significantly decreased from small to a very large, negative effect size ($d = -1.07$; Z = 3.10, $p < .001$). Notably, this observed effect was derived from a single study (Moser et al., 2005) and this effect size was identified as an outlier and trimmed to its current value of -1.07; thus, this is unlikely to be an accurate reflection of the true population effect size at this time point. Small, non-significant effect sizes were observed in the 9-30 day and 31-89 day time strata. Mirroring the previous analyses, a non-significant increase in effect size (Z = .676, $p = .50$) was observed after 90 days. After 90 days, a small, but significant effect size was observed ($d = .249$), This effect size did not differ from the non-significant effect size observed the initial 24 hours post-MTBI (Z = .17, $p = .86$). No significant between-study heterogeneity was observed.

***Attention and Working Memory*.** The analogue-to-ANOVA was significant (*Q Between*(4) = 12.838, $p = .012$), suggesting differences in observed effect sizes across time strata. A medium effect size was observed in the first 24 hours post-MTBI ($d = .520$). A non-significant decrease to a medium-small effect size ($d = .348$) was observed in the 1-8 day time strata. A small, but significant, effect size was observed after 9-30 days ($d = .191$) and a near-zero effect size was observed after 31-89 days ($d = .054$). Both of these observed effect sizes were significantly smaller than the effect size observed in the first 24 hours post-MTBI (all p's $< .05$). A non-significant increase in observed effect size was observed after 90 days ($d = .270$, Z = 1.74, $p = .08$). The small effect size

observed after 90 days was significantly smaller than the medium effect size observed in the first 24 hours post-MTBI (Z = 2.06, *p* = .04). Significant between-study heterogeneity was observed in all time strata except the 31-89 day stratum.

Processing Speed. The analogue-to-ANOVA was significant (*Q Between*(4) = 10.667, *p* .031), suggesting differences in observed effect sizes across time. A medium-large effect size was observed in the first 24 hours post-MTBI (*d* = .605). A non-significant decrease to a medium effect size (*d* = .472) was observed after 1-8 days (Z = .956, *p* = .33). A significant decrease to a small effect size was observed in the 9-30 day time strata (*d* = .203; Z = 2.07, *p* = .0381). Small, but significant, effect sizes were observed across the remaining time strata (*d* = .260 and .274). Significant between-study heterogeneity was observed in all time points.

Executive Functioning. The analogue-to-ANOVA was not significant (*Q Between*(4) = .326, *p* = .99), suggesting there were no differences in observed effect sizes over time. In the first 24 hours post-MTBI, a small, non-significant effect size was observed (*d* = .259). Small effect sizes were observed across the remaining time strata; however, only the effect sizes from the 1-8 day stratum and > 90 day stratum reach statistical significance (*d* = .245 and .201, respectively). Significant between-study heterogeneity was observed in all time strata.

Immediate Memory. The analogue-to-ANOVA failed to reach statistical significance (*Q Between*(4) = 6.61, *p* = .158). In the first 24 hours post-MTBI, a medium-large effect size was observed (*d* = .605). This was reduced to a medium-small effect size after 1-8 days (*d* = .334). Non-significant, medium-small effect sizes were observed in the 9-30 day and 31-89 day strata (*d* = .275 and .300, respectively). However, a medium-

small effect size after 90 days did reach statistical significance (*d* = .274). Significant between-study heterogeneity was observed in all time strata except the 9-30 day and 31-89 day time strata.

Delayed Memory. The analogue-to-ANOVA failed to reach statistical significance (*Q Between* (4) = 8.289, *p* = .082). In the first 24 hours post-MTBI a medium-large effect size was observed (*d* = .723). Significant, medium-large effect sizes were observed across the remaining time strata (*d* range = .332-.425). Significant between-study heterogeneity was evident in all strata except the > 90 day time strata.

Visuospatial Skills. The analogue-to-ANOVA failed to reach statistical significance (*Q Between* (4) = .245, *p* = .970), suggesting no differences in observed effect sizes across time points. A non-significant, medium-small effect size (*d* = .375) was observed 1-8 days post-MTBI. Non-significant, small (*d* = .238) and medium-small (*d* = .312) were observed in the 9-30 and 31-89 day time strata. After 90 days, a significant, medium-small effect size was observed (*d* = .345). Between-study heterogeneity was evident across all time strata.

Fine Motor Movement. The analogue-to-ANOVA failed to reach statistical significance (*Q Between*(4) = 7.608, *p* = .107). A medium-large effect size was observed in the first 24 hours post-MTBI; however, this effect failed to reach significance, likely due to the small number of included studies. Similarly, the observed effect sizes for the remaining time strata failed to reach statistical significance (*d* range = .078 - .459).

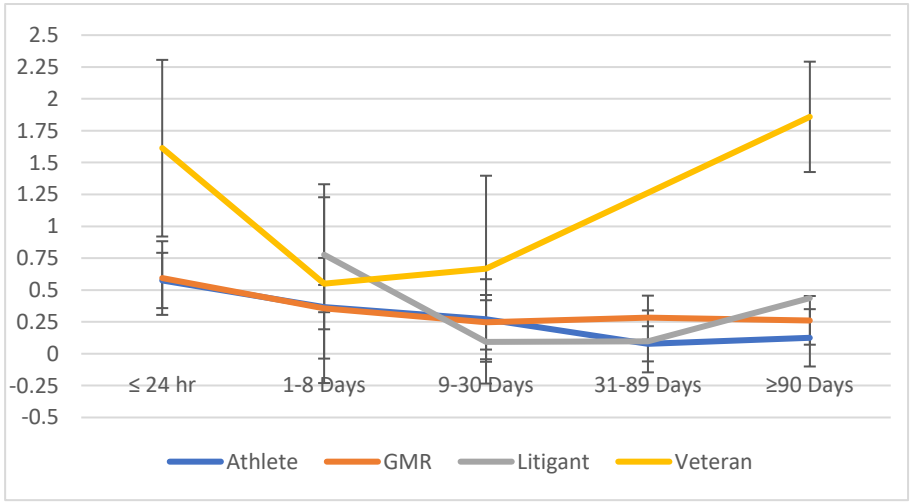
Population. Random effects Analogue-to-ANOVA was conducted to examine differences in overall cognitive functioning across different populations (See Table 7). In

Table 7
Overall Cognitive Dysfunction Post-MTBI Stratified by Time and Population

	≤ 24 Hours					1-8 Days					9-30 Days					31-89 Days					≥ 90 Days				
	k	d	95% CI	Q	I^2	k	d	95% CI	Q	I^2	k	d	95% CI	Q	I^2	k	d	95% CI	Q	I^2	k	d	95% CI	Q	I^2
Athletes	13	0.575*	.357-.792	49.64*	75.82	27	0.366*	.192-.540	65.76*	60.46	7	0.271	-.044-.585	25.74*	76.69	9	0.078	-.060-.216	13.02	38.56	13	0.125	-0.099-0.35	3.02	0.00
GMR	8	0.594*	.305-.883	18.96*	63.08	5	0.357	-0.038-0.752	5.22	23.43	18	0.247*	.033-.461	46.2*	63.21	9	.283*	.110-.456	4.92	0	18	0.262*	0.071-0.453	22.61	24.82
Litigants						3	0.777*	.291-1.264	57.79*	96.54	3	0.093	-.358-.544	4.39	54.45	2	0.097	-.230-.424	0	0	11	0.437*	0.193-0.68	29.81*	66.46
Veterans	1	1.613*	.920-2.306	-	-	1	0.55	-0.231-1.33	-	-	1	0.667	-.065-1.397	-	-						3	1.859*	1.425-2.292	35.1*	94.30
Q Between				8.022*					2.632					1.724					3.426					51.292*	

Notes. GMR = General Medical Referral
Values that are bolded and have an * indicate values with $p < .05$; Significance levels were not futher stratified

Figure 5.
Line Graph of Overall Cognitive Dysfunction Over Time by Population



contrast to the analyses reported above, there is no violation of independence as the between-study analyses did not examine the effects of time, but rather population membership.

In general, differences in sample population were found in the first 24-hours post-MTBI and after 90 days, with samples that included Veterans having the largest effect sizes. Samples that included athletes tended to have smaller effect sizes than samples with general medical referrals (GMR) in the post-acute periods after the injury; though these differences were not significant. Samples that included Veterans and individuals involved in litigation continued to have medium to large effect sizes 90 days after injury. *Hypothesis 2A, that differences across populations would be evident, was partially fulfilled.* More detailed analyses regarding the overall effect of sustaining an MTBI across various populations are provided below.

***Population: 24 Hours or Less Post-Injury*.** Medium effect sizes were observed for the athlete and GMR populations (d = .575 and .594, respectively). A very large effect size was observed for Veteran populations (d = 1.613), though this estimate was derived from a single study (French, McCrea, & Baggett, 2008). The analogue-to-ANOVA (Q *Between* (2) = 8.022, p = .018) was significant suggesting differences in in effect sizes across populations. The observed effect sizes for the GMR and athlete populations were similar in magnitude (Z = .104, p = .92). However, the effect size for the Veteran populations was significantly larger than the athlete and GRM populations (Z =2.80 and 2.66, all p's < .05). Significant between-study heterogeneity was observed for the athlete and GMR populations, with 63-75% of the variability unexplained. Given there was a

single study across the Veteran population, metrics of between-study heterogeneity cannot be calculated.

Population: 1-8 Days Post-Injury. The analogue-to-ANOVA failed to reach significance (*Q Between*(3) = 2.63, *p* = .45), suggesting no differences in observed effect sizes across populations. After 1-8 days, a medium-to-large effect size was observed for studies that include individuals involved in litigation (*d* = .777). A significant medium-small effect size was observed for studies that included athletes (*d* = .366), and a non-significant medium-small effect size was observed for GMR populations (*d* = .357). A medium, non-significant effect size was observed in the Veteran population, though only one study contributed to this effect. Significant between-study heterogeneity was observed the athlete and litigant populations, with 60-97% of the variability unexplained.

Population: 9-30 Days Post-Injury. The analogue-to-ANOVA failed to reach significance (*Q Between*(3) = 2.632, *p* = .452), suggesting no differences in observed effect sizes across populations 9-30 days post-MTBI. A small, significant effect size was observed for the GMR population (*d* = .247), while studies that included athletes also had a small effect that failed to reach significance (*d* = .271). A non-significant, medium-large effect size was observed in Veteran population (*d* = .667), though only a single study contributed to this estimate. Finally, a near-zero effect size was observed for studies that included individuals involved in litigation (*d* = .093). Significant between-study heterogeneity was evident for studies involving athletes and GRM with 63-80% of the variability left unexplained.

Population: 31-89 Days Post-Injury. The analogue-to-ANOVA failed to reach significance (*Q Between* (2) = 3.426, *p* = 0.18), suggesting no differences in observed

effect sizes across populations after 31-89 days post-MTBI. A near-zero effect size was observed for studies involving athletes (d = .078) and individuals involved in litigation (d = .097). A small, significant effect size was observed for studies involving GMR (d = .283). Significant between study-heterogeneity was evident in studies involving athletes, with 39% of the variance between studies left unexplained.

Population: 90 Days or More Post-Injury. The analogue-to-ANOVA was significant (Q *Between*(3) = 51.292, $p < .001$), suggesting differences in observed effect sizes across populations 90 days after injury. A near-zero effect size was observed for studies that involved athletes (d = .125). A small, significant effect size was observed for studies involving GRM (d = .262). A significant, medium-small effect size was observed for studies that included individuals involved in litigation (d = .437). A very large effect size was observed for studies involving Veterans (d = 1.895), which was significantly larger than the observed effect sizes across the other populations (all p's < .05). Significant between-study heterogeneity was observed for studies involving litigants and Veterans with 66-94% of the variability left unexplained.

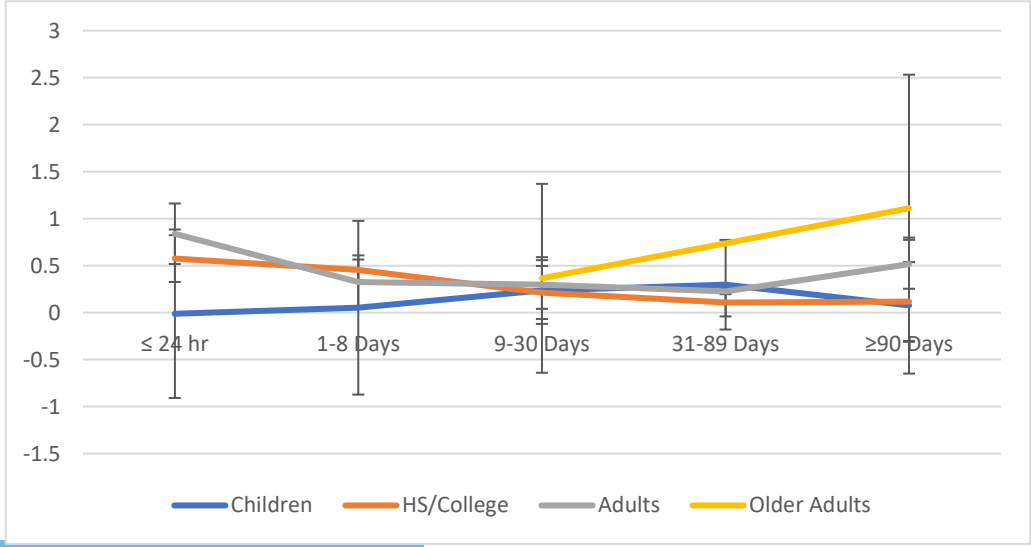
Age. A random-effects meta-analysis was conducted to compare the overall cognitive sequalae of sustaining an MTBI across different age groups and time points (See Table 7). In general, *consistent with Hypothesis 2B, there were no significant differences in the observed effect sizes across different age groups.* While the differences were not significant, samples that included older adults tended to have the largest effect sizes, followed by samples that included adults. Drawing conclusions about these apparent differences were difficult given the small number of studies in certain groups.

Table 8
Overall Cognitive Dysfunction Post-MTBI Stratified by Time and Age

	≤ 24 Hours					1-8 Days					9-30 Days					31-89 Days					≥ 90 Days				
	k	d	95% CI	Q	I^2	k	d	95% CI	Q	I^2	k	d	95% CI	Q	I^2	k	d	95% CI	Q	I^2	k	d	95% CI	Q	I^2
Children	1	-0.01	-.908-.884	-	-	1	0.052	-.872-.976	-	-	6	0.235	-.120-.590	11.04	54.72	2	0.297	-.179-.774	0.19	0.00	4	0.075	-0.648-0.798	2.07	0.00
HS/College	13	0.575*	.326-.824	49.64*	75.82	26	0.454*	.243-.565	126.58*	80.25	10	0.214	-.068-.496	26.52*	66.07	10	0.108	-.040-.256	14.09	36.12	11	0.119	-0.301-0.538	1.68	0.00
Adults	8	0.839*	.516-1.161	44.57*	84.30	9	.326*	.044-.609	11.86	32.53	12	0.299*	.041-.558	50.35*	78.15	8	0.226*	-.040-.256	5.30	0.00	29	0.514*	0.254-0.774	302.53*	90.74
Older Adults											1	0.365	-.636-1.37	-	-						1	1.110	-0.311-2.531	-	-
Q Between				3.757					1.155					0.254					1.347					4.201	

Notes. HS/College = High School and College
Values that are bolded and have an * indicate values with $p < .05$; Significance levels were not futher stratified

Figure 6.
Line Graph of Overall Cognitive Dysfunction Post-MTBI Over Time by Age



More detailed analyses regarding the age and the overall effects of sustaining an MTBI are provided below.

Age*: 24 Hours or Less Post-Injury*. The analogue-to-ANOVA failed to reach significance (*Q Between*(2) = 3.76, *p* = .15), suggesting no differences in overall effect size across age groups in the first 24 hours post-MTBI. A near-zero effect size was observed for the single study that included children (*d* = -.01). A significant, medium effect size was observed for studies that included samples with high school and college-aged students (*d* = .575). A significant, large effect size was observed with studies that included adults. Significant between-study heterogeneity was observed for studies that included high school and college-aged students as well as adults, with 76-84% of the variability left unexplained.

Age*: 1-8 Days Post-Injury*. The analogue-to-ANOVA failed to reach significance (*Q Between*(2) = 1.155, *p* = .561), suggesting no differences in overall effect size across age groups in the 1-8 days post-MTBI. A near-zero effect size was observed for the single study that included a sample of children (*d* = .052). Significant medium-small effect sizes were observed for studies that included high school and college-aged students (*d* = .454) and adults (*d* = .326). Significant between-study variability was observed for studies that included high school and college-aged students, with 80% of the variability left unexplained.

Age*: 9-30 Days Post-Injury*. The analogue-to-ANOVA failed to reach significance (*Q Between*(3) = 0.25, *p* = .0.97), suggesting no differences in overall effect size across age groups in the 9-30 days post-injury. Small, but non-significant effect sizes were observed in studies that included children (*d* = .235) and high school and college-

aged students (*d* = .214). A significant, medium-small effect size was observed in studies that included adults (*d* = .299). And a non-significant, medium-small effect size was observed in the single study that included older adults (*d* = .365). Significant between-study heterogeneity in studies that included high school and college-aged students and adults with 66-78% of variance in observed effect sizes within these groups left unexplained.

Age*: 31-89 Days Post-Injury*. The analogue-to-ANOVA failed to reach significance (*Q Between*(2) = 1.347, *p* = 0.51), suggesting no differences in overall effect size across age groups in the 31-89 days post-injury. Small, non-significant effect sizes were observed for samples that included children (*d* = .297) and high school and college-aged students (*d* = .108). A small, but significant effect size was observed for studies that included adults (*d* = .226). Between-study heterogeneity was not found across any of the age groups.

Age*: 90 Days or More Post-Injury*. The analogue-to-ANOVA failed to reach significance (*Q Between*(3) = 4.201, *p* = .241), suggesting no differences in overall effect size across age groups 90 days or more post-MTBI. A near-zero effect size and small, non-significant effect size was observed for studies that included children and high-school and college-aged students, respectively (*d* = .075 and .119). A medium effect size was observed in samples that included adults (*d* = .514) and a very large, but non-significant effect size was observed in the single study that included older adults (*d* = 1.110). Significant between-study heterogeneity was evident in studies that included adults, with 91% of the variance in observed effect sizes within these groups left unexplained.

Psychological Comorbidity. A random-effects analogue-to-ANOVA meta-analysis was conducted to examine the presence of psychological comorbidity on the overall cognitive effects of sustaining an MTBI (see Table 9). *Contrary to Hypothesis 2C, studies that included participants without comorbid mental health disorders did not have smaller effect sizes than studies where mental health disorders may have been present.* These unexpected findings may be the result of the methodological decisions regarding these data. That is, most studies were coded as "mixed" if the authors did not specifically note that subjects were included/excluded for having mental health disorders or if the composition fell anywhere between 1 and 99%. Additional details of the analyses are presented below.

Psychological Comorbidity*: 24 Hours or Less Post-Injury*. The analogue-to-ANOVA failed to reach statistical significance (Q *Between*(1) = 1.239, p = .266), suggesting there were no differences in the observed effect sizes between individuals with and without psychological comorbidities in the first 24 hours post-MTBI. A medium-small effect size was observed for studies where participants did not have psychological comorbidities (d = .428) and a medium-large effect size was observed in studies where psychological comorbidities were not excluded (d = .701). Significant between-study heterogeneity was evident in studies where participants had psychological comorbidities, with 84.34% of the variance in observed effect sizes within these groups left unexplained.

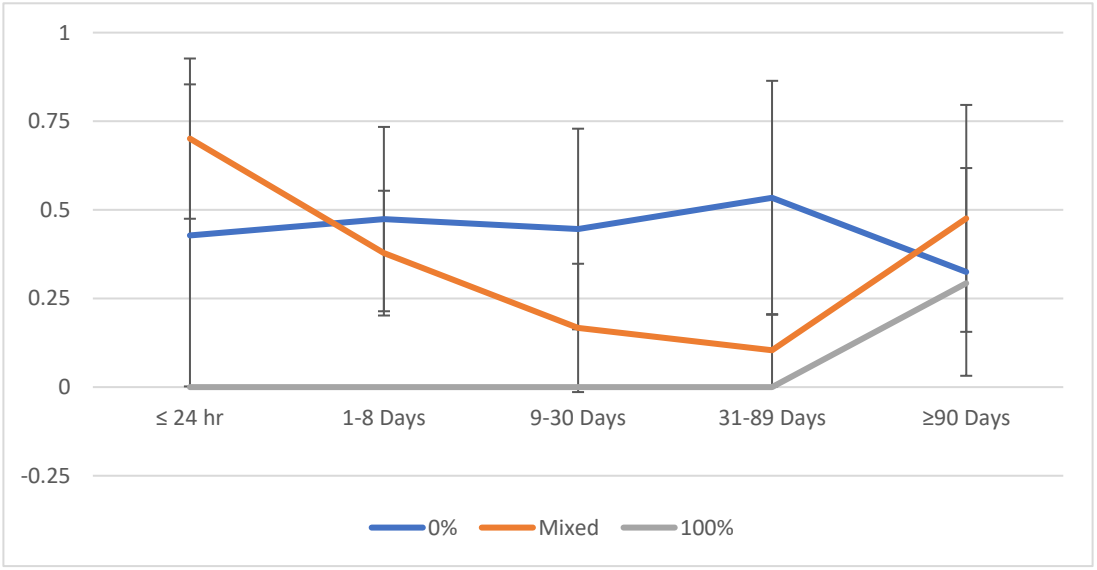
Psychological Comorbidity*: 1-8 Days Post-Injury*. The analogue-to-ANOVA failed to reach statistical significance (Q *Between*(1) = .362, p = .547), suggesting there were no differences in the observed effect sizes between individuals with and without

Table 9
Overall Cognitive Dysfunction Post-MTBI Stratified by Time and Psychological Comorbidity

	≤ 24 Hours					1-8 Days					9-30 Days					31-89 Days					≥ 90 Days				
	k	d	95% CI	Q	I^2	k	d	95% CI	Q	I^2	k	d	95% CI	Q	I^2	k	d	95% CI	Q	I^2	k	d	95% CI	Q	I^2
0%	5	0.428*	0.002-0.854	5.44	26.51	12	0.474*	0.215-0.734	22.28*	50.64	10	0.446*	0.162-0.729	14.90	39.58	4	0.534*	0.204-0.864	2.50	0.00	25	0.325*	0.033-0.618	28.69	16.34
Mixed	17	0.701*	0.476-0.927	102.19*	84.34	24	0.378*	0.202-0.554	116.24*	80.21	19	0.167	-0.013-0.348	66.7*	73.01	16	0.104*	0.002-0.206	13.55	0.00	19	0.476*	0.156-0.796	305.61*	94.11
100%																					1	0.293	-1.277-1.863	-	-
Q Between				1.239					0.362					2.639					5.954*					0.481	

Notes. Values that are bolded and have an * indicate values with p < .05; Significance levels were not futher stratified

Figure 7.
Line Graph of Overall Cognitive Dysfunction Post-MTBI Over Time by Psychological Comorbidity



psychological comorbidities 1-8 days post-MTBI. A medium-small effect size was observed in studies where subjects had no psychological comorbidities (d = .474) and studies where psychological comorbidities were not excluded (d = .378). For both groups, significant between-study heterogeneity was evident, leaving 50-80% of the variability in observed effect sizes within these groups left unexplained.

Psychological Comorbidity*: 9-30 Days Post-Injury.* The analogue-to-ANOVA failed to reach statistical significance (Q *Between*(1) = 2.64, p = .100), suggesting there were no differences in the observed effect sizes between individuals with and without psychological comorbidities 9-30 days post-MTBI. While the effect sizes did not significantly differ, there was an unexpected finding in which a significant small-medium effect size was observed in studies where participants did not have psychological comorbidities (d = .446); whereas, a small, non-significant effect size was observed for studies where psychological comorbidity may have been evident (d = .167). Significant between-study heterogeneity was evident for studies with mixed psychological comorbidities, leaving 73% of the variability in observed effect sizes within this group left unexplained.

Psychological Comorbidity*: 31-89 Days Post-Injury.* The analogue-to-ANOVA did reach statistical significance (Q *Between*(1) = 5.954, p = .015), suggesting there were differences in the observed effect sizes between individuals with and without psychological comorbidities 31-89 days post-MTBI. Contrary to expectation, the samples with no psychological comorbidities yielded a significantly larger effect size (d = .534) than studies that included participants with psychological comorbidities (d =.104). Significant between-study heterogeneity was not evident.

Psychological Comorbidity*: 90 Days or More Post-Injury.* The analogue-to-ANOVA failed to reach statistical significance (*Q Between*(2) = .481, *p* = .786, suggesting there were no differences in the observed effect sizes between individuals with and without psychological comorbidities after 90 days post-MTBI. Medium-large effect sizes were observed for studies where participants did not have psychological comorbidities (*d* = .325) and studies where psychological comorbidities may have been evident (*d* = .476). A small, non-significant effect size was observed for the single study where all study participants had a comorbid mental health disorder (*d* = .293). Significant between-study heterogeneity was evident for studies where psychological comorbidities were not excluded, leaving 94% of the variability in observed effect sizes within this group left unexplained.

Performance Validity Testing. A random-effects analogue-to-ANOVA meta-analysis was conducted to examine if the utilization of PVTs on the overall cognitive effects of sustaining an MTBI (see Table 10). *In general, the results showed no significant differences in observed effect sizes between groups, contrary to Hypothesis 2D. While the differences did not reach statistical significance, studies that utilized PVTs tended to have smaller effect sizes than studies that did not screen for suboptimal effort with PVTs*. Further details of the analyses are outlined below.

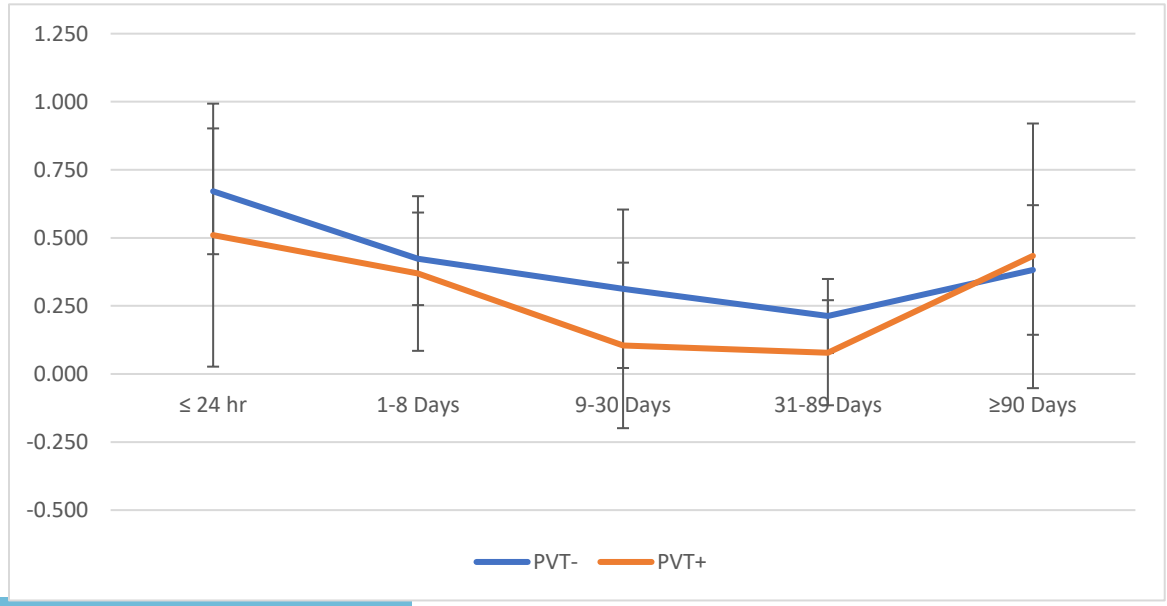
***PVT: 24 Hours or Less Post-Injury*.** The analogue-to-ANOVA failed to reach statistical significance (*Q Between*(1) = .347, *p* = .556, suggesting there were no differences in the observed effect sizes between studies that did and did not utilize PVTs in the first 24 hours post-MTBI. A medium effect size was observed for studies that utilized PVTs (*d* = .510) and a medium-large effect size was observed for studies that did

Table 10
Overall Cognitive Dysfunction Post-MTBI Stratified by Time and Performance Validity Testing

	≤ 24 Hours					1-8 Days					9-30 Days					31-89 Days					≥ 90 Days				
	k	d	95% CI	Q	I^2	k	d	95% CI	Q	I^2	k	d	95% CI	Q	I^2	k	d	95% CI	Q	I^2	k	d	95% CI	Q	I^2
PVTs Not Used	18	0.671*	0.441-0.902	100.27*	83.05	27	0.423*	0.252-0.593	113.12*	77.01	22	0.313*	0.123-0.504	55.77*	62.35	13	0.213*	0.076-0.349	20.79	42.29	37	0.382*	0.143-0.62	321.47*	88.80
PVTs Used	4	0.51*	0.028-0.993	15.8*	81.01	9	0.369*	0.086-0.653	25.95*	69.18	7	0.105	-0.198-0.409	34.58*	82.65	7	0.078	-0.115-0.271	0.34	0.00	8	0.434	-0.052-0.92	14.41*	51.43
Q Between				0.347					0.1					1.299					1.252					0.036	

Notes. PVT = Performance Validity Test
Values that are bolded and have an * indicate values with $p < .05$; Significance levels were not futher stratified

Figure 8.
Line Graph of Overall Cognitive Dysfunction Post-MTBI Over Time by Performance Validity Testing



not utilize PVTs (*d* = .671). Significant between-study heterogeneity was evident, with 81-83% of the variability in observed effect sizes within each group left unexplained.

PVT: 1-8 Days Post-Injury. The analogue-to-ANOVA failed to reach statistical significance (*Q Between*(1) = 0.100, *p* = .752), suggesting there were no differences in the observed effect sizes between studies that did and did not utilize PVTs 1-8 days post-MTBI. Small-medium effect sizes were observed for studies that did utilize PVTs (*d* = .369) and for studies that did not utilize PVTs (*d* = .423). Significant between-study heterogeneity was evident for both groups, leaving 68-77% of the variability in observed effect sizes within each group left unexplained.

PVT: 9-30 Days Post-Injury. The analogue-to-ANOVA failed to reach statistical significance (*Q Between*(1) = 1.30, *p* = 0.25), suggesting there were no differences in the observed effect sizes between studies that did and did not utilize PVTs 9-30 days post-MTBI. A small-medium effect size was observed for studies that did not utilize PVTs (*d* = .313), whereas a small, non-significant effect size was observed for studies that utilized PVTs (*d* = .105). Significant between-study heterogeneity was observed for both groups, with 62-85% of the variability in observed effect sizes within each group left unexplained.

PVT: 31-89 Days Post-Injury. The analogue-to-ANOVA failed to reach statistical significance (*Q Between*(1) = 1.252, *p* = 0.263), suggesting there were no differences in the observed effect sizes between studies that did and did not utilize PVTs 31-89 days post-MTBI. A small, significant effect size was observed for studies that did not utilize PVTs (*d* = .213), whereas a non-significant, near-zero effect size was observed

for studies that utilized PVTs (d = .078). Significant between-study heterogeneity was not observed for either group.

PVT: 90 Days or More Post-Injury. The analogue-to-ANOVA failed to reach statistical significance (Q *Between*(1) = .036, p = 0.85), suggesting there were no differences in the observed effect sizes between studies that did and did not utilize PVTs 90 days after injury. A significant small-medium effect size was observed for studies that did not utilize PVTs (d = .382), whereas a non-significant, small-medium effect size was observed for studies that utilized PVTs (d = .434). This seemingly incongruous findings that the larger effect size (PVTs used) failed to reach significance is likely an issue of power as only 8 studies were included; whereas, 37 studies were included in the former analysis. Significant between-study heterogeneity was not observed for both groups, with 51-89% of the variability in observed effect sizes within each group left unexplained.

Aim 1 Summary. When considering a heterogenous population and not stratifying based on moderator variables, medium to large effect sizes were observed across all cognitive domains in the acute stages of MTBI recovery. The effect size decreased over the first 90 days. Contrary to expectation, the overall effect size appeared to increase 90 days after injury. Subsequent analyses suggested this was likely driven by the medium and very large effect sizes observed in studies during this time strata that included individuals involved in litigation and Veterans, respectively. Across most time strata, significant differences were not observed across age categories, studies that utilized PVTs, and the composition of psychological comorbidities.

Hypothesis 1: *Consistent with the previous literature, a medium overall effect is expected in the acute period post-MTBI that will fail to reach significance after three months*. This

hypothesis was partially supported. A medium overall effect was observed in the acute stages, but it remained significant and increased after three months.

Hypothesis 2: *It is expected that (a) effect sizes will differ across the different "populations;" (b) effect sizes will not differ for the different age groups (c) effect sizes will differ for individuals with psychological comorbidities (d) effect sizes will differ for studies where effort testing is implemented.* This hypothesis was partially upheld. Between-group differences were observed across the different populations (a) and effect sizes did not generally differ across age groups (b). Contrary to expectation, neither psychological comorbidities (c) nor utilization of PVTs (d) resulted in differences in observed effect sizes.

Hypothesis 3: *Despite stratifying by these different effect modifiers and performing multiple sub-group analyses, it is hypothesized that between-study heterogeneity will still exist*. This hypothesis was upheld. Across most comparisons, significant between-study heterogeneity was evident, with I^2 values as high as 94%. This suggests that stratifying by an effect modifier across different time points is not sufficient to explain the variability observed across the heterogenous population.

Aim 2: Meta-Regression Analyses

A random-effects meta-regression was conducted utilizing the furthest, most non-acute time point from each study, yielding 152 unique observations. Variables of interest were first entered into the regression equation alone. Then, all significant variables were entered into a single regression model (See Table 11; Etnier et al., 2006; Lee et al., 2012).

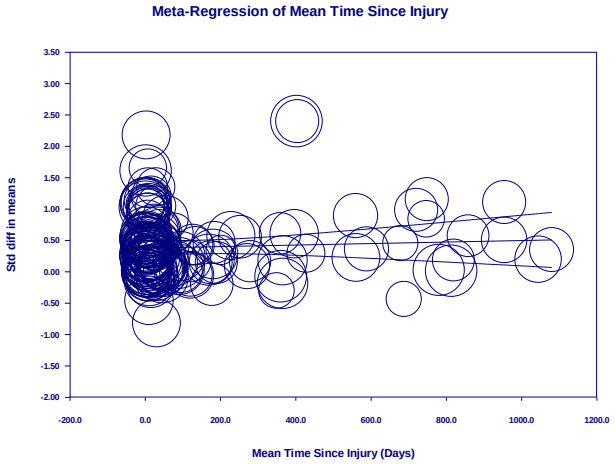
Table 11
Meta-Regression Models Predicting Overall Neurocognitive Dysfunction After MTBI

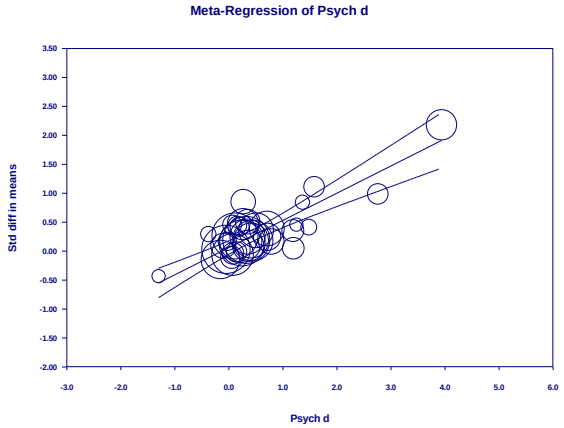
	Model 1			Model 2			Model 3			Model 4			Model 5			Model 6			Model 7		
	B	SE	t	B	SE	t	B	SE	t	B	SE	t	B	SE	t	B	SE	t	B	SE	t
Intercept	0.395	0.044	9.06***	0.393	0.062	6.30***	0.222	0.117	1.89	0.287	0.087	3.28***	0.062	0.046	0.183	0.338	0.056	6.01***	0.437	0.244	1.79
MTSI	0	0	0.67	0	0	0.23															
$MTSI^2$				0	0	0.06															
Age							0.007	0.005	1.55												
PVT										0.143	0.101	1.42									
Psych d													0.47	0.052	9.01***				0.457	0.054	8.51***
Population																F(3,148) = 9.76***			F(3, 31) = 1.55		
GMR																-0.012	0.085	-0.14	-0.414	0.247	-1.68
Litigant																0.08	0.121	0.66	-0.303	0.251	-1.21
Veteran																0.976	0.185	5.26	-0.626	0.403	-1.55
k		152			152			144			152			36			152			36	
Model F		0.04			0.22			2.39			2.01			81.18***			9.76***			21.46***	
Q		805.29***			803.19***			771.05***			803.23***			24.1			592.06***			19.45	
I^2		81.37%			81.45%			81.58%			81.33%			0.01%			81.28%			0.01%	
R^2 Analog		0.00			0.00			0.01			0.01			0.99			0.30			0.99	

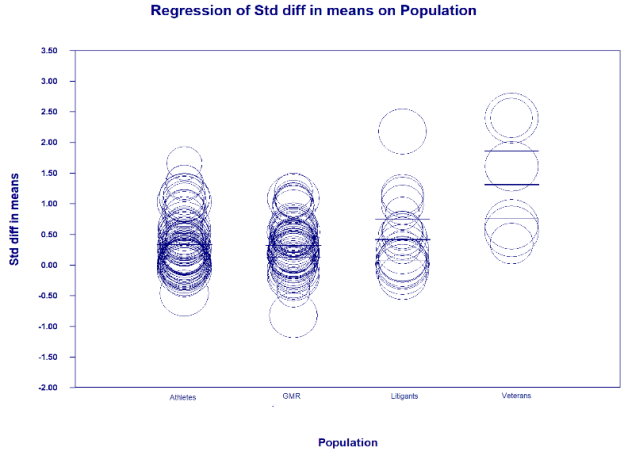
Notes. MTSI = Mean Time Since Injury; PVT = Performance Validity Testing; GMR = General Medical Referall; Psych d = The effect size of psychological distress
For PVT, the reference group is studies that utilized PVTs to screen for adequate effort; For Population, the reference group were studies that included Athletes
* = $p < .05$; ** = $p < .01$; *** = $p < .001$

Figures 9-11

Scatterplots of Moderator Variables and Overall Cognitive Dysfunction







Note. The size of the circles in the plot represent the relative weight each study has on the overall observed effect size

Time Since Injury. The average amount of time that had passed since sustaining an MTBI was entered into the regression equation as a continuous variable (Models1and 2). For the linear and non-linear models, the data were centered about the mean of 138.09 days. Contrary to expectation, neither the linear nor quadratic (i.e., $Time^2$) equation for mean time since injury was a significant predictor of the overall effect size ($F(1,150) = 0.44$, $p = .51$; $F(1,150) = .022$, $p = .80$). This unexpected finding is likely due to increasing observed effect size after 90 days that was observed in analysis from Aim 1 (see Figure 4). For both models, nearly 0% of the between-study variability is explained by the models (R^2 Analog = 0.01 for both models). Given that time since injury is not a significant predictor, it was not entered into subsequent regression analyses as proposed.

Age. The average age of the study samples was entered into the regression equation as a continuous variable (Model 3). Consistent with Aim 1 analyses, this model failed to reach statistical significance ($F(1,142) = 2.39$, $p = .12$) and again almost no between-study variability explained by the model (R^2 Analog = 0.01).

PVT. Performance validity testing was entered into the regression equation as a categorical variable (Model 4). Studies that utilized performance validity testing to exclude subjects with sub-optimal effort was used as the reference group. Consistent with Aim 1 analyses, this model failed to reach statistical significance ($F(1,150) = 2.01$, $p = .16$). Almost no between-study variance was explained by the model (R^2 Analog = 0.01).

Psychological Functioning. A regression model using the composition of psychological comorbidities as a categorical variable (0%, mixed, 100%) was first entered into a meta-regression (not modelled). Consistent with the results of Aim 1, the model failed to reach statistical significance ($F(2,149) = .06$, $p = .9448$).

Next, the overall effect size of self-reported psychological functioning across all domains (e.g., depression, anxiety, SUD) was entered into the regression equation as a continuous variable (Model 5; Figure 5). There was one observed outlier that was > 3 standard deviations above the average of all effect sizes (d = 13.289). It was trimmed to the next nearest group of effect sizes (d = 4.05). This model reached statistical significance ($F(1,34) = 81.18$, $p < .001$). Based on this model, studies where the differences in psychological functioning between the MTBI and control group was almost non-existent (Psych d = 0.00) or the differences were small (Psych d = 0.20) a small-medium effect size was predicted (d = .338 and .432, respectively). When the effect size in self-reported psychological functioning between MTBI and control groups is medium (Psych d = .50), then a medium effect size for cognitive functioning is predicted (d = .573). When the differences in psychological wellbeing between the two groups are large (Psych d = .80), the predicted effect size is medium-large (d = .714). This model explains nearly 100% of the between-study variance (R^2 Analog = .99). While this model was extremely predictive, it is worth noting that this analysis included a minority (k = 36) of the extracted studies.

Population. Population membership (i.e., Athlete, Veteran, GMR, Litigant), was entered into the meta-regression as a categorical variable with studies that included athletes as the reference group (Model 6; Figure 6). Athletes were selected as the reference group based on *a priori* knowledge that athletes tend to recovery faster than other populations after an MTBI (Belanger, Curtiss, et al., 2005; Belanger & Vanderploeg, 2005). The overall model was significant ($F(3,148) = 9.76$. $p < .001$). However, of the sub-groups, only studies that included Veterans was a significant

predictor (t(148) = 5.26, $p < .001$), suggesting studies that included individuals involved in litigation and GRM did not differ in observed effect size from athletes. Based on the model, a small-medium overall cognitive effect size ($d = .338$) is observed for athletes after sustaining an MTBI, whereas a very large effect size ($d = 1.314$) is observed for Veterans who sustain an MTBI. This model explains 30% of the between-study variance (R^2 Analog = .30). A Time x Population interaction, however, failed to reach significance (F(4, 147) = 1.19, $p = 0.31$).

Combined Models. A regression model with self-reported psychological functioning (Psych *d*) and population membership were simultaneously entered into the regression equation (Model 7). The overall model was significant (F(4,31) = 21.46, $p < .001$) with nearly all of the between-study variance explained by the model (R^2 Analog = .99). The observed differences in psychological well-being between MTBI and control groups (Psych *d*) was a significant predictor (t(31) = 8.51, $p < .001$), whereas population membership was not a significant predictor (F(3,31) = 1.55, *p* .221). Similar to Model 5, no differences in self-reported psychological functioning between the MTBI and control groups (Psych $d = 0.00$) resulted in a small-medium overall cognitive effect size ($d = .437$). Small (Psych $d = .20$) and medium (Psych $d = .50$) differences in psychological functioning resulted in medium predicted effect size of overall cognitive functioning ($d = .528$ and .665, respectively). Large differences in psychological well-being (Psych $d = .80$) resulted in a large predicted effect size of overall cognitive functioning ($d = .802$).

Aim 2 Summary. A meta-regression to control for potential between-study heterogeneity and quantify the effect of covariates on the overall neuropsychological functioning post-MTBI was conducted. Surprisingly, the mean time since sustaining an

MTBI was not a significant predictor; though this is likely due the increase in observed effect sizes in the chronic periods (> 90 days) post-MTBI. Consistent with Aim 1 analyses, the age of the study sample and the utilization of PVTs were not significant predictors. This differences in self-reported psychological functioning was a significant predictor that explained most between-study variance. Population was a significant predictor, with Veterans exhibiting larger effect sizes than athletes. However, population was not a significant predictor when simultaneously entered into the regression equation with psychological functioning. Overall, across heterogenous populations, the biggest predictor of over overall cognitive functioning post-MTBI is psychological functioning.

Hypothesis 4: *When entered into a meta-regression, time since injury, psychological comorbidities, and PVT testing will be significant covariates. Effect sizes are expected to decrease over time but increase in the presence of psychological comorbidities and increase if PVT are not implemented. Whereas, population and age will not reach significance.* This hypothesis was partially upheld. Psychological functioning was a significant predictor of overall cognitive effect size. As predicted, the average age of the study sample was not a significant predictor, and population membership was not a significant predictor after controlling for psychological functioning. However, mean time since injury and utilization of PVTs were not significant predictors.

Supplemental Analyses

Meta-Regression for Acute-Only Studies. Given the unexpected finding that the average time since injury was not a significant predictor over overall neurocognitive dysfunction, exploratory analyses examined the predictive ability of the various effect moderators in the acute (< 90 days) and post-acute (> 90 days) periods post-MTBI. Table

12 displays the results of the meta-regression models when considering studies in the acute phase, only.

In contrast to the model that include all time points, mean time since injury is a significant predictor in the meta-regression model for the acute-period, only (Model 1; $F(1, 106) = 7.49$, $p < .01$). Based on this model, a medium effect size is observed in the first 24 hours after injury ($d = .490$), which drops to a small effect size ($d = .20$) 41 days post-MTBI.

When controlling for average time since injury, neither age ($t(99) = 0.92$, $p > .05$) nor utilization of PVTs ($t(106) = 1.69$, $p > .05$) were significant predictors of overall neurocognitive dysfunction in the first 90 days after sustaining an MTBI (Model 2, Model 3). Consistent with the previous models, psychological functioning was a significant predictor ($t(19) = 7.96$, $p < .001$) with nearly all between-study variability accounted for by the model (R^2 Analog = .99). When entered into the same model with psychological functioning, mean time since injury fails to reach significance (Model 4; $t(19) = 0.42$, $p > .05$)[5]. In contrast to the previous models, population membership was not a significant predictor of overall neurocognitive dysfunction in the acute periods post-MTBI ($F(3, 102) = 1.93$, $p > .05$). This may be due to the absence of studies with Veteran populations, which was a significant predictor in the previous models.

[5] It is worth noting that CMA 3 eliminates studies in a list-wise fashion. When considering the 20 studies that included measures of psychological functioning, mean time since injury, by itself, was not a significant predictor. Thus, the lack of significance of time to be a significant predictor is not necessarily an indication that psychological functioning accounting for all of the variability, making time since injury non-significant.

Table 12

Meta-Regression Models Predicting Overall Neurocognitive Dysfunction in the First 90 Days Post-MTBI

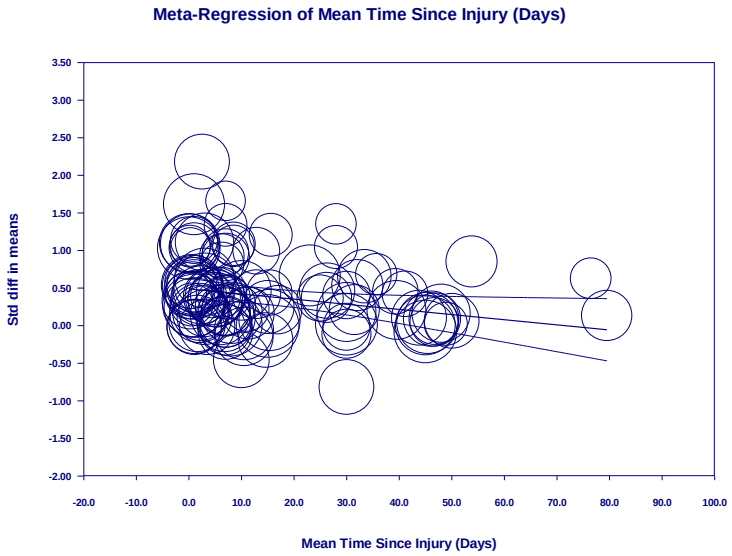
	Model 1			Model 2			Model 3			Model 4			Model 5		
	B	SE	t	B	SE	t	B	SE	t	B	SE	t	B	SE	t
Intercept	0.49	0.057	8.56***	0.378	0.128	2.95**	0.365	0.094	3.90***	0.027	0.091	0.3	0.459	0.067	6.90***
MTSI	-0.007	0.003	-2.74**	-0.007	0.003	-2.56*	-0.007	0.003	-2.59**	0.001	0.003	0.42	-0.007	0.003	-2.61**
Age				0.005	0.005	0.92									
PVT							0.164	0.097	1.69						
Psych d										0.512	0.064	7.96***			
Population													F(3,102) = 1.93		
GMR													0.004	0.093	0.04
Litigant													0.032	0.157	0.21
Veteran													0.536	0.225	2.38
k		107			100			107			20			107	
Model F		7.49**			3.60*			5.14**			32.30***			3.40*	
Q		410.2***			384.16***			409.63***			17.72			468.2***	
I^2		74.40%			74.75%			77.36%			4.05%			77.36%	
R^2 Analog		0.14			0.15			0.13			0.99			0.22	

Notes. MTSI = Mean Time Since Injury; PVT = Performance Validity Testing; GMR = General Medical Referall*;* Psych d = The effect size of psychological distress

For PVT, the reference group is studies that utilized PVTs to screen for adequate effort; For Population, the reference group were studies that included Athletes

* = $p < .05$; ** = $p < .01$; *** = $p < .001$

Figure 12
Scatterplots of Time Since Injury and Acute Overall Cognitive Dysfunction



Note. The size of the circles in the plot represent the relative weight each study has on the overall observed effect size

Meta-Regression for Post-Acute Studies. Meta-regression models were conducted when considering studies in the post-acute periods after sustaining an MTBI (> 90 days) and results are described below.

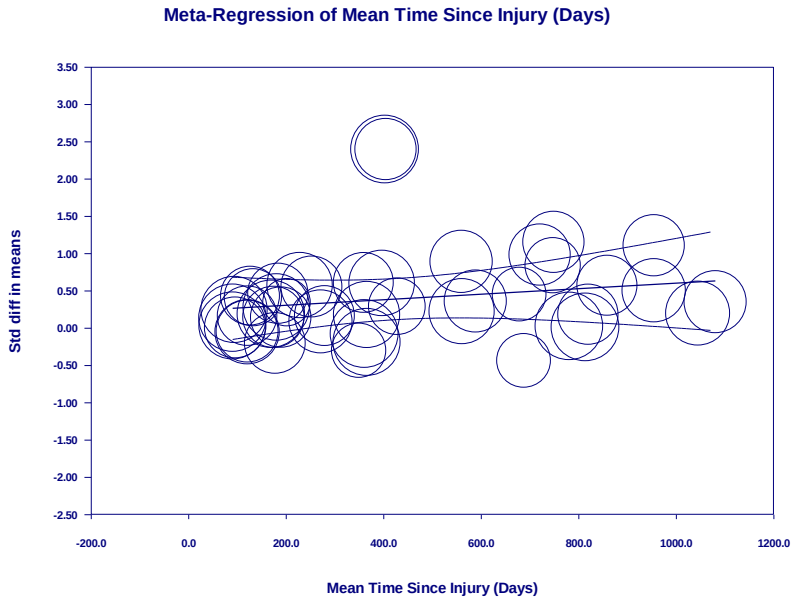
Mirroring the results from meta-regression model with all time points considered, the models with time since injury ($F(1, 44) = 1.02$, $p > .05$), age ($F(1, 43) = 1.81$, $p > .05$), or the utilization of PVTs ($F(1, 44) = .04$, $p > .05$) failed to reached statistical significance. Similar to the earlier models, psychological functioning ($F(1, 15) = 14.35$, $p < .001$) and population ($F(3, 41) = 17.01$, $p < .001$) were significant when these variables were modeled alone. When both variables were entered into the same equation, psychological functioning remained a significant predictor ($t(15) = 3.81$, $p < .01$), whereas population membership failed to reach significance ($F(3, 11) = 0.22$, $p > .05$).

Table 13
Meta-Regression Models Predicting Overall Neurocognitive Dysfunction 90 Days or More After MTBI

	Model 1			Model 2			Model 3			Model 4			Model 5			Model 6		
	B	SE	t	B	SE	t	B	SE	t	B	SE	t	B	SE	t	B	SE	t
Intercept	0.234	0.191	1.22	0.024	0.298	0.08	0.434	0.248	1.75	0.087	0.074	1.17	0.125	0.115	1.09	-0.18	0.471	-0.38
MTSI	0	0	1.01															
Age				0.013	1.35	0.185												
PVT							-0.052	0.276	-0.19									
Psych d										0.372	0.098	3.79**				0.401	0.105	3.81**
Population													F(3,41) = 17.10***			F(3,11) = 0.22		
GMR													0.137	0.15	0.91	0.266	0.47	0.57
Litigant													0.311	0.169	1.84	0.272	0.467	0.58
Veteran													1.733	0.249	6.96***	0.059	0.549	0.11
k		45			44			45			16			45			16	
Model F		1.02			1.81			0.04			14.35**			17.10***			3.75*	
Q		335.48***			334.67***			335.88***			19.08			337.43***			4.06	
I^2		87.18%			87.45%			86.96%			21.38%			86.96%			0.01%	
R^2 Analog		0.01			0.01			0.01			0.99			0.80			0.99	

Notes. MTSI = Mean Time Since Injury; PVT = Performance Validity Testing; GMR = General Medical Referall; Psych d = The effect size of psychological distress
For PVT, the reference group is studies that utilized PVTs to screen for adequate effort; For Population, the reference group were studies that included Athletes
* = $p < .05$; ** = $p < .01$; *** = $p < .001$

Figure 13
Scatterplots of Time Since Injury and Post-Acute Overall Cognitive Dysfunction



Note. The size of the circles in the plot represent the relative weight each study has on the overall observed effect size

Demographic Variables: Neither the meta-regression model with the mean education level as a covariate($F(1,85) = 1.49$, $p = .225$), percentage of females included in the study sample ($F(1,139) = .13$, $p = .717$), nor the percent of ethnic minorities included in the study sample ($F(1,45) = .17$, $p = .069$) were significant predictors of the overall cognitive effect size post-MTBI.

Injury Parameters. Neither the meta-regression model with the percentage of individual who reported LOC as a covariate ($F(1,63) = .01$, $p = .928$) nor the percentage of individuals who reported PTA ($F(1,45) = 1.75$, $p = .193$) reached statistical significance.

Post-Concussive Symptomology. Seven studies had two independent sub-groups comprised of individuals who were identified as having PCS and individuals who did not have PCS. A large overall cognitive effect was observed in the sub-groups that included individuals with PCS (d = .890 after average of 167.2 days) and a medium-large effect was observed in the sub-group of participants who did not report PCS (d = .649 after average of 168.4 days). However, the Analogue-to-ANOVA failed to reach significance (Q *Between*(1) = .155, p = .693), suggesting no difference between the two groups.

In contrast, the effect size of self-reported PCS in the MTBI group relative to the control group did significantly predict the overall neurocognitive effect size, with 76% of the between-study variability accounted for by the covariate (See Table 14; Model 1). However, this variable failed to reach significance once psychological functioning was entered into the model simultaneously (Model 2).

Study Characteristics: Consistent with previous studies, there was a significant difference in the observed effect sizes based on the control groups (Q *Between*(4) = 12.469, p = .014). Studies with non-injured control groups (d = .497) yielded an effect size that was significantly larger than the effect size from all other control groups. Control groups that consisted of individuals with orthopedic injuries yielded the next largest effect size (d = .257), though the magnitude of this effect was not significantly larger than any of the estimated effect sizes from other control groups. Studies that utilized both non-injured controls and pre-injury baselines yielded the next highest effect size (d = .216), though this failed to reach significance. The studies utilizing individuals who sustained a trauma and individuals with chronic pain as their control group yielded small, non-significant effect sizes (d = .038 and -0.063, respectively).

Table 14
Meta-Regression Models Predicting Overall Neurocognitive Dysfunction After MTBI

	Model 1			Model 2		
	B	SE	t	B	SE	t
Intercept	-0.031	0.047	0.508	0.013	0.07	0.19
PCS d	0.393	0.043	9.03***	-0.013	0.15	-0.08
Psych d				0.521	0.162	3.21**
k		73			22	
Model F		81.47***			36.28***	
Q		113.81***			10.32	
I^2		37.62%			1.00%	
R^2 Analog		0.76			0.99	

Notes. PCS = Post-Concussive Symptomology; Psych d = the effect size indicating overall psychological functioning
* = $p < .05$; ** = $p < .01$; *** = $p < .001$

Table 15.
Overall Cognitive Dysfunction Post-MTBI Stratified by Control Group

	k	d	95% CI	Q	I^2
Non-Injured Control	100	0.497***	.394-.599	499.055***	80.163
Non-Injury Control & Pre-Injury Baseline	14	0.216	-.030-.463	36.788***	64.663
Orthopedic Injury	30	0.257**	.080-.435	132.047***	78.038
Chronic Pain	3	-0.063	-.601-.475	18.237***	89.033
Trauma Control	3	0.038	-.517-.592	0.702	0.01
Q Between	12.469*				

Notes. * = $p < .05$; ** = $p < .01$; *** = $p < .001$

Discussion

Mild traumatic brain injuries are a significant public health issue with respect to pervasiveness (Cassidy et al., 2004) and economic burden (Ma et al., 2014; Max et al., 1991). While it is well documented that many individuals recover from MTBI in as little as nine days (e.g., McCrea, 2008), there are others who take up to 3 months for complete neurocognitive recovery (e.g., Belanger, Curtiss, et al., 2005), and still others who fail to return to their cognitive baseline years after their injury (Ruff, Camenzuli, & Mueller, 1996). Emerging research has identified a multitude of factors that might contribute to protracted cognitive recovery from MTBI. However, due to differences in study methodology, discrepant findings are pervasive in this broad literature, which creates challenges for clinical researchers and healthcare professionals in management of MTBI. Due to the number of potential factors that are likely to modify cognitive recovery, empirical studies controlling for each of these factors would be difficult. Rather, quantitative reviews have attempted to elucidate the effects of such variables (e.g., Belanger, Curtiss, et al., 2005; Belanger & Vanderploeg, 2005; Dougan et al., 2014). These studies have been instrumental in furthering our understanding MTBI recovery across different variables of interest. However, these meta-analytic studies examined homogenous populations with restricted time frames, somewhat limiting their generalizability.

The present study was an updated quantitative review of the MTBI literature that simultaneously utilized traditional and contemporary meta-analytic techniques. This study sought to determine how demographic factors (e.g., age), individual differences (e.g., psychological functioning), and study designs (e.g., utilization of PVTs) might

explain the apparent differences in neurocognitive recovery from MTBI across a heterogenous population (e.g., athletes, Veterans, GMR, litigants). Capitalizing on the recent explosion of literature, this study is the largest MTBI meta-analytic review to date.

Aim 1

The first aim of this study was to utilize traditional meta-analytic techniques to determine if differences in observed effect sizes differed across various moderator variables of interest. This was done by conducting multiple analyses via Analogue-to-ANOVA across each time point and effect modifier. Regarding overall neurocognitive dysfunction, a medium-large effect size was observed in the initial 24 hours post-MTBI that decreased to a small effect size over the first 90 days. Contrary to expectation, however, the observed effect size appeared to increase from small to small-medium for studies where assessments were conducted 90 days post-injury. This, however, was likely driven by the larger proportion of studies with samples consisting of Veterans and individuals involved in litigation in this time strata (k = 14 of 45). Effect sizes across cognitive domains followed this general pattern with significant effect sizes for every domain except orientation and fine motor movement after 90 days post-injury.

While this finding is surprising, it is not unique within the meta-analytic literature. In Belanger, Curtiss, and colleagues' (2005) meta-analysis, which included a heterogenous clinical sample (individuals involved in litigation, prospectively recruited patients, and patients selected due to continued symptom report), significant effect sizes were observed, even in the post-acute (>90 day) periods across nearly all cognitive domains (*d* range =.15 to .71). After multiple pair-wise analyses were conducted, the authors determined that this effect was driven by an increase in observed effect sizes

from individuals involved in litigation and patients recruited due to persistent symptomology. Similarly, the overall effect sizes in the present study diminish with time until the most post-acute time point (> 90 days) when there were a larger number of studies that included individuals involved in litigation and Veterans.

Further moderator analyses in Aim 1 sought to examine differences in the observed effect size of overall cognitive functioning across various effect modifiers. Consistent with expectation, differences in observed effect sizes were evident across the various populations of interest (i.e., athletes, Veterans, GRM, litigants), with studies that included Veterans having a significantly larger effect sizes than studies that included other populations. This is unsurprising given the exceedingly high rate of psychological comorbidities that accompany Veterans post-deployment (Brenner et al., 2010), MTBI might not be treated or detected in combat theater in favor of treating other injuries (Belanger, Scott, et al., 2005), and the inherent medicolegal nature of obtaining medical services for US Veterans.

Similar to Belanger, Curtiss, and colleagues' (2005) study, the observed effect size for studies with litigant populations increased in the post-acute (> 90 days) periods after an MTBI. For reasons not entirely clear, the observed effect sizes in the present study for this population in the post-acute period (> 90 days) is meaningfully smaller than what was observed in Belanger's study (d = .437 vs .777). This may due to methodological differences in the authors using a fixed-effect analysis, which tends to lead to higher effect sizes. More likely, this is due to the author's decision to include studies with complicated MTBI, which were excluded in the present study. Complicated MTBI (i.e., evidence of skull fracture or brain hemorrhage), has a prolonged recovery

course more like moderate TBI than MTBI. The smaller-than-expected effect size for litigant samples may explain why the differences in effect size between litigant, GRM, and athlete samples only trended towards significance. While the observed effect sizes were not statistically smaller than litigant samples, the effect sizes for athlete samples failed to reach significance after 8 days, which is consistent with the well-established empirical literature (Belanger & Vanderploeg, 2005; Dougan et al., 2014; McCrea, 2008).

There is an increased recognition of the importance of administering PVTs during clinical evaluations to detect suboptimal effort, which may confound results (Chafetz et al., 2015). While studies that screened for invalid performance yielded smaller effect sizes than studies that did not utilize PVTs, unexpectedly, these differences failed to reach statistical significance at any timepoint. However, a similar pattern was found in Belanger and Curtis' (2005) analysis. For studies that involved litigant samples, they found that the studies that screened for insufficient effort had a smaller observed effect size (d = .50) than studies that did not utilize PVTs (d = .66), though this difference failed to reach significance. Most striking is the overwhelming majority of studies (77%) that reported no utilization of PVTs to screen for poor effort despite multiple professional organizations imploring their utilization in clinical work and research (e.g., Chafetz et al., 2015).

It is clear that most of the MTBI research included in these analyses focused on adolescents and adults, which is problematic given that that children aged 0-4 years and adults aged 75 are particularly prone to head injuries (Faul et al., 2010). Given the discrepancy in empirical findings (e.g., Anderson et al., 2001; Grubenhoff et al., 2010; Ponsford et al., 1999), it was important to evaluate age as a potential effect modifier ,

Consistent with our hypotheses, age was not a significant predictor of neurocognitive dysfunction post-MTBI. Notably, however, there was a much smaller percentage of studies in the present study that included pediatric and geriatric populations. Thus, it is difficult to make definitive conclusions regarding the effect of age from the present analysis.

Unexpectedly, studies that excluded individuals with psychological or psychiatric comorbidities did not yield higher effect sizes than studies where comorbidities were excluded or presumed to exist. This finding is inconsistent with the rapidly emerging literature that psychological functioning largely predicts MTBI outcomes (e.g., Combs et al., 2015; Nelson et al., 2012; Verfaellie et al., 2014). This unexpected finding may be the result of the lack of nuance from this categorical variable and the assumptions associated with coding this variable. That is, most of the included studies were coded as "mixed." Studies were conservatively coded as having a mixed composition if any study participant was reported to have a mental health disorder. Thus, there is incredible variability in this outcome as studies could be coded as "mixed" if 1 to 99% of their study participants were reported to have a comorbid mental health disorder. Additionally, studies were coded as mixed if the authors did not report specific inclusion/exclusion criteria associated psychological comorbidities. Thus, studies could have been incorrectly coded if the authors did not formally measure psychological outcomes. Altogether, this unexpected finding may be a result of methodological decisions associated with developing a categorical coding of this variable, which may not be particularly meaningful.

Notably, limitations associated with methodological approaches utilized in Aim 1 are consistent with most prior MTBI meta-analyses conducted. Analogue-to-ANOVA analyses require categorical data, restricting the variability of the effect modifiers. This type of analysis also requires a separate analysis for each covariate and time point of interest. Altogether, 20 separate analyses were needed to examine the impact of the various effect modifiers on MTBI recovery over time, likely resulting in Type I errors. Additionally, there is an inherent reduction in power as included studies are split among the various analyses (largest k = 45). Consistent with nearly every previous MTBI meta-analysis, significant between-study heterogeneity (Cochran's Q) was evident after most analyses, leaving a significant majority of the variability left unexplained (I^2) (Belanger, Curtiss, et al., 2005; Belanger & Vanderploeg, 2005; Frencham et al., 2005; Rohling et al., 2011).

Aim 2

The second aim of this study was to utilize meta-regressive techniques to quantify the relative effect in overall neurocognitive functioning post-MTBI for each covariate, and more fully account for the between-study heterogeneity evident in the literature and replicated in Aim 1. Unlike the pairwise analyses from Aim 1, meta-regression analyses can quantify the relative effect of each covariate on neurocognitive recovery with much fewer analyses. Furthermore, the covariates can be examined continuously, rather than categorically, maintaining important variability.

When considering all studies with time of assessment ranging from immediately post-injury to three years, average time since injury did not predict overall neurocognitive dysfunction. This held true when considering linear and non-linear equations. Again, this

surprising finding was likely due to the comparatively large effect sizes for studies that included individuals involved in litigation and Veterans. To further explore this issue, supplemental analyses revealed that the average time that had elapsed since sustaining an MTBI was a significant predictor only when examining the first 90 days after injury. This variable, however, failed to be predictive when examining studies in the post-acute (>90 days) period. Taken together, this seems to suggest that in the post-acute periods after an MTBI, when symptoms are not typically present, the amount of time that has passed since the injury is no longer important in predicting overall cognitive functioning. Rather, other key variables are likely to account for any residual differences between MTBI populations and controls.

Given the consistent findings demonstrating a deleterious effect of psychological distress and MTBI recovery (e.g., Combs et al., 2015; Nelson et al., 2012; Verfaellie et al., 2014) it was important to evaluate emotional well-being in more systematic and objective manner than in Aim 1. Uniquely, this is the first meta-analysis to systematically examine psychological functioning after sustaining an MTBI. Analyses revealed that psychological functioning was a significant predictor of neurocognitive dysfunction, accounting for nearly 100% of the between-study variability despite only including 36 studies ranging from 2 to 954 days post-MTBI. While population membership was a significant predictor, accounting for 30% of the between-study variability when considered alone, this variable failed to reach significance when entered to the regression equation simultaneously with psychological functioning.

The effect of psychological functioning seems to be primarily driven by studies including individuals who have depression and/or PTSD (see Table 16). This is generally

consistent with emerging MTBI research (e.g., Combs et al., 2015; Nelson et al., 2012; Verfaellie et al., 2014) For example, Nelson and colleagues (2012) found that 3.5 years post-injury, Veterans who sustained an MTBI did not differ in overall neurocognitive dysfunction compared to controls; whereas, Veterans with MTBI and a comorbid Axis I disorder performed much worse than controls, but did perform similar to Veterans with no head injury and a comorbid mental health disorder. Similarly, other research has found that cognitive and psychological functioning predicted functional outcomes 10 years after sustaining an MTBI (Ponsford, Draper, & SchÖNberger, 2008). The importance of psychological functioning in predicting cognitive functioning post-MTBI is also consistent with research that demonstrates reliable decrements in neuropsychological test performance for individuals with mental health disorders in the absence of head injuries. For example, it is well-established that depression in older adults is a risk factor for cognitive impairment (e.g., Dotson, Resnick, & Zonderman, 2008a). In addition, meta-analyses have found consistent neurocognitive decrements across the lifespan for individuals with depression (Snyder, 2013) and PTSD (Johnsen & Asbjørnsen, 2008). What remains unclear is if poor psychological functioning fully explains persistent neurocognitive dysfunction in those with protracted recovery, or if continued dysfunction may be attributed to the actual head trauma sustained during MTBI (e.g., neurometabolic deficiencies, diffuse axonal injuries).

Table 16.
Effect Sizes of Various Psychological Constructs

Construct	Depression	Anxiety	PTSD	SUD	Somatiziation	Internalizing Behavior	Externalizing Behavior	Overall Psych Fx
k	24	14	6	3	2	12	15	36
d	0.908	0.387	1.926	0.236	0.385	0.230	0.145	0.546

Notes. PTSD = Post-Traumatic Stress Disorder; SUD = Substance Use Disorder; Psych Fx = Psychological Functioning

While the importance of psychological well-being in predicting cognitive functioning post-MTBI is consistent with the existent literature, this finding differs from the pair-wise analyses from Aim 1. This difference is likely due to the lack of nuance and variability from the categorical variable of the percentage of individuals with psychological comorbidities utilized in Aim 1. The variable utilized in Aim 2, however, represents overall self-reported psychological functioning and well-being in the MTBI group compared to the controls. This continuous variable does not require a diagnosis of a mental health disorder to be made as the variable from Aim 1 does. This does, however, highlight the importance of psychological assessment as part of routine clinical care for MTBI.

Previous studies with homogenous samples have found that various demographic factors, such as sex (Bazarian et al., 2010), education (Dougan et al., 2014), and race (Shafi et al., 2007), may modify MTIB recovery. However, supplemental analyses from the present study found that demographic variables (percentage of females and ethnic minorities included in the study sample, age, education), injury parameters (percentage of participants reporting LOC and PTA), and study characteristics (utilization of PVTs) did not predict overall neurocognitive outcomes post-MTBI. Similar to some published

studies (Collie et al., 2006; Iverson et al., 2004; Sterr et al., 2006) supplemental analysis did indicate that the report of PCS in the MTBI group relative to the control group did predict cognitive functioning. However, much like the other variables, this failed to reach significance when simultaneously entered with psychological functioning. Perhaps, the initial PCS finding was driven by the affective symptomology of PCS (e.g., irritability, fatigue) versus pain (e.g., headache, photophobia), which was better explained by overall psychological functioning.

Overall, the meta-regression models from Aim 2 suggest the time that has elapsed after sustaining an MTBI is predictive of neurocognitive dysfunction only in the first 90 days post-injury. However, psychological functioning is the most important predictor of neurocognitive outcomes post-MTBI. That is, across a heterogenous population of individuals who sustain MTBI, psychological functioning better predicts neurocognitive recovery, over and above the latency from the initial injury.

Methodological Considerations

The present study diverged from methodology utilized in prior MTBI meta-analyses in several meaningful ways. First, a random-effects meta-analysis was conducted instead of fixed-effects analysis, which can result in smaller, more conservative estimates of effect sizes since two sources of error (within-study and between-study) are considered. Additionally, outcomes from multiple time points were not averaged as was done in other studies (e.g., Belanger, Curtiss, et al., 2005; Binder et al., 1997). Rather, in line with study aims, the time point with the greatest latency since the initial injury was selected from each study for analysis. This was done to better understand the factors that moderated cognitive recovery as opposed to documenting the

more acute effects of MTBI, per se. This decision may have led to systematically smaller estimates of effect sizes than if we were to have averaged all the time point comparisons. Notably, due to the large number of studies that met potential inclusionary criteria, a random sample of articles were reviewed until a specified number (k = 45) of studies per population were included. Given that a random-effects analysis assumes a random distribution of effects, and the process of reviewing articles was also randomized, we do not believe that this process biased the observed effects in any particular direction. Finally, in an effort to ensure the construct validity of the cognitive outcomes, this study only included validated neuropsychological assessments and excluded experimental measures (e.g., fMRI paradigms; Pertab et al., 2009). The ability to be selective with psychological assessments is a luxury that previous meta-analyses were not afforded given the recent increase in published MTBI research. It is uncertain if this decision would lead to a systematic bias in observed effect sizes in either direction. Despite these potentially meaningful differences, most of the outcomes were consistent with prior analyses. When there were differences, however, the effect sizes tended to be larger; though this is most likely due to the increased heterogeneity of study populations relative to previous analyses.

As outlined above, despite these methodological differences, most of the analyses from the present study are consistent with the findings from previous meta-analytic reviews. A notable discrepancy in our findings from prior meta-analytics studies was the small, but statistically significant effect size that remained in the GMR group after 90 days, which differed from most meta-analytic studies that divided outcomes by a similar time frame (Belanger, Curtiss, et al., 2005; Pertab et al., 2009; Rohling et al., 2011; c.f.,

Frencham et al., 2005). This finding may be due to the relatively larger inclusion of studies in the present analysis (k = 18) compared to previous analyses (mean k = 10.5). Notably, most of these previous studies investigated a "mixed" population that included some athletes, likely decreasing the observed effect sizes. The only study with a "true" GMR sample was Belanger's (2005a) analysis that included eight studies, which found a negligible effect size (d = .04) after 90 days. Perhaps, the small, but significant effect size observed in the present study is a more accurate representation of MTBI recovery for this group, and this study has the power to detect such finding. Alternatively, this finding may be due to a cultural shift in our understanding of the deleterious effects of MTBI in the nearly 10 years since the previous GMR study was published, and individuals may be more likely to seek medical care when their "bell is rung" rather than "walking it off."

While it was consistent with our hypotheses, another divergent finding from previous MTBI research was that age was not a significant predictor of post-injury cognitive functioning. Dougan and colleagues (2014) found that, in athletes, higher age resulted in lower neuropsychological effect sizes. Their study, however, had a relatively restricted age range (15-33 years vs. 4.87-69.1 years) and was limited to athletes in the acute phases of the injury (1-10 days). The present finding is consistent with a systematic review, which found no consistent evidence that age was not a reliable predictor of long-term neurocognitive functioning. Notably, there was a relative dearth of pediatric and older adult studies in the present analysis. This is particularly problematic for generalizability as epidemiological studies have found a bimodal distribution in TBI prevalence with children and older adults having the highest rate of injury (Faul et al., 2010).

The differences in results from the present study relative to previous meta-analytic reviews may also be due to the uniqueness of the variables of interest. To our knowledge, this is the first published study that included Veteran samples in a quantitative review of cognitive functioning after sustaining an MTBI. These analyses found that studies that included Veteran populations exhibited significantly larger cognitive sequalae after an MTBI relative to their non-injured counterparts. This is likely due to the "cumulative model" in which the physical, emotional, cognitive, vocational, and psychosocial stressors Veterans face when returning from deployment may exacerbate premorbid risk factors, leading to worse outcomes (Evered, Ruff, Baldo, & Isomura, 2003; Ruff et al., 1996). Additionally, the methodological decision to exclude studies with assessments greater than three years post-injury resulted in the exclusion of many Veteran studies, which preludes a comprehensive understanding of how Veteran recovery from MTBI. For example, a preliminary unpublished project stemming from the methodology and article selection of the present study found a much smaller effect size (Hedges g = .34) across 18 studies when there were no exclusions based on time of assessment (mean time since injury = 43.59 months; Marston, 2019). Nonetheless, the current project is the first meta-analytic study that attempts to understand the neurocognitive trajectory for Veterans and factors that may modify cognitive recovery.

Another novelty is the inclusion of psychological variables in this meta-analytic study. While many empirical studies (e.g., Combs et al., 2015; Nelson et al., 2012; Verfaellie et al., 2014) and systematic reviews (e.g., Carroll et al., 2004) have examined the role of psychological functioning in post-MTBI cognitive recovery, this is the first meta-analysis, to our knowledge, that attempted to control for the effect of psychological

functioning on neurocognitive outcomes. Despite this analysis only including 36 studies, the overwhelming ability of psychological functioning to predict study-level data, speaks to the importance of emotional well-being for cognitive recovery after an MTBI.

Despite attempts to systematically integrate a broad literature to derive findings that will generalize across populations, the study is not without limitations. One limitation of this research is the relatively restricted age ranges of selected samples and relatively small number of Veteran samples included, potentially reducing generalizability. On the other hand, this study included an extremely heterogenous study sample, which has inherent potential for generalizability across many other variables. Another limitation is the small number of studies used for the analysis of psychological functioning in Aim 2 (k = 36). Given that most studies included did not directly measure psychological functioning (>70%) efforts to replace these data (e.g., imputations) were not conducted. Nonetheless, the ability of this variable to explain nearly all between-study variability speaks to its robustness and predictive ability across samples.

Additionally, a notable criticism of all MTBI meta-analyses is that the methods of aggregating outcomes across studies may mask the minority of individuals who experience protracted recovery (the so-called “miserable minority”), giving the false impression that no one experiences residual cognitive sequalae after three months (Pertab et al., 2009). On the contrary, our significant cognitive findings after 90 days suggest that these individuals may not be lost in our analyses. Finally, it is important to note that meta-regression analyses are inherently observational in nature. The data from the present study are study-level data, not patient-level data. Thus, caution needs to be taken in over-

generalizing these findings and assuming that psychological functioning *causes* protracted cognitive recovery after MTBI.

Clinical Implications

Recognizing the significance of psychological functioning status-post injury has great clinical utility and should result in improved care and management of individuals after an MTBI. Assessment of emotional well-being and psychological functioning should be part of routine clinical care for management of MTBI across all populations. Individuals who screen high for psychological distress may benefit from a referral for brief Cognitive Behavioral Therapy (CBT) or another therapeutic intervention. Brief CBT has been found to reduce the duration and severity of PCS after MTBI (Miller & Mittenberg, 1998; Silverberg et al., 2013). For example, a small pilot study found that individuals who were at high risk for persistent PCS and received brief CBT reported fewer symptoms and were less likely to be diagnosed with Post-Concussive Syndrome than patients who received treatment as usual (Silverberg et al., 2013). Additionally, this study suggests that patients who suffer an MTBI may benefit from psychoeducation regarding the overall in the non-specific symptomology between MTBI and mental health disorders (e.g., fatigue, inability to concentrate, irritability).

Patients should be empowered to seek mental health treatment in the acute recovery process, especially if there are pre-morbid psychological concerns, rather than waiting three months or more. Neuropsychologists, who are uniquely trained to assess cognitive, biological, and psychological factors, should be a part of all multi-disciplinary MTBI teams. The present research also speaks to the growing need for acute MTBI detection and care for military Veterans. Given the high rate of PTSD symptomology

(Carlson et al., 2009) and other mental health disorders, our research suggests this population is particularly vulnerable to poorer neurocognitive functioning after MTBI. In recent years, emphasis on Veteran care and research has increased. For example, the Defense and Veterans Brain Injury Center published clinical guidelines for the management and clinical care of Veterans with MTBI in 2006 (Moy, Martin, Scwhab, & Malik, 2018). Within 30 days of returning from deployment, Veterans meet with a health care provider to assess current health functioning and evaluate for deployment-related occupational and environmental exposure (Brenner, Vanderploeg, & Terrio, 2009). In 2008, head injuries were added to the list of environmental exposures that Veterans were to be screened. Positive exposure would result in referrals to appropriate services (e.g., Poly-Trauma, neuropsychology). Nonetheless, careful and effective screening for mental health disorders and expansion of therapeutic services may be beneficial for improving Veteran's long-term functioning after MTBI.

Summary

In sum, this study is the largest MTBI meta-analysis to date, which utilized contemporary analytic techniques to assess changes in cognitive functioning status-post MTBI. A medium-large decrement was observed in overall neurocognitive functioning in the very acute (< 24 hours) period post-MTBI. Meta-regression showed time to be significant predictor of cognitive functioning in the first 90 days, predicting a small (d = .20) effect size after 41 days. After, 90 days, time since injury was no longer a significant predictor of cognitive functioning. Psychological functioning was found to be the most robust predictor of overall cognitive functioning after MTBI across heterogenous samples. Future research should further elucidate and attempt to validate the specific

psychological constructs that may confound cognitive recovery. Finally, given the high prevalence of MTBI and the general lack of access to healthcare in the US, especially with minority groups, CBT or Prolonged Exposure, to treat MTBI via computer or telemedicine should be developed.

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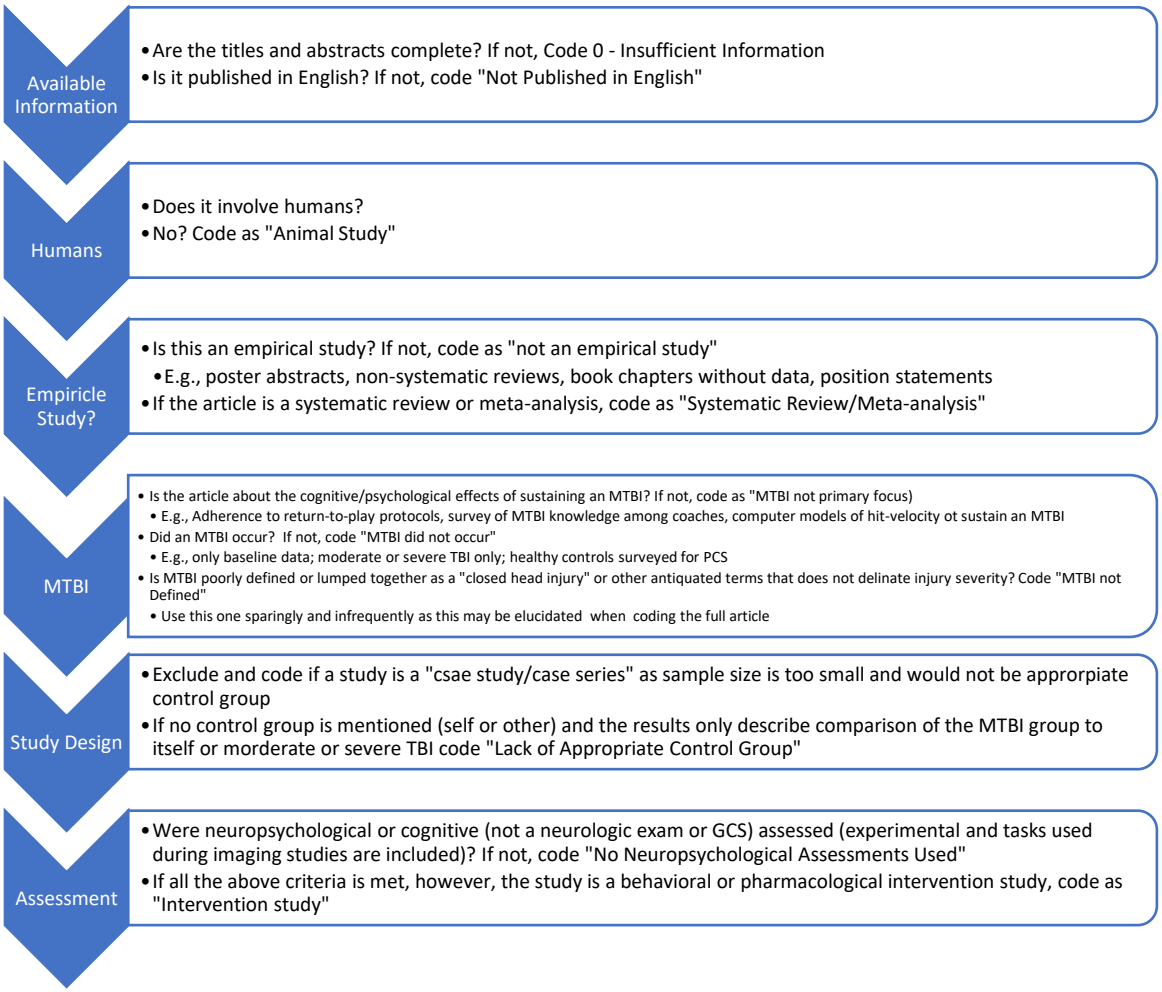
Appendix A

Flowsheet Outlining Approach to Initial Abstract Review and Article Coding



Appendix B

MTBI Data Entry Code Sheet

Identifying Information:

Author – Type in the last name of the first author.

Year – The year the article was first published. If article was published in print first, then online (i.e., re-print), enter the year that the article first appeared in print.

***Note: If there are multiple articles included in the study with the same first author published the same year, differentiate the articles by placing letters (in alphabetical order) after the year. Example: Belanger 2005a; Belanger 2005b; Belanger 2005c

Country – The country that data collection took place. If it took place in multiple countries, enter the country that the first author is from.

Study Characteristics:

Appropriate Method of Defining MTBI – Enter either "Yes" or "No." MTBIs must be generally aligned with the ACRM or WHO guidelines (i.e., acute mental alterations, GCS 13-15, LOC < 30 minutes, PTA < 24 hours). If unsure, ask David Marra

Method Used – Briefly described how MTBI was defined (e.g., "Blunt head trauma; LOC < 30 minutes)

Imaging Study – Enter either "Yes" or "No." If the study included neuroimaging (i.e., MRI, CT, MEG) or EEG, enter "Yes." If no neuroimaging is reported as part of the study, enter "No."

PVTs Used to Exclude Invalid Performance – Enter either "Yes" or "No." If the study specifically states that subjects were removed due to invalid performance, then enter "Yes." If not, enter "No."

Types of PVTs Used: If "Yes" to "PVTs Used to Exclude Invalid Performance," then enter the types of PVTs used. Enter either, "Stand-alone" (e.g., VSVT, TOMM, WMT), "Embedded" (e.g., Reliable Digit Span, CVLT-FC), "Both" (e.g., used both embedded and stand-alone), or "Unspecified" if the article did not directly state how they assessed effort.

Control Group: Enter the appropriate control group used in the study. Either "Non-Injured Controls," "Pre-Injury Baseline," "Non-Injured Controls & Pre-Injury Baseline," or "Orthopedic Injury."

MTBI Sample Demographics:

Population - Enter either: Athlete, Veteran, General Medical Referral, Litigant, or Mixed: General Medical/Litigant.

Mean Age – Enter the mean age of the MTBI sample

Age Category – Based on the mean age of the MTBI sample, select: Children (Ages 0-13), High School/College (Ages 14-22), Adults (Ages 23-64), Older Adults (Ages 65+)

Mean Education – Enter mean educational attainment of the MTBI sample

Based on the MTBI sample, enter the percentage of females, percentage of Caucasians, percentage of Blacks, percentage of Latinos, and percentage of individuals of other races

Mechanism of Injury – based on the MTBI sample, calculate the percentage of individuals who suffered an MTBI due to play an Impact Sport (i.e., Football, Lacrosse, Boxing, Hockey, Rugby, MMA), Other Sport (e.g., Soccer, Basketball, Baseball, Wrestling), Motor Vehicle Accident (MVA), Falls, Blast Injury, Veteran Blunt Trauma (Veterans who suffered an MTBI due to blunt force trauma – but not due to a blast), Civilian Assault (i.e., victims of a crime/mugging), Other Mechanisms (i.e., any other mechanism of injury not covered above)

Complicated TBI – the percentage of individuals who suffered a complicated MTBI (i.e., skull fracture, subdural hematoma) as confirmed by neuroimaging

Psychological Comorbidity & Personality Constructs:

Composition of Psych Comorbidity – the study specifically states that subjects were excluded due to a psychological comorbidity (e.g., depression, PTSD, anxiety), then select "0%." If the sample or subsample of individuals have a diagnosed psychological comorbidity, then select "100%." If the article does not specify, or some individuals (but not all) have a mental health disorder, then select "Mixed."

Based on the MTBI sample, enter the percentage of the MTBI sample with a diagnosis of Depression, Anxiety, PTSD, and Substance Use Disorder (SUD).

Time and Time Points:

Mean Time Since Injury - Enter the mean time since MTBI occurred (in months) from the MTBI sample. If multiple measurements occurred during the course of the study, average the time points together. Example: if measurements an evaluation took place at 1 month and 6 months, then enter "3.5 months."

***Note: if the evaluation took place days (rather than months) after the initial evaluation, then convert the number of days into months by dividing by 30. If the evaluation took place hours after the evaluation, first convert the number of hours post-TBI into days, then into months by dividing by 30.

Example:

7 days = .233 months (7/30)

6 hours = .0083 Months (6 / 24 / 30)

Time Category: Based on the Mean Time Since Injury, enter the following: < 24 hours, < 7days, < 3 months, > 3 months

Number Post-Injury Time Points: Enter the number of evaluations that took place over the course of the study.

Appendix C

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