MILD TRAUMATIC BRAIN INJURY (MTBI) CHRONICALLY IMPAIRS COGNITIVE FUNCTION

IN MORE FIRST-TIME CONCUSSED INDIVIDUALS THAN PREVIOUSLY ESTABLISHED: A

SCOPING REVIEW

by

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Abstract

Mild traumatic brain injury (mTBI) has long been characterized as a "mild" injury without long-term consequences. Despite our growing understanding of its long-term consequences, the current estimate of individuals with mTBI that will develop persisting symptoms (i.e., 15%) may be an underestimation. We therefore designed a scoping review to reveal what the literature as a whole reports about long-term cognitive impairment following a single mTBI. We systematically reviewed the literature that behaviourally assesses cognition in individuals with chronic phase (i.e., ≥ 3 months) mTBI. We show that approximately half of individuals with a single mTBI continue to demonstrate chronic cognitive impairments. We also show that the mTBI literature is plagued with a lack of homogeneity with respect to the use of cognitive outcome measures. Our findings highlight the need to establish a thorough understanding of the long-term implications of a single mTBI.

List of Abbreviations Used

ABI: Acquired brain injury

CHI: Closed head injury

Conflict SP: Conflict slow potential

CT: Computed Tomography

CTE: Chronic Traumatic Encephalopathy

DAI: Diffuse axonal injury

DTI: Diffusion Tensor Imaging (DTI)

EEG: Electroencephalogram

ERP: Event-related potential

FA: Fractional Anisotropy

fMRI: Functional Magnetic Resonance Imaging

GCS: Glasgow Coma Scale

ImPACT: Immediate Post-Concussion Assessment and Cognitive Testing

LOC: Loss of Consciousness

LTP: Long-term potentiation

MeSH: Medical Subject Headings

MRI: Magnetic Resonance Imaging

mTBI: Mild Traumatic Brain Injury

PET: Positron Emission Tomography

PPCS: Persistent Post-Concussion Syndrome

PCS: Post-Concussion Syndrome

PTA: Post-traumatic Amnesia

PTSD: Post-traumatic stress disorder

ROI: Region of Interest

RTP: Return-to-play

Acknowledgements

Enrolling in a Master's degree in Rehabilitation Research was not part of my original life plan. At the time, however, my "life plan" was discombobulated and unelucidated. Having just completed an undergraduate degree in Neuroscience and beginning to flirt with the idea of starting the clinical Physiotherapy degree, I conducted a quick Google search of "Neuroscience" and "Physiotherapy" to see what an amalgamation of the two fields might bring. Enter Shaun Boe and his Laboratory for Brain Recovery and Function.

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Chapter 1: Introduction

1.1 Executive Summary

Mild traumatic brain injury (mTBI), more commonly known as concussion, is the most common type of traumatic brain injury [1]. What was once seen as a temporary condition without long-term consequences is now understood as a contributor to the onset of the neurodegenerative pathologies, Chronic Traumatic Encephalopathy (CTE) and dementia, as well as long-term impairments in cognition [2]–[5]. Consequently, mTBI is gaining critical attention from researchers, clinicians, the military, sports organizations, and athletes alike [6].

The Mild Traumatic Brain Injury Committee of the American Congress of Rehabilitation Medicine (1993) describes mTBI as a mild insult to the head that results in a brief period of unconsciousness followed by impaired cognitive function. Mild TBI causes an array of signs and symptoms, most notably: headaches, fatigue, depression, anxiety, irritability, and cognitive impairments [7]. Mild TBI is a misnomer in that the consequences of the injury are anything but mild. Those recovering from mTBI have difficulty returning to work and engaging in activities of daily living [8]. The time it takes to recover in the majority of individuals is approximately 3 months, however, a subset of individuals continue to experience symptoms well past 1 year post-injury [9]. Moreover, subjective disappearance of symptoms does not account for the subtle changes to cognition that may persist for years following an mTBI. The incidence of individuals who experience chronic cognitive impairment following mTBI has been estimated to be 15%. In this work, however, we will elaborate on the limitations in the literature that supports the "15% estimate hypothesis", as it will be referred to hereon.

There are many signs and symptoms implicated with mTBI. For the purposes of this work, we will use the term "symptoms" to describe both the subjective (i.e., those the individual experiences or reports) and objective (i.e., those detectable on cognitive outcome measures) ongoing issues that are characteristic of mTBI. Cognitive impairment, particularly learning and memory impairment, are paramount to mTBI [1]. As will be discussed in greater detail, even a single concussion can disrupt the

neurological mechanisms underlying learning and memory. Acutely post-injury, these neurological changes manifest behaviourally as learning and memory impairment. The impairment is robust and easy to detect in the early phase post-injury; how or if these changes to neurological function manifest behaviourally in the long-term, however, is less clear. Few studies examine the long-term cognitive outcomes of individuals with mTBI. Fewer still have been able to detect long-term cognitive impairments using standard cognitive outcome measures. Despite the limited evidence linking a single concussion to long-term cognitive impairment, studies similarly examining long-term cognitive outcomes in individuals with a history of multiple concussions have yielded more fruitful findings. That is, each successive injury in an individual's concussion history contributes to worse long-term cognitive outcomes.

The somewhat limited findings of long-term cognitive impairment in individuals with a single mTBI may stem from (1) inter-study and (2) intra-study methodological limitations. Inter-study limitations include: a small number of studies looking at long-term cognitive impairment and difficulties comparing across studies owing to the use of a variety of outcome measures. Intra-study limitations include small cohorts and/or low power, as well as a lack of sensitivity of each outcome measure to detect subtle behavioural changes in cognition. Further, limitations in the assessment tools used to detect cognitive impairment may indicate that the incidence of long-term cognitive impairment following mTBI may be grossly underestimated in the literature.

To date, the literature is void of a comprehensive review examining the long-term cognitive outcomes in singly-concussed individuals. Gathering the evidence from multiple studies would help reveal the incidence of long-term cognitive impairment by overcoming limitations of single studies. Further, examining assessment tools used in this body of literature would facilitate an investigation of their sensitivity for detecting long-term impairment in cognitive function. Therefore, the purpose of this work is to systematically review the literature reporting cognitive outcomes in first-time concussed individuals in the chronic phase (i.e., > 3 months post-injury) of mTBI. Specifically, we will look at studies behaviourally assessing cognition in individuals at discrete time

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points in the chronic phase post-injury. To this end, our primary research objective is to assess the evidence linking a single mTBI with long-term cognitive impairment and secondarily, to reveal differences in the sensitivities of various cognitive paradigms used to assess learning and memory impairment.

To achieve these objectives, we searched three databases, Embase, CINAHL, and Medline, for studies relating to two broad concepts: mTBI and cognitive impairment. The resulting studies from the scoping search were then assessed for their adherence to the following major inclusion criteria: (1) outcome measures assessed at discrete time points in chronic-stage (>3 mo. post-injury) mTBI; and (2) use of cognitive outcome measures that behaviourally assess cognition. Relating to our primary objective, we found evidence for long-term cognitive impairment on select outcome measures in individuals with a history of a single mTBI. Relating to our secondary objective, we were unable to show differences in the sensitivities of the outcome measures. This was owing to the limited homogeneity of outcome measures used in the studies in our review. Thus, we found that the mTBI literature is systematically lacking in homogeneity of outcome measures. This was an unexpected finding of our review but important nonetheless. Finally, our study was not designed to overcome the limitation of insensitive methodology — the studies we review rely on those very methods that are potentially insensitive to behaviourally assess cognition — our review was able to address the other intra- and inter-study limitations, as described above. That is, by gathering the evidence from all the single-studies looking at long-term cognitive impairment in individuals with mTBI, we were able to conduct a thorough synthesis of the evidence linking chronic mTBI with cognitive impairment. In turn, we have furthered our understanding of the long-term consequences of mTBI.

1.2 Background Information

1.2.1 Incidence, Underreporting, and Cost of mTBI

As indicated above, mTBI, more commonly known as concussion, is the most common type of traumatic brain injury. In recent years, the incidence and prevalence of mTBI has increased. The incidence of mTBI is disproportionately high in military and athletic populations. In deployed soldiers, particularly those returning from Iraq and Afghanistan where blast-related injuries are routine, the incidence of TBI is somewhere between 7.6% and 22.8% [10]. These estimates are for TBI, however, mTBI has been coined the "signature injury" for deployed soldiers returning from combat in Iraq and Afghanistan [11], [12]. Among high school football players, three quarters will sustain at least one concussion while about one third of all children sustain at least one mTBI prior to adulthood [13], [14]. These incidence estimates vary across sources and unfortunately are notoriously confounded by misdiagnoses and underreporting [15], [16]. In a study examining concussion underreporting in high school football players, McCrea et al (2004) found that only half of athletes reported their concussions [17].

Despite widespread underreporting, the social and economic costs of mTBI are still significant. The economic burden associated with treating mTBIs is around $3 billion in Canada and $16.5 billion in the US — and rising [18], [19]. In the past decade, emergency rooms in the US have seen a 200% increase in visits from concussed youths [20]. While this study specifically was looking at emergency room visits in the United States, it is apparent that the consequences of mTBI — both to the patient's health and economically speaking — are increasing.

While treating mTBI is costly to society at large and the health care system, the personal costs to individuals with mTBI is greatly impactful. Many individuals with mTBI are unable to return to work during the first 3 months post-injury. One study found that the unemployment rate following mTBI was 34% at 3 months post-injury and 9% at 1 year post-injury [21], [22]. These numbers fail to account for individuals who return to work despite persisting headaches, cognitive problems, and restless sleeps among other continuing signs or symptoms. Furthermore, those who experience mTBI co-morbidly

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with depression or post-traumatic stress disorders (PTSD), particularly combat personnel exposed to blast-related mTBI in theatre, are more likely to develop persisting signs or symptoms [23].

1.2.2 Defining Concussion

The precise definition of mTBI differs depending on the source. Further, there are many terms used interchangeably with mTBI, even though the varying terms may have differing definitions. Terms used interchangeably with mTBI include the following: mild closed-head injury (CHI), diffuse axonal injury (DAI), concussion, post-concussion syndrome (PCS), and acquired brain injury (ABI) [24], [25]. Differing definitions of mTBI complicate the comparison of results across studies. Most sources will adhere to a definition of mTBI that includes the following three requirements: an initial (lowest) Glasgow Coma Scale (GCS) score of 13-15 (with a GCS of 9-12 representing moderate TBI and 3-8 as severe TBI), an insult to the head accompanied by an alteration or loss of consciousness (LOC) for no more than 30 minutes, and a resulting post-traumatic amnesia (PTA) lasting no more than 24 hours [25]. The presence or absence of positive neuroimaging findings such hemorrhages, contusions, and fractures following mTBI are not consistent across definitions of mTBI [25]. While some studies will classify mTBI patients with positive neuroimaging findings as "complicated mTBI" others will simply slot those patients into the "moderate" TBI category regardless of a lowest recorded GCS between 13-15 [25]–[28]. Furthermore, not all positive neuroimaging findings are created equal. A linear skull fracture, for example, often accompanies TBI and is thus sometimes disregarded as a "positive neuroimaging finding" that would otherwise define the TBI as complicated (mild) or moderate [28]. Consequently, selected studies define complicated mTBI as having positive neuroimaging findings, not including a linear skull fracture.

Finally, assessing positive neuroimaging findings is also complicated by methodological limitations. While traditional neuroimaging techniques such as MRI and CT are effective for finding macro-structural injuries (e.g., hemorrhages, fractures, contusions, etc.), they are not adequately sensitive to detect microstructural injury,

most notably, diffuse axonal injury (DAI) — the pathological hallmark of concussion [29]. DAI is characterized by subtle structural damage to the axon fibers. During a concussive insult, the accelerational force of the impact selectively damages the vulnerable white matter tracts in the brain. The resulting diffuse axonal damage is thought to be responsible for the cognitive impairments that follow concussion [29], [30]. Indeed, studies that assess DAI following concussion using specialized neuroimaging techniques (i.e., diffusion tensor imaging (DTI)) found that the majority of mTBI patients present with microstructural white matter tract damage in the absence of macro-structural damage [31].

In summary, most researchers will agree that concussion is accompanied by microstructural damage in the form of DAI. Disagreement prevails, however, regarding the classification of TBIs that otherwise fit the criteria for mTBI but are accompanied by positive neuroimaging results (i.e., gross anatomical changes) such as contusions, hemorrhages, and skull fractures. For the purposes of this work, we will adhere to the mostly widely accepted definition of concussion where individuals must meet three criteria: (1) a GCS of 13-15; (2) LOC for less than 30 minutes; and (3) PTA for less than 24 hours. For our scoping review, we will not exclude studies with participants presenting with complicated mTBI. Instead, we will review all sudies regardless of their inclusion of positive neuroimaging findings in their definition of mTBI.

The next section will further define concussion by describing the stages of chronicity — that is, the acute and chronic stages post-injury.

1.2.3 Concussion Chronicity

Among individuals with concussion, there is great variability in the time it takes for post-injury issues to resolve. Given the variability in symptom persistence, it is difficult to classify individuals into the acute versus chronic phases post-injury. The literature discusses two phases of recovery following an mTBI: the acute phase and the chronic phase (International Brain Injury Association). Unfortunately, the timeline of each phase is not consistent in the literature. While some studies define the acute phase

as the period during the first 2 months post-injury, others use the first 3 months post-injury [32]–[34]. For the purposes of our work, we will adhere to the 3-month time point for acute mTBI whereby the majority of individuals experience symptom resolution. It follows that individuals who continue to exhibit symptoms during the chronic phase post-injury — or past the 3-month time point — are experiencing persistent post-concussion syndrome (PPCS) [7].

According to most reports, PPCS occurs in about 15% of patients [35], [36], [9], [37], [38]. Factors such as comorbidity, injury severity, medical history, age, and gender have been shown to contribute to the length of symptom persistence [39]. Specifically, mTBI patients that have depression, more severe mTBIs, and previous concussions are less likely to see symptoms disappear within 3-months. Similarly, women and older patients are also more likely to experience persisting symptoms [39]. The number of mTBI patients who have persistent symptoms, however, may be grossly underestimated due to methodological limitations. It may not be possible to quantify the degree of cognitive impairments late post-injury using the same paradigms that we use to show impairments early post-injury. In other words, cognitive impairments may persist undiagnosed owing to our limited ability to detect them using standard paradigms [40], [41]. This notion of a lack of sensitivity in assessment tools will be revisited in a later section.

1.2.3.1 The 15% Hypothesis

Myriad sources cite the 15% estimate hypothesis — that is, that approximately 15% of individuals with an mTBI will go on to develop PPCS [35], [36], [9], [37], [38]. In fact, this estimate has become common knowledge in the mTBI literature: the Center for Disease Control and Prevention (CDC) has stated that "15% of patients diagnosed with mTBI may have experienced persistent disabling problems" [35]. Unfortunately, there are several limitations to the literature supporting this hypothesis. Consequently, the limitations to the 15% estimate may equate to an underestimation of the incidence of PPCS in the literature. First, the literature inconsistently characterizes PPCS with respect

to whether the syndrome describes those with ongoing subjective issues (e.g., headaches, sleep problems, subjective memory impairment), ongoing objective issues (e.g., behaviourally tested cognitive deficits, neurophysiolgically detected impairments), or both. Without a clear and consistent definition of PPCS in the literature, estimates of the incidence of PPCS are prone to error. For example, the primary research underlying the 15% estimate demonstrates the incidence of PPCS in those with ongoing subjective symptoms. Subsequent studies citing the primary research may have misinterpreted the findings. One study often cited as demonstrating the 15% estimate, by Rutherford et al (1979), assessed the subjective presence of post-concussion symptoms in 131 participants with mTBI at 12 months post-injury [36]. They found that 14.5% of their sample continued to subjectively endorse persistent post-concussion symptoms at the 12-month interview.

In a process that could be likened to a game of broken telephone, subsequent studies have directly and indirectly cited Rutherford et al. (1979) over the last few decades, extrapolating their findings. One study cites Rutherford et al. (1979) as evidence that "a minority [15%] of patients are not fully recovered 12 months post mTBI" [42]. This statement implies that the presence or absence of subjective post-concussive symptoms is indicative of recovery and fails to account for the difference between recovery of subjective symptoms and recovery of cognitive impairment as demonstrated by cognitive testing. Moreover, Daneshvar et al. (2011) indirectly cite Rutherford et al. (1979) through an intermediate study by Rees et al., 2005 and interpret the Rutherford et al. (1979) findings as follows: "it is believed that as many as 15% of people with a history of mTBI still suffer from deficits one year after injury" [36], [43], [44]. It is therefore easy to see how the Rutherford et al (1979) findings demonstrating persistent subjective symptoms one year post-injury have been extrapolated to include persistent cognitive deficits. Without consideration for the primary literature demonstrating the 15% finding, this estimate has become common knowledge in the mTBI literature.

Other limitations have stemmed from overinterpreting the results of the primary literature demonstrating the 15% estimate and may be contributing to a large underestimation of the incidence of PPCS. The primary research demonstrating the 15% estimate lacks evidence from cohorts with chronic mTBI long after the injury (i.e., past the 1 year mark). Few studies have assessed cognition in individuals with mTBI well past the 1 year post-injury mark. For example, the Rutherford et al. (1979) study only followed participants until 1 year post-injury [36]. While their research did not claim to assess individuals past that point, it has been cited as evidence that 15% of individuals will develop PPCS in the long-term. Thus, while the primary literature has assessed PPCS in the chronic phase (i.e., 1 year post-injury), the studies citing this work may only specify that 15% of individuals experience PPCS in the long-term rather than denoting the precise post-injury interval from the primary literature. In turn, the initial findings have been extrapolated to include the "long-term" rather than simply the "chronic phase at 1 year post-injury".

Finally, the major limitation to the research demonstrating the 15% estimate is unrelated to misinterpretations of the primary research. While the misinterpretations described above may contribute to an underestimation of the incidence of PPCS, methodological limitations in our ability to detect long-term cognitive impairments may be overwhelmingly at fault for the potential underestimation of PPCS in the literature. While the Rutherford et al. (1979) study is not the only piece of primary research describing the 15% hypothesis (or similar estimates), most studies describing the incidence of persistent cognitive impairments rely on imperfect outcome measures. In other words, the 15% estimate is only as accurate as the sensitivity of the cognitive testing used to detect cognitive impairment. In short, the tests we use to detect cognitive impairment and consequently those we use to estimate the incidence of PPCS may be insufficiently sensitive. This idea will be further discussed in a later section. Regardless, it is important to note that the primary literature describing the 15% estimate has been subject to: (1) misinterpretation by secondary sources citing their

findings; and (2) methodological limitations. Taken together, the widely reported 15% estimate may, in fact, be a misconception, or at the very least an underestimation.

1.3 Cognitive Impairment in mTBI

1.3.1 Types of Cognitive Impairment in mTBI

Rabinowitz & Levin (2014) describe four cognitive domains that are impaired in individuals following mTBI [45]. These include executive function, memory, attention, and processing speed. Attention and processing speed are relatively easy to define. Attention refers to the "state of focused awareness on a subset of the available perceptual information" [46]. Processing speed refers to "the speed of cognitive processes and response output" [47].

Executive function (EF) refers to a set of higher-order cognitive functions, involving the prefrontal cortex and its related circuitry that help control lower-level cognitive functions such as learning, memory, attention, planning, and decision making [48]. There are three main EFs: inhibitory control, working memory, and cognitive flexibility [48]. These EFs form the scaffolding for other cognitive functions such as reasoning, problem-solving, and planning [48]. For example, inhibitory control, or the ability "to control one's attention, behavior, thoughts, and/or emotions" facilitates selective attention [48]. That is, in order to selectively attend to a given stimulus, we need to inhibit our awareness of outside distractions. Working memory, or holding information in the forefront of our minds, allows us to work with information that is no longer "perceptually present" [48]. Mental math, for example, requires working memory as we rely on our ability to hold pieces of information (i.e., numbers) while we work with them to solve an equation. Finally, cognitive flexibility, or the ability to adjust our thinking processes, builds on inhibitory control and working memory. Take, for example, a situation where we are required to change perspectives. First, we must inhibit our previous perspective (i.e., inhibitory control), then we must recruit the information needed to change perspectives into our working memory. Executive functions, and its

sub-components are thus higher-order cognitive function that facilitates the use of other cognitive functions such as attention, processing speed, and learning and memory.

Memory can be defined as the "behavioural change caused by an experience" while learning can be defined as the "process for acquiring memory" [49]. In our work, we discuss learning and memory as one cognitive domain since they are inextricably linked. One cannot remember information without having learned nor can one learn information without working memory. Memory can be sub-defined as explicit memory and implicit memory. Explicit memories concern the conscious storage of events and facts while implicit memories concern the storage of motor skills [49]. Interestingly, explicit and implicit memories are functionally and anatomically distinct. That is, they serve a different functional purpose and they are stored and maintained in different areas of the brain. We know this not because we have localized the precise anatomical loci of a given memory. Instead, we have seen how individuals with brain damage will often show amnesia for one form of memory but not the other [50]. At the cognitive level, explicit and implicit memory can be further defined into sub-categories (i.e., working memory, immediate memory, verbal memory, long-term memory). Operationally defining each sub-form of memory is beyond the scope of this thesis. Moreover, at the neurobiological level, all forms of memory are essentially equal in that they require structural changes to the brain's synapses. This scoping review will thus adhere to the broad operational definition of neurobiological learning and memory. That is, learning is the ability to acquire memory while memory is the ability to encode information through structural changes to the brain and access this information for later use.

Interestingly, the definition of executive function — namely, that it is involved in controlling learning, memory, and attention — reveals the inextricable relationship between the cognitive domains that are impaired in mTBI. In other words, executive function, learning/memory, attention, and processing speed are all interrelated cognitive functions. Specifically, learning, memory, and attention rely on intact executive functions while processing of executive function is limited by an individual's processing

speed [48], [51]. This overlap (or intersection) of cognitive processes complicates our discussion of cognitive impairments in mTBI in that attributing a measurable impairment to say, memory, in an individual with mTBI could stem from a direct impairment to memory alone or it might stem from a deficit to executive function that in turn, impairs memory. The goal of our work, however, is not to understand the relationship between executive function and its inextricably related types of cognition. Our work will therefore not attempt to determine the cognitive etiology of a given cognitive impairment. Rather, the purpose of our scoping review will be to describe cognitive impairments as they appear in the literature. For the purposes of our work, we will operationally define cognitive impairment as any impairment to the cognitive processes related to executive function. Nevertheless, our work will describe the long-term cognitive outcomes that are related to the cognitive processes described above (i.e., executive function, learning/memory, attention, and processing speed).

Impairments to executive function and its related cognitive processes in individuals with mTBI can be assessed using a variety of outcome measures. Standardized neuropsychological testing may involve one or multiple cognitive tests that are designed to detect impairment to any given cognition. Any neuropsychological test is subject to limitations in validity and reliability and thus they are not perfect detectors of cognitive impairment. In a later section, I will discuss the possibility that insufficiently sensitive neuropsychological tests may contribute to the underestimation of long-term cognitive impairment in individuals with mTBI. Prior to this discussion, the next section will delve into the underlying pathophysiological and behavioural changes to learning and memory. We have chosen to focus the next section on learning and memory impairments since the literature comprehensively details the underlying pathophysiological mechanisms that account for the behavioural impairment to learning and memory that ensues mTBI. In our review, however, we will not limit our study selection to those assessing learning and memory only.

1.3.2 Learning & Memory Impairment

A concussive injury induces pathophysiological changes to the underlying neural mechanisms responsible for learning and memory. In the acute phase post-injury, these pathophysiological changes definitively translate to behavioural changes in the form of learning and memory impairment. Whether or not these changes persist past the acute phase of mTBI (i.e., 3 months post-injury) or have any meaningful functional impact in the chronic phase post-injury remains to be established [52]. *Figure 1* summarizes the general findings in the mTBI literature reporting on the pathophysiological and behavioural changes (to learning and memory) that have been measured in the acute and chronic phases post-injury in individuals with single and multiple mTBIs. Please note, *Figure 1* is only a representation of the findings after a scoping search of the literature — it does not represent the findings from a comprehensive and systematic literature search. In the following sections, the level of evidence supporting the claims made in each quadrant will be elaborated upon. First, we will provide a brief explanation of the figure prior to delving deeper into the evidence supporting the claim in each quadrant.

Figure 1. Pathological and Behavioural Changes Ensuing mTBI. Presence of pathological (i.e., cellular and molecular) and behavioural changes in singly- and multiply-concussed individuals with both chronic- and acute-stage mTBI, as evidenced by the mTBI literature.

To briefly explain *Figure 1*: there is evidence in the literature showing changes to the underlying pathophysiological processes of learning and memory in individuals with both one and multiple previous concussions. These pathophysiological changes have been detected both in the acute and chronic phases post-injury (*Quadrants A and C*), [31], [53], [54]. Similarly, the literature also reports definitive behavioural changes to learning and memory in individuals with both single and multiple concussions — albeit only in the acute phase post-injury (*Quadrant B*) [55]–[57]. Behavioural changes to learning and memory in the chronic stage post-injury have not consistently been reported in the literature (*Quadrant D*) [58], [59]. Individuals with a history of multiple concussions often demonstrate chronic behavioural changes to learning and memory [60]. Demonstrating these same chronic, behavioural changes to learning and memory in individuals with one (or very few) previous concussion(s) has been more difficult [58]. This may be because a single concussion does not induce any measurable long-term

changes to learning and memory at the behavioural level. Alternatively, the behavioural changes might be very subtle and difficult to detect.

1.3.3 Pathophysiological Changes (Figure 1: Quadrants A & C)

The pathophysiology of learning and memory deficits differ according to the severity of the TBI. Moderate and severe TBI are accompanied by excitotoxicity-induced apoptosis of hippocampal cells and consequently, hippocampal atrophy [61], [62]. Excitotoxicity is a form of cellular stress whereby cells experience damage and/or death from over-excitation. In turn, the function of the hippocampus, a sub-cortical structure involved in learning and memory formation, is impaired. Thus, the changes in gross anatomy following moderate to severe TBI, at least in part, account for the observed learning and memory deficits. Interestingly, mTBI is not associated with any gross anatomical changes to the brain or excitotoxic cell death [63]. In mTBI, however, similar amnesia immediately follows the traumatic event and subsequent learning and memory deficits occur in the absence of excitotoxicity and cell death [64]. It follows that brain trauma can negatively impact the neurobiology of learning and memory at the cell's functional level. Indeed, research into both the molecular and cellular levels have revealed the disrupting impact of mTBI.

At the molecular level, mTBI research has focused on the changes to the biochemical pathways involved in long-term potentiation (LTP) — the best understood molecular correlate of learning and memory [65]. LTP impairment following mTBI has been well substantiated in the literature [66]. While the mechanisms involved in mTBI learning and memory impairments are not entirely understood, impaired calcium homeostasis is the best understood molecular contributor to the cognitive deficits [67], [68]. In addition, intracellular calcium levels have been shown to be elevated in the hippocampus for up to 30 days following experimentally induced mTBI in rodents [68]. Elevated calcium is thought to alter the function of hippocampal cells following mTBI thus contributing to learning and memory deficits following brain trauma [67], [69].

At the cellular level, mTBI is infamous for disrupting axonal function in the form of DAI. Prior to its coining, DAI, the microscopic injury to white matter tracts in the brain

resulting from the shearing forces of the brain injury, had been described in the literature as early as 1899 when a closed-head injury patient's brain was described as having widespread white-matter damage [70]. In 1956, a paper published by Sabina Strich first noted the relationship between closed-head injuries, the resulting DAI described as "diffuse degeneration of white matter", and the development of dementia [70]. Since then, DAI has been continually discussed in the mTBI literature. Today, DAI is thought to not only ensue concussion, but it also may be the underlying etiology of both short- and long-term cognitive impairments associated with mTBI [30], [71].

1.3.3.1 Measuring Pathophysiological Changes

The microscopic nature of the damage means that DAI cannot be assessed using conventional neuroimaging methods such as MRI and CT. Instead, DAI is assessed using DTI. DTI reveals white matter tract damage by capitalizing on the nature of water diffusion along axonal tracts. Specifically, the predictable movement (diffusion) of water molecules along the parallel axon tracts that make up white matter is compromised after DAI. Consequently, water diffusion along the axon tracts is no longer ordered and predictable and the direction of water diffusion becomes increasingly random. The most common DTI measure, fractional anisotropy (FA), quantifies the randomness of water diffusivity in axonal tracts. FA values are inversely related to the chaoticity of water diffusion and thus lower FA is indicative of white matter tract damage [71]. Many studies have shown compromised white matter tract integrity in individuals post-injury as evidenced by lower FA values using DTI [53], [72], [73].

1.3.3.2 Acute Pathophysiological Changes (Figure 1: Quadrant A)

Research into the cellular and/or molecular changes that ensue mTBI have painted a clear picture of the pathologically impairing impact of mTBI. There are two stages of pathophysiological damage following TBI. The primary stage of pathophysiological injury involves the microstructural damage of axons resulting from the mechanical forces applied to the brain during injury. This phase of injury is

unavoidable and irreversible [74]. During mTBI, the brain's axons endure damaging mechanical forces that twist and tear at their structural integrity. Axons, or white matter tracts, rely on networks of microtubules spanning their length to provide a route of communication between the cell's body and its distant dendrites. These microtubules provide the essential service of transporting proteins and other molecules necessary for synaptic transmission (cell-cell communication) and molecular up-regulation required for Hebbian learning (LTP). During DAI, the axon's infrastructure, such as the microtubules themselves and the proteins that facilitate the movement of materials within them become compromised [75]. As indicated above, this damage occurs in the absence of structural abnormalities detectable on conventional neuroimaging such as CT [31], [75].

The secondary stage of pathophysiological injury results from the reactionary neurometabolic cascade of events that follow primary injury. For example, when nerve cells are damaged, the delicate balance of ions across the neuronal membrane shifts to allow dangerously high concentrations of intracellular sodium and calcium. These shifts in ionic balance can induce indiscriminate glutamate release — the underlying mechanism of excitotoxic death of neurons in moderate and severe TBI. In mild TBI, as discussed in the introduction to this section, excitotoxic death does not happen during this secondary pathophysiological phase. Nevertheless, similar metabolic cascades and ionic imbalances still occur in damaged nerve cells. This is evidenced by studies demonstrating changes to the ionic balance across the neuronal membrane in individuals early-post injury [54], [76]. In mTBI, the extent to which secondary pathophysiological injury induces long-term damage is not well understood. Currently, most researchers believe that secondary pathophysiological injury in mTBI resolves and thus do not cause long-term damage. They do, however, concede that this may not be the case in individuals with multiple mTBIs. This will be further discussed in a later section.

Nevertheless, the primary phase of pathophysiological injury in mTBI does cause definitive damage in the form of DAI. Interestingly, the pattern of damage from DAI is

not random. Specific brain regions appear to be selectively vulnerable to DAI during mTBI such as the corpus callosum, the internal capsule, the uncinate faciculus, and the superior and inferior longitudinal fasciculi [77] [78]. Further, the cognitive and behavioural impairments that follow mTBI, such as learning and memory deficits are directly related to the damage of brain regions most vulnerable to DAI. In a study using DTI to examine white matter integrity in participants with acute stage mTBI (approximately 1 month post-injury), Xiong et al (2014) found a significant correlation between DAI in the aforementioned brain regions and performance on various cognitive measures such as working memory and processing speed [77]. This is just one example of a study demonstrating how changes to the underlying pathophysiological mechanisms of learning and memory parallel changes to behavioural measures of learning and memory in the acute phase post-injury. The section looking at acute behavioural changes in concussed individuals will further explore the supporting evidence. First, the next section will shift our discussion to the pathophysiological changes that persist chronically post-injury.

1.3.3.3 Chronic Pathophysiological Changes (Figure 1: Quadrant C)

There are myriad studies documenting pathophysiological changes to the brain in individuals with both single- and multiple-mTBI histories [54], [77], [79], [80]. DTI is allowing researchers to assess the relationship between chronic mTBI and DAI. Moreover, they are able to assess differences in FA, for example, between individuals who present with persistent cognitive impairments versus those who have successful and quick recoveries. In a sample of pediatric patients with chronic (6-12 months post-injury) mild to moderate TBI, Wozniak et al (2007) found a significant correlation between low FA values in white matter ROIs and correspondingly low scores on tests of cognitive function [72]. Similarly, another study assessed FA in a group of 10 individuals with PPCS and cognitive impairment who were at least 2 years post-injury [71]. They specifically excluded patients who had structural abnormalities on conventional neuroimaging (i.e., MRI and CT) at the time of injury. Thus, their patient sample

represented those with uncomplicated, mild TBI. Compared to controls, they found individuals with chronic mTBI and persistent cognitive impairments had significantly lower FA values in the corpus callosum but not other regions of interest (ROI). These results nevertheless demonstrate how changes to cellular function are not necessarily reversible and damage can persist chronically post-injury.

Another study looking at chronic mTBI (at least 6 months post-injury) and DAI also found FA to be reduced in several ROIs including the superior longitudinal fasciculus, sagittal stratum, and corticospinal tract [81]. Unlike the previous study, the sample of participants with mTBI was not selected based on their cognitive impairment status. Despite demonstrating chronic microstructural damage (i.e., DAI) using DTI, this study did not find that their mTBI sample had any persisting cognitive impairments on any of their implemented standardized neuropsychological test [81]. This inability to show cognitive impairment on neuropsychological tests despite the DTI evidence demonstrating persistent pathophysiological changes may be an artifact of methodological limitations. Nevertheless, these results demonstrate how a single concussive event can induce lasting changes to the underlying pathology of learning and memory. In the next section, the focus of our conversation will shift from the pathophysiological changes to the behavioural changes following mTBI.

1.3.4 Behavioural Changes (Figure 1: Quadrants B & D)

1.3.4.1 Acute Behavioural Changes (Figure 1: Quadrant B)

In the acute phase post-injury, the neurophysiological changes are accompanied by definitive cognitive and behavioural changes. While the time course to full recovery is not consistent across studies, the literature conclusively shows that learning and memory are impaired acutely post-injury. A meta-analysis conducted in 2005 by Belanger and Vanderploeg examining the neuropsychological impact of sport-related concussions found large effect sizes across all studies for cognitive impairments in the first 7-days post-injury [82]. In their study, cognitive impairment was defined using a variety of outcome measures that assess nine cognitive domains (e.g., orientation,

attention, memory acquisition, delayed memory) [82]. The authors found these cognitive impairments to subside following the 7-day time point, however, memory impairment persisted until 10-days post-injury. This meta-analysis encompassed 21 studies ranging in publication date from 1996-2004. While this study did not show lasting cognitive impairments in the sub-acute and chronic phases post-injury, it was limited by the agglomerative nature of a meta-analysis whereby many different cognitive outcome measures were used to make sweeping comparisons.

Nevertheless, the breadth of research examining cognitive function acutely post-mTBI has demonstrated considerable differences in cognition across many domains including working memory, delayed memory, executive function, verbal fluency, reaction time, and many other cognitive measures [31], [73], [83]. The true debate, however, lies in whether or not these differences persist chronically. Thoroughly understanding the time course of symptom resolution in mTBI is important for advising those with mTBI whether they should continue resting or return to their normal activities. A successful recovery from mTBI relies on ample rest and abstinence from physically and mentally taxing activities (e.g., sports, large social gatherings, etc.) [84]. Thus, premature return to these activities will impair recovery. The next section will elaborate.

1.3.4.2 Symptom Resolution and Return-to-Play (RTP)

Being able to assess symptom resolution is particularly important for athletes who are deciding when to continue their sports practice, or "return-to-play" (RTP) [85]. As will be discussed in a later section, experiencing a second mTBI while still recovering from the first injury is detrimental to a successful recovery [86]. Moreover, researchers and clinicians agree that sufficient rest and symptom resolution following concussion is paramount to a successful recovery without development of PPCS [20]. RTP guidelines, the criteria clinicians, coaches, and athletes use to determine when an athlete may return to their normal activities/sports, rely on both neuropsychological testing and subjective reporting of symptoms to determine when an athlete has fully recovered. The

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past few decades of concussion research has seen mounting evidence that concussions have serious health implications. Consequently, RTP guidelines have become more strict [15].

RTP guidelines essentially define recovery in that they exist to quantify full symptom resolution. Unfortunately, our ability to detect persistent cognitive impairments may be limited by inadequately sensitive methodology. Thus, athletes presenting with cognitive impairments that undergo insufficiently sensitive neuropsychological testing may exhibit a false positive for recovery. Premature RTP is associated with poorer long-term recovery and increased severity of subsequent concussive events [15], [20]. A 2013 narrative review examining RTP in athletes post-injury found that most athletes showed persistent cognitive impairments despite having already returned to play [15]. Thus, cognitive impairments may persist despite traditional neuropsychological testing showing otherwise. This idea will be further explored in a later section. The take home message here, however, is as follows: concussed individuals demonstrate better long-term outcomes when they refrain from premature RTP; and RTP guidelines are limited by the concussed individual's subjective complaints and potentially inadequately sensitive cognitive testing.

1.3.4.3 Chronic Behavioural Changes (Figure 1: Quadrant D)

Measuring cognitive impairments early post-injury is relatively easy given the robust impact mTBI has on cognitive function in the acute stage. Whether or not cognitive impairments persist in the later stages of recovery is the topic of much debate. While some studies have shown persistent cognitive impairments in a subset of individuals, others discuss the possibility that concussion impairs many more individuals in the long-term. The latter hypothesis can be supported with three arguments. First, molecular and cellular studies have successfully shown how a single concussive episode can induce lasting changes to neurological function post-injury, despite disagreements as to whether these changes result in measurable cognitive impairments. Second, there is mounting evidence revealing how multiple concussions have a cumulative effect on

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both molecular and cellular changes as well as cognitive and behavioural sequelae. Thus, if a single mTBI can induce lasting molecular and cellular changes, and if these changes cumulate following multiple mTBIs and begin manifesting in robust cognitive impairments, it follows that a single mTBI can change cognitive function despite our limited ability to detect those changes. Third and finally, it is possible that inter- and intra-study methodological limitations have hindered our ability to adequately assess the long-term impact of mTBI. These limitations include the following: a limited number studies looking at long-term cognitive impairment; difficulties comparing differential outcome measures between studies; small cohorts and/or low power; and a limited ability of each outcome measure to detect subtle behavioural changes to cognition. The following sections will discuss the evidence linking multiple concussions with long-term cognitive impairment as well as the methodological limitations that may have hindered our ability to assess the real long-term impact of mTBI.

1.3.5 Multiple Concussions — Do they have cumulative effects?

It is well established that an individual's concussion history is a robust predictor in the outcomes of subsequent concussions. Simply, each concussion contributes negatively to the severity and recovery length of successive concussions. For example, Covassin et al (2013) found that individuals with a history of two or more concussions were more impaired on cognitive measures in the acute phase post-injury compared to their previously non-concussed counterparts [87]. They also found that those with a history of three or more concussions demonstrated impairments in measures of verbal memory that had resolved in participants with a history of 1 or 2 concussions. Another study that also looked at differences in cognitive measures between previously concussed and non-previously concussed individuals in the acute phase post-injury found similar results. Iverson et al (2004) found that individuals with a history of 3 or more concussions were eight times more likely to experience disorientation or post-traumatic amnesia (PTA) during subsequent concussions [88]. Further, those individuals

also performed significantly worse on cognitive measures of memory tested in the acute phase post-injury.

These studies, and others, highlight the detrimental impact previous concussions have on the outcome of subsequent concussions. While these studies were specifically looking at the acute phase post-injury, they nevertheless reveal how concussions induce lasting changes to neurological function. Indeed, other studies looking at the impact of concussion history on both neurological and cognitive indices in the long-term have similarly found an impairing and cumulative effect of concussions. For example, Aungst et al (2014) used an experimental model of mTBI in rodents to demonstrate how repeated head trauma compromised the hippocampi's ability to express LTP *ex vivo* [89]. Interestingly, they were able to attribute this finding to the impaired mediation of NMDA receptors in hippocampal synapses. LTP is reliant on NMDA receptor-mediation such that synaptic plasticity requires NMDA receptor activation and up-regulation. These findings show a direct relationship between repeated head trauma and the neurological correlate of learning and memory — LTP. Corroborating these neurophysiological findings, they also showed that rodents exposed to repeated head trauma had impaired performance on the Morris Water Maze and the Novel Object Recognition test — indices of spatial learning/memory and recognition memory, respectively [89]. While the findings in this study and others using experimental models of head injury are significant, the most compelling and ecologically valid evidence demonstrating how repeated head trauma can contribute to long-term and lasting neurological changes comes from human studies revealing Alzheimer's and Parkinson's disease-like pathologies in contact-sport athletes.

1.3.5.1 Chronic Traumatic Encephalopathy (CTE)

Historically, anecdotal evidence from athletes suggested a relationship between multiple mTBIs and long-term learning and memory impairment. In fact, a physician treating boxers published an article in 1928 in the Journal of the American Medical Association titled, *Punch Drunk,* where he discusses the behavioural consequences of repeated head trauma during boxing [90]. His article describes the chronic condition

"punch drunk" that affects boxers who sustain repeated head trauma. Punch drunk, as he reports, closely resembles Parkinson's disease and demonstrates mental deterioration that often necessitates institutionalization. Interestingly, the condition "punch drunk" was then named "dementia pugilistica", and "psychopathic deterioration of pugilists" before it was finally named chronic traumatic encephalopathy (CTE) in 1966 [5], [91], [92].

Recently, researchers have been focusing their attention on the similarities in brain pathology between athletes who have sustained repetitive mTBIs and Alzheimer's patients. Chronic traumatic encephalopathy (CTE), like Alzheimer's disease, is a tauopathy which is a neurodegenerative disease characterized by the aggregation of tau proteins in the brain [93]. This aggregation of tau protein leads to neuronal activity disruption and structural destruction that accompany a host of symptoms including mood changes, Parkinsonian motor symptoms, and cognitive impairments such as dementia [60]. Consequently, CTE is often misdiagnosed as its symptoms are similar to other pathologies (i.e., Alzheimer's and Parkinson's disease) [93]. Unfortunately, as of today, CTE can only be diagnosed by examining post-mortem brains [60]. That being said, [F18]FDDNP PET, a positron emission tomography (PET) technique that specifically detects the insoluble protein aggregates characteristic of CTE, has been used to diagnose CTE in *vivo* [94]. [F18]FDDNP PET is therefore a promising new tool for detecting CTE in the clinical setting.

The development of CTE following repetitive head trauma has been most thoroughly documented in cohorts of retired athletes [3], [5], [95]–[100]. For example, McKee et al. (2013) examined 85 brains taken from individuals with a history of multiple mTBIs from the brain bank at the Center for the Study of Traumatic Encephalopathy at the Boston University School of Medicine [98]. Of those 85 brains, 80% showed pathological evidence of CTE. Moreover, a subset of 35 brains represented those of retired professional football players. Interestingly, only one of those 35 brains showed no evidence of disease [98]. This study's findings are not unique. That is, many other

studies also examining the link between repeated lifetime concussion exposure and development of CTE have shown similar findings [95], [96], [99], [101], [102].

Sport-related concussion is not the only documented contributor to the onset of CTE. A study conducted by Goldstein et al. (2012) examined post-mortem brains from three groups: (1) military personnel who experienced blast injury and/or concussion; (2) athletes with a history of repetitive concussion; and (3) age-matched controls with no history of neurological injury [101]. They found evidence of CTE in the brains of both military personnel with blast injury and athletes with concussion, but not in the age-matched controls [101]. Most notably, they found no differences between the athletes' and military personnel's brains.

While CTE is currently only diagnosed by examining the post-mortem brain, cognitive signs and symptoms, including irritability, impulsivity, aggression, depression, memory loss, and suicidal thoughts typically begin manifesting a decade after repeated head trauma [98]. As the pathology progresses, cognition deteriorates and individuals develop dementia. Thus, the spectrum of learning and memory impairment in individuals with mTBI histories ranges from mild, post-injury amnesia in the hours following head trauma, to residual cognitive difficulties that persist in the days and weeks following trauma, to late-onset neurodegenerative dementia. The mere fact that this spectrum exists has made researchers rethink the initial placement of mTBI as a mild and inconsequential injury.

Taken together, the findings from studies assessing cognitive impairments in those with a history of multiple mTBIs and those examining the link between lifetime repetitive concussion exposure and development of CTE both support a similar conclusion. That is, repeated head trauma has a cumulative and detrimental impact on cognitive function. So far in this chapter we have seen how a single mTBI can induce lasting changes to neurological function. We have also seen how repetitive mTBIs can have a cumulative effect on those changes to neurological function. Importantly, we

have seen how the cumulative effects of neurological function translate to more robust and measurable changes to cognitive and behavioural function. These conclusions support our working hypothesis that mTBI impairs cognition in the long-term by inducing changes to neurological function that become more pronounced and severe with each subsequent mTBI. Thus, a comprehensive review gathering all the evidence linking long-term cognitive impairment with concussion history is a necessary addition to the literature. A scoping review of this type would also aid in our understanding of the long-term impact of a single concussion — represented by quadrant D in *Figure 1*. Before elaborating on our work, there is one final point that has not been addressed. If a single mTBI induces changes to neurological function, why do these changes not consistently translate into measurable cognitive and behavioural impairment? The third and final section in this chapter will explore the potential limitations in the methodology used to assess cognitive impairment and whether those limitations may account for the difficulty many researchers have showing persistent cognitive impairment in chronic mTBI.

1.3.6 Sensitivity of Methodologies — Are they sufficiently sensitive?

The figures reported in the literature pertaining to mTBI and symptom persistence vary greatly. For example, Miles et al., (2008) report that anywhere from 7 to 33% of individuals with mTBI will show persistent cognitive changes following full recovery [103]. The existing methodology used to assess persistent cognitive changes following mTBI, however, may not be adequately sensitive. This may account for the wide range of reported individuals who experience symptom persistence. Moreover, there is similar discrepancy in the figures reported on the time to full recovery and disappearance of symptoms following mTBI. Some studies demonstrate that individuals with mTBI recover from all cognitive disturbances within one year of the initial injury while others demonstrate symptoms that persist well beyond one year [40], [66], [103], [104]. Rather than attributing these ranging figures to differential individual ability to recover following mTBI, researchers are exposing the shortcomings in our methodology that may be at fault. In other words, insensitive methodology may account for the

studies that previously demonstrated that the majority of individuals with mTBI cease to show cognitive impairments one year post-injury.

Several studies have demonstrated this idea by juxtaposing results from two different cognitive assessment methods where only one detects impairment. For example, Pontifex et al. (2009) used a modified flanker task to assess cognitive control — the "goal-directed, self-regulatory operations involved in the selection, scheduling, and coordination of [...] perception, memory, and action" — in a subset of college-aged athletes who had previously sustained a mTBI but who were currently symptom-free [40]. During the flanker task, participants were asked to respond to a set of arrows presented on a computer screen by determining whether they were congruent (i.e., all pointing in the same direction) or incongruent (i.e., the middle arrow pointing in the opposite direction). They found that the athletes with a previous mTBI were significantly slower and less accurate in their responses than non-concussed controls. This demonstrates that mTBI impairs cognitive control in the long-term despite the absence of self-reported symptoms. The authors also tested the participants on the ImPACT (Immediate Post-Concussion Assessment and Cognitive Testing), which is the "most-widely used and most scientifically validated computerized concussion evaluation system" (ImPACT Applications Inc., 2015). While the ImPACT is not designed to specifically detect residual cognitive impairment in individuals with PPCS, its proprietors tout it as an effective tool for measuring "subtle changes in cognitive functioning" (ImPACT Applications Inc., 2015). They found that both athletes with a previous mTBI and the age-matched controls scored equally on the ImPACT. Thus, the modified flanker task and the ImPACT test differed in their ability to assess cognitive changes in individuals that were otherwise considered fully recovered.

Another group conducted a similar study wherein they used two methodologies to assess cognitive function and impairment in both individuals with and without a prior mTBI. Larson et al. (2010) assessed conflict monitoring and conflict adaptation using behavioural (i.e., response time) and neurophysiological (i.e., event-related potentials; ERPs) measures during the Stroop task [104]. The Stroop task requires individuals to

examine a set of words on a screen that are each in a different colour and that spell out a colour. Thus, the words can either be congruent (e.g., brown written with brown font) or incongruent (e.g., brown written with green font) in their spelling and font colour. This task is effective in assessing conflict monitoring and conflict adaptation. They define conflict monitoring as the ability to detect a conflict within a stimulus and conflict adaptation as the ability to increase one's cognitive control in order to respond to a stimulus with a conflict. In the Stroop task, an individual displays conflict monitoring when they detect the incongruency of the spelling/colour of the words. Similarly, they demonstrate conflict adaptation when they begin responding to the incongruent stimuli.

Larson et al. (2010) recruited 29 individuals with a prior mTBI and 36 age-matched controls. These participants were asked to perform the Stroop task with either a congruent trial followed by an incongruent trial or an incongruent trial followed by an incongruent trial. Successful conflict adaptation is evidenced by a slower reaction time on incongruent trials that succeed congruent trials and a faster reaction time on incongruent trials that succeed incongruent trials. Interestingly, both mTBI and control groups demonstrated successful conflict adaptation when tested behaviourally with reaction times. The authors, however, also tested participants on the same task while using electroencephalography (EEG) to measure two ERPs. The two ERPs they examined were the N450 and the Conflict Slow Potential (SP). The N450 is a negative deflection that becomes more negative following incongruent trials and is thus marker of conflict detection or monitoring. The Conflict SP is a positive deflection that becomes more positive following incongruent trials therefore demonstrating the recruitment of cognitive control and thus successful conflict adaptation.

When mTBI and control participants were tested on the Stroop task with EEG, the authors found that both groups had similar N450 ERPs. They took this finding to imply that both groups were equal in their ability to monitor a conflicted stimulus. The patterns of the conflict SP ERP, however, significantly differed between groups. That is, control participants demonstrated an increase in the conflict SP amplitude on an incongruent trial that followed a congruent trial. Dissimilarly, mTBI participants did not

show an increase in the conflict SP amplitude during incongruent trials that followed congruent trials. The authors interpreted this finding as mTBI participants demonstrating an inability to recruit cognitive control and adapt to a conflicted stimulus.

What these studies collectively demonstrate, is that methods used to measure cognitive impairment post-mTBI differ in their ability to detect subtle differences. The take away message from this section is threefold. First, neurophysiological evidence maintains that mTBI impairs the underlying physiological processes of cognition. These changes are not only evident in the acute phase post-injury, but persist chronically. Second, these neurophysiological changes —and thus the cognitive and behavioural changes — cumulate with repeated mTBIs. This explains why individuals with a history of multiple mTBIs are more likely to show cognitive impairments on behavioural indices alone. Third and finally, the methodology used to assess cognition is limited. Consequently, the likelihood that a single mTBI impairs cognition — albeit in a subtle way — despite our limited ability to detect these changes is high.

1.4 Tying it all Together

Evidently, the increasing sensitivity of cognitive testing along with DTI studies confirming microstructural brain damage following mTBI is revealing the long-lasting changes to cognitive function in individuals with a history of one or multiple mTBIs. This body of research makes us rethink our previous understanding of concussion as a transient disability without long-term consequence. Moreover, multiple mTBIs are now understood as a contributor to long-term cognitive impairment and devastating pathologies such as CTE. Despite these findings, the literature variably reports the presence of long-term cognitive impairments in individuals with a history of a single concussion. As we have seen, the somewhat limited findings showing long-term cognitive impairment in individuals with a single concussion may be a result of inter-and intra-study methodological limitations. These include: a limited number of studies looking at long-term cognitive impairments; difficulties comparing across studies using variable outcome measures; small cohorts and/or low power as well as the limited ability of each outcome measure to detect subtle behavioural changes to cognition. In turn, these limitations contribute to what may be a vast underestimation of the incidence of PPCS (i.e., the 15% estimate hypothesis). Furthermore, numerous studies assess cognition in individuals with chronic mTBI but their primary research goal is to report on the validity of cognitive outcome measures. While the data from these studies would be helpful for revealing the long-term impact of mTBI on cognition, their results have not yet been analyzed to that end.

To date, a comprehensive review of the evidence characterizing the cognitive recovery — or lack thereof — in individuals with a history of mTBI has yet to be conducted. Such a review will allow researchers and clinicians to better understand: (1) the relationship between concussion history and long-term cognitive impairment; and (2) which cognitive outcome measures are more effective for detecting subtle changes to cognitive impairment in the long-term. Thus, the primary goal of this review is to *assess the evidence linking mTBIs with long-term cognitive impairment*, and the

secondary goal is to _reveal differences in the sensitivities of various cognitive paradigms used to assess learning and memory ability_.

To meet our research objectives we will systematically review the literature that reports on cognitive function in individuals with mTBI in the chronic phase (> 3 months) post-injury. We will only include studies that administer outcome measures at discrete time points post-injury. This inclusion criterion will allow our review to specifically determine the relationship between post-injury intervals and the residual cognitive impairment. We believe that addressing these research objectives will provide insight into the relationship between mTBI history and long-term cognitive impairment. We expect our findings to show that cognitive impairments persist chronically post-injury. We also expect to show that cognitive impairments are subtle and highly specific, and thus the deficits will likely manifest as specific measures on the cognitive tests. In other words, we do not expect to show that individuals in the chronic phase of mTBI will demonstrate large deficits on multiple outcome measures assessing a wide array of cognitive domains. Moreover, we expect selective cognitive assessment methods to show a more robust relationship between a single mTBI and impairment that is otherwise undetectable using other methods. This scoping review will be a unique contribution to the mTBI literature as well as a tool for researchers and clinicians seeking to find the most effective and sensitive methods for detecting subtle changes in cognition.

Chapter 2: Methods

2.1 Methods at Large — An Executive Summary

This section briefly clarifies the methodological approach taken in this scoping review, as the methods described here were designed in two stages: (1) prior to our scoping search (i.e., *Scoping Search Methods*); and (2) following the first two stages of article selection and an initial assessment of our preliminary results (i.e., *Post-Scoping Search Methods*). The nature of a scoping review requires a large portion of the methodology to be developed only after the preliminary results are available since the literature must first be assessed for its ability to address research objectives identified a priori. The *Scoping Search Methods* section thus outlines the steps we took to design our initial scoping search of the literature (i.e., the search terms and strategies we developed) and the first set of inclusion/exclusion criteria for selecting relevant citations. The *Post-Scoping Search Methods* section described the methods that were designed only after a critical assessment of the first group of studies that made it past our first two stages of exclusions. For this reason, our methods section contains the results pertaining to (1) above.

2.2 Scoping Search Methods

2.2.1 Scoping Search

A broad search of the literature was performed to identify all keywords and search terms for two concepts: concussion and cognitive impairment. Additionally, the search strategies from other reviews related to mTBI were studied to ensure all related terms were considered. Three scoping searches were performed in the following electronic databases: CINAHL, Embase, and Medline/Ovid. Prior to conducting the scoping searches, the keywords and search terms were organized into a search translation table (see *Table 1*). The search translation table organizes both keywords and controlled vocabulary terms to assist in maintaining equivalent searches. For example, each database uses its own idiosyncratic form of controlled vocabulary terms (i.e.,

CINAHL uses CINAHL headings, EMBASE uses EMTREE terms, and Medline uses Medical Subject Heading (MeSH) terms).

Table 1. Scoping Search Translation Table

	CINAHL	EMBASE	Medline
Concept 1: Concussion	**Controlled Vocabulary Terms***		
	(MH "Brain Concussion")	'brain concussion'/exp	exp brain concussion/
	(MH "Postconcussion Syndrome")	'postconcussion syndrome'/exp	exp post-concussion syndrome/
	Keywords & Phrases		
	(mild N5 (head OR crani* OR cerebr* OR brain* OR skull* OR hemispher* OR intra?cran* OR inter?cran* OR intracran* OR intercran* OR "diffuse axonal") N3 (injur* OR trauma* OR damag* OR ?edema* OR contusion* OR concus*))	mild NEAR/5 (head OR crani* OR cerebr* OR brain* OR skull* OR hemispher* OR intra?cran* OR inter?cran* OR intracran* OR intercran* OR 'diffuse axonal') NEAR/3 (injur* OR trauma* OR damag* OR ?edema* OR contusion* OR concus*)	(mild adj5 (head or crani* or cerebr* or brain* or skull* or hemispher* or intra?cran* or inter?cran* or intracran* or intercran*) adj3 (injur* or trauma* or damag* or oedema* or edema* or contusion* or concus*)).ab,ti.
Concept 2: Cognitive Impairment	**Controlled Vocabulary Terms***		
	(MH "Neurobehavioral Manifestations+")	mild cognitive impairment'/exp	exp mild cognitive impairment/
	(MH "Memory+")	memory'/exp	exp memory/
	(MH "Learning+")	learning'/exp	exp learning/
	Keywords & Phrases		
	(Learn* OR memor* OR neurobehavio* OR cogniti* OR neurologi*) N3 (Impair* OR deficit* OR disturb* OR impact* OR disorder* OR outcome*)	(learn* OR memor* OR neurobehavio* OR cogniti* OR neurologi*) NEAR/3 (impair* OR deficit* OR disturb* OR impact* OR disorder* OR outcome*)	((learn* or memor* or neurobehavio* or cogniti* or neurologi*) adj3 (impair* or deficit* or disturb* or impact* or disorder* or outcome*)).mp.

*Controlled Vocabulary Terms: CINAHL = CINAHL Headings, EMBASE = Emtree terms, and Medline/Ovid = Medical Subject Headings (MeSH) terms

As illustrated in *Table 1*, each concept (i.e., concussion and cognitive impairment) yielded controlled vocabulary terms that were equivalent across databases. Concept 1 — concussion — translated into the identical CINAHL headings, EMTREE terms, and MeSH terms as "brain concussion" and "postconcussion syndrome". Concept 2 — cognitive impairment — translated into the controlled terms "neurobehavioural manifestations" (CINAHL) and "mild cognitive impairment" (EMTREE and MeSH). Each controlled vocabulary term for all three databases was exploded to include related terms. Since the initial focus of this thesis was on learning and memory, we additionally

used controlled vocabulary terms for each "learning" and "memory" in all three databases (*Table 1*). The expansion of focus from one cognitive domain (learning/memory) to include four other cognitive domains (executive functions, attention, and processing speed, and language function) was established after assessing the final group of articles included in our review. To clarify — we did not select these five cognitive domains; the outcome measures used to assess cognition in our final group of studies could be categorized into these cognitive domains. Thus, we merely describe the cognitive domains as they appear in the literature. This should not pose any limitations since our initial search criteria were developed to include all types of cognitive testing, regardless of their respective cognitive domains.

To ensure our search was comprehensive, we also included keywords and phrases for each concept. We used the adjacent ("ADJ#") and "near" ("NEAR/#" or "N#") search functions within the keywords and phrases to capture terms that would appear within several words of each other. For example, mild brain injury and mild closed head injury could be searched using the following strategy: "mild NEAR/3 (brain OR closed head) injury". The number beside the near or adjacent functions specifies the maximum number of words that may separate the two terms. The search strategy outlined in *Table 1* was entered into each corresponding database with the Boolean operators "or" within each concept and "and" between each concept.

The three scoping searches (i.e., one for each database) were performed on July 25th, 2015. The search yielded 5900 citations, 579 from CINAHL, 2167 from EMBASE, and 3154 from Medline/Ovid. The 5900 citations were exported into a reference manager database (Mendeley). After the duplicates were removed, 3741 citations remained.

2.2.2 Refining the Literature — Phases 1 & 2

The citation review and selection process for which studies to include was broken down into four phases. In the first phase, two independent reviewers assessed the 3741 citations for inclusion in the scoping review. Both independent reviewers read the 3741 titles/abstracts and indicated their decision for inclusion/exclusion in an Excel spreadsheet (Microsoft Office, 2015) based on the primary inclusion/exclusion criteria

outlined in *Table 2*. Briefly, citations included following phase 1 had to have human participants with chronic (i.e., ≥3 month post-injury interval) mTBI that underwent cognitive testing. At this stage, we did not discriminate against cognitive testing for specific cognitive domains — a study with any kind of cognitive testing was included. Where differences existed for inclusion/exclusion amongst the two reviewers, a third reviewer resolved disagreements about study inclusion/exclusion. As illustrated in *Figure 2*, following phase 1, 648 citations remained.

Table 2. Inclusion/exclusion criteria for each selection phase process.

Phase	Inclusion Criteria	Exclusion Criteria
1: Titles/abstracts reviewed* *Two-reviewer process*	• Human participants with chronic (post-injury interval of ≥3 mo.) mild TBI • Participants tested for cognitive impairments using neurocognitive testing	• Foreign language articles • Articles without accompanying full texts (i.e., conference abstracts/posters) • Subjective questionnaires used for cognitive testing
2: Full-text articles reviewed	• *Same as above*	• *Same as above*
3. Full-text articles reviewed	• Participants assessed at discrete time points post-injury (i.e., exclude studies only reporting on mean/SD for post-injury interval) • Specific number of concussions reported (within 1 concussion)	• Participants suspected of malingering cognitive deficits or those involved in litigation for their injuries
4. Post-analysis	• Participants with a history of a single concussion	• Studies recruiting participants based on their positive mTBI symptomology • Participants with multiple or lifetime incidence of concussions

Stage 1 inclusions were identified using the limited information provided in an abstract. Thus, the second phase required a single reviewer to re-assess the citations, this time reading the full text articles to ensure they still met the primary inclusion/exclusion criteria outlined in *Table 2*. While the criteria were the same as stage 1 (i.e., chronic mTBI and cognitive testing), we were able to exclude studies that only made it past stage 1 because of their potential (rather than their ability) to satisfy our criteria upon further examination of the full texts. The dual-reviewer and dual-phase

approach ensured an unbiased and focused literature search. As illustrated in *Figure 2*, 274 full-text articles remained following stage 2 review.

Throughout the review process during stage 2, information was extracted from the articles that satisfied the primary inclusion/exclusion criteria (i.e., those going on to stage 3) and entered into the Excel spreadsheet. This will hereon be referred to as the "preliminary data spreadsheet". Specifically, the preliminary data spreadsheet included the following pieces of information from each article: number and age of participants, mTBI mechanism of injury (e.g., blast related versus motor-vehicle accident (MVA)-induced), concussion history (e.g., number of previous concussions, time since last concussion), cognitive test(s)/subtest(s) used to assess cognitive impairment, participant's litigation status and/or suspected malingerers, and use of treatment/intervention (e.g., hyperbaric oxygen treatment). Other pertinent information such as comorbidities (e.g., PTSD, depression, Alzheimer's disease) was also noted in the preliminary data spreadsheet. During our analysis, data from treatment/intervention studies was limited to the pre-treatment or pre-intervention time points. In other words, we only used baseline scores on cognitive assessments for participants being tested on their cognition following a treatment/intervention. This will ensure that confounding treatments/interventions will not affect our results.
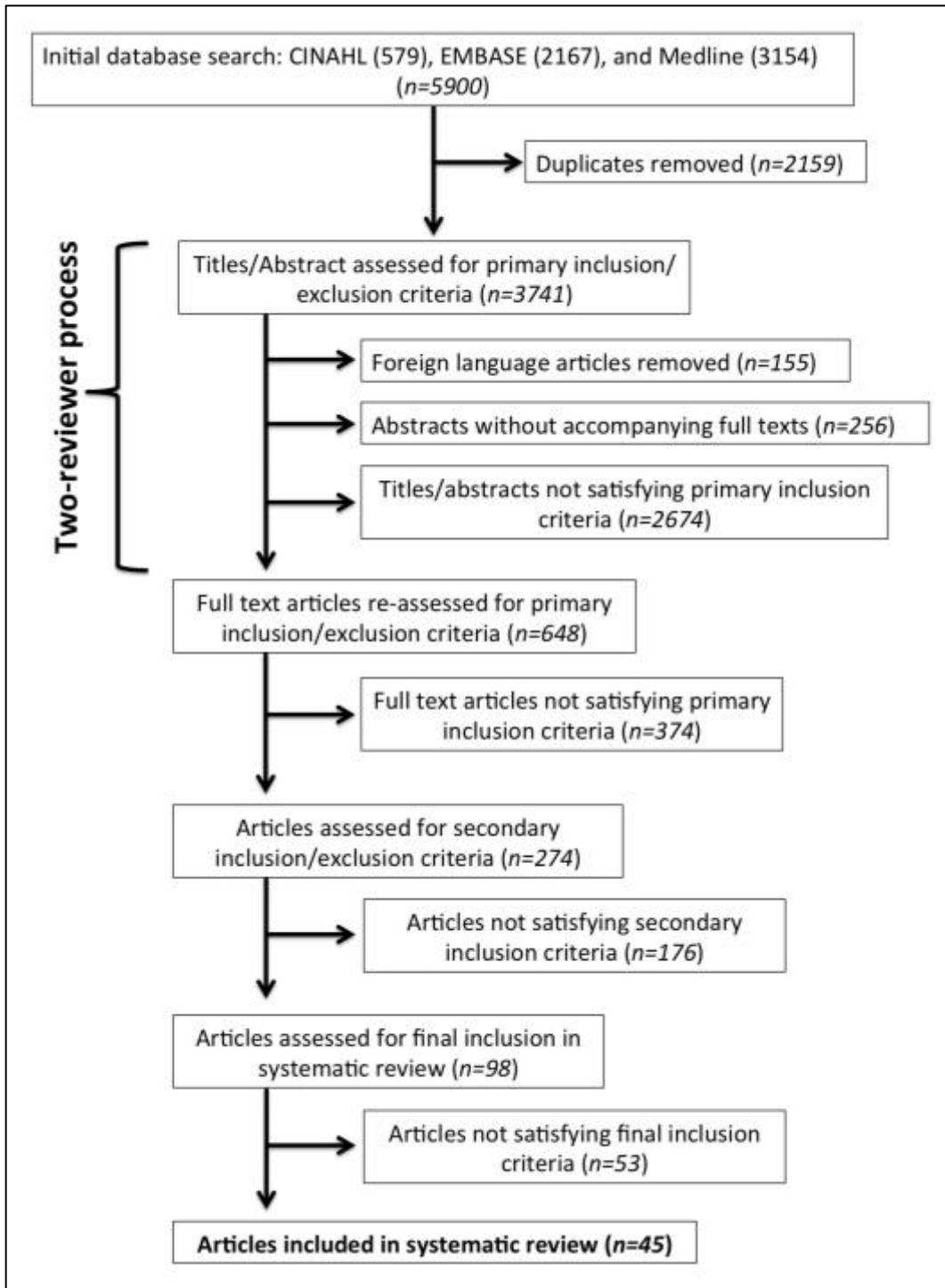
Figure 2. Scoping Search and Article Selection. Flow chart representing each stage of the article selection process of the scoping search and citation review.

2.3 Post-Scoping Search Methods

2.3.1 Refining the Literature — Phase 3

In the third phase of review, we re-assessed the remaining articles with a second set of inclusion/exclusion criteria (*Table 2*). These inclusion/exclusion criteria were developed to narrow our focus and address our research objectives of (1) assessing cognitive impairment in chronic stage mTBI and (2) revealing differences in the sensitivity of various outcome measures used to assess learning/memory ability. Specifically, to assess the long-term neuropsychological outcomes of mTBI with temporal specificity (i.e., precise post-injury intervals), we decided to only include articles that performed assessments of cognitive function at discrete time points post-injury. Thus, we have excluded studies that only report a mean and/or range of post-injury intervals for a group of individuals with mTBI.

We have, however, opted to include studies reporting only means or ranges of post-injury intervals if the mean and/or range corresponded to a post-injury interval of greater than 5 years. The reason for this exception is twofold. First, cognitive outcomes will not continue to improve long after the most recent injury — cognitive outcomes after the first five years will likely not change in the next five (or more) years [105], [106]. In other words, the precision of the post-injury interval becomes less relevant in the long-term. Second, the majority of studies reporting long-term cognitive outcomes in individuals with mTBI are not often temporally specific with respect to post-injury intervals. Excluding these studies would greatly diminish our ability to comprehensively review the literature reporting on long-term cognitive outcomes in mTBI. Fortunately, our preliminary analysis revealed that our studies contained a spread of post-injury intervals (*Figure 3*) with large groups of participants in each post-injury interval. Since there were fewer studies assessing individuals at a post-injury interval of greater than 12 months, we decided to collapse those together as a post-injury interval of "> 12 mo." (*Figure 3*). After our final exclusions, the spread of participants across each of our frou post-injury intervals (i.e., 3 mo., 6 mo., 12 mo., and >12 mo.) stayed consistent (*Figure 3*).
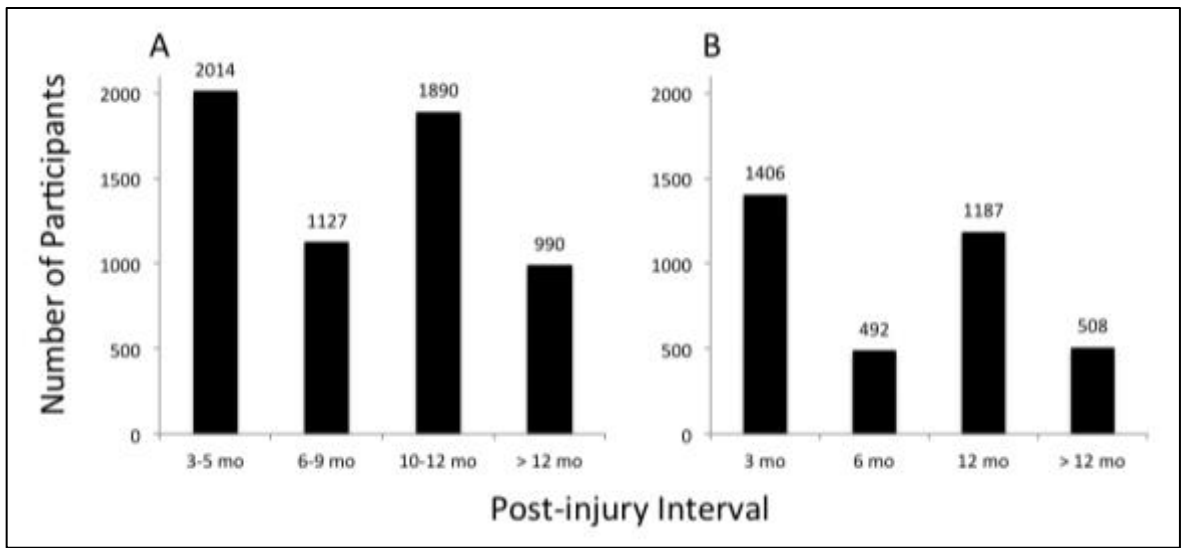
Figure 3. Participants And Their Post-Injury Intervals. Number of participants at various post-injury intervals in the group of studies selected following: (A) the first three stages of the article selection process (n=98 studies); and (B) the post-analysis (final) exclusions (n=48 studies). Thus, Figure 3 (B) represents the number of participants at each post-injury interval included in our final review.

In order to assess the relationship between number of previously sustained concussions and cognitive function, we also chose to exclude studies that only specify a range and/or mean number of concussions. Thus, studies reporting that their participants sustained, for example, between 1-5 concussions would be excluded from our analysis. Studies noting a range of concussions within 1 (i.e., between 1-2 concussions) will be included. This exception, like that for the post-injury interval, is meant to minimize exclusions and ensure that our review is comprehensive so that we can better synthesize the wide breadth of research.

During phase 3, we also excluded participants who were engaged in litigation associated with their injury, or those suspected of malingering (i.e., exaggerating or fabricating) their neurocognitive deficits. Excluding participants engaged in litigation or suspected of malingering ensures our sample of participants is not confounded with individuals who have an incentive to perform poorly on the cognitive outcome measures. To meet this criterion, we excluded studies (or groups of participants) that

specifically stated that the participants were involved in litigation or that they were suspected of malingering. Following this phase of review, 98 articles remained.

2.3.2 Preliminary Analysis & Further Refining the Literature — Phase 4

We developed a fourth stage of article selection with a set of inclusion/exclusion criteria (see *Table 2*) to reflect the viability of the remaining studies to address our research objectives. To develop these criteria, we scrutinized the preliminary data spreadsheet containing information from the 98 articles remaining after phase 3 of the article selection process. Specifically, we were looking at the homogeneity of the articles with respect to the following variables: number of concussions sustained by participants; outcome measures used to assess cognitive impairment; method of participant recruitment (i.e., whether the participants were recruited based on their positive symptomology of cognitive impairment); and method for determining cognitive impairment (i.e., comparison groups, author-defined normative data, or author-provided cut-off scores on given outcome measures).

From our analysis of the preliminary data spreadsheet, we found that the majority of the participants (i.e., 4196 of 4239) had a history of a single concussion while only 43 participants had a history of more than one concussion (i.e., 2 with 2 mTBIs, 1 with 3 mTBIs, 39 with 4 mTBIS, and 1 with 5 mTBIs). Given the disproportional spread of our data with respect to concussion history, we decided we would focus our analysis on the cognitive outcome measures in individuals with a history of a single concussion. Thus, in our final exclusion criteria outlined in the last row of *Table 2*, we excluded studies examining cognitive outcome measures in individuals with a history of multiple concussions or lifetime concussion exposure. In order to minimize exclusion, we chose to include studies where the participants were likely (but not certainly) first-time concussed. Those included studies that: (1) did not specify whether their participants were exclusively singly concussed or (2) did not exclude participants based on their history of a previous concussion. Nevertheless, we do include this as a variable in our data analysis. This will be elaborated on in the results section.

During our preliminary analysis, we also found that several studies had specifically recruited their participants on the basis of their persisting cognitive symptoms. This presents an unnecessary confound to our data, as these studies would artificially exaggerate the presence of persisting cognitive impairment among the average singly concussed participant. Thus, we excluded case studies and other studies recruiting participants for positive symptomology. Finally, our preliminary analysis also revealed that not all of our studies presented their data in a way that would facilitate the dichotomization of participants into cognitively impaired and cognitively unimpaired groups (see below for methods on dichotomization process). Thus, we decided to only include studies that included comparison groups (i.e., healthy controls or trauma controls), normative data, or cut-off scores on cognitive outcome measures. This is further discussed below. Following these post-analysis exclusions, there were 45 studies remaining for the final scoping review (*Figure 2*) [103], [107]–[150].

2.3.3 Addressing the Primary Research Objective

The primary research objective of this scoping review is to assess the evidence linking mTBI with long-term cognitive impairment. To address this objective, we analyzed the information pertaining to concussion histories (i.e., post-injury interval and number of previous concussion parameters) and cognitive outcomes (i.e., presence versus absence of cognitive impairment). In order to make inferences about cognitive ability, we dichotomized participants, assigning them the status of either "cognitively unimpaired" (CU) or "cognitively impaired" (CI) for each cognitive outcome measure and post-injury interval at which an assessment of cognitive impairment was performed. Cognitive impairment status was assigned to groups of participants based on group outcome measure data. An assignment of CU/CI was made using one of three comparison scores. Those include: studies that provided outcome measure data from control groups (i.e., healthy controls or trauma controls); studies that provided normative data for a given outcome measure; or studies that provided cut-off scores for a given outcome measure. Thus, groups of participants were classified as CI if their

outcome measure score significantly differed from those of the control groups or the normative data, or if they were below author-identified cut-off scores. We recognize the limitation posed by dichotomizing participants into CI/CU groups based on their group data. This will be addressed in the discussion (see *Limitations*).

A final consideration must be addressed while dichotomizing participants into CU/CI groups. The majority of our studies assessed groups of participants using multiple outcome measures. For studies showing differential cognitive impairment on multiple outcome measures, we will define "CI" as participants that show impairment on *any* outcome measure. In other words, if a participant shows impairment on 1 of 3 outcome measures, they will be assigned to the CI group. Our justification for this decision is as follows. Each outcome measure assesses a different aspect of cognition. If an individual shows impairment on the CVLT but not the ImPACT, for example, this might be because these two outcome measures are measuring different aspects of cognition. Even though the individual is not impaired on the ImPACT, their impairment on the CVLT still ascertains them as having cognitive impairment. Since our study is primarily concerned with demonstrating *any* form of cognitive impairment, it is not important if their impairment only manifests as a specific impaired function to say, verbal, short-term memory or divided attention. In short, an individual who is impaired on one function still exhibits cognitive impairment.

2.3.4 Addressing the Secondary Research Objective
The second research objective of the current work was to reveal differences in the sensitivities of various cognitive paradigms used to assess learning and memory impairment. After our analysis of the preliminary data spreadsheet, we found that our sample of studies was lacking homogeneity with respect to outcome measures. Across the 48 studies included in our review, there were a total of 74 cognitive outcome measures (not including subtests). These outcome measures are illustrated in *Tables 4.1* to *4.4*. Further, the majority of the cognitive outcome measures only appeared in a very small subset of the sample (i.e., one or two studies) while only a few outcome measures

were used across more than three studies. Thus, while our intent was to comment on the sensitivities of various outcome measures, the studies included in our final review did not facilitate this analysis. We therefore added to our secondary objective in order to extract more information from our limited data. In addition to discussing the difficulties posed by analyzing the sensitivity of outcome measures in the available literature, we will also use our data to discuss which cognitive domains are most often impaired following mTBI.

To examine the cognitive domains that are most often impaired in individuals with mTBI, we translated each of the cognitive outcome measures in *Tables 4.1* to *4.4* into the corresponding cognitive domains that were being assessed. For example, the Auditory Verbal Learning Test (AVLT) measures learning/memory and therefore corresponds to that cognitive domain [151]. While there were 74 outcome measures in our sample, these only corresponded to five cognitive domains (i.e., executive functions, learning/memory, attention, processing speed, and language function). Thus, translating the cognitive outcomes into their corresponding cognitive domains allowed us to increase the homogeneity of the data for the purposes of our analysis and discussion. To address our secondary objective, we analyzed each CU/CI group to see if specific cognitive outcome measures appear more often in the CU/CI group and are thus more often impaired in individuals with mTBI.

While translating the cognitive outcome measures from *Tables 4.1* to *4.4* into cognitive domains (see *Tables 5.1* to *5.4*), we had to exclude several studies for the purposes of this analysis only. We excluded studies using test batteries for which the subtests were not specified. For example, impairment on the Wechsler Adult Intelligence Scale (WAIS) could be attributed to impairment to any combination of the four cognitive domains assessed in the WAIS subtests. Similarly, The ImPACT assesses four cognitive domains across its subtests (i.e., attention, learning/memory, processing speed, and executive functions) [152]. A study reporting CI or CU on the WAIS or ImPACT, for example, without specifying which subtests were impaired would be excluded. Finally, we also excluded studies that provided binarized impairment (i.e.,

author-identified participant CI or CU) for a group of outcome measures. Studies using cognitive impairment binaries, indicated in italics throughout *Tables 4.1* to *4.4*, were not informative of the specific cognitive domains that were impaired or unimpaired. For example, Xu et al (2014) state that 40 of their participants were CI and 78 participants were CU based each participant's results from seven cognitive outcome measures. They did not, however, state which tests each participants in the CI group were impaired.

After translating the outcome measures illustrated in *Tables 4.1-4.4* into the corresponding cognitive domains (presented in *Tables 5.1-5.4*), we tallied up the results (i.e., the number of instances a cognitive domain is tested as impaired or unimpaired) and presented the findings in *Table* 6. Since our findings did not facilitate an analysis of outcome measure sensitivity and since our analysis of cognitive domains was designed as a discussion topic rather than a methodologically sound analysis, we use our results to discuss the limitations in the mTBI literature. Specifically, we will discuss how our findings (or lack thereof) are indicative of a major limitation in the mTBI literature and, in turn, in our understanding of the cognitive outcomes in individuals with mTBI.

Chapter 3: Results

3.1 Objective 1: Global Cognitive Impairment

To address our primary research objective — that is, to assess the evidence linking mTBI with long-term cognitive impairment — we dichotomized participants into two groups based on their presence or absence of cognitive impairment as evidenced by any cognitive outcome measure. Information pertaining to each CI/CU group was extracted from each study and presented in *Tables 3.1-3.4*. Specifically, *Tables 3.1-3.4* present the following pieces of information: (1) the number of participants cognitively impaired or unimpaired at each post-injury interval; (2) the method we used to determine cognitive impairment (i.e., comparison groups, author-provided normative data, or author-provided cut-off scores for a given outcome measure; (3) the mean age and SD of the participants; (4) how the authors defined mTBI (note: "Standard" refers to three criteria: GCS = 13-15, a LOC < 30 minutes, and a PTA < 24 hours); (5) whether the participants had complicated (i.e., presence of radiological findings not including a linear skull fracture) or uncomplicated mTBI; and (6) the participant inclusion criteria given for number of previous concussion.

Tables 3.1-3.4. Study and Participant Information

Table 3.1. Study information for all participants at 3 months post-injury.

CI	Study	N	Control/Method of Comparison	Age (M, SD)	mTBI Definition	C/UC	# mTBIs
	Rieger et al., 2013	39	OI: A/G/R	8-17 yr.	Standard (GCS = 14-15)	UnC	1[a]
	Phillipou et al., 2014	26	HC: A	12.8 (2.1)	Standard	—	1[b]
	Tay et al., 2010	31	A/G/E/R	40.6 (14.7)	Standard (LOC < 20 min)	UnC	1[c]
	Kwok et al., 2006	15	HC: A/G/E	38.6 (12.4)	Standard	C	—
	Su et al., 2014	54	Cut-off scores	39.8 (0.7)	Standard	—	1[a]
	Siman et al., 2013	17	HC: A/G/E	20.2 (5.4)	Standard	—	1[b]
	Ponsford et al., 2011	90	Trauma controls	35.0 (13.1)	Standard	UnC	—
	Paré et al., 2009	37	A/G/E	26.7 (10.3)	Standard	—	1[d]
CI	Kinsella et al., 2014	50	OI & HC: A/G/E	76.5 (7.6)	Standard	C	1[b]
	Marsh & Smith 1995	15	A/E	27.1 (12.6)	"Diagnosis of concussion"; LOC < 20 min	UnC	1[f]
	Xu et al., 2014	40	Cut-off scores	39.3 (13.1)	Standard	UnC	1[a]
	De Boussard et al., 2005	29	Normative data	37.2 (—)	Standard (GCS = 14-15)	C	—
	Hanten et al., 2013	59	OI & HC: A/G/R/SES	18.2 (4.6)	Standard	UnC	1[b]
	Heitger et al., 2006	37	A/G/E	29.1 (12.7)	Standard	UnC	1[e],[α]
	Bohnen et al., 1993	8	Normative data	27.2 (14.0)	Standard (GCS = 15)	UnC	1[a]
	Rotarescu & Ciurea 2008	96	Normative data	10.5 (3.4)	GCS = 14-15 w amnesia	—	—
	Ponsford et al., 1999	119	HC: A/G/E/SES	11.3 (2.9)	Standard	—	≥1[c]
	Su et al., 2014	159	Cut-off scores	39.8 (0.7)	Standard	—	1[a]
	Ponsford et al., 2000	84	HC: A/G/E/SES	26.4 (13.9)	Standard	—	≥1[c][α]
CU	Xu et al., 2014	78	Cut-off scores	39.3 (13.1)	Standard	UnC	1[a]
	De Boussard et al., 2005	68	Normative data	37.2 (—)	Standard (GCS = 14-15)	C	—
	Maillard-Wermelinger et al., 2005	186	OI: A/G/E/SES	12.0 (2.2)	Standard	C	1[b]
	Bohnen et al., 1993	33	Normative data	27.2 (14.0)	Standard (GCS = 15)	UnC	1[a]
	Levin et al., 1996	36	A/G	9.8 (3.1)	GCS = 13-15	—	—

Table 3.2. Study information for all participants at 6 months post-injury.

CI	Study	N	Control/Method of Comparison	Age (M, SD)	mTBI Definition	C/UC	# mTBIs
	Phillipou et al., 2014	26	HC: A	12.8 (2.1)	Standard	—	1[b]
	Wong et al., 2010	4	A/G/E	52 (17.9)	Standard	UnC	1[a]
	Muller et al., 2009	19	Defined norms	35.1 (—)	GCS 13-15; LOC/retrograde amnesia	C	—
	Ellemberg et al., 2007	10	A/G/E/Sport**	22.7 (—)	AAN Grade II concussion	—	—
CI	Miles et al., 2008	4	Cut-off scores	33.4 (—)	Standard	UnC	1[a]
	Wrightson et al., 1995	59	A/G/SES	3.38	"Mild head injury" diagnosis	—	1[a]
	Heitger et al., 2006	37	A/G/E	29.1 (12.7)	Standard	UnC	1[g, α]
	Bohnen et al., 1993	7	Normative Data	27.2 (14.0)	Standard (GCS = 15)	UnC	1[a]
	Babikian et al., 2011; 2013	36	Normative Data	12.7 (2.0)	Standard; AIS level 1-2	—	≥1
	Rotarescu & Ciurea 2008	96	Normative data	10.5 (3.4)	GCS = 14-15 with amnesia	—	—
	Muller et al., 2009	36	Normative Data	35.1 (—)	GCS 13-15; LOC/retrograde amnesia	C	—
	Miles et al., 2008	8	Cut-off Scores	33.4 (—)	Standard	UnC	1[a]
CU	Barrow et al., 2006	28	A/E/R	41 (—)	Standard	UnC	1[a]
	Bohnen et al., 1993	34	Normative Data	27.2 (14.0)	Standard (GCS = 15)	UnC	1[a]
	Babikian et al., 2011; 2013	88	Normative Data	12.7 (2.0)	Standard; AIS level 1-2	—	≥1

Table 3.3. Study information for all participants at 12 months post-injury.

CI	Study	N	Control/Method of Comparison	Age (M, SD)	mTBI Definition	C/UC	# mTBIs
	Catale et al., 2009	15	A/G/E/SES	8.3 (1.3)	GCS = 15; LOC < 10 min; PTA < 1 hr.	UnC	1[a]
	Lee et al., 2008	28	A/G/E	30.2 (8.0)	Standard	C	1[a]
	Polissar et al., 1994	53	A/G/E/SES	*"Children"*	GCS = 13-15	C	—
	Kashluba et al., 2008	102	Normative data	48.6 (16.4)	Standard	C	—
	Romero et al., 2015	49	Normative data	30.9 (12.4)	Standard	C	1[a]
CI	Stålnacke et al., 2007	69	A/G/E	40.9 (19.5)	GCS = 13-15; LOC < 30 min.	UnC	1[c]
	Chadwick et al., 1981	29	A/G/SES	9.6 (2.5)	1 hour < PTA < 7 days	C	—
	Wrightson et al., 1995	57	A/G/SES	3.38	"Mild head injury" diagnosis	—	1[a]
	Heitger et al., 2006	37	A/G/E	29.1 (12.7)	Standard	UnC	1[g]
	Anderson et al., 2001	17	A/G/SES	5.1 (1.5)	GCS = 13=15; "alteration of consciousness"	UnC	1[a]
	Babikian et al., 2011; 2013	21	Normative Data; OI: A/G/E/SES	12.7 (2.0)	Standard; AIS level 1-2	—	≥1
	Rotarescu & Ciurea 2008	96	Normative data	10.5 (3.4)	GCS: 14-15 w amnesia	—	—
	Wäljas et al., 2015	103	A/G	37.8 (13.5)	Standard	C	—
	Dikmen et al., 2001	157	TC: A/G/E	28.1 (11.1)	GCS = 13-15	C	—
	Zhou et al., 2013	19	A/G/E	34 (11.5)	Standard	UnC	1[a]
	Croall et al., 2014	18	A/G/E	33.9 (14.8)	Standard	—	—
CU	Maillard-Wermelinger et al., 2005	186	OI: A/G/E/SES	12.0 (2.2)	Standard	C	1[b]
	Babikian et al., 2011; 2013	55	Normative Data	12.7 (2.0)	Standard; AIS level 1-2	—	≥1
	Jaffe et al., 1995	40	A/G/E/SES	6-15 yrs	"Mild head injury with LOC"	—	1[b]
	Levin et al., 1996	36	A/G	9.8 (3.1)	GCS = 13-15	—	—

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Table 3.4. Study information for all participants at >12 months post-injury.

	Study	PII (Yr.)	N	Control/Method of Comparison	Age (M, SD)	mTBI Definition	C/UC	# mTBIs
CI	Mangels et al., 2002	1.5	10	A/G/E	29.4 (3.3)	GCS = 13-15	C	—
	Chadwick et al., 1981	2.25	29	A/G/SES	9.6 (2.5)	1 hour < PTA < 7 days	C	—
	Anderson et al., 2001	2.5	17	A/G/SES	5.1 (1.5)	GCS = 13=15; "alteration of consciousness"	UnC	1[a]
	Mangels et al., 2002	3.7	11	A/G/E	29.4 (3.3)	GCS = 13-15	C	—
	Wrightson et al., 1995	3-4	57	A/G/SES	3.38	"Mild head injury" diagnosis	—	1[a]
	McCauley & Levin (2004)	5	17	OI: A/G/SES	15.3 (2.1)	GCS = 13-15	C	—
	Geary et al., 2010	5	40	A/G/E	29.6 (1.7)	Standard	UnC	—
	Konrad et al., 2011	6	14	A/G/E	36.7 (12.4)***	Standard	C	1[a]
	Vanderploeg et al., 2005	8	254	MVA & HC: A/E/R	37.8 (2.5)	"mTBI with LOC"	—	—
CU	Jaffe et al., 1995	3	40	A/G/E/SES	6-15 yr.	"Mild head injury with LOC"	—	1[b]
	Konrad et al., 2011	6	19	A/G/E	36.7 (12.4)***	Standard	C	1[a]

A: Age; **AAN**: American Academy of Neurology; **AIS**: Abbreviated Injury Score; **C**: Complicated **E**: Education; **G**: Gender; **GCS**: Glasgow Coma Scale; **HC**: Healthy Controls; **LOC**: Loss of Consciousness; **MVA**: Motor-vehicle accident; **OI**: Orthopedic Injury Control; **PTA**: Post-Traumatic Amnesia; **SES**: Socioeconomic Status; **UnC**: Uncomplicated

AAN Grade II concussion: No LOC, transient confusion, concussion symptoms, or mental status abnormality lasting more than 15 minutes.

1[a]: No previous TBI
1[b]: No previous TBI requiring hospitalization
1[c]: Previous head injuries not excluded
1[d]: No previous TBI resulting in the loss of consciousness for >5 min
1[e]: No previous TBI with persisting symptoms
1[f]: No previous TBI requiring hospitalization in the last 6 mo.
1[g]: No previous TBI with persisting symptoms
* Impairment defined as score below 10th percentile for an age and education matched norm.
** Sport matched for type and length of involvement
***Time of testing

From *Tables 3.1-3.4*, it is apparent that the studies included in our scoping review were not completely homogeneous with respect to any of the outlined variables. For example, while we included studies that used three different methods of comparison for determining cognitive impairment (i.e., comparison groups, normative data, and cut-off scores), there was variability within the comparison groups. Some studies used a healthy control group while others used either an orthopedic injury control group or a trauma control group. Further, those that did use a healthy control group may have included different variables that were equivalent across groups (i.e., any combination of the following: age-matched, gender-matched, education-matched, and socioeconomic status-matched controls). Similarly, the studies did not all adhere to one definition of mTBI. The majority of studies used the standard definition (i.e., GCS 13-15, LOC < 30 min, PTA < 24 hours), however, some studies either adhered to a variation of the standard definition (i.e., standard definition with the exception of a GCS = 14-15) or an entirely different definition (i.e., PTA > 1 hour and < 24 hours). Further to the above, it is also apparent from *Tables 3.1-3.4* that the studies included in our review were not consistent in their inclusion or exclusion of participants with complicated mTBI. Some studies included those with complicated mTBI, others excluded them, and the remaining studies failed to provide this information. Finally, *Tables 3.1-3.4* also show that the studies in our review were not consistent regarding their inclusion/exclusion criteria of participants with previous mTBIs. Interestingly, 18 studies did not specify whether or not their participants had sustained a previous mTBI. This entertains the possibility that the participants in these studies were not first-time concussed. For this reason, and since some studies specifically did not exclude those with previous concussions, we included this variable in our data analysis (discussed below).
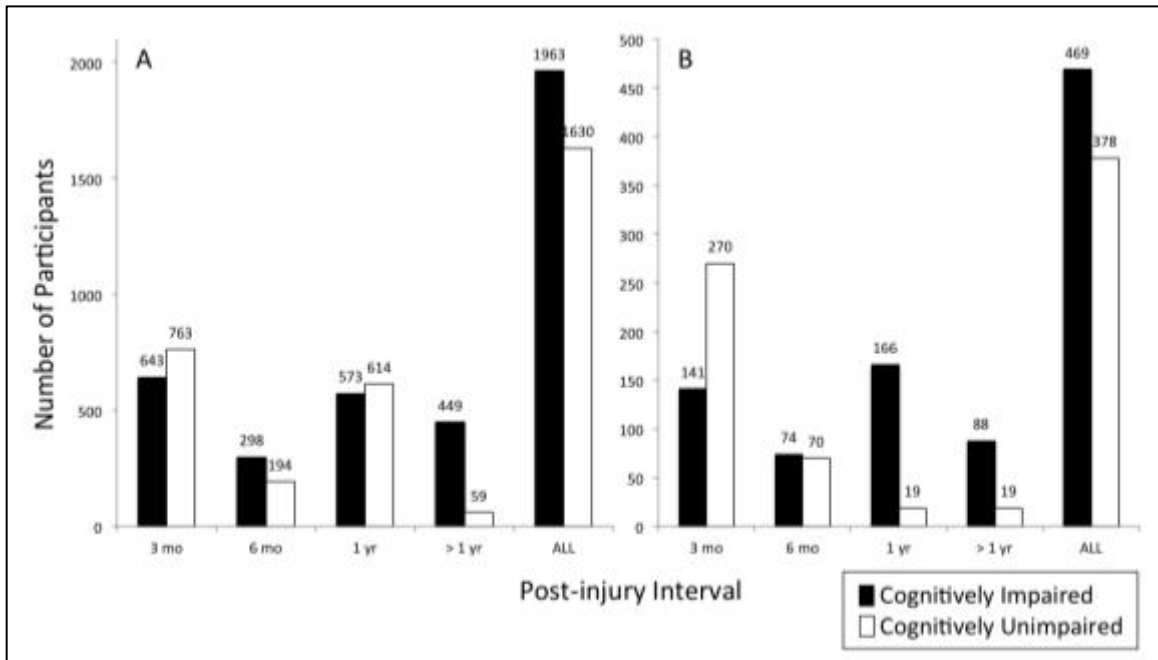
Figure 4. Global Cognitive Impairment. (A) Presence of cognitive impairment in individuals at various time points post-injury from studies reporting cognitive outcomes using either author-supplied normative data or comparison groups (i.e., healthy or trauma controls). (B) Presence of cognitive impairment in individuals with a history of a single concussion only.

Figure 4, A illustrates the overall incidence of cognitive impairment in individuals with mTBI at various post-injury intervals for all studies included in our scoping review. *Figure 4, B* illustrates the overall incidence of cognitive impairment at the same post-injury intervals, however, only for participants who had a reported history of a single concussion. In other words, this analysis exclusively included studies that stated that they excluded participants with previous mTBIs. This criteria is represented in the final column of *Tables 3.1-3.4* as 1[a], or "no previous TBI". The results from each post-injury interval are collapsed together in the final cluster of columns in each *Figure 4, A* and *B* to yield a total number of participants who show long-term cogntive impairment across all studies and all time points in our scoping review. It is important to note, however, that participants who were tested across multiple time points are accounted for more than once in *Figure 4*. For example, prospective studies that assess participants at say, both 3- and 6-months post injury would be represented at both time points in *Figure 4*. Thus, when we collapse all post-injury intervals in the last cluster of columns, participants from those studies will have been accounted for more than once.

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Figure 4 collectively demonstrates that the incidence of individuals who show persitent cognitive impairment following an mTBI is much higher than previous estimates (i.e., around 15%) in the literature [35], [36], [9], [37], [38], [153]. While our methodology was not designed to determine the incidence of individuals who will present with long-term cognitive impairment following an mTBI, our results do not support the conclusions that mTBI only causes persistent cognitive impairment in a small subset of individuals. Specifically, 1963 participants out of 3593, or approximately 55% of our sample collapsed across all time points showed cognitive impairment. Interestingly, after filtering out the studies that did not ensure their participants were first-time concussed (*Figure 4, B*), we still show 55% of our participant sample collapsed across all time points were cognitively impaired (i.e., 469 participants out of 847). Thus, *Figure 4, B* demonstrates that the high incidence of long-term cognitive impairment in our results cannot be attributed to the possibility that a subset of participants in *Figure 4, A* may have experienced more than one mTBI. Interestingly, our results do not hint towards a temporal relationship of cognitive impairment wherein participants were less likely to be cognitively impaired at later post-injury intervals. This is evident in both *Figure 4, A* and *B* in that the incidence of cognitive impairment did not wither over time — however, our participant sample was not representative of only studies using prospective and longitudinal study designs. Specifically, *Figure 4, A* demonstrates that 46% of the participant sample was cognitively impaired at 3 months, 61% at 6 months, 48% at 12 months, and 88% at >12 months post-injury. We do not take the particularly high percentage of participants that were cognitively impaired at the >12 months post-injury interval to show that individuals are more likely to be cognitively impaired after 12 months. Instead, this finding is likely attributable to the limited number of studies assessing individuals past one year.

To determine whether our results were similar in both children (<18 years) and adults (≥18 years), we present the data from *Figure 4, A* again in *Figure 5*, this time additionally demonstrating age as a third variable. Based on this analysis, it does not appear that age had any impact on the high incidence of long-term cognitive impairment

in individuals with mTBI. While there does appear to be many more adults in the CI group than in the CU group at the >12 months post-injury interval, this is likely due to the limited number of studies we had reporting cognitive outcomes at this time interval. The last cluster of columns in *Figure 5* can be quantified as follows: 786 children with cognitive impairment; 786 children without cognitive impairment; 1177 adults with cognitive impairment; and 844 adults without cognitive impairment. In other words, 50% of the children and aproximately 58% of the adults in our scoping review showed some form of cognitive impairment.
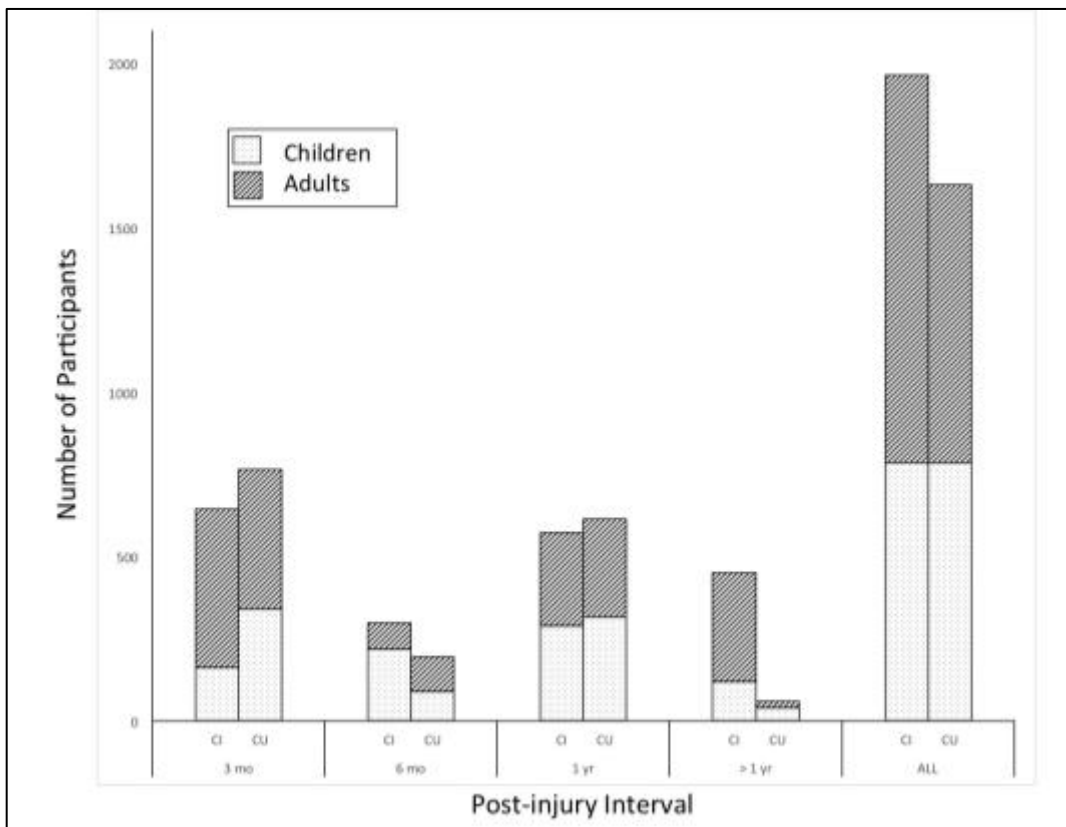

Figure 5. Child Versus Adult Global Cognitive Impairment. Cognitive impairment in children and adults at each post-injury interval (i.e., 3 mo, 6 mo., 12 mo., and greater than 12 mo.) and overall.

3.2 Objective 2: Outcome Measures and Impaired Cognitive Domains

3.2.1 Outcome Measures

After determining the CI/CU status of the participants in each study, we organized the outcome measure information into four tables for each post-injury interval (i.e., 3 mo., 6 mo., 12 mo., and > 12 mo.; see *Tables 4.1-4.4*, respectively). Unfortunately, there were few outcome measures that were repeated across multiple studies: of our 48 studies, there were 74 outcome measures excluding subtests and few were repeated across multiple studies. Moreover, a glance through *Tables 4.1-4.4* reveals how two studies using the same outcome measure reported their results differently thus further limiting the homogeneity of the studies. For example, *Table 4.1* shows that Phillipou et al. (2014) and Ponsford et al. (2011) each administered the ImPACT to their participants but presented the data differently. While Phillipou et al. (2014) provide the data from each subtest of the ImPACT (i.e., the immediate design memory task, the immediate word memory task, the delayed word memory task, and the delayed design memory task), Ponsford et al (2011) provide the composite scores for verbal memory, visual memory, motor speed, and reaction time. The composite scores provided by Ponsford et al (2011) are derived from the ImPACT subtests but the differential presentation of the results makes comparison difficult. Thus, while our intent was to use the data presented in *Tables 4.1-4.4* to discuss how certain outcome measures were more effective in demonstrating cognitive impairment than others, the data did not facilitate this analysis.

Tables 4.1-4.4 indicate in italics the studies where the authors provided cognitive impairment binary information for a group of cognitive outcome measures. For example, Xu et al. (2014) in *Table 4.1* used seven cognitive tests to binarize their participants into CI/CU groups. Unlike studies providing the raw data from the administered cognitive outcome measures, we classified these participants into *our* CI/CU groups according to the study authors' classification of CI/CU. Thus, participants from these studies were easy to binarize, however, we were unable to determine which cognitive outcome measures account for their classification as CI/CU. In the case of Xu et al (2014), 40 of

their participants were CI and 78 were CU based on their performance on seven cognitive outcome measures. It remains unknown which combination of the seven outcome measures detected impairment in the 40 participants in the CI group.

While we were unable to conduct the intended analysis, our findings are still revealing of the general inconsistencies in the mTBI literature. Specifically, the lack of homogeneity we found in our scoping review is reflective of the lack of homogeneity among the mTBI literature with respect to the use of outcome measures to assess long-term cognitive impairments in individuals with mTBI. This finding was not anticipated but it is nonetheless important. The Discussion section will elaborate on the implications.

Tables 4.1-4.4. Cognitively Impaired/Unimpaired Outcome Measures. Outcome measures showing cognitive impairment (CI) and not showing cognitive impairment (CU) across all studies assessing participants at 3 months post-injury (*Table 4.1*), 6 months post-injury (*Table 4.2*), 12 months post-injury (*Table 4.3*), and >12 months post-injury (*Table 4.4*).

Table 4.1.

CI	Study ID	N	Outcome Measures Showing CI **Test:** Subtest (Measure)	Outcome Measures Showing CU **Test:** Subtest (Measure)
CI	Rieger et al., 2013	39	**ImPACT:** (Visual memory composite) **PPVT-III***	**ImPACT:** (Overall)
	Phillipou et al., 2014	26	**ImPACT:** Immediate Design Memory Task (Correct responses); Delayed word memory task (Correct responses); Immediate word memory task (Correct responses)	**ImPACT:** Immediate design memory (Processing speed); Delayed word memory (Processing speed); Delayed design memory (% correct & Processing speed); **PPVT**
	Tay et al., 2010	31	**Memory for Intentions Screening Test**	—
	Kwok et al., 2006	15	**Digit Vigilance Test; Chinese AVLT**	**Colour Trails; Stroop; SDMT; WAIS:** Digit Span; **Verbal Fluency; Benton Visual Retention Test; Figural Fluency Test**
	Su et al., 2014	54	**MoCA**	—
	Siman et al., 2013	17	**SDMT; KTT**	—
	Ponsford et al., 2011	90	**ImPACT**: (Visual Memory)	**ImPACT**: (Verbal Memory; Motor Speed; RT)
	Paré et al., 2009	37	**TAPI:** (RT)	—
	Kinsella et al., 2014	50	**CAMPROMPT; TMT** ***Verbal Fluency:** Word & Letter; **HVLT-R**	—
	Marsh & Smith 1995	15	**PASAT; Stroop; Verbal Fluency:** COWAT	**WAIS-R** (short form); **TMT:** Part B; **SRT; CFT**
	Xu et al., 2014	40	*Concept Shifting Test; TMT; Stroop; VVLT; Verbal Fluency; LDST; RT:* Motor Choice	—
	De Boussard et al., 2005	29	*WAIS-R: Information, Digit Span, Digit Symbol, Block Span; SRT; Stroop; PASAT; TMT: Part A. Part B*	—
	Hanten et al., 2013	59	**KTT**	—
	Heitger et al., 2006	37	**CVLT**: SDFR; SDCR; LDFR; LDCR; (Total Standard Score)	**PASAT; TMT:** Part A, Part B; **WAIS**: Vocabulary, Matrix Reasoning; **SDMT**
	Bohnen et al., 1993	8	**Stroop**	—
	Rotarescu & Ciurea 2008	96	**RAVLT**	**WAIS:** Digit Span
CU	Ponsford et al., 1999	119		**WRAML; WAIS**: Digit Span, Coding; **CHIPASAT; Contingency Naming Task**
	Su et al., 2014	159		**MoCA**
	Ponsford et al., 2000	84		**Reaction Time Tests**: Four-choice; **WAIS-R**: Digit Span, Digit Symbol; **PASAT; RAVLT; Speed and Capacity of Language Processing Test:** Speed of Comprehension
	Xu et al., 2014	78	—	*Concept Shifting Test; TMT; Stroop; VVLT; Verbal Fluency; LDST; RT:* Motor Choice
	De Boussard et al., 2005	68		*WAIS-R: Information, Digit Span, Digit Symbol, Block Span; Buschke SRT; Stroop; PASAT; TMT: Part A, Part B*
	Maillard-Wermelinger et al., 2005	186		**CANTAB:** Stocking of Cambridge. Spatial Working Memory Task
	Bohnen et al 1993	33		**Stroop**
	Levin et al., 1996	36		**Verbal Fluency**: Word, Category; **CVLT; WISC-R:** Vocabulary; **Semantic Verification**

Table 4.2.

CI	Study ID	N	Outcome Measures Showing CI Test: Subtest (Measure)	Outcome Measures Showing CU Test: Subtest (Measure)
CI	Phillipou et al., 2014	26	**Immediate Design Memory Task** (Processing speed)	**PPVT; Immediate Design Memory** (Correct responses)**; Delayed Word Memory** (Correct responses, Processing speed)**; Delayed Design memory** (Correct responses, Processing Speed)**; Immediate Word Memory** (Correct responses, Processing speed)
	Wong et al., 2010	4	2 of 4: **NCCEA**: Token Test	3 of 4: **BNT**
			1 of 4: **Verbal fluency; BNT; SCATBI**: Orientation, Recall, Reasoning; (Total Score)	2 of 4: **SCTABI**
			4 of 4: **TLC-E** ; **TWT-R**	
	Muller et al., 2009	19	*WMS-R; TMT: Part A; Grooved Pegboard; CVLT; Verbal Fluency: COWAT; RT: Simple, Complex; TAP: Go/No-go; Stroop; WCST*	—
	Ellemberg et al., 2007	10	**Stroop:** (Inhibition time, Accuracy); **TOL** (Planning time, Accuracy); **RT:** Complex	**CVLT; Ruff 2&7; Brief Test of Attention; SDMT; TOL** (Execution time)
	Miles et al., 2009	4	*Weinberg Visual Cancellation Test; RIRMS; Stroop; PriA; PriB; WTT; Verbal Fluency: COWAT; Headminder Cognitive Stability Index*	—
	Wrightson et al., 1995	59	**Illinois test of Psycholinguistic Abilities**: Visual Closure Test	**Illinois test of Psycholinguistic Abilities**: Auditory reception, Visual reception, Visual sequential memory, Auditory association, Auditory memory, Visual association, Verbal expression, Grammatical closure, Manual expression
	Heitger et al., 2006	37	**CVLT**: SDCR; LDFR; (Total standard score) ***CVLT:** SDFR, LDCR	**PASAT; TMT:** Part A, Part B; **WAIS:** Vocabulary, Matrix Reasoning; **SDMT**
	Bohnen et al., 1993	7	**Stroop**	—
	Babikian et al., 2011; 2013	36	*Prospective Memory Test; Picture Memory Test; Word List Memory Test; SDMT; Colour Trails (Child's Version): Part B ; Pin Test; Span of Apprehension Test; Stroop; DS-CPT; PPVT-R*	—
	Rotarescu & Ciurea 2008	96	**RAVLT** (Attention volume)	**RAVLT** (Memory volume); **WAIS:** Digit span
CU	Muller et al., 2009	36		*WMS-R; TMT: Part A; Grooved Pegboard; CVLT; COWAT; RT: Simple, Complex; TAP: Go/No-go; Stroop; WCST*
	Miles et al., 2009	8		*Weinberg Visual Cancellation Test; RIRMS; Stroop; PriA; PriB; WTT; Verbal Fluency: COWAT; Headminder Cognitive Stability Index*
	Barrow et al., 2006	28	—	**Speeded Naming Task**: Simple, Complex (Response latencies and accuracy)
	Bohnen et al., 1993	34		**Stroop**
	Babikian et al., 2011; 2013	88		*Prospective Memory Test; Picture Memory Test; Word List Memory Test; SDMT; Colour Trails (Child's Version): Part B ; Pin Test; Span of Apprehension Test; Stroop; DS-CPT; PPVT-R*

Table 4.3.

CI	Study	N	Outcome Measures Showing CI **Test:** Subtest (Measure)	Outcome Measures Showing CU **Test:** Subtest (Measure)
	Catale et al., 2009	15	**TAP**: Visual selective attention task (Correct responses); Auditory selective attention task (Accuracy); Divided Attention task (Accuracy); **Go/No-go task**; **Working Memory Task**	**WISC-III**: Similarities, Vocabulary, Block Design, Picture arrangement; **Tonic & Phasic alertness**; **TAP**: Visual selective attention task (RT, False responses); Auditory selective attention task (RT; False responses); Divided Attention task (RT, False responses); **Go/No-go task** (RT); **Working Memory** (RT)
	Lee et al., 2008	28	**CVLT**: LDCR; (Total recall Trials 1-5) *CVLT*: SDFR, SDCR, LDFR	—
	Polissar et al., 1994	53	**WISC-R**: Vocabulary, Block design; **CVLT**: SDFR, SDCR, LDFR, SDCR; (Long-term recognition)	**WISC-R**: Information, Similarities, Arithmetic, Comprehension, Digit Span, Picture Completion, Picture Arrangement, Object Assembly; (Full scale IQ; Verbal Scale IQ; Performance IQ); **Category Test**; **Generic progressive figures**; **General colour form**
	Kashluba et al., 2008	102	**Logical memory I; RAVLT; SDMT; TMT**: Part A, Part B**; WAIS**: Block design**; WCST Stroop**	**Logical memory II; WAIS**: Digit backwards**; Verbal Fluency**: COWAT
	Romero et al., 2015	49		—
	Stålnacke et al., 2007	69	**Stroop**: (Processing speed); **TMT**: Part A *TMT*: Part B	**Stroop**: (Interference, % Adaptation); **Automated Psychological Test System**: Finger-tapping; RT (Auditory, Visual, Two-choice, Inhibition); **PASAT**
CI	Chadwick et al., 1981	29	**WISC**: Coding; (Verbal IQ)	**WISC**: Digit Span; (Performance IQ)
	Wrightson et al., 1995	57	**Illinois test of Psycholinguistic Abilities**: Visual Closure Test	**Illinois test of Psycholinguistic Abilities**: Auditory reception, Visual reception, Visual sequential memory, Auditory association, Auditory memory, Visual association, Verbal expression, Grammatical closure, Manual Expression
	Heitger et al., 2006	37	**CVLT**: (total standard score)	**PASAT; TMT**: Part A, Part B**; WAIS**: Vocabulary, Matrix Reasoning**; SDMT; CVLT**: SDFR, SDCR, LDFR, LDCR
	Anderson et al., 2001	17	**WMS-R**: Story Recall	**WISC-III/WPPSI-R**: Information, Similarities, Vocabulary, Comprehension, Picture Completion, Block Design, Object Assembly, Sentences, Arithmetic, Animal Pegs; (Performance IQ, Full Scale IQ); **Verbal Fluency Test; EOWPVT; PPVT-R; Test of Auditory Comprehension of Language-Revised; Spatial Learning Test**
	Babikian et al., 2011; 2013	21	*Prospective Memory Test; Picture Memory Test; Word List Memory Test; SDMT Colour Trails (Child's Version): Part B; Pin Test; Span of Apprehension Test; Stroop; DS-CPT; PPVT-R*	—
	Rotarescu & Ciurea 2008	96	**RAVLT** (Attention volume)	**RAVLT** (Memory volume); **WAIS**: Digit Span
	Wäljas et al., 2015	103		**RAVLT**
	Dikmen et al., 2001	157		**Seashore Rhythm Test; SRT; TMT**: Part B**; WAIS**: (Performance IQ)
	Zhou et al., 2013	19		**SDMT; WAIT**: Digit span**; TMT**: Part A, Part B**; CVLT; Rey's CFT; PASAT**
	Croall et al., 2014	18		**Verbal Fluency**: Letter, Category; **PASAT; WAIS**: Digit span (backwards); **List Learning; Design Learning; TOL; Stroop**
	Maillard-Wermelinger et al., 2005	186		**CANTAB**: Stockings of Cambridge; Spatial Working Memory
CU	Babikian et al., 2011; 2013	55	—	*Prospective Memory Test; Picture Memory Test; Word List Memory Test; SDMT; Colour Trails (Child's Version): Part B; Pin Test; Span of Apprehension Test; Stroop; DS-CPT; PPVT-R*
	Jaffe et al., 1995	40		**WISC-R/WAIS-R**: Information, Similarities, Arithmetic, Vocabulary, Comprehension, Digit Span, Picture Completion, Picture Arrangement, Coding, Object Assembly; (Full Scale IQ, Verbal IQ, Performance IQ); **Category Test; TMT**: Part B**; CVLT**: SDFR, SDCR, LDFR, LDCR; (Long-term recognition); **Tactual Performance Test**
	Levin et al., 1996	36		**Verbal Fluency Test**: Category, Word; **CVLT; Semantic Verification; WISC-R**: Vocabulary

Table 4.4.

CI	Study	N	PII (Yr.)	Outcome Measures Showing CI Test: Subtest (Measure)	Outcome Measures Showing CU Test: Subtest (Measure)
CI	Mangels et al., 2002	10	1.5	**Verbal Fluency Test**: Phonemic	**WAIS-R**: Information, Vocabulary, Digit Span, Digit Symbol; **WMS-R**: Figural memory (Immediate & Delayed); Paired Association (Immediate & Delayed); Story Recall (Immediate & Delayed); **WCST**
	Chadwick et al., 1981	29	2.25	**WISC**: Coding	**WISC**: Digit Span; (Verbal IQ, Performance IQ)
	Anderson et al., 2001	17	2.5	**Story Recall Test; Verbal Fluency Test**	**WISC-III/WPPSI-R**: Information, Similarities, Vocabulary, Comprehension, Picture Completion, Block Design, Object Assembly, Sentences, Arithmetic, Animal Pegs; (Performance IQ, Full Scale IQ); **EOWPVT**; **PPVT-R**; **Test of Auditory Comprehension of Language-Revised**; **Spatial Learning Test**
	Mangels et al., 2002	11	3.7	**Free Recall Task:** Divided attention; (Recognition memory performance)	**BNT; Stroop; TMT**: Part A, Part B; **Digit Monitoring Task; Free Recall Task:** Focussed attention; **Scene-Cued Recall Task**: Focussed & Divided attention
	Wrightson et al., 1995	57	3-4	**Illinois test of Psycholinguistic Abilities:** Visual Closure Test	**WISC**: Coding; **WMS**: Visual memory test, Paired Associate learning; **Verbal memory passage; Frostig development test of visual perception; Letter knowledge and writing; Neale analysis of reading ability**
	McCauley & Levin, 2004	17	5	**Prospective Memory Task**	—
	Geary et al., 2010	40	5	**CVLT-II**: (Trial 1 (List A), Learning slope)	**CVLT-II**: SDFR, SDCR, LDFR, LDCR; (Trials 2-5 (List B))
	Konrad et al., 2011	14	6	*AVLT (German); WMS-R (German): Digit Span; TAP (German): Working memory, Divided Attention, Go/No-go; TMT: Part A, B;* **Verbal Fluency Test**: *Letter, Category;* **Word Memory Test** *(German adaptation): (Immediate recognition, Delayed recognition, Consistency)*	—
	Vanderploeg et al., 2005	254	8	**PASAT**: (Rate of continuation); **CVLT**: (Proactive Interference)	**Grooved Pegboard Test; PASAT; WAIS-R**: Information, Block Design); **Verbal Fluency**: COWAT (FAS) **Animal Naming Test; Rey's CFT; CVLT**: LDFR (Total correct words, Recognition Hits)**; WCST**
CU	Jaffe et al., 1995	40	3		**WAIS-R**: Information, Similarities, Arithmetic, Vocabulary, Comprehension, Digit Span, Picture Completion, Picture Arrangement, Coding, Object assembly; **Category Test; TMT**: Part B; **CVLT**: SDFR, SDCR, LDFR, LDCR; (Long-term recognition)
	Konrad et al., 2011	19	6	—	*AVLT (German); WMS-R (German): Digit Span; TAP (German): Working memory, Divided Attention, Go/No-go; TMT: Part A, B;* **Verbal Fluency Test**: *Letter, Category;* **Word Memory Test** *(German adaptation): (Immediate recognition, Delayed recognition, Consistency)*

AVLT: Auditory Verbal Learning Test; **BNT**: Boston Naming Test; **CAMPROMPT**: Cambridge Prospective Memory Test; **CANTAB**: Cambridge Neuropsychological Test Automated Battery; **CFT**: Complex Figure Test; **CHIPASAT**: Children's Paced Auditory Serial Addition Test; **COWAT**: Controlled Oral Word Associated Test; **CPT**: Continuous Performance Test; **CVLT** California Verbal Learning Test; **DS-CPT**: Degraded Stimulus Continuous Performance Test; **EOWPVT**: Expressive One Word Picture Vocabulary Test; **HVLT-R**: Hopkins Verbal Learning Test-Revised; **ImPACT**: Immediate Post-Concussion Assessment and Cognitive Testing; **KTT**: Keep Track Task; **LDCR**: Long-Delay Cued Recall; **LDFR**: Long-Delay Free Recall; **LDST**: Letter Digit Substitution Test; **MoCA**: Montreal Cognitive Assessment; **NCCEA**: Neurosensory Center Comprehensive Examination for Aphasia; **PASAT**: Paced Auditory Serial Addition Test; **PPVT**: Peabody Picture Vocabulary Test; **PriA/PriB**: Prioritization Form A/B; **RAVLT**: Rey's Auditory Verbal Learning Test; **RIRMS**: Rusk Institute Rehab Medicine Similarities; **RT**: Reaction time; **SCATBI**: Scales of Cognitive Ability for Traumatic Brain Injury; **SDCR**: Short-Delay Cued Recall; **SDFR**: Short-Delay Free Recall; **SDMT**: Symbol Digit Modalities Test; **SRT**: Selective Reminding Test; **TAP**: Test of Attentional Performance; **TAPI**: Test d'Attention Partagée Informatisé; **TLC-E**: Test of Language Competence: Expanded Edition; **TMT**: Trail Making Test; **TOL**: Tower of London; **TWT-R**: The Word Test-Revised; **VVLT**: Visual Verbal Learning Test; **WAIS**: Wechsler Adult Intelligence Scale; **WCST**: Wisconsin Card Sorting Test; **WISC-R**: Wechsler Intelligence Scale for Children; **WMS-R**: Wechsler Memory Scale — Revised; **WPPSI-R**: Wechsler Preschool and Primary Scale of Intelligence; **WRAML**: Wide Range Assessment of Memory and Learning; **WTT**: Will Temperament Test;

3.2.2 Cognitive Domains

To increase the homogeneity of the data for the purpose of analysis and discussion, we translated each cognitive outcome measure from *Tables 4.1-4.4* into its corresponding cognitive domain (being measured) and input this information into *Tables 5.1-5.4*. The information from *Tables 5.1-5.4* was extracted and summarized in *Table 6*. *Table 6* therefore illustrates the number of times a cognitive domain was tested and either did show cognitive impairment (CI) or did not show cognitive impairment (CU) at each post-injury interval and overall (i.e., collapsed across all post-injury intervals). In the final column of *Table 6*, we present the incidence, as a percent, of a given cognitive domain that detected cognitive impairment across all time points.

Unfortunately, this analysis provided no more information than the analysis from *Tables 4.1-4.4*. This is owing to the multitude of limitations posed by this analysis. Those will be further examined in the *Discussion*. Without regard of the limitations, the numbers alone may suggest that executive functions, attention, and learning/memory are more prone to cognitive impairment than processing speed and language function. Outcome measures assessing the former three cognitive domains (EFs, attention, and learning/memory) detected cognitive impairment 32%, 31.5%, and 29% of the time, respectively (*Table 6*). Outcome measures assessing the latter two cognitive domains (processing speed and language function) only detected cognitive impairment 22% and 14.3% of the time, respectively (*Table 6*). We caution a literal interpretation of these numbers, however, because of the limitations posed by this analysis. Nonetheless, this analysis further supports our finding that the mTBI literature is lacking in homogeneity with respect to the cognitive outcome measures used to detect cognitive impairment as well as the cognitive domains that are being assessed.

Tables 5.1-5.4. Cognitively Impaired/Unimpaired Cognitive Domains. Cognitive domains that were impaired (CI) and unimpaired (CU) across all studies assessing individuals at 3 months post-injury (*Table 5.1*), 6 months post-injury (*Table 5.2*), 12 months post-injury (*Table 5.3*), and >12 months post-injury (*Table 5.4*).

Table 5.1.

CI	Study ID	N	Outcome Measures Showing CI Test: Subtest (Measure)	Outcome Measures Showing CU Test: Subtest (Measure)
	Tay et al., 2010	31	**L&M**	—
	Kwok et al., 2006	15	**Attention** **L&M**	**Attention, EFs** **EFs** **Attention, Processing Speed** **L&M** **EFs** **L&M** **EFs**
	Siman et al., 2013	17	**Processing Speed, Attention** **L&M, EFs**	—
	Ponsford et al., 2011	90	**L&M**	**L&M; Processing Speed**
	Paré et al., 2009	37	**Attention**	—
	Kinsella et al., 2014	50	**L&M** **Attention, Processing Speed, EFs** ***EFs; L&M**	—
	Marsh & Smith 1995	15	**Processing Speed, Attention, L&M** **EFs, Attention** **EFs**	**L&M** **Attention, Processing Speed, EFs** **L&M** **L&M**
	Hanten et al., 2013	59	**L&M, EFs**	—
	Heitger et al., 2006	37	**L&M**	**Attention, Processing Speed, L&M** **Attention, Processing Speed, EFs** **Language Function, EFs** **Processing Speed; Attention**
	Bohnen et al., 1993	8	**EFs, Attention**	—
	Rotarescu & Ciurea 2008	96	**L&M**	**L&M**
	Ponsford et al., 1999	11 9		**L&M** **L&M; Processing Speed** **Processing speed, Attention, L&M** **Processing Speed, EFs**
	Ponsford et al., 2000	84		**Processing Speed** **L&M; Processing Speed** **Processing speed, Attention, L&M** **L&M** **Language Function, Processing Speed**
CU			—	
	Maillard-Wermelinger et al., 2005	18 6		**EFs, L&M**
	Bohnen et al 1993	33		**EFs, Attention**
	Levin et al., 1996	36		**EFs** **L&M** **Language Functions** **L&M; Language Function**

60

Table 5.2.

CI	Study ID	N	Outcome Measures Showing CI **Test:** Subtest (Measure)	Outcome Measures Showing CU **Test:** Subtest (Measure)
	Phillipou et al., 2014	26	**L&M, Processing Speed**	**Language Function** **L&M, Processing Speed**
	Wong et al., 2010	4	<u>2 of 4:</u> **Language Function**	<u>3 of 4:</u> **Language Function**
			<u>1 of 4:</u> **EFs** **Language Function** **EFs**	<u>2 of 4:</u> **EFs**
			<u>4 of 4:</u> **Language Function** **Language Function**	
CI	Ellemberg et al., 2007	10	**EFs, Attention** **EFs** **Processing Speed**	**L&M** **Attention** **Attention** **EFs** **Processing Speed, Attention**
	Wrightson et al., 1995	59	**EFs**	**Language Function, L&M**
	Heitger et al., 2006	37	**L&M**	**Processing speed, Attention, L&M** **Attention, Processing Speed, EFs** **EFs, Language Function** **Processing Speed, Attention** (Divided)
	Bohnen et al., 1993	7	**EFs, Attention**	—
	Rotarescu & Ciurea 2008	96	**Attention**	**L&M** **L&M**
	Barrow et al., 2006	28		**Processing Speed**
	Bohnen et al., 1993	34		**EFs, Attention**

Table 5.3.

CI	Study	N	Outcome Measures Showing CI Test: Subtest (Measure)	Outcome Measures Showing CU Test: Subtest (Measure)
	Catale et al., 2009	15	**Attention (Visual, selective, divided), EFs L&M (Working)**	**Language Function, EFs** **Processing Speed, Attention** **Attention** **EFs** **L&M (Working)**
	Lee et al., 2008	28	**L&M (Verbal)**	—
	Polissar et al., 1994	53	**Language Function, EFs** **L&M** (Verbal)	**Language Functions, L&M (Working), EFs** **EFs** **Processing Speed, EFs** **Processing Speed, EFs**
	Kashluba et al., 2008	10 2	**L&M** **L&M (Verbal)** **Attention** (Visual)**, Processing Speed, EFs** **EFs** **EFs**	**L&M** **L&M (Working)** **EFs**
	Romero et al., 2015	49	**EFs, Attention**	—
CI	Stålnacke et al., 2007	69	**EFs, Attention** **Attention** (Visual)**, Processing Speed** ***Attention** (Visual)**, Processing Speed, EFs**	**EFs, Attention** **Processing Speed** **Processing speed, Attention, Memory** (Immediate)
	Chadwick et al., 1981	29	**Processing Speed**	**L&M (Working)**
	Wrightson et al., 1995	57	**EFs**	**Language Function, L&M**
	Heitger et al., 2006	37	**L&M (Verbal)**	**Processing speed, Attention, Memory** (Immediate) **Attention** (Visual)**, Processing Speed, EFs** **Language Function, EFs** **Processing Speed, Attention (Divided)** **L&M (Verbal)**
	Anderson et al., 2001	17	**L&M**	**Language Function, Processing Speed, EFs, L&M** (Working) **EFs** **Language Function** **Language Function** **Language Function** **L&M** (Spatial)
	Rotarescu & Ciurea 2008	96	**L&M (Verbal)**	**L&M (Verbal)** **L&M (Working)**
	Wäljas et al., 2015	10 3		**L&M (Verbal)**
	Dikmen et al., 2001	15 7		**Attention (Sustained)** **Memory (Verbal)** **Attention** (Visual)**, Processing Speed, EFs**
	Zhou et al., 2013	19		**Processing Speed, Attention** (Divided) **Memory (Working)** **Attention** (Visual)**, Processing Speed, EFs** **L&M (Verbal)** **L&M (Visual)** **Processing speed, Attention, Memory** (Immediate)
CU			—	
	Croall et al., 2014	18		**EFs** **PS, Attention, L&M** (Immediate) **L&M (Working)** **EFs** **EFs, Attention**
	Maillard-Wermelinger et al., 2005	18 6		**EFs; L&M (Working)**

Jaffe et al., 1995	40	**L&M** (Working); **Processing Speed, EFs, Language Function** **EFs** **Attention** (Visual), **Speed of Processing, EFs** **L&M (Verbal)** **EFs**
Levin et al., 1996	36	**EFs** **L&M (Verbal)** **L&M, Language Function** **Language Function**

Table 5.4.

CI	Study	N	PII (Yr.)	Outcome Measures Showing CI **Test:** Subtest (Measure)	Outcome Measures Showing CU **Test:** Subtest (Measure)
	Mangels et al., 2002	10	1.5	**EFs**	**Language Function, L&M (Working), Processing Speed L&M EFs**
	Chadwick et al., 1981	29	2.25	**Processing Speed**	**L&M (Working); Language Function, Processing Speed, EFs**
	Anderson et al., 2001	17	2.5	**L&M** **EFs**	**L&M (Working); Language Function, Processing Speed, EFs** **Language Function** **Language Function** **Language Function** **L&M** (Spatial)
	Mangels et al., 2002	11	3.7	**Attention (Divided), L&M**	**Language Function** **EFs, Attention** **Attention** (Visual), **Processing Speed, EFs** **Attention** (Divided) **Attention** (Focused, Divided) **Attention** (Focused, Divided)
CI	Wrightson et al., 1995	57	3-4	**EFs**	**Processing Speed** **L&M (Visual)** **L&M (Verbal)** **EFs** **Language Function** **Language Function**
	McCauley & Levin, 2004	17	5	**L&M**	—
	Geary et al., 2010	40	5	**L&M**	**L&M**
	Vanderploeg et al., 2005	25 4	8	**Processing speed, Attention, L&M** (Immediate Memory) **L&M**	**Processing Speed, Attention, L&M (Immediate)** **Language Function, EFs** **EFs** **L&M (Visual Memory)** **L&M** **EFs**
CU	Jaffe et al., 1995	40	3	—	**Language Function, L&M, Processing Speed, EFs** **EFs** **Attention, Processing Speed, EFs** **L&M**

EFs: Executive Functions

Table 6. Cognitive Domain Summary Data. Number of cognitive domains showing cognitive impairment (CI) or cognitive unimpairment (CU) at each post-injury interval and overall, as measured using cognitive outcome measures that target given cognitive domains.

		3 mo	6 mo	12 mo	> 12 mo	Overall	% CI
Attention	CI	7	3	5	2	17	31.5
	CU	8	7	15	7	37	
EFs	CI	6	6	9	3	24	32
	CU	11	5	23	12	51	
Language Function	CI	0	4	1	0	5	14.3
	CU	4	4	11	11	30	
L&M	CI	9	2	8	6	25	29
	CU	17	6	26	12	61	
Processing Speed	CI	3	2	4	2	11	22
	CU	11	5	15	8	39	

Chapter 4: Discussion

The last several decades of mTBI research has seen an expansion in our understanding of the injury's long-term consequences. While mTBI used to be thought of as an inconsequential "mild" injury, it is now more closely associated with the latter three letters of its acronym — "traumatic brain injury". This shift in our understanding of mTBI and its long-term consequences is owing to several revelations in the research, as outlined in *Figure 1* (see *Introduction*). Briefly, researchers have shown the following: first, both single and multiple mTBI(s) induce pathophysiological changes to the brain that can be detected in both the acute and chronic phases post-injury (*Figure 1, Quadrants A & C*). They have also shown how these pathophysiological changes manifest as measurable cognitive impairment in both single or multiple mTBI(s) in the acute phase post-injury (*Figure 1, Quadrant B*). Further, researchers have shown how individuals with multiple mTBIs or lifetime mTBI exposure develop chronic pathological cognitive impairment in tandem with neurodegeneration (i.e., CTE; *Figure 1, Quadrant D, lower half*). Interestingly, the mTBI literature has not consistently shown measurable chronic behavioural impairments to cognition in individuals with a single mTBI (*Figure 1, Quadrant D, upper half*) despite showing definitive chronic changes to the brain's underlying pathophysiology (*Figure 1, Quadrant C, upper half*).

We have discussed how this inconsistency in the literature can be explained in two ways. First, it is possible that the pathophysiological changes induced by a single mTBI does not manifest behaviourally. Second, it is also possible that a single mTBI does impair cognition in the long-term but intra- and inter-study methodological limitations have limited our ability to reveal the true cognitive cost associated with mTBI. Thus, this thesis set out to address two research objectives relating to this inconsistency in the literature. First, we aimed to reveal the incidence of long-term cognitive impairment associated with a single mTBI in the literature. By systematicaly reviewing the literature and synthesizing the findings from all studies meeting our inclusion criteria, we were able to overcome the limitations posed by single studies. Second, we aimed to reveal differences in the sensitivities of the outcome measures used to detect cognitive

impairment in the long-term. While the homogeneity of our studies limited our ability to address our second objective, we discuss the meaning of our null findings in relation to the mTBI literature at large.

4.1 Overall Findings

The main finding from our scoping review relates to the incidence of persistent cognitive impairment as evidenced by the literature that reports on individuals with chronic stage mTBI following a single concussion. Contrary to myriad previous reports that a single mTBI leads to persistent cognitive impairment in 15% of individuals, and that the other 85% will see cognitive symptoms disappear within the acute phase (i.e., the first 3 months post-injury), the findings from our scoping review do not support this conclusion [35], [36], [9], [37], [38]. Based on our results, we show that a larger proportion of individuals with a single mTBI will continue to demonstrate measurable impairment in various measures of executive functioning, learning/memory, attention, processing speed, and language function long after the initial injury. We also show that the cognitive impairments that persist in individuals with mTBI do not manifest in all outcome measures and across all cognitive domains. Thus, our review supports the hypothesis that a single mTBI has a strong likelihood of impairing cognitive function in the chronic phase post-injury — albeit in subtle and often highly specific ways. Finally, we show that cognitive impairment in the chronic phase post-injury is not temporally related — cognitive impairments appear to persist chronically and are no more likely to be present 3 months post-injury than 12 months post-injury. This finding, however, is limited by the lack of prospective and longitudinal studies in our review — that is, the participants in our review were not each tracked across multiple post-injury intervals. The following sections elaborate on these findings and implications for future mTBI research.

4.2 Main Findings — Objective 1

As mentioned in our overall findings, we show that a single mTBI results in a measurable impairment to cognitive function in the majority of studies assessing cognitive outcome measures in individuals with chronic stage mTBI. Further, we show that our finding holds true in our sample of both children and adults (*Figure 5*), and in studies both controlling for, and failing to control for, previous concussion exposure (*Figure 4*). Most surprisingly, we did not find that cognitive impairment was more likely to appear at earlier post-injury intervals (*Figure 4*). While the methods used in this scoping review are not appropriate for determining the precise incidence of persistent cognitive impairments following mTBI, our results still highlight a major contradiction in the mTBI literature. While the 15% estimate — that is, that about 15% of individuals with an mTBI will go on to develop persistent symptoms — is widely reported in the mTBI literature, our results suggest this hypothesis is an underestimation of the true incidence. Interestingly, by juxtaposing the results from pathophysiological studies demonstrating how a single mTBI induces long-lasting changes to the underlying learning and memory neurophysiology, it is not surprising that our findings show a parallel behavioural impairment in cognition in the chronic phase post-injury. The next section will further discuss these contradictory findings as well as providing a methodological explanation for the "15% hypothesis".

4.2.1 Rethinking 15%

Our findings challenge the previous estimates that only about 15% of individuals with mTBI will go on to develop persistent issues [36], [154]. While countless reports quote the 15% estimate, the primary research demonstrating this finding suffers from several limitations. First, those studies have relied on methods that, as we have discussed, may be insufficiently sensitive to detect subtle changes to cognition following mTBI. Our study relies on gathering the evidence from research that has used those very methods. Consequently, our scoping review was not designed to overcome this limitation. This work did, however, help overcome other limitations that may have

contributed the 15% estimate being an underestimation of the cognitive costs associated with mTBI.

Specifically, our scoping review overcame single-study limitations such as low power, a limited number of participants, and lack of generalizability of the study's sample population. Furthermore, our review was able to gather evidence from a wide array of studies that may or may not have intended to examine the long-term cognitive outcomes in individuals with a single mTBI. For example, some studies gather cognitive outcome measure data secondarily to gathering, say, electrophysiological recordings of brain activity. Our scoping review was able to assess the literature as a whole including studies that were primarily designed to assess cognitive outcomes and those that only assessed cognition as a secondary objective. Moreover, our study was able to assess cognitive outcomes at multiple time points when the majority of the individual studies only examined one post-injury interval. Taken together, our study was able to overcome many, but not all, of the limitations that have contributed to the research supporting the 15% estimate. Furthermore, given the inability of our study to overcome the limitation of insufficiently sensitive methodology used to assess cognition, it is likely that our results represent an underestimation of the incidence of persistent cognitive impairment following a single mTBI. In other words, our results showing that around half of individuals with mTBI will suffer persistent cognitive impairment may still be an underestimation.

4.3 Main Findings — Objective 2

The main finding related to our secondary objective is not revealing of either the sensitivities of outcome measures (our initial secondary objective) nor the cognitive domains impaired following mTBI (our additional secondary objective). Instead, our main finding reveals the extent to which limitations in the mTBI literature have hindered our ability to estimate the true cognitive costs associated with a single mTBI. The fact that we were unable to draw any conclusions after analyzing the studies from our

scoping search demonstrates how the mTBI literature, to date, has not adhered to a standard method of assessing the long-term cognitive outcomes of individuals with mTBI. In fact, our results show how (1) there is no established set of outcome measures or test batteries that are used consistently across studies in individuals with mTBI; and (2) test batteries do not appear to focus on specific cognitive domains that are impaired following mTBI. A detailed discussion of the secondary objectives is included below.

4.3.1 Sensitivities of Outcome Measures — Initial Secondary Objective

Our initial secondary objective was to examine the sensitivities of outcome measures in detecting cognitive impairment in individuals in the chronic phase of mTBI. We expected to gather the cogntive testing data from our sample of studies and demonstrate how certain outcome measures were more effective in detecting cognitive impairment. Instead, we found that our study sample was lacking in homogeneity with respect to the outcome measures that were selected to assess individuals with chronic stage mTBI. Of our 48 studies, there were 74 outcome measures (not including subtests) and few were repeated across multiple studies. Moreover, those that were repeated across multiple studies were difficult to compare for two reasons. First, studies were not always consistent in their method of reporting the results from the outcome measures. For example, Heitger et al. (2006) reported their participants' CVLT data as z-scores whereas Levin et al., (1996) reported the same test data as mean group scores. Second, studies using the same test battery used different subtests therefore eliminating the ability to compare their results.

As a result of the limited repeatability of outcome measures across studies, and limited comparability between those studies using the same outcome measures, *Tables 4.1-4.4* are uninformative for addressing our secondary research objective. Take, for example, the CVLT. Heitger et al., (2006) tested 37 individuals with mTBI at three time points in the first year post-injury (i.e., 3 mo, 6 mo, and 12 mo) on the CVLT, the Paced Auditory Serial Addition Test (PASAT), the Symbol Digit Modalities Test (SDMT), the Trail Making Test (TMT), and two subtests of the Wechsler Adult Intelligence Scale (WAIS)

assessing language and executive function. At three months post-injury, only the CVLT (albeit all four subtests of the CVLT) showed impairment while all other outcome measures showed no difference compared to controls. At 6 months, only two of the four CVLT subtests showed impairment (with the other two subtests failing to reach significance at $p < 0.07$) and by 12 months, only the total standard score of the CVLT showed cognitive impairment yet the scores from each of the subtests were equivalent to the controls. This study in isolation demonstrates that the CVLT was more effective than the other cognitive tests in detecting cognitive impairment. When Levin et al., (1996) tested 36 chidlren on the CVLT, Verbal Fluency, the Wechsler Intelligence Scale for Children - Revised (WISC-R), and Semantic Verification at 3 and 12 months post-injury, they did not show cognitive impairment on any of their measures at either the 3 or 12 month testing session. While this finding does not place the CVLT as an insensitive measure per se, it demonstrates how drawing conclusions about sensitivities in our study was not possible.

This pattern, of an outcome measure showing cognitive impairment in some studies but not in others, reveals how the cognitive outcome measures we use, unlike DTI and other measures of DAI, are inconsistent and prone to false negatives and/or false positives. For example, De Boussard et al. (2005) used two test batteries to assess cognitive impairment in their sample of 97 mTBI participants at 3 months post-injury. The first test battery, the Automated Psychological Test (APT) contained four subtests that each measured processing speed, attention (focused and selective), executive function (i.e., auditory inhibition task), and long-term associative memory. The second test battery, the extended neuropsychological test, included three subtests of the WAIS, the Buschke Selective Reminding Test, the Stroop test, the PASAT, and the TMT. They showed that only 8% of their patients had CI when tested with the first battery while 30% showed CI on the extended (second) test battery. While they did not elaborate which subtests specifically accounted for the cognitive impairment, it does show that extensive neuropsychological testing is more effective in demonstrating subtle impairments to cognition.

The results from the De Boussard et al. (2005) study show that at least 23% of their patients had a false negative for cognitive impairment when tested with the first battery. Alternatively, it is also possible that the extensive neuropsychological test battery (i.e., the second test battery) unconvered 23% false positives for cognitive impairment. While the latter is unlikely the case, chronic cognitive impairments in individuals with mTBI nevertheless do not appear to manifest as robust and consistent changes to cogntion — at least in individuals with a history of a single concussion. Instead, chronic cognitive impairment following mTBI is subtle and often difficult to detect. This begs the question, if chronic cognitive impairment following mTBI manifests in highly specific and subtle ways, is the cognitive impairment clinically relevant? That is, does the cognitive impairment matter if it bypasses standardized cognitive testing batteries and if it does not have an impact on the patient's quality of life? This question will be addressed in the section, "Cognitive Impairment in mTBI — Is it Clinically Relevant?". First, we discuss the findings from our additional component of the secondary objective.

4.3.2 Impaired Cognitive Domains — Additional Secondary Objective

To our surprise, the results showing the cognitive domains tested in the CI/CU groups, displayed in *Tables 5.1-5.4,* did not show that specific cognitive domains are more or less likely to be impaired in individuals with mTBI. In fact, these tables clearly show how two outcome measures assessing the same cognitive domain may show impairment on one and unimpairment on the other. Kwok et al. (2008), for example, tested 31 participants with mTBI 3 months post-injury using multiple cognitive tests including two tests designed to probe sustained attention: the Digit Vigilance Test and the Colour Trails Test (*Table 4.1*). While their participants showed a deficit compared to controls on the Digit Vigilance Test, they did not show impairment on the Colour Trails task. There are two interpretations to be drawn from these findings. First, it is possible that this finding supports our initial hypothesis that the cognitive outcome measures we use to assess cognitive impairment are not adequately sensitive. Thus, while the

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participants with CI in the Kowk et al. (2008) study show an impairment on one measure of sustained attention (i.e., the Digit Vigilance Test) but not on another (i.e., Colour Trails), it is possible that the Digit Vigilance Test is a more sensitive measure of sustained attention than the Colour Trails.

Alternatively, it is possible that cognitive impairment long after a single mTBI manifests as a highly specific impairment to a single aspect within a cognitive domain. In other words, a highly specific and subtle impairment to sustained attention may not manifest as an impairment to all outcome measures assessing sustained attention. Thus, two outcome measures assessing sustained attention in slightly different ways may differentially pick up on the impairment depending on their methodological design. If this holds true, this might provide an explanation for the null findings in our first analysis of the secondary objective — that is, if a first-time concussed individual has an impairment to, say, sustained attention that is highly specific and only manifests when tested under conditions that probe that aspect of sustained attention, it is understandable that simply looking at the outcome measures only is not adequately informative. Further, it is possible that concussion impairs cognition in different ways between individuals. Consequently, our method of organizing participants into CI/CU groups based on their group data for a given outcome measure would be an ineffective way to determine the nuanced impairment for a single participant. This highlights a major limitation of our study — analysing group data is likely uninformative in participants with individualized and highly specific impairments that differ from participant to participant. This is further discussed in the section titled, *Limitations*.

Finally, it is important to stress the limitations posed by our analysis of the impaired cognitive domains. We conducted this analysis as a qualitative discussion point and understand that the numbers presented in *Table 6* should not be statistically or quantitatively analysed. Most cognitive outcome measures in our review assess multiple cognitive domains. Moreover, they assess multiple aspects within each cognitive domain (discussed above). An impairment to, say, the PASAT, which assesses aspects of three cognitive domains (i.e., attention, memory, and processing speed) does not necessarily

mean that the individual is impaired on all three cognitive domains. Thus, our tally of the impaired cognitive domains in *Table 6* may include those that were not cognitively impaired. This is an inevitable limitation of the current analysis.

4.3.3 Secondary Objective Findings in a Nutshell

While we were unable to analyze the studies in our scoping review to show differences in sensitivities of outcome measures, our findings are still illuminative. We show three main findings. First, we show that the mTBI literature describing the long-term cognitive outcomes in first-time concussed individuals is not homogeneous. There does not exist a standard set of outcome measures that are universally used to assess cognition in individuals with mTBI. For this reason, a scoping review gathering and analysing the literature is limited by the lack of homogeneity in the primary studies. Second, we show that long-term cognitive impairment in first-time concussed individuals likely manifests in highly specific and subtle ways. Thus, extensive neuropsychological testing is more likely to reveal impairments when the testing is comprehensive and covers many aspects of cognition that may be impaired in individuals with mTBI. Finally, we discuss the possibility that chronic cognitive impairment in individuals with mTBI is not necessarily equal. That is, every mTBI is unique and thus the consequential cognitive impairments will be unique. There is a plausible mechanistic explanation for this hypothesis — the twisting and shearing of axons during an mTBI will not consistently cause DAI in the exact same brain loci between individuals [30]. While specific brain regions are more succeptible to DAI, the injury will not damage the same precise loci within a given vulnerable region (e.g., the hippocampus). As a result, examining cognitive impairments at the group level in individuals with mTBI is likely not the best approach.

4.4 Cognitive Impairment in mTBI — Is it Clinically Relevant?

We have shown that a single mTBI impairs cognition in subtle and often highly specific ways. This was most evident in that the majority of studies showing cognitive impairment in their participants only demonstrated a deficit on select measures of their

test batteries. Further, our results contradict the 15% estimate; instead, we show that persistent cognitive impairment following mTBI likely impacts a large portion of concussed individuals. Our study methodology, however, was not designed to quantify the incidence of persistent cognitive impairment. Importantly, the introduction of this thesis discussed how standard behavioural measures may not detect cognitive impairment while other measures (e.g., neurophysiological testing) may consistently detect robust change. Our work focussed on cognitive impairment assessed using behavioural measures only and thus we emphasize this limitation and caution that our results may represent an underestimation of the presence of long-term cognitive impairment. If, however, chronic cognitive impairment is difficult to detect on the majority of cognitive tests, is the cognitive impairment clinically relevant? That is, should we care?

Addressing the question of clinical relevance depends on how the results are interpreted. A subtle impairment to cognition may not hinder the individual's ability to carry out activities of daily living nor might it impact their quality of life. If, for example, an individual shows a statistically significant difference on a measure of working memory compared to a control, this does not necessarily translate to a noticeable change in their working memory ability throughout their day. In this sense, chronic cognitive impairment following mTBI may not be clinically relevant. If, however, a single mTBI results in a subtle change to cognition that persists long after the injury, this is indicative of the underlying neurological damage (e.g., DAI) caused by mTBI. Further, this challenges the notion that mTBI is a "mild" injury devoid of long-term consequence that can be completely resolved in less than 3 months. Most disconcerting, however, are the implications this has on individuals with multiple mTBIs. To explain, if a single mTBI results in neurological damage that impairs cognition, and if multiple mTBIs result in slower recoveries and worse cognitive outcomes, and finally, if lifetime mTBI exposure leads to pathological neurodegeneration and deterioration of cognitive function (i.e., CTE), it follows that neurological damage from a single mTBI forms the foundation for the cumulative degradation of neurological function that occurs with multiple mTBIs.

Thus, the clinical relevance of mTBI is as follows. It is unlikely that a single and isolated mTBI will have any meaningful impact on an individual's cognitive function. A first-time mTBI will, however, cause lasting changes to the underlying neural structures that will accummulate with each subsequent concussion. Regardless of its clinical relevance on the patient's quality of life, their presence of subtle and/or specific cognitive impairment long after injury is indicative of change. A first-time mTBI in athletes, soldiers, or other populations at risk for concussion exposure becomes a risk-factor for CI following subsequent mTBIs. In this work, we did not focus on potential interventions or methods for reversing the chronic cognitive changes. By identifying the existence of chronic changes in individuals with a single mTBI, however, we emphasize the point that the pathological neurodegeneration experienced by individuals with lifetime mTBI exposure begins with the first mTBI. Consequently, the changes we see following a single mTBI may be considered as a first marker for the detrimental changes to come with each subsequent concussion.

Finally, a discussion of mTBI recovery and clinical relevance would be incomplete without considering persistant subjective complaints. While the focus of this review and thesis has been on the cognitive outcomes in mTBI, it would be inaccurate to characterize recovery following mTBI strictly in terms of cognitive outcomes rather than subjective symptoms and the effect of the injury on an individual's quality of life. An individual with subjective symptoms who scores within the normal range on cognitive impairment measures cannot be considered recovered. Complete recovery from an mTBI should also account for ongoing subjective issues that contribute to the individual's quality of life.

Levin et al. (1987) tested 57 first-time concussed participants on multiple measures of cognition at 1- and 3-months post-injury [33]. In addition to the neuropsychological testing, they also interviewed participants and collected data regarding their subjective endorsement of common post-concussion symptoms (e.g., memory loss, dizziness, headaches). By 3 months post-injury, their mTBI participants showed no group differences from controls on any neuropsychological test, however,

the participants with mTBI continued to report the presence of post-concussion symptoms. Despite the finding of most participants subjective reporting of post-concussion symptoms, the authors concluded that their results "suggest that a single uncomplicated minor head injury produced no permanent disabling neurobehavioural impairment in the great majority of patients" [33]. This demonstrates how the conclusions drawn from research findings can highlight specific findings while diminishing others. This thesis focussed on the evidence for persistent cognitive impairment following mTBI rather than subjectively experienced persistent concussion symptoms. A holistic approach to understanding the clinical relevance of persistant issues following mTBI would benefit from an analysis of both objective measures (i.e., measures of cognitive impairment) and subjective measures (patient endorsed symptoms). We therefore caution that our discussion of clinical relevance was strictly in relation to objective measures.

4.5 Limitations

There are several limitations to the current work that should be considered when interpreting the results. The first major limitation pertains to the article selection process used in our scoping review. In creating inclusion and exclusion criteria, scoping review style studies will inevitably suffer from trade-offs between selecting articles that are both representative of the literature but also have a degree of homogeneity to facilitate comparison across studies. Our exclusion of studies reporting only group data for post-injury interval or number of concussions did greatly diminsh our sample size. Including these studies, however, would have greatly increased the difficulty of comparing the studies. Further, we would not have been able to temporally organize our data (i.e., with respect to post-injury interval) had we included studies reporting mean post-injury intervals. While we believe these exclusions were necessary for facilitating comparison across studies, we do recognize the limitations posed by mass exclusions. Unfortunately, the mTBI literature to date has not emphasized the reporting of individual participant data for post-injury intervals or number of previous concussions.

This artefact of the mTBI literature reveals the lack of importance placed on understanding the temporal relationship between mTBI exposure and persitent cognitive impairment. In other words, the primary interest of mTBI research has not been focussed on establishing the relationship between post-injury interval and dissapearance of cognitive symptoms, particularly in studies looking at post-injury intervals within the chronic phase. This relates to another limitation of our work — the participants in our review were not all gathered from longitudinal studies assessing the same participants across each post-injury interval. Ideally, all the participants in our study would have had their cognitive testing repeated at each post-injury interval. Solely looking at data from longitudinal studies, however, would have greatly diminshed our sample size. The other exclusions, namely eliminating participants involved in litigation and studies recruiting participants based on their positive symptomology of subjective ongoing symptoms, also diminshed the number of studies in our sample. These exclusions, however, were necessary in avoiding confounds that would have hindered our ability to assess the long-term impact of a single mTBI.

Study homogeneity, as we have seen, poses inevitable limitations during scoping reviews. We decided to include studies using three different methods of comparison for assessing outcome measures — that is, those using normative data, those using cut-off scores, and those providing control groups. While the control group method of comparison is applied to group data, the cut-off score and normative data methods were applied to individual data. Thus, for studies providing control groups, the entire mTBI group would be assigned to either the CI/CU group whereas studies providing cut-off scores or normative data, individual participants were allocated to each CI/CU group. Individual participant binarization is not prone to the limitations posed by group data binzarization using control groups. Take, for example, a study examining 100 participants on a given outcome measure where the group means fail to differ from that of the control group despite the presence of cognitive impairment in a subset of the sample. In this case, all 100 participants would be dichotomized as CU. Fortunately, this limitation is balanced by the fact that group dichotomization can equally sway the

results in both directions. For example, if the same hypothetical study of 100 participants did yield significant differences between control and mTBI group data, all 100 participants would be classified as CI despite the possibility that only a subset of the participants with lower cognitive outcomes are accounting for the group difference. Thus, the binarization of participants to each CI/CU group based on group data introduces the possibility of a false positive for CI, or a Type 1 statistical error.

Despite this obvious limitation of working with group data, excluding these studies would have greatly diminished our sample size. Further, had we focused solely on studies that were highly homogeneous with respect to their cognitive outcome measures and their data, we would have also greatly diminish the sample size. Given our main research objective — that is, to synthesize the breadth of literature reporting on long-term cognitive outcomes in individuals with mTBI — we opted for a methodological approach that would maximize the inclusions while still balancing the need to control for limitations. In any case, the limitations posed by group homogeneity (or lack thereof) should be taken into consideration when interpreting the results.

A review of *Tables 3.1* to *3.4* illustrates the myriad variables within our studies with respect to the way mTBI was defined across studies, whether or not the participants had a complicated (i.e., radiological findings not including linear skull fractures) or uncomplicated mTBI, and the parameters studies gave for inclusion of participants with a possible history of TBI. From our analyses, it does not appear that these variables had a measurable impact on our results. Nevertheless, we understand the potential these variables have on cognitive outcomes in individuals with mTBI. As discussed in the introduction, the number of concussions an individual has is negatively associated with cognitive outcomes and positively associated with length of recovery. Simply put, multiple mTBIs are associated with worse cognitive outcomes and longer recovery periods. While we did control for this variable by reanalyzing our data exclusively using studies that ensured their participants were first-time concussed (see *Figure 4, B)*, the overall data from our review should be analyzed in light of this variable.

A final limitation relates to the mTBI literature itself. During the first two phases of the article selection process (i.e., assessing abstracts and then full texts for their adherence to our primary inclusion/exclusion criteria), it became evident that the number of studies reporting on cognitive outcomes in individuals in the chronic stage of mTBI were the minority. The majority of studies in the initial scoping search were reporting on the cogntive outcomes of individuals in the first three months post-injury. The saliency of the 15% estimate in the literature may be at fault for this finding. Since the 15% estimate is so widely accepted, researchers designing their studies that assess symptom recovery in concussed individuals will opt to test participants only in the first three months. Many studies thus make the assumption that cognitive testing in individuals in the chronic phase is redundant seeing as they are already supposed to have exhibited complete symptom recovery. This last limitation is very revealing of the underlying assumptions made in the mTBI literature. Namely, it is assumed that the 15% estimate is accurate and that the methods we used to test cognitive impairment are sufficiently sensitive. Our results and our subsequent discussion of these limitations highlight an important consideration for future mTBI research. These considerations are discussed in the next section.

4.6 Future Directions

In light of the current findings as well as the pathophysiological research demonstrating long-lasting changes to the neurophysiology in individuals with mTBI, the 15% hypothesis should be re-examined with a more critical approach to the methodology used to assess cognitive impairment in mTBI. While our study methodology is not adequate for determining the incidence of persiting cognitive impairments or making claims about the sensitivies of conventional outcome measures used to detect cognitive impairment, our results do highlight the need for future research to address these issues. Specifically, future research should aim to clarify two main points of contention in the literature. First, it should focus on understanding the

true cognitive costs associated with a single mTBI. That is, which cognitive domains or sub-domains are most likely impaired following an mTBI? Second, in order to address the former point, future research should also address the methodological limitations that have plagued mTBI research to date with respect to insufficiently sensitive outcome measures. As we have discussed throughout this work, the homogeneity of the use of cognitive outcome measures is limited. Future work would benefit from the development of a standardized neuropsychological test battery that is methodologically designed to maximize the detection of the subtle cognitive impairments that are characteristic of chronic mTBI. Furthermore, a standardized neuropsychological test battery would be useful for prospective and longitudinal studies assessing cognitive impairments at multiple post-injury intervals in the same participants. Longitudinal studies should also not be limited to a 1-year post-injury interval — few studies to date have assessed mTBI participants after 1 year post-injury. While our work was unable to provide an assessment of outcome measure sensitivity, identifying outcome measures that are highly sensitive to the subtle changes to cognition that persist following an mTBI would be useful for designing a standardized neuropsychological test battery for chronic mTBI.

As we have seen when addressing our secondary research objective, characterizing the long-term cognitive outcomes in individuals with mTBI is difficult considering the vast number of cognitive outcome measures that are used across mTBI. Our understanding of the long-term cognitive outcomes in individuals with mTBI would benefit from a more consistent approach in future research. It is possible that cognitive testing will never be sensitive enough to detect the cognitive changes that follow mTBI will adequate consistency and reliabilty. Perhaps the cognitive changes in mTBI require neurophysiological methods in their detection. Nevertheless, our understanding of the impact of a single mTBI on cognitive impairment is far from complete in the current literature. Addressing the methodological concerns we have outlined in this thesis would be a great first step towards unraveling the relationship between mTBI and cognitive impairment.

References

[1]   N. A. Shaw, "The neurophysiology of concussion," *Prog. Neurobiol.*, vol. 67, no. 4, pp. 281–344, Jul. 2002.

[2]   M. Kiraly and S. J. Kiraly, "Traumatic brain injury and delayed sequelae: a review-- traumatic brain injury and mild traumatic brain injury (concussion) are precursors to later-onset brain disorders, including early-onset dementia.," *ScientificWorldJournal.*, vol. 7, pp. 1768–76, Jan. 2007.

[3]   B. E. Gavett, R. A. Stern, R. C. Cantu, C. J. Nowinski, and A. C. McKee, "Mild traumatic brain injury: a risk factor for neurodegeneration.," *Alzheimers. Res. Ther.*, vol. 2, no. 3, p. 18, Jan. 2010.

[4]   J. S. Cheng, R. Craft, G.-Q. Yu, K. Ho, X. Wang, G. Mohan, S. Mangnitsky, R. Ponnusamy, and L. Mucke, "Tau reduction diminishes spatial learning and memory deficits after mild repetitive traumatic brain injury in mice.," *PLoS One*, vol. 9, no. 12, p. e115765, Jan. 2014.

[5]   B. E. Gavett, R. a. Stern, and A. C. McKee, "Chronic Traumatic Encephalopathy: A Potential Late Effect of Sport-Related Concussive and Subconcussive Head Trauma," *Clin. Sports Med.*, vol. 30, no. 1, pp. 179–188, Jan. 2011.

[6]   S. T. DeKosky, M. D. Ikonomovic, and S. Gandy, "Traumatic brain injury--football, warfare, and long-term effects.," *N. Engl. J. Med.*, vol. 363, no. 14, pp. 1293–6, Sep. 2010.

[7]   O. Ghaffar, S. McCullagh, D. Ouchterlony, A. Feinstein, G. O., M. S., O. D., and F. A., "Randomized treatment trial in mild traumatic brain injury.," *J. Psychosom. Res.*, vol. 61, no. 2, pp. 153–160, Aug. 2006.

[8] I. Emanuelson, E. Holmkvist, R. Bjorklund, and D. Stalhammar, "Quality of life and post-concussion symptoms in adults after mild traumatic brain injury: a population-based study in western Sweden.," *Acta Neurol Scand*, vol. 108, no. 5. (1)Department for Health of Women and Children, Goteborg University, Goteborg, Sweden, (C) 2003 Munksgaard International Publishers Ltd., pp. 332–338, 2003.

[9] R. C. W. R. C. W. W. R. C. W. Hall, R. C. W. R. C. W. W. R. C. W. Hall, M. J. Chapman, H. R.C.W., H. R.C.W., and C. M.J., "Definition, diagnosis, and forensic implications of postconcussional syndrome," *Psychosomatics*, vol. 46, no. 3, pp. 195–202, 2005.

[10] R.-S. T.M., V. A.S., T. D.A., L. B.W., L. M., F. K.E., G. S.J., S. R.E., and G. K., "Cognitive change associated with self-reported mild traumatic brain injury sustained during the OEF/OIF conflicts.," *Clin. Neuropsychol.*, vol. 26, no. 3, pp. 473–489, 2012.

[11] A. Kontos, R. J. Elbin, R. Kotwal, P. MD, R. Lutz, P. MD, S. Kane, P. Benson, R. Forsten, and M. Collins, "The effects of combat-related mild traumatic brain injury (mTBI): Does blast mTBI history matter?.," *J. trauma acute care surg.* From the Department of Orthopaedic Surgery/UPMC Sports Medicine Concussion Program, University of Pittsburgh Medical College Sports Medicine Concussion Program (A.P.K., M.W.C.), Pittsburgh, Pennsylvania; Office for Sport Concussion Research (R.E.), Univer, (C) 2015 Lippincott Williams & Wilkins, Inc., 2015.

[12] L. S.R., "Epidemiology of concussion and mild traumatic brain injury," *PM R*, vol. 3, no. 10 SUPPL. 2, pp. S354–S358, 2011.

[13] S. R. Laker, "Epidemiology of concussion and mild traumatic brain injury.," *PM R*, vol. 3, no. 10 Suppl 2, pp. S354–8, Oct. 2011.

[14] E. Dahl, L. von Wendt, and I. Emanuelson, "A prospective, population-based, follow-up study of mild traumatic brain injury in children.," *Injury*, vol. 37, no. 5, pp. 402–9, May 2006.

[15] N. Porcher J. and T. Sotecki J., "A narrative review of sports-related concussion and return-to-pray testing with asymptomatic athletes.," *J. Chiropr. Med.*, vol. 12, no. 4, pp. 260–268, Dec. 2013.

[16] D. Ellemberg, L. C. Henry, S. N. Macciocchi, K. M. Guskiewicz, and S. P. Broglio, "Advances in sport concussion assessment: from behavioral to brain imaging measures.," *J. Neurotrauma*, vol. 26, no. 12, pp. 2365–2382, 2009.

[17] M. McCrea, T. Hammeke, G. Olsen, P. Leo, and K. Guskiewicz, "Unreported concussion in high school football players: implications for prevention.," *Clin. J. Sport Med.*, vol. 14, no. 1, pp. 13–7, Jan. 2004.

[18] C. M. Rockhill, J. R. Fann, M.-Y. Fan, W. Hollingworth, and W. J. Katon, "Healthcare costs associated with mild traumatic brain injury and psychological distress in children and adolescents.," *Brain Inj.*, vol. 24, no. 9, pp. 1051–60, Jan. 2010.

[19] D. Smith, "Mild traumatic brain injury, Part 1: Assessment and management," *BC Med. J.*, vol. 48, no. 9, pp. 440–441, 2006.

[20] R. C. Sabini, D. N. Nutini, M. Nutini, S. R.C., N. D.N., and N. M., "Return-to-play guidelines in concussion: revisiting the literature," *Phys. Sportsmed.*, vol. 42, no. 3, pp. 10–19, 2014.

[21] A. N. Guthkelch, "Posttraumatic amnesia, post-concussional symptoms and accident neurosis.," *Eur. Neurol.*, vol. 19, no. 2, pp. 91–102, Jan. 1980.

[22] R. W. Rimel, B. Giordani, J. T. Barth, T. J. Boll, and J. A. Jane, "Disability caused by minor head injury.," *Neurosurgery*, vol. 9, no. 3, pp. 221–8, Sep. 1981.

[23] A. P. Kontos, R. Elbin, R. S. Kotwal, R. H. Lutz, S. Kane, P. J. Benson, R. D. Forsten, and M. W. Collins, "The effects of combat-related mild traumatic brain injury (mTBI)," *J. Trauma Acute Care Surg.*, vol. 00, no. 00, p. 1, 2015.

[24] M. P., T. M., M. J., P. McCrory, M. Turner, and J. Murray, "A punch drunk jockey?," *Br. J. Sports Med.*, vol. 38, no. 3, p. e3, 2004.

[25]   D. J. Schretlen and A. M. Shapiro, "A quantitative review of the effects of traumatic brain injury on cognitive functioning.," *Int. Rev. Psychiatry*, vol. 15, no. 4, pp. 341–349, 2003.

[26]   M. A.R., Y. Z., Y. R.A., P. A., L. J.M., M. M.V., S. M., and M. K., "A functional MRI study of multimodal selective attention following mild traumatic brain injury," *Brain Imaging Behav.*, vol. 6, no. 2, pp. 343–354, 2012.

[27]   E. Hessen, K. Nestvold, K. Sundet, H. E., N. K., and S. K., "Neuropsychological function in a group of patients 25 years after sustaining minor head injuries as children and adolescents," *Scand. J. Psychol.*, vol. 47, no. 4, pp. 245–251, 2006.

[28]   H. S. Levin, G. Hanten, G. Roberson, X. Li, L. Ewing-Cobbs, M. Dennis, S. Chapman, J. E. Max, J. Hunter, R. Schachar, T. G. Luerssen, P. Swank, L. H.S., H. G., R. G., X. L.I., E.-C. L., D. M., C. S., M. J.E., H. J., S. R., L. T.G., and S. P., "Prediction of cognitive sequelae based on abnormal computed tomography findings in children following mild traumatic brain injury.," *J. Neurosurg. Pediatr.*, vol. 1, no. 6, pp. 461–70, 2008.

[29]   C. W. Wallesch, N. Curio, S. Kutz, S. Jost, C. Bartels, H. Synowitz, W. C.-W., C. N., K. S., J. S., B. C., and S. H., "Outcome after mild-to-moderate blunt head injury: effects of focal lesions and diffuse axonal injury.," *Brain Inj.*, vol. 15, no. 5, pp. 401–412, 2001.

[30]   J. M. Meythaler, J. D. Peduzzi, E. Eleftheriou, and T. A. Novack, "Current concepts: diffuse axonal injury-associated traumatic brain injury.," *Arch. Phys. Med. Rehabil.*, vol. 82, no. 10, pp. 1461–71, Oct. 2001.

[31]   S. N. Niogi, P. Mukherjee, J. Ghajar, C. Johnson, R. A. Kolster, R. Sarkar, H. Lee, M. Meeker, R. D. Zimmerman, G. T. Manley, B. D. McCandliss, N. S.N., M. P., G. J., J. C., K. R.A., S. R., L. H., M. M., Z. R.D., M. G.T., and M. B.D., "Extent of microstructural white matter injury in postconcussive syndrome correlates with impaired cognitive reaction time: A 3T diffusion tensor imaging study of mild traumatic brain injury," *Am. J. Neuroradiol.*, vol. 29, no. 5, pp. 967–973, 2008.

[32] N. Gosselin, C. Bottari, J.-K. K. Chen, M. Petrides, S. Tinawi, E. de Guise, A. Ptito, G. N., B. C., C. J.-K., P. M., T. S., D. G. E., and P. A., "Electrophysiology and functional MRI in post-acute mild traumatic brain injury," *J Neurotrauma*, vol. 28, no. 3, pp. 329–341, 2011.

[33] H. S. Levin, S. Mattis, R. M. Ruff, H. M. Eisenberg, L. F. Marshall, K. Tabaddor, W. M. J. High, and R. F. Frankowski, "Neurobehavioral outcome following minor head injury: a three-center study.," *J. Neurosurg.*, vol. 66, no. 2, pp. 234–243, Mar. 1987.

[34] B. L.M. and L. M. Binder, "A review of mild head trauma. Part II: Clinical implications," *J. Clin. Exp. Neuropsychol.*, vol. 19, no. 3, pp. 432–457, 1997.

[35] M. S., B. M., M. S., V. D., and B. L., "Clinical practice guidelines for mild traumatic brain injury and persistent symptoms," *Can. Fam. Physician*, vol. 58, no. 3, pp. 257–267+e128–e140, 2012.

[36] W. H. Rutherford, J. D. Merrett, and J. R. McDonald, "Symptoms at one year following concussion from minor head injuries," *Injury*, vol. 10, no. 3, pp. 225–230, Feb. 1979.

[37] P. Spinos, G. Sakellaropoulos, P. MD, M. Georgiopoulos, K. Stavridi, K. Apostolopoulou, J. Ellul, P. MD, C. Constantoyannis, and P. MD, *Postconcussion Syndrome After Mild Traumatic Brain Injury in Western Greece.*, vol. 69, no. 4. (C) 2010 Lippincott Williams & Wilkins, Inc.: From the Departments of Neurosurgery (P.S., M.G., K.S., K.A., C.C.), Medical Physics (G.S.), and Neurology (J.E.), Patras Medical School, Patras, Greece., 2010, pp. 789–794.

[38] A. Sterr, K. A. Herron, C. Hayward, D. Montaldi, S. A., H. K.A., H. C., M. D., A. Sterr, K. A. Herron, C. Hayward, and D. Montaldi, "Are mild head injuries as mild as we think? Neurobehavioral concomitants of chronic post-concussion syndrome.," *BMC Neurol.*, vol. 6, p. 7, 2006.

[39] S. J. Preiss-Farzanegan, B. Chapman, T. M. Wong, J. Wu, and J. J. Bazarian, "The relationship between gender and postconcussion symptoms after sport-related mild traumatic brain injury.," *PM R*, vol. 1, no. 3, pp. 245–53, Mar. 2009.

[40] M. B. Pontifex, P. M. O'Connor, S. P. Broglio, and C. H. Hillman, "The association between mild traumatic brain injury history and cognitive control.," *Neuropsychologia*, vol. 47, no. 14, pp. 3210–6, Dec. 2009.

[41] S. P. Broglio, M. S. Ferrara, S. G. Piland, R. B. Anderson, and A. Collie, "Concussion history is not a predictor of computerised neurocognitive performance.," *Br. J. Sports Med.*, vol. 40, no. 9, pp. 802–805, Sep. 2006.

[42] B. Y. and V. M., "Cognitive sequelae of blast-induced traumatic brain injury: Recovery and rehabilitation," *Neuropsychol. Rev.*, vol. 22, no. 1, pp. 4–20, 2012.

[43] D. H. Daneshvar, D. O. Riley, C. J. Nowinski, A. C. McKee, R. A. Stern, and R. C. Cantu, "Long-Term Consequences: Effects on Normal Development Profile After Concussion," *Phys. Med. Rehabil. Clin. N. Am.*, vol. 22, no. 4, pp. 683–700, Nov. 2011.

[44] P. M. Rees and R. P.M., "Contemporary issues in mild traumatic brain injury.," *Arch. Phys. Med. Rehabil.*, vol. 84, no. 12, pp. 1885–1894, 2003.

[45] A. R. Rabinowitz and H. S. Levin, "Cognitive sequelae of traumatic brain injury.," *Psychiatr. Clin. North Am.*, vol. 37, no. 1, pp. 1–11, Mar. 2014.

[46] R. J. Gerrig and P. G. Zimbardo, *Psychology and Life*. Boston, MA US: Pearson Education, 2002.

[47] T. Soto, *Encyclopedia of Autism Spectrum Disorders*. New York, NY: Springer New York, 2013.

[48] A. Diamond, "Executive functions.," *Annu. Rev. Psychol.*, vol. 64, pp. 135–68, Jan. 2013.

[49] H. Okano, T. Hirano, and E. Balaban, "Learning and memory.," *Proc. Natl. Acad. Sci. U. S. A.*, vol. 97, no. 23, pp. 12403–4, Nov. 2000.

[50] L. R. Squire, "The legacy of patient H.M. for neuroscience.," *Neuron*, vol. 61, no. 1, pp. 6–9, Jan. 2009.

[51] L. Nelson, R. Yoash-Gantz, T. Pickett, and T. Campbell, "Relationship Between Processing Speed and Executive Functioning Performance Among OEF/OIF Veterans: Implications for Postdeployment Rehabilitation.," *J Head Trauma Rehabil*, vol. 24, no. 1. From the Mental Health Service, Hunter Holmes McGuire Department of Veterans Affairs Medical Center, Richmond, Virginia (Drs Nelson, Pickett, and Campbell); Defense and Veterans Brain Injury Center, Richmond, Virginia (Drs Nelson and Pickett); Hefner Vete, (C) 2009 Lippincott Williams & Wilkins, Inc., pp. 32–40, 2009.

[52] M. M., I. G.L., M. T.W., H. T.A., P. M.R., B. W.B., and K. J.P., "An integrated review of recovery after mild traumatic brain injury (MTBI): Implications for clinical management," *Clin. Neuropsychol.*, vol. 23, no. 8, pp. 1368–1390, 2009.

[53] M. Inglese, S. Makani, G. Johnson, B. A. Cohen, J. A. Silver, O. Gonen, R. I. Grossman, and L. H. Hospital, "Diffuse axonal injury in mild traumatic brain injury: a diffusion tensor imaging study.," *J. Neurosurg.*, vol. 103, no. 2, pp. 298–303, Aug. 2005.

[54] G. Barkhoudarian, D. A. Hovda, and C. C. Giza, "The molecular pathophysiology of concussive brain injury.," *Clin. Sports Med.*, vol. 30, no. 1, pp. 33–48, vii–iii, Jan. 2011.

[55] T. W. McAllister, M. B. Sparling, L. A. Flashman, S. J. Guerin, a C. Mamourian, a J. Saykin, M. T.W., S. M.B., F. L.A., G. S.J., M. A.C., S. A.J., T. W. McAllister, M. B. Sparling, L. A. Flashman, S. J. Guerin, a C. Mamourian, and a J. Saykin, "Differential working memory load effects after mild traumatic brain injury.," *Neuroimage*, vol. 14, no. 5, pp. 1004–1012, 2001.

[56] T. Mcallister, M. Sparling, and L. Flashman, "Changes in frontal lobe activation after mild traumatic brain injury (MTBI) are related to performance on a fMR1 working memory task," *Neuroimage*, no. 5, p. 2189, 2000.

[57] S. Kumar, S. L. Rao, B. A. Chandramouli, S. Pillai, K. S., R. S.L., C. B.A., P. S., S. Kumar, S. L. Rao, B. A. Chandramouli, and S. Pillai, "Reduced contribution of executive functions in impaired working memory performance in mild traumatic brain injury patients.," *Clin. Neurol. Neurosurg.*, vol. 115, no. 8, pp. 1326–1332, 2013.

[58] H. G. Belanger, E. Spiegel, and R. D. Vanderploeg, "Neuropsychological performance following a history of multiple self-reported concussions: a meta-analysis.," *J. Int. Neuropsychol. Soc.*, vol. 16, no. 2, pp. 262–267, 2010.

[59] L. J. Carroll, J. D. Cassidy, C. Cancelliere, P. Côté, C. A. Hincapié, V. L. Kristman, L. W. Holm, J. Borg, C. Nygren-de Boussard, J. Hartvigsen, C. L., C. J.D., C. C., C. P., H. C., K. V., H. L., B. J., N.-D. B. C., H. J., C. L.J., C. J.D., C. C., C. P., H. C.A., K. V.L., H. L.W., B. J., N.-D. B. C., and H. J., "A systematic review of the prognosis after mild traumatic brain injury in adults: Cognitive, psychiatric and mortality outcomes. Results of the International Collaboration on MTBI Prognosis (ICoMP)," *Arch. Phys. Med. Rehabil.*, vol. 95, no. 5–6, pp. S152–S173, Mar. 2014.

[60] C. M. Baugh, J. M. Stamm, D. O. Riley, B. E. Gavett, M. E. Shenton, A. Lin, C. J. Nowinski, R. C. Cantu, A. C. McKee, R. A. Stern, B. C.M., S. J.M., R. D.O., G. B.E., S. M.E., L. A., N. C.J., C. R.C., M. A.C., and S. R.A., "Chronic traumatic encephalopathy: Neurodegeneration following repetitive concussive and subconcussive brain trauma," *Brain Imaging Behav.*, vol. 6, no. 2, pp. 244–254, 2012.

[61] A. V Goryunova, N. A. Bazarnaya, E. G. Sorokina, N. Y. Semenova, O. V Globa, Z. B. Semenova, V. G. Pinelis, L. M. Roshal', and O. I. Maslova, "Glutamate receptor autoantibody concentrations in children with chronic post-traumatic headache.," *Neurosci. Behav. Physiol.*, vol. 37, no. 8, pp. 761–4, Oct. 2007.

[62] F. Tomaiuolo, G. A. Carlesimo, M. Di Paola, M. Petrides, F. Fera, R. Bonanni, R. Formisano, P. Pasqualetti, and C. Caltagirone, "Gross morphology and morphometric sequelae in the hippocampus, fornix, and corpus callosum of patients with severe non-missile traumatic brain injury without macroscopically detectable lesions: a T1 weighted MRI study.," *J. Neurol. Neurosurg. Psychiatry*, vol. 75, no. 9, pp. 1314–22, Sep. 2004.

[63] T. J. Sick, M. A. Pérez-Pinzón, and Z.-Z. Z. Feng, "Impaired expression of long-term potentiation in hippocampal slices 4 and 48 h following mild fluid-percussion brain injury in vivo," *Brain Res.*, vol. 785, no. 2, pp. 287–292, Mar. 1998.

[64] W. C. Taft, K. Yang, C. E. Dixon, and R. L. Hayes, "Microtubule-Associated Protein 2 Levels Decrease in Hippocampus Following Traumatic Brain Injury," *J. Neurotrauma*, vol. 9, no. 3, pp. 281–290, Jan. 1992.

[65] E. Schwarzbach, D. P. Bonislawski, G. Xiong, and A. S. Cohen, "Mechanisms underlying the inability to induce area CA1 LTP in the mouse after traumatic brain injury.," *Hippocampus*, vol. 16, no. 6, pp. 541–50, Jan. 2006.

[66] L. De Beaumont, S. S. Tremblay, J. Poirier, M. Lassonde, H. Théoret, D. B. L., T. S., P. J., L. M., T. H., L. De Beaumont, S. S. Tremblay, J. Poirier, M. Lassonde, H. Théoret, and H. Th??oret, "Altered bidirectional plasticity and reduced implicit motor learning in concussed athletes," *Cereb. Cortex*, vol. 22, no. 1, pp. 112–121, Jan. 2012.

[67] D. A. Sun, L. S. Deshpande, S. Sombati, A. Baranova, M. S. Wilson, R. J. Hamm, and R. J. DeLorenzo, "Traumatic brain injury causes a long-lasting calcium (Ca2+)-plateau of elevated intracellular Ca levels and altered Ca2+ homeostatic mechanisms in hippocampal neurons surviving brain injury.," *Eur. J. Neurosci.*, vol. 27, no. 7, pp. 1659–72, Apr. 2008.

[68] L. S. Deshpande, D. A. Sun, S. Sombati, A. Baranova, M. S. Wilson, E. Attkisson, R. J. Hamm, and R. J. DeLorenzo, "Alterations in neuronal calcium levels are associated with cognitive deficits after traumatic brain injury," 2008.

[69] D. Ozdemir, B. Baykara, I. Aksu, M. Kiray, A. R. Sisman, F. Cetin, A. Dayi, T. Gurpinar, N. Uysal, and M. N. Arda, "Relationship between circulating IGF-1 levels and traumatic brain injury-induced hippocampal damage and cognitive dysfunction in immature rats," 2012.

[70] S. J. STRICH, "Diffuse degeneration of the cerebral white matter in severe dementia following head injury.," *J. Neurol. Neurosurg. Psychiatry*, vol. 19, no. 3, pp. 163–85, Aug. 1956.

[71] C. Lo, K. Shifteh, T. Gold, J. A. Bello, M. L. Lipton, L. C., S. K., G. T., B. J.A., L. M.L., C. Lo, K. Shifteh, T. Gold, J. A. Bello, M. L. Lipton, and P. MD, "Diffusion Tensor Imaging Abnormalities in Patients With Mild Traumatic Brain Injury and Neurocognitive Impairment.," *J. Comput. Assist. Tomogr.*, vol. 33, no. 2, pp. 293–297, 2009.

[72] J. R. Wozniak, L. Krach, E. Ward, B. A. Mueller, R. Muetzel, S. Schnoebelen, A. Kiragu, K. O. Lim, W. J.R., K. L., W. E., M. B.A., M. R., S. S., K. A., L. K.O., J. R. Wozniak, L. Krach, E. Ward, B. A. Mueller, R. Muetzel, S. Schnoebelen, A. Kiragu, and K. O. Lim, "Neurocognitive and neuroimaging correlates of pediatric traumatic brain injury: a diffusion tensor imaging (DTI) study.," *Arch. Clin. Neuropsychol.*, vol. 22, no. 5, pp. 555–568, 2007.

[73] G. E.J., G. Y., J. J.H., B. J.S., M. L., R. J., S. J.M., G. R.I., and I. M., "Thalamus and cognitive impairment in mild traumatic brain injury: A diffusional kurtosis imaging study," *J. Neurotrauma*, vol. 29, no. 13, pp. 2318–2327, 2012.

[74] M. L.L., S. K.K., C. K.E., L. L. Mechtler, K. K. Shastri, and K. E. Crutchfield, "Advanced neuroimaging of mild traumatic brain injury," *Neurol. Clin.*, vol. 32, no. 1, pp. 31–58, 2014.

[75] B. J.J., B. B., C. L., J. J. Bazarian, B. Blyth, and L. Cimpello, "Bench to bedside: evidence for brain injury after concussion--looking beyond the computed tomography scan.," *Acad. Emerg. Med.*, vol. 13, no. 2, pp. 199–214, 2006.

[76] C. C. Giza and D. A. Hovda, "The Neurometabolic Cascade of Concussion.," *J. Athl. Train.*, vol. 36, no. 3, pp. 228–235, Sep. 2001.

[77] X. K., Z. Z. Y., Z. Z. Y., Y. Z., Z. J., Q. M., Z. W., K. Xiong, Y. Zhu, Y. Zhang, Z. Yin, J. Zhang, M. Qiu, and W. Zhang, "White matter integrity and cognition in mild traumatic brain injury following motor vehicle accident.," *Brain Res.*, vol. 1591, no. 1, pp. 86–92, Dec. 2014.

[78] P. Arenth, K. Russell, J. Scanlon, L. Kessler, and J. Ricker, "Corpus Callosum Integrity and Neuropsychological Performance After Traumatic Brain Injury: A Diffusion Tensor Imaging Study.," *J Head Trauma Rehabil*, vol. 29, no. 2. School of Medicine, Department of Physical Medicine and Rehabilitation (Drs Arenth, Russell, Scanlon, and Ricker and Ms Kessler); Center for the Neural Basis of Cognition (Drs Arenth, Russell, and Ricker); School of Medicine, Safar Center for Resuscitatio, (C) 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins, pp. E1–E10, 2014.

[79] Y. Asano, J. Shinoda, W. T., A. Y., and S. J., "Decreased fractional anisotropy evaluated using tract-based spatial statistics and correlated with cognitive dysfunction in patients with mild traumatic brain injury in the chronic stage," *Am. J. Neuroradiol.*, vol. 33, no. 11, pp. 2117–2122, 2012.

[80] J. Strain, N. Didehbani, C. M. Cullum, S. Mansinghani, H. Conover, M. A. Kraut, J. J. Hart, and K. B. Womack, "Depressive symptoms and white matter dysfunction in retired NFL players with concussion history.," *Neurology*, vol. 81, no. 1, pp. 25–32, 2013.

[81] M. F. Kraus, T. Susmaras, B. P. Caughlin, C. J. Walker, J. A. Sweeney, and D. M. Little, "White matter integrity and cognition in chronic traumatic brain injury: a diffusion tensor imaging study.," *Brain*, vol. 130, no. Pt 10, pp. 2508–19, Oct. 2007.

[82] B. H.G., V. R.D., H. G. Belanger, and R. D. Vanderploeg, "The neuropsychological impact of sports-related concussion: a meta-analysis.," *J. Int. Neuropsychol. Soc.*, vol. 11, no. 4, pp. 345–357, 2005.

[83] M. L. Keightley, R. S. Saluja, J.-K. Chen, I. Gagnon, G. Leonard, M. Petrides, A. Ptito, K. M.L., S. S. R., C. J.-K., G. I., L. G., P. M., and P. A., "A functional magnetic resonance imaging study of working memory in youth after sports-related concussion: is it still working?," *J. Neurotrauma*, vol. 31, no. 5, pp. 437–451, 2014.

[84] J. J. Leddy, H. Sandhu, V. Sodhi, J. G. Baker, and B. Willer, "Rehabilitation of Concussion and Post-concussion Syndrome.," *Sports Health*, vol. 4, no. 2, pp. 147–54, Mar. 2012.

[85] M. Makdissi, P. McCrory, A. Ugoni, D. Darby, and P. Brukner, "A prospective study of postconcussive outcomes after return to play in Australian football.," *Am. J. Sports Med.*, vol. 37, no. 5, pp. 877–883, 2009.

[86] A. K. Connery, D. A. Baker, J. W. Kirk, and M. W. Kirkwood, "The Effects of Multiple Mild Traumatic Brain Injuries on Acute Injury Presentation and Neuropsychological Recovery in Children.," *Neurosurgery*, vol. 75, no. 1, pp. 31–36, 2014.

[87] T. Covassin, R. Moran, K. Wilhelm, C. T., M. R., and W. K., "Concussion Symptoms and Neurocognitive Performance of High School and College Athletes Who Incur Multiple Concussions.," *Am. J. Sports Med.*, vol. 41, no. 12, pp. 2885–2889, Dec. 2013.

[88] G. L. Iverson, M. Gaetz, M. R. Lovell, M. W. Collins, I. G.L., G. M., L. M.R., and C. M.W., "Cumulative effects of concussion in amateur athletes," *Brain Inj.*, vol. 18, no. 5, pp. 433–443, May 2004.

[89]   S. L. Aungst, S. V Kabadi, S. M. Thompson, B. A. Stoica, A. I. Faden, A. S.L., K. S.V., T. S.M., S. B.A., and F. A.I., "Repeated mild traumatic brain injury causes chronic neuroinflammation, changes in hippocampal synaptic plasticity, and associated cognitive deficits," *J. Cereb. Blood Flow Metab.*, vol. 34, no. 7, pp. 1223–1232, Jul. 2014.

[90]   H. S. MARTLAND, "PUNCH DRUNK," *J. Am. Med. Assoc.*, vol. 91, no. 15, p. 1103, Oct. 1928.

[91]   L. Chin, G. Toshkezi, and R. Cantu, "Traumatic Encephalopathy Related to Sports Injury," *Brain Trauma*, vol. 7, no. 1, pp. 33–6, 2011.

[92]   H. Miller, "Mental after-effects of head injury.," *Proc. R. Soc. Med.*, vol. 59, no. 3, pp. 257–61, Mar. 1966.

[93]   P. H. Montenigro, D. T. Corp, T. D. Stein, R. C. Cantu, and R. A. Stern, "Chronic Traumatic Encephalopathy: Historical Origins and Current Perspective.," *Annu. Rev. Clin. Psychol.*, Jan. 2015.

[94]   B. J.R., S. G.W., W. K.-P., H. S.-C., L. J., M. D.A., G. C.C., F. R.P., O. B., B. J., and K. V., "In vivo characterization of chronic traumatic encephalopathy using [F-18]FDDNP PET brain imaging," *Proc. Natl. Acad. Sci. U. S. A.*, vol. 112, no. 16, pp. E2039–E2047, 2015.

[95]   J. M. Coughlin, Y. Wang, C. A. Munro, S. Ma, C. Yue, S. Chen, R. Airan, P. K. Kim, A. V Adams, C. Garcia, C. Higgs, H. I. Sair, A. Sawa, G. Smith, C. G. Lyketsos, B. Caffo, M. Kassiou, T. R. Guilarte, and M. G. Pomper, "Neuroinflammation and brain atrophy in former NFL players: An in vivo multimodal imaging pilot study.," *Neurobiol. Dis.*, vol. 74C, pp. 58–65, Nov. 2014.

[96]   R. A. Stern, D. O. Riley, D. H. Daneshvar, C. J. Nowinski, R. C. Cantu, and A. C. McKee, "Long-term consequences of repetitive brain trauma: chronic traumatic encephalopathy.," *PM R*, vol. 3, no. 10 Suppl 2, pp. S460–7, Oct. 2011.

[97]   S. A.M., S. J.H., B. A.J., B. E.C., A. M. Spiotta, J. H. Shin, A. J. Bartsch, and E. C. Benzel, "Subconcussive impact in sports: A new era of awareness," *World Neurosurg.*, vol. 75, no. 2, pp. 175–178, Feb. 2011.

[98]   A. C. McKee, T. D. Stein, C. J. Nowinski, R. A. Stern, D. H. Daneshvar, V. E. Alvarez, H. S. Lee, G. Hall, S. M. Wojtowicz, C. M. Baugh, D. O. Riley, C. A. Kubilus, K. A. Cormier, M. A. Jacobs, B. R. Martin, C. R. Abraham, T. Ikezu, R. R. Reichard, B. L. Wolozin, A. E. Budson, L. E. Goldstein, N. W. Kowall, and R. C. Cantu, "The spectrum of disease in chronic traumatic encephalopathy," *Brain*, vol. 136, no. 1, pp. 43–64, 2013.

[99]   E. J. Lehman, M. J. Hein, S. L. Baron, and C. M. Gersic, "Neurodegenerative causes of death among retired National Football League players.," *Neurology*, vol. 79, no. 19, pp. 1970–4, Nov. 2012.

[100]   A. C. McKee and M. E. Robinson, "Military-related traumatic brain injury and neurodegeneration," *Alzheimer's Dement.*, vol. 10, no. 3 SUPPL., pp. S242–S253, Jun. 2014.

[101]   L. E. Goldstein, A. M. Fisher, C. A. Tagge, X.-L. Zhang, L. Velisek, J. A. Sullivan, C. Upreti, J. M. Kracht, M. Ericsson, M. W. Wojnarowicz, C. J. Goletiani, G. M. Maglakelidze, N. Casey, J. A. Moncaster, O. Minaeva, R. D. Moir, C. J. Nowinski, R. A. Stern, R. C. Cantu, J. Geiling, J. K. Blusztajn, B. L. Wolozin, T. Ikezu, T. D. Stein, A. E. Budson, N. W. Kowall, D. Chargin, A. Sharon, S. Saman, G. F. Hall, W. C. Moss, R. O. Cleveland, R. E. Tanzi, P. K. Stanton, and A. C. McKee, "Chronic traumatic encephalopathy in blast-exposed military veterans and a blast neurotrauma mouse model.," *Sci. Transl. Med.*, vol. 4, no. 134, p. 134ra60, May 2012.

[102] D. R. Seichepine, J. M. Stamm, D. H. Daneshvar, D. O. Riley, C. M. Baugh, B. E. Gavett, Y. Tripodis, B. Martin, C. Chaisson, A. C. McKee, R. C. Cantu, C. J. Nowinski, R. A. Stern, S. D.R., S. J.M., D. D.H., R. D.O., B. C.M., G. B.E., T. Y., M. B., C. C., M. A.C., C. R.C., N. C.J., S. R.A., D. R. Seichepine, J. M. Stamm, D. H. Daneshvar, D. O. Riley, C. M. Baugh, B. E. Gavett, Y. Tripodis, B. Martin, C. Chaisson, A. C. McKee, R. C. Cantu, C. J. Nowinski, and R. A. Stern, "Profile of self-reported problems with executive functioning in college and professional football players.," *J. Neurotrauma*, vol. 30, no. 14, pp. 1299–304, 2013.

[103] L. Miles, R. I. Grossman, G. Johnson, J. S. Babb, L. Diller, and M. Inglese, "Short-term DTI predictors of cognitive dysfunction in mild traumatic brain injury.," *Brain Inj.*, vol. 22, no. 2, pp. 115–122, Feb. 2008.

[104] M. J. Larson, T. J. Farrer, P. E. Clayson, L. M.J., F. T.J., and C. P.E., "Cognitive control in mild traumatic brain injury: conflict monitoring and conflict adaptation.," *Int. J. Psychophysiol.*, vol. 82, no. 1, pp. 69–78, Oct. 2011.

[105] M. McCrea, K. M. Guskiewicz, S. W. Marshall, W. Barr, C. Randolph, R. C. Cantu, J. A. Onate, J. Yang, J. P. Kelly, M. M., G. K.M., M. S.W., B. W., R. C., C. R.C., O. J.A., Y. J., K. J.P., M. McCrea, K. M. Guskiewicz, S. W. Marshall, W. Barr, C. Randolph, R. C. Cantu, J. A. Onate, J. Yang, and J. P. Kelly, "Acute effects and recovery time following concussion in collegiate football players: the NCAA Concussion Study.," *JAMA*, vol. 290, no. 19, pp. 2556–63, Nov. 2003.

[106] M. McCrea, K. Guskiewicz, C. Randolph, W. B. Barr, T. A. Hammeke, S. W. Marshall, M. R. Powell, K. Woo Ahn, Y. Wang, J. P. Kelly, M. M., G. K., R. C., B. W.B., H. T.A., M. S.W., P. M.R., A. K.W., W. Y., and K. J.P., "Incidence, clinical course, and predictors of prolonged recovery time following sport-related concussion in high school and college athletes.," *J. Int. Neuropsychol. Soc.*, vol. 19, no. 1, pp. 22–33, 2013.

[107] M. Wäljas, G. Iverson, R. Lange, U. Hakulinen, P. Dastidar, H. Huhtala, S. Liimatainen, K. Hartikainen, and J. Ohman, "A Prospective Biopsychosocial Study of the Persistent Post-Concussion Symptoms Following Mild Traumatic Brain Injury," *J. Neurotrauma*, vol. 547, pp. 1–54, 2014.

[108] C. O., R. M., B. G., O. Chadwick, M. Rutter, G. Brown, D. Shaffer, and M. U. Traub, "A prospective study of children with head injuries: II. Cognitive sequelae.," *Psychol. Med.*, vol. 11, no. 1, pp. 49–61, 1981.

[109] R. B.P., L. L.J., C. J.M., S. L., T. A., G. R., M. L.A., B. Rieger P., L. Lewandowski J., J. Callahan M., L. Spenceley, A. Truckenmiller, R. Gathje, L. Miller A., B. P. Rieger, L. J. Lewandowski, J. M. Callahan, L. Spenceley, A. Truckenmiller, R. Gathje, and L. A. Miller, "A prospective study of symptoms and neurocognitive outcomes in youth with concussion vs orthopaedic injuries.," *Brain Inj.*, vol. 27, no. 2, pp. 169–178, Feb. 2013.

[110] C. C., M. P., C. A., M. T., C. Catale, P. Marique, A. Closset, and T. Meulemans, "Attentional and executive functioning following mild traumatic brain injury in children using the Test for Attentional Performance (TAP) battery.," *J. Clin. Exp. Neuropsychol.*, vol. 31, no. 3, pp. 331–338, 2009.

[111] P. A., D. J., K. D., A. A. L., A. A. L., A. PHILLIPOU, J. DOUGLAS, D. KRIESER, L. AYTON, and L. ABEL, "Changes in saccadic eye movement and memory function after mild closed head injury in children.," *Dev Med Child Neurol*, vol. 56, no. 4, pp. 337–345, 2014.

[112] F. Y. Kwok, T. M. C. Lee, C. H. S. Leung, W. S. Poon, K. F.Y., L. T.M.C., L. C.H.S., P. W.S., F. Y. Kwok, T. M. C. Lee, C. H. S. Leung, and W. S. Poon, "Changes of cognitive functioning following mild traumatic brain injury over a 3-month period.," *Brain Inj.*, vol. 22, no. 10, pp. 740–751, 2008.

[113] T. S.Y., A. B.T., L. X.Y., M. A., C. S.L., S. Y. Tay, B. T. Ang, X. Y. Lau, A. Meyyappan, and S. L. Collinson, "Chronic impairment of prospective memory after mild traumatic brain injury," *J. Neurotrauma*, vol. 27, no. 1, pp. 77–83, 2010.

[114] J. Ponsford, C. Willmott, A. Rothwell, P. Cameron, G. Ayton, R. Nelms, C. Curran, K. T. Ng, P. J., W. C., R. A., C. P., A. G., N. R., C. C., N. K.T., J. Ponsford, C. Willmott, A. Rothwell, P. Cameron, G. Ayton, R. Nelms, C. Curran, and K. T. Ng, "Cognitive and behavioral outcome following mild traumatic head injury in children.," *J. Head Trauma Rehabil.*, vol. 14, no. 4, pp. 360–372, Aug. 1999.

[115] J. A. Mangels, F. I. M. Craik, B. Levine, M. L. Schwartz, D. T. Stuss, M. J.A., C. F.I.M., L. B., S. M.L., and S. D.T., "Effects of divided attention on episodic memory in chronic traumatic brain injury: a function of severity and strategy.," *Neuropsychologia*, vol. 40, no. 13, pp. 2369–2385, 2002.

[116] S.-H. Su, W. Xu, M. Li, L. Zhang, Y.-F. Wu, F. Yu, J. Hai, S. S.-H., X. W., L. M., Z. L., W. Y.-F., Y. F., and H. J., "Elevated C-reactive protein levels may be a predictor of persistent unfavourable symptoms in patients with mild traumatic brain injury: a preliminary study.," *Brain. Behav. Immun.*, vol. 38, pp. 111–117, 2014.

[117] R. Siman, N. Giovannone, G. Hanten, E. A. Wilde, S. R. McCauley, J. V. Hunter, X. Li, H. S. Levin, D. H. Smith, S. R., G. N., H. G., W. E.A., M. S.R., H. J.V., L. X., L. H.S., and S. D.H., "Evidence that the blood biomarker SNTF predicts brain imaging changes and persistent cognitive dysfunction in mild TBI patients," *Front. Neurol.*, vol. 4 NOV, no. November, pp. 1–8, 2013.

[118] J. Ponsford, C. Willmott, A. Rothwell, P. Cameron, A. M. Kelly, R. Nelms, C. Curran, K. Ng, P. J., W. C., R. A., C. P., K. A.-M., N. R., C. C., and K. N.G., "Factors influencing outcome following mild traumatic brain injury in adults.," *J. Int. Neuropsychol. Soc.*, vol. 6, no. 5, pp. 568–579, 2000.

[119] H. Lee, M. Wintermark, A. D. Gean, J. Ghajar, G. T. Manley, P. Mukherjee, L. H., W. M., G. A.D., G. J., M. G.T., and M. P., "Focal lesions in acute mild traumatic brain injury and neurocognitive outcome: CT versus 3T MRI.," *J. Neurotrauma*, vol. 25, no. 9, pp. 1049–56, Sep. 2008.

[120] M. N. Wong, B. Murdoch, B.-M. Whelan, W. M.N., M. B., W. B.-M., M. N. Wong, B. Murdoch, and B.-M. Whelan, "Language disorders subsequent to mild traumatic brain injury (MTBI): Evidence from four cases," *Aphasiology*, vol. 24, no. 10, pp. 1155–1169, Oct. 2010.

[121] K. C., G. A.J., R. F., B. H., F. B., H. I., A. V., S. H., L. H., C. Konrad, A. Geburek, F. Rist, H. Blumenroth, B. Fischer, I. Husstedt, V. Arolt, H. Schiffbauer, and H. Lohmann, "Long-term cognitive and emotional consequences of mild traumatic brain injury.," *Psychol. Med.*, vol. 41, no. 6, pp. 1197–1211, 2011.

[122] V. R.D., C. G., B. H.G., H. G. Belanger, G. Curtiss, J. A. Demery, B. K. Lebowitz, R. D. Vanderploeg, B. H.G., C. G., D. J.A., L. B.K., V. R.D., R. D. Vanderploeg, G. Curtiss, and H. G. Belanger, "Long-term neuropsychological outcomes following mild traumatic brain injury," *J. Int. Neuropsychol. Soc.*, vol. 11, no. 3, pp. 215–227, 2005.

[123] J. Ponsford, P. Cameron, M. Fitzgerald, M. Grant, A. Mikocka-walus, P. J., C. P., F. M., G. M., and M.-W. A., "Long-term outcomes after uncomplicated mild traumatic brain injury: a comparison with trauma controls.," *J. Neurotrauma*, vol. 28, no. 6, pp. 937–946, 2011.

[124] P. Wrightson, V. McGinn, D. Gronwall, W. P., M. V., and G. D., "Mild head injury in preschool children: evidence that it can be associated with a persisting cognitive defect.," *J. Neurol. Neurosurg. Psychiatry*, vol. 59, no. 4, pp. 375–380, 1995.

[125] S. Dikmen, J. Machamer, and N. Temkin, "Mild head injury: facts and artifacts.," *J. Clin. Exp. Neuropsychol.*, vol. 23, no. 6, pp. 729–738, 2001.

[126] P. N.L., F. G.C., J. K.M., L. S., M. K.M., S. H.A., R. J.B., and W. H.R., "Mild pediatric traumatic brain injury: Adjusting significance levels for multiple comparisons," *Brain Inj.*, vol. 8, no. 3, pp. 249–263, 1994.

[127] A. Maillard-Wermelinger, K. O. Yeates, H. Gerry Taylor, J. Rusin, B. Bangert, A. Dietrich, K. Nuss, M. Wright, M.-W. A., Y. K.O., G. T. H., R. J., B. B., D. A., N. K., W. M., A. Maillard-Wermelinger, K. O. Yeates, H. Gerry Taylor, J. Rusin, B. Bangert, A. Dietrich, K. Nuss, and M. Wright, "Mild traumatic brain injury and executive functions in school-aged children.," *Dev. Neurorehabil.*, vol. 12, no. 5, pp. 330–341, 2009.

[128] N. Paré, L. a Rabin, J. Fogel, M. Pépin, N. Pare, L. a Rabin, J. Fogel, and M. Pepin, "Mild traumatic brain injury and its sequelae: characterisation of divided attention deficits.," *Neuropsychol. Rehabil.*, vol. 19, no. 1, pp. 110–137, 2009.

[129] G. J. Kinsella, J. Olver, B. Ong, R. Gruen, E. Hammersley, K. G.J., O. J., O. B., G. R., and H. E., "Mild traumatic brain injury in older adults: early cognitive outcome.," *J. Int. Neuropsychol. Soc.*, vol. 20, no. 6, pp. 663–671, 2014.

[130] Z. Y., K. A., K. D., G. Y., R. R. J., R. R. J., G. R.I., and L. Y.W., "Mild traumatic brain injury: Longitudinal regional brain volume changes," *Radiology*, vol. 267, no. 3, pp. 880–890, 2013.

[131] M. H. Heitger, R. D. Jones, J. C. Dalrymple-Alford, C. M. Frampton, M. W. Ardagh, T. J. Anderson, H. M.H., J. R.D., D.-A. J.C., F. C.M., A. M.W., and A. T.J., "Motor deficits and recovery during the first year following mild closed head injury.," *Brain Inj.*, vol. 20, no. 8, pp. 807–24, Jul. 2006.

[132] S. Kashluba, R. A. Hanks, J. E. Casey, S. R. Millis, K. S., H. R.A., C. J.E., and M. S.R., "Neuropsychologic and functional outcome after complicated mild traumatic brain injury.," *Arch. Phys. Med. Rehabil.*, vol. 89, no. 5, pp. 904–11, May 2008.

[133] R. K., L. N.J., B. S.E., E. L., F. A., K. Romero, N. J. Lobaugh, S. E. Black, L. Ehrlich, and A. Feinstein, "Old wine in new bottles: Validating the clinical utility of SPECT in predicting cognitive performance in mild traumatic brain injury," *Psychiatry Res. - Neuroimaging*, vol. 231, no. 1, pp. 15–24, 2015.

[134] B. M. Stålnacke, E. Elgh, P. Sojka, B.-M. Stalnacke, E. Elgh, P. Sojka, S. B.-M., E. E., and S. P., "One-year follow-up of mild traumatic brain injury: cognition, disability and life satisfaction of patients seeking consultation.," *J. Rehabil. Med. (Stiftelsen Rehabiliteringsinformation)*, vol. 39, no. 5, pp. 405–411, May 2007.

[135] V. Anderson, C. Catroppa, S. Morse, F. Haritou, J. Rosenfeld, A. V., C. C., M. S., H. F., and R. J., "Outcome from mild head injury in young children: a prospective study.," *J. Clin. Exp. Neuropsychol. Off. J. Int. Neuropsychol. Soc.*, vol. 23, no. 6, pp. 705–717, 2001.

[136] B. N., T. A., J. J., N. Bohnen, A. Twijnstra, and J. Jolles, "Persistence of postconcussional symptoms in uncomplicated, mildly head-injured patients: A prospective cohort study," *Neuropsychiatry, Neuropsychol. Behav. Neurol.*, vol. 6, no. 3, pp. 193–200, 1993.

[137] N. V Marsh, M. D. Smith, M. N.V., and S. M.D., "Post-concussion syndrome and the coping hypothesis," *Brain Inj.*, vol. 9, no. 6, pp. 553–562, 1995.

[138] K. Miller, T. Ingebrigtsen, T. Wilsgaard, G. Wikran, T. Fagerheim, B. Romner, K. Waterloo, M. K., I. T., W. T., W. G., F. T., R. B., W. K., K. Muller, T. Ingebrigtsen, T. Wilsgaard, G. Wikran, T. Fagerheim, B. Romner, and K. Waterloo, "Prediction of time trends in recovery of cognitive function after mild head injury," *Neurosurgery*, vol. 64, no. 4, pp. 698–704, 2009.

[139] L. Xu, J. V Nguyen, M. Lehar, A. Menon, E. Rha, J. Arena, J. Ryu, N. Marsh-Armstrong, C. R. Marmarou, and V. E. Koliatsos, "Repetitive mild traumatic brain injury with impact acceleration in the mouse: Multifocal axonopathy, neuroinflammation, and neurodegeneration in the visual system.," *Exp. Neurol.*, Nov. 2014.

[140] B. T., M. D., A. R.F., T. Babikian, D. McArthur, and R. F. Asarnow, "Predictors of 1-month and 1-year neurocognitive functioning from the UCLA longitudinal mild, uncomplicated, pediatric traumatic brain injury study.," *J. Int. Neuropsychol. Soc.*, vol. 19, no. 2, pp. 145–154, 2013.

[141] D. Ellemberg, S. Leclerc, S. Couture, and C. Daigle, "Prolonged neuropsychological impairments following a first concussion in female university soccer athletes.," *Clin. J. Sport Med.*, vol. 17, no. 5, pp. 369–374, Sep. 2007.

[142] S. R. McCauley, H. S. Levin, M. S.R., and L. H.S., "Prospective Memory in Pediatric Traumatic Brain Injury: A Preliminary Study," *Dev. Neuropsychol.*, vol. 25, no. 1–2, pp. 5–20, 2004.

[143] V. Rotarescu and A. V Ciurea, "Quality of life in children after mild head injury.," *J. Med. Life*, vol. 1, no. 3, pp. 307–322, 2008.

[144] K. M. Jaffe, N. L. Polissar, G. C. Fay, S. Liao, J. K.M., P. N.L., F. G.C., and L. S., "Recovery trends over three years following pediatric traumatic brain injury.," *Arch. Phys. Med. Rehabil.*, vol. 76, no. 1, pp. 17–26, 1995.

[145] C. N. De Boussard, A. Lundin, D. Karlstedt, G. Edman, A. Bartfai, C. de Boussard, A. Lundin, D. Karlstedt, G. Edman, A. Bartfai, J. Borg, N. de B. C., L. A., K. D., E. G., B. A., and B. J., "S100 AND COGNITIVE IMPAIRMENT AFTER MILD TRAUMATIC BRAIN INJURY.," *J Rehabil Med*, vol. 37, no. 1, pp. 53–57, 2005.

[146] H. S. Levin, J. M. Fletcher, L. Kusnerik, J. A. Kucera, A. Matthew, F. F. Duffyl, S. Chapman, D. Mendelsohn, D. Bruce, L. H.S., F. J.M., K. L., K. J.A., L. M.A., D. F.F., C. S., M. D., B. D., H. S. Levin, J. M. Fletcher, L. Kusnerik, J. A. Kufera, M. A. Lilly, F. F. Duffy, S. Chapman, D. Mendelsohn, and D. Bruce, "Semantic memory following pediatric head injury: relationship to age, severity of injury, and MRI.," *Cortex.*, vol. 32, no. 3, pp. 461–478, 1996.

[147] I. Barrow, J. Collins, F. MD, L. Britt, M. P. H. MD, and F. FACS, "The Influence of an Auditory Distraction on Rapid Naming After a Mild Traumatic Brain Injury: A Longitudinal Study.," *J Trauma*, vol. 61, no. 5. From the Department of Communicative Sciences and Disorders, Hampton University, Hampton, Virginia (I.M.B.); Department of Surgery, Eastern Virginia Medical School, Norfolk, Virginia (J.N.C., L.D.B.)., (C) 2006 Lippincott Williams & Wilkins, Inc., pp. 1142–1149, 2006.

[148] G. Hanten, X. Li, A. Ibarra, E. a Wilde, A. Barnes, S. R. McCauley, J. McCarthy, S. Hoxhaj, D. Mendez, J. V Hunter, H. S. Levin, D. H. Smith, H. G., L. X., I. A., W. E.A., B. A., M. S.R., M. J., H. S., M. D., H. J.V., L. H.S., and S. D.H., "Updating memory after mild traumatic brain injury and orthopedic injuries.," *J. Neurotrauma*, vol. 30, no. 8, pp. 618–24, 2013.

[149] E. K. Geary, M. F. Kraus, N. H. Pliskin, D. M. Little, G. E.K., K. M.F., P. N.H., and L. D.M., "Verbal learning differences in chronic mild traumatic brain injury," *J. Int. Neuropsychol. Soc.*, vol. 16, no. 3, pp. 506–516, 2010.

[150] I. Croall, C. J. A. Cowie, J. He, A. Peel, J. Wood, B. Aribisala, P. Mitchell, A. Mendelow, F. Smith, D. Millar, T. Kelly, A. Blamire, C. I.D., C. C.J.A., H. J., P. A., W. J., A. B.S., M. P., M. A.D., S. F.E., M. D., K. T., B. A.M., I. Croall D, C. J. A. Cowie, J. He, A. Peel, J. Wood, B. Aribisala S, P. Mitchell, A. Mendelow David, F. Smith E, D. Millar, T. Kelly, and A. Blamire M, "White matter correlates of cognitive dysfunction after mild traumatic brain injury.," *Neurology*, vol. 83, no. 6, pp. 494–501, Aug. 2014.

[151] E. D. Bigler, L. Rosa, F. Schultz, S. Hall, and J. Harris, "Rey-Auditory Verbal Learning and Rey-Osterrieth Complex Figure Design performance in Alzheimer's disease and closed head injury.," *J. Clin. Psychol.*, vol. 45, no. 2, pp. 277–280, 1989.

[152] P. Schatz, J. E. Pardini, M. R. Lovell, M. W. Collins, K. Podell, S. P., P. J.E., L. M.R., C. M.W., P. K., P. Schatz, J. E. Pardini, M. R. Lovell, M. W. Collins, and K. Podell, "Sensitivity and specificity of the ImPACT Test Battery for concussion in athletes," *Arch. Clin. Neuropsychol.*, vol. 21, no. 1, pp. 91–99, Jan. 2006.

[153] M. Alexander, "Mild traumatic brain injury.," *Neurology*, vol. 46, no. 5. Braintree, MA, (C) 1996 American Academy of Neurology, pp. 1489–1490, 1996.

[154] M. P. Alexander, "Mild traumatic brain injury: pathophysiology, natural history, and clinical management.," *Neurology*, vol. 45, no. 7, pp. 1253–60, Jul. 1995.