The Investigation of Long-term Cognitive Changes after Mild Traumatic Brain Injury using Novel and Sensitive Measures

by
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A thesis
presented to the University of Waterloo
in fulfillment of the
thesis requirement for the degree of
Doctor of Philosophy
in
Psychology - Behavioural & Cognitive Neuroscience

Waterloo, Ontario, Canada, 2012

AUTHOR'S DECLARATION

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners. I understand that my thesis may be made electronically available to the public.

Abstract

Memory and concentration problems are frequently reported long after experiencing a mild traumatic brain injury (mild TBI), though conflict with null findings of deficits on standard neuropsychological tests. Experimental research shows that these inconsistencies are, in part, due to the simplicity of neuropsychological tests. As well, past research suggests that when neuropsychological deficits are occasionally detected within this population, they could be influenced by diagnosis threat: an expectation bias for impaired performance when individuals are merely informed that cognitive problems may be experienced following a mild TBI. The main goal of this thesis was to specify the long-term cognitive effects of mild TBI, with the prediction that, while cognitive complaints may be over-reported due to diagnosis threat, significant deficits can be detected using sensitive measures in experimental paradigms. Experiment 1 sought to document whether diagnosis threat influenced self-report of everyday attention and memory problems and neuropsychological task performance in individuals with a remote history of mild TBI. We found that undergraduate students with a mild TBI were significantly more likely to report having attention and memory failures in their daily lives when exposed to diagnosis threat, compared to undergraduate students not exposed to diagnosis threat. These findings call into question the efficacy of using of self-report measures to identify long-term cognitive deficits following a mild TBI. In an attempt to further specify persistent significant cognitive deficits, we designed two different experimental paradigms that uniquely manipulated the demand place on executive processes, as past research suggested deficits emerge only when tasks require considerable cognitive resources. In Experiment 2a, we manipulated processing load on a visual working memory task, across two conditions, while also limiting the potential effect of diagnosis threat. While self-report and neuropsychological measures of attention and memory did not differentiate the groups, the mild TBI group took significantly longer to accurately detect repeated targets on our working memory task. Accuracy was comparable in the low-load condition and, unexpectedly, mild TBI performance surpassed that of controls in the high-load condition. Temporal analysis of target identification suggested a strategy difference between groups: mild TBI participants made a significantly greater number of accurate responses following

the target's offset, and significantly fewer erroneous distracter responses prior to target onset, compared to controls. In Experiment 2b we also examined whether manipulating executive processing demands would differentiate mild TBI from controls, this time on a routine action task that required participants to learn a sequence of hand movements to targets. While not significant, we found a trend such that mild TBI participants were slower to respond on trials with a large executive demand compared controls, while no differences were found on trials with relatively low executive requirements. Results from Experiments 2a and 2b provide stronger evidence for mild TBI-related slowing during a working memory task with an executive component compared to a skilled action task that also had an executive component, but placed minimal demand on memory. To more precisely identify the brain basis of this cognitive slowing, in Experiment 3 we administered a visual *n*-back task in which we systematically increased working memory demands from 0- to 3-item loads. We found that, compared to controls, mild TBI participants showed a reduction in P300 amplitude, conceptualized as an index of available cognitive resources for stimulus classification. While no late stage response differences were found between groups, P300 amplitude was negatively correlated with response times at higher loads in both control and mild TBI participants. Findings suggest that high functioning young adults who sustained a mild TBI in their remote past, have a reduced amount, or inefficient recruitment of, cognitive resources for target detection; a potential mechanism underlying mild TBI-related response slowing on tasks that place a heavy demand on processing resources. Similar to the effects of mild TBI, aging is also known to negatively impact cognition. In Experiment 4, we examined whether TBI-related deficits persist into older adulthood, and compound the negative effect of aging on cognition. We administered the same working memory task as in Experiment 2a, along with a variety of neuropsychological tests in order to investigate the effect of a TBI sustained an average of 50 years in the past. While no group differences emerged on our experimental working memory task, older adults with a history of 1 or 2 TBIs performed significantly worse than non head-injured older adults only on neuropsychological measures of attention that had an executive component. Such results suggest that a remote TBI sustained early in life further compounds normal age-related cognitive decline. Together, these experiments

help specify the measures that best detect long lasting cognitive changes following TBI. Particularly, our findings provide a potential explanation for why long-term cognitive deficits are difficult to identify in the young mild TBI population: the majority of neuropsychological tests are insensitive to minor changes in information processing speed and, as a result, the execution of slowing strategies to maintain accuracy may go undetected. Our findings also demonstrate the importance of investigating longer-term effects of TBI, as they may be chronic and impact cognitive task performance in old age, amplifying normal age-related cognitive deficits.

Acknowledgements

I would like to start by acknowledging my supervisor, Dr. Myra Fernandes, for her unwavering reliability, enthusiasm for research, and overall support for the past four years. I would also like to thank Dr. Eric Roy and Dr. Roxane Itier for sitting on my committing and for their many contributions to my research projects. In addition, I extend thanks to every member of the Fernandes lab who has willingly provided me with support and encouragement during my journey through graduate school. To each research assistant who has helped me along the way, your dedication, reliability, and exceptional work are all greatly appreciated. I also give great thanks to NSERC and the University of Waterloo for funding my research.

A special thanks to Michelle Manios, Shahnaz Koji, Amanda Clark and Frank Preston, not only for each of your specific contributions to my research, but more importantly, for your friendship. I am also grateful for the ongoing support of my closest friends, Elena Rauda, Palki Arora, and Crystal Gelsinger. To my dad, thank you for your endless reassurance, your compassion and for continually making an effort to ensure I am not overworking. To my mom, I am most grateful for your love, encouragement and your ability to console me during the tough times. Dean and Anne, I deeply value our relationships and the support you have both provided me over the years.

It is with great gratitude that I acknowledge Melissa Felteau. Your positive words, advice and academic support have paved a path for me to pursue my research interests. I am thrilled to say that I have found a wonderful lifelong friend. Lastly, thank you Paul for always being there for me no matter what time of the day it is or how many miles apart we may be. Your genuine kindness is an extremely valuable quality and I am very fortunate that our paths crossed.

Dedication

This dissertation is dedicated to Marilyn Perdue. Her support, guidance and wisdom encouraged me to find inner strength and pause to appreciate the beauty of the present moment. I am forever grateful for her acceptance and compassion.

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Chapter 1: General Introduction

The prevalence of traumatic brain injury (TBI) is high, with the majority of injuries classified as mild in severity. Mild TBIs have recently been referred to the as a silent epidemic in North America, as the incidence is much higher, and the effects more persistent, than once thought. For example, mild TBIs (i. e., concussions) are especially common in sports, but until recently, were often overlooked. Such disregard may not come as a surprise to clinical psychologists and cognitive researchers as traditional neuropsychological assessments most often failed to detect any residual cognitive impairment following mild TBI. Recently, experimental research has had more success at identifying long-lasting deficits by increasing task complexity and sensitivity. Research directed at specifying such deficits is important in order to understand the reasons for inconsistent neuropsychological findings documented in the literature, as well as for persistent memory and concentration complaints in individuals long after experiencing a mild TBI. The purpose of my thesis is to better specify residual cognitive impairment following a mild TBI by implementing sensitive and novel experimental tasks in otherwise healthy young and older adults.

The introduction to this PhD thesis is organized into various sections. I begin by defining TBI and classifying the injuries according to severity. Next, I briefly review the neural imaging literature and discuss what is currently known about the structural damage caused by TBI. Following this section, I provide evidence for persistent cognitive impairment following moderate to severe TBIs. The short- and long-term cognitive deficits due to a mild TBI are then discussed in the subsequent sections. I then go into detail about precisely how experimental research has increased task complexity in order to identify lingering cognitive problems after mild TBI and relate these findings to working memory and attentional control theories widely accepted by the psychology community. This section is followed by a review of an electrophysiological technique, event-related potential recording, used in TBI research to identify the brain-basis of persistent cognitive changes. Next, I discuss the overlap in TBI- and healthy age-related cognitive changes, and emphasize the importance of considering these similarities when studying long-term cognitive impairment in TBI population. Finally, I provide a brief overview of my thesis experiments.

Prevalence of Traumatic Brain Injury

Each year, approximately 120, 000 people sustain a traumatic brain injury (TBI) in Canada (Iverson & Lange, 2011). In the United States, reports show that between 1995 and 2001, 1.4 million people each year were admitted to the emergency department after a TBI (Iverson & Lange, 2011). Traumatic brain injuries affect people of all ages, with incident rates being the highest in young adults from 15-24 years of age and older adults over the age of 75 (Thurman, Coronado, & Selassie, 2007). While the criteria for determining the severity of TBI is highly dependent on the referral institution, when taken as a whole, an American estimate shows that over a recent 25-year period, 80% of all TBIs were mild, 10% moderate and 10% severe (Kraus & Chu, 2005). The high prevalence of mild TBI largely contributes to the economic burden of all head injuries, accounting for an estimated 44% of the 56 billion dollar cost annually in the United States (Thurman, 2001). Another source approximates that 90% of all brain injuries are classified as mild, with an estimate of 1.5 million non-institutionalized new mild to moderate cases each year in the United States (Sosin, Sniezek, & Thurman, 1996). Rates based on hospital admissions are thought to be an underestimate of mild TBI prevalence as many individuals do not seek medical assistance (Sosin et al., 1996). Sports players are an example of a group who commonly experience mild TBIs (i. e., concussions), but are not admitted to a hospital or emergency department. It has recently been reported that 30% of high school football players sustained a minimum of one previous concussion and 15% of players reported a concussion in the current football season (McCrea, Hammeke, Olsen, Leo, & Guskiewicz, 2004). In fact, the incidence is so high that mild TBI has been described as an epidemic in the United States (Kushner, 1998).

What is Traumatic Brain Injury?

Severity Index

Traumatic brain injury is another term for closed head injury and results from the head being hit, the head striking an object, or the brain undergoing an acceleration/deceleration force without direct external trauma to the head (Kay et al., 1993). Severity of the TBI is most commonly determined by the Glascow Coma Scale (GCS), duration of loss of consciousness

(LOC) and post-traumatic amnesia (PTA). Developed by Teasdale & Jennett, 1974, the GCS is a screening tool administered to independently measure three aspects of behavior: motor responsiveness, verbal performance, and eye opening, yielding a score anywhere from 3 to 15 (most to least severe). The most widely used criteria to determine a mild TBI status is based on the definition put forth by The American Congress of Rehabilitative Medicine (Kay et al., 1993). In order to be classified as a mild TBI, the GCS score must be between 13-15 and the head injury must result in at least one of the following: LOC not exceeding 30 minutes, or any period of memory loss, confusion or disorientation, all not exceeding 24 hours. While there is less agreement on the exact duration of LOC and post traumatic amnesia (PTA) to distinguish more severe injuries, a TBI has been classified as moderate if the GCS score is between 9 and 12, LOC is between 30 min and 6 hours or PTA between 1-7 days (Bond, 1986; Lezak, 1995). If the GSC score is less than 9, LOC is longer than 6 hours or PTA lasts more than 6 days, a TBI is categorized as severe (Bond, 1986; Gerstenbrand & Stepan, 2001).

Neuroimaging: Understanding the Brain Damage

Many brain areas are susceptible to TBI, but diffuse damage is most likely in the frontal and temporal regions of the brain (Adams, 1975). These areas are more vulnerable to injury in part due to the high frequency of hits to the front of the head and in part due to larger forces exerted on the anterior portion of the brain as a result of the internal shape of the skull. The likely cognitive impairment resulting from TBI appears to be associated with primary (axonal injury, vascular injury and hemorrhage) and secondary pathophysiologies (cellular damage, hypotension or hypoxia; Iverson & Lange, 2011). Diffuse axonal injury is a frequent result of TBI (Ommaya & Gennarelli, 1974), especially when caused by severe rotational and/or linear acceleration/deceleration forces on the brain (Iverson & Lange, 2011). A commonly used term to describe damage after TBI is axonal shearing. It is now known that this ‘shearing’ is most often a gradual process, not an instant tearing of axons at the time of injury. Instead, axons that are stretched and twisted may swell and either recover, remain damaged (Christman, Grady, Walker, Holloway, & Povlishock, 1994; Povlishock & Becker, 1985) or eventually separate (Povlishock, Becker, Cheng, & Vaughan, 1983) depending on the force to the brain.

Common in moderate to severe cases, magnetic resonance imaging (MRI) has provided evidence for abnormalities in mesial temporal and lateral frontal lobes, as well as ventricle enlargement (Crosson, Sartor, Jenny, Nabors, & Moberg, 1993). Moreover, changes in ventricular size and white matter are frequently reported (Anderson & Bigler, 1995; Levin, Meyers, Grossman, & Sarwar, 1981), as well as hippocampal atrophy (Bigler et al., 1996; Kotapka, Graham, Adams, & Gennarelli, 1992). Yet, even in severe cases, it is possible for an individual to experience persistent cognitive impairment with no evidence of neural damage on a computed tomography (CT) scan (Gean, 1994; Harris & Harris, 2000). Using MRI quantitative techniques, white matter atrophy is the most common source of persistent damage, with the genu and splenium of the corpus callosum found to be most vulnerable (Huisman et al., 2004; Le et al., 2005; Nakayama et al., 2006; Wilde et al., 2006). Most recently, a high resolution MRI technique, diffusion tensor imaging (DTI), has been useful for examining white matter at a microscopic level and has also consistently found evidence of damage in white matter of the corpus callosum (Inglese et al., 2005; Miles et al., 2008).

Moderate to Severe TBI: Persistent Cognitive Deficits

For the purpose of this thesis, I will focus on the issue of cognitive deficits associated with TBI, though there are many other long-term problems related to remote TBI, some of the most common being headaches, fatigue, troubles sleeping, as well as anxiety and depression disorders (see Iverson & Lange, 2011 for review). Memory impairment is one of the most common cognitive deficits that persists after TBI (Levin & Goldstein, 1986) and is also one of the most frequent complaints reported by survivors and family members (Arcia & Gualtieri, 1993; Oddy, Coughlan, Tyerman, & Jenkins, 1985). Not all aspects of memory are equally affected and neuropsychological assessments carried out over the past five decades have specified those memory functions that tend to be preserved and those that are more susceptible to impairment following TBI.

Working memory deficits have been identified using various tasks that require the manipulation of information temporarily stored in mind (e. g., random generation task; Azouvi, Jokic, Van der Linden, Marlier, & Bussel, 1996) Sternberg's paradigm (Haut, Petros, Frank, &

Lamberty, 1990); the Paced Auditory Serial Addition Test [PASAT]; Christodoulou et al., 2001). On the other hand, relatively simple working memory tasks that involve short-term storage with minimal manipulation have been shown to be spared following a moderate to severe TBI. For example, compared to controls, TBI patients had similar performance on the digit span forward task (short-term storage; Wechsler, 1997), but showed deficits on digit span backwards (storage plus manipulation; Brooks, 1976; Haut et al., 1990). Moreover, dual-task paradigms have shown that while TBI performance is no different from controls on a simple reaction time test, significant slowing in reaction time is evident in TBI participants when it is concurrently performed with either a counting task or digit span task (McDowell, Whyte, & D'Esposito, 1997). Together, these findings suggest that complex working memory tasks, those that require additional processing of information, are more sensitive to TBI compared to relatively simple tasks with no such additional processing demands.

Verbal memory deficits have also been identified long after moderate to severe TBI including deficits in neuropsychological measures of immediate and delayed recall (Baddeley, Harris, Sunderland, Watts, & Wilson, 1987; Bennett-Levy, 1984; Kersel, Marsh, Havill, & Sleigh, 2001; Zec et al., 2001), paired-associate learning ((Baddeley et al., 1987; Brooks, 1976), and slower learning rates for verbal material (Blachstein, Vakil, & Hoofien, 1993; DeLuca, Schultheis, Madigan, Christodoulou, & Averill, 2000; Gardner & Vrbancic, 1998; Geffen, Butterworth, Forrester, & Geffen, 1994; Haut & Shutty, 1992; Levin, Grossman, Rose, & Teasdale, 1979; Novack, Kofoed, & Crosson, 1995; Zec et al., 2001). Visual recognition and recall problems have also been identified in this population using several visual memory tests (Brooks, 1976; Brooker & George, 1984; Hannay, Levin, & Grossman, 1979; Zec et al., 2001). Moreover, prospective memory, the ability to remember to perform a previously planned action at the right time, has been shown to be poorer in TBI patients compared to controls (Groot, Wilson, Evans, & Watson, 2002; Kinsella et al., 1996; Shum, Harris, & O'Gorman, 2000). On the other hand, the majority of studies investigating priming, a measure of implicit memory, in this population suggest that it is spared (Perri, Carlesimo, Loasses, & Caltagirone, 2000; Schmitter-Edgecombe, 1996; Vakil & Oded, 2003; Vakil & Tweedy, 1994; Watt, Shores, & Kinoshita, 1999).

In addition to the many memory impairments evident after moderate to severe TBI, slowing during simple and complex information processing speed measures have been identified (Axelrod, Fichtenberg, Liethen, Czarnota, & Stucky, 2001; Ferraro, 1996; Fisher, Ledbetter, Cohen, Marmor, & Tulsky, 2000; Gronwall & Wrightson, 1981), as well as deficits in selective attention (Cremona-Meteyard, Clark, Wright, & Geffen, 1992; Schmitter-Edgecombe & Kibby, 1998; van Zomeren, 1981), divided attention (Leclercq et al., 2000; Park, Moscovitch, & Robertson, 1999), and sustained attention (Loken, Thornton, Otto, & Long, 1995). The extensive research over the years has confirmed that long after a moderate to severe TBI, individuals show cognitive deficits when task are demanding (i. e., when active or effortful strategies require more cognitive processing), but show little or no impairment compared to healthy controls on less demanding tasks (i. e., when passive strategies or automatic processing is sufficient; Levin, 1990; Perri et al., 2000; Vakil, Arbell, Gozlan, Hoofien, & Blachstein, 1992).

Mild TBI: Neuropsychological Impairment in the Acute Phase

Mild TBI has also been shown to result in neuropsychological dysfunction in many cognitive domains; however, due to the mild nature of the injury, these impairments have been thought to largely resolve by at least three months post-injury. This claim has been supported over the years by several studies which have reported that while cognitive impairments may be apparent in the first weeks following injury, they typically resolve within the first 1-3 months (Alexander, 1995; Dikmen, McLean, & Temkin, 1986; Macciocchi, Barth, Alves, Rimel, & Jane, 1996; McLean, Temkin, Dikmen, & Wyler, 1983; Ponsford et al., 2000; Reitan & Wolfson, 1999; Stewart, Kaylor, & Koutanis, 1996; Voller et al., 1999). Several recent meta-analyses have examined the effect of mild TBI on neuropsychological functioning by including studies conducted both within 3 months (acute phase) and after 3months (post-acute phase). For example, Frencham, Fox, and Maybery (2005) showed that mild TBI had a significant effect on working memory, attention, recall and recognition, executive functioning and speed of processing in the acute phase of mild TBI (Frencham et al., 2005), but not in post-acute phase. Moreover, a separate meta-analysis conducted in the same year confirmed significant effects of mild TBI within the first three months of injury, which were greatest for delayed memory and

fluency (Belanger, Curtiss, Demery, Lebowitz, & Vanderploeg, 2005). Most recently, Rohling and colleagues (2011) also found a significant effect of mild TBI on neuropsychological functioning during the acute phase, with the largest effects on verbal and visual memory domains. Mild TBI participants in the acute phase of injury (1 month) have also been shown to have slower reaction times compared to controls on a battery of neuropsychological tasks with a significant working memory component (McAllister, Flashman, Sparling, & Saykin, 2004). More recent controlled experiments have further identified the specific cognitive impairments within the acute phase. Mild TBI participants have been shown to produce significantly fewer words and perform at lower rates compared to controls during an association word test (Crawford, Knight, & Alsop, 2007). Mild TBI-related deficits have also been evident in visuospatial attention tasks, specific to decrements in disengaging (Drew et al., 2007), orienting and executing attention (Halterman et al., 2006). Together, these findings show that mild TBI impairs various aspects of cognitive functioning shortly after injury.

Mild TBI: Neuropsychological Impairment in the Post-Acute Phase

Compared to the acute findings in the mild TBI literature and the many long-term consequences of moderate to severe TBI, only a handful of empirical studies have identified residual deficits using standard neuropsychological measures at least 3 months post- mild TBI limited to the cognitive domains of attention (Chan, 2002; Potter, Jory, Bassett, Barrett, & Mychalkiw, 2002; Solbakk, Reinvang, Nielsen, & Sundet, 1999) and information processing speed (Bernstein, 2002; Johansson, Berglund, & Ronnback, 2009; Potter et al., 2002). In fact, the meta-analyses mentioned above found that any significant effects of mild TBI on cognitive functioning resolved by three months (Belanger et al., 2005; Frencham et al., 2005; Rohling et al., 2011). An earlier meta-analysis yielded similar results, but found a significant, although small, effect of mild TBI on the domain of attention (Binder, Rohling, & Larrabee, 1997). Such inconsistencies in neuropsychological findings highlight the difficulty in assessing the residual effects of mild TBI. Moreover, when lingering problems are detected, they are frequently confounded by extraneous variables, such as pre-existing factors (Vanderploeg, Curtiss, Luis, & Salazar, 2007), co-morbid psychosocial factors (Chan, 2002; Dischinger, Ryb, Kufera, &

Auman, 2009; Fann, Uomoto, & Katon, 2001; Rapoport, McCullagh, Shammi, & Feinstein, 2005; Stulemeijer, Vos, Bleijenberg, & van der Werf, 2007) and litigation (for review, see (Belanger et al., 2005; Binder & Rohling, 1996; Tsanadis et al., 2008).

While researchers and neuropsychologists are well aware of these confounds and often take appropriate steps to ensure they are controlled for, an additional variable known to affect cognitive performance in other populations has recently been shown to affect self-report and neuropsychological assessment in the mild TBI population. I will briefly discuss how expectation bias has been shown to affect neuropsychological impairment after mild TBI, as it is most often not controlled for and may be a large contributor to persistent deficits observed in this population. Suhr and Gunstad (2002) coined this phenomenon 'diagnosis threat,' which they relate to the term 'stereotype threat': a member of a specific group may display poor task performance simply because he/she is aware that the task is thought to be performed poorly by members of that group. For example, Spencer, Steele, and Quinn (1999) found that women performed worse on the math Graduate Record Exam compared to men when they were told to expect gender differences, but had equal performance when gender differences were not mentioned. Similarly, 'diagnosis threat' was evident in a study of undergraduate students who self-reported a past head injury (Suhr & Gunstad, 2002; Suhr & Gunstad, 2005). The 'diagnosis threat' mild TBI group, who were told that they may be experiencing cognitive problems post-injury, had lower performance on tests of general intellect, memory, and attention, as well as slower average psychomotor speed compared to 'neutral' mild TBI participants. Together, these studies demonstrate that negative expectations are substantial enough to result in cognitive impairment.

Increasing Sensitivity and Complexity Measures in the Post-Acute Phase of Mild TBI

While cognitive performance may be negatively affected by diagnosis threat, this does not suggest that the head injury itself results in no lasting deficits. Results may be null or inconsistent across studies utilizing neuropsychological measures because the effects are small, the tests are insensitive, and/or the measures of functioning are too coarse. The lack of neuropsychological evidence for lasting impairments is in contrast to the persistent memory and

concentration complaints often documented through self-report measures long after experiencing a mild TBI (Alves, 1993; Meares et al., 2011; Vanderploeg et al., 2007; Villemure, Nolin, & Le Sage, 2011). Research using non-standard, as well as more sensitive and complex, measures of cognitive functioning, have started to provide empirical evidence for such complaints. For instance, using standard accuracy measures, Vanderploeg, Curtiss and Belanger (2005) reported no deficits in individuals who sustained a mild TBI at least one year prior to testing compared to non head-injured controls on a neuropsychological task measuring attention and working memory abilities (i. e., the Paced Auditory Serial Addition Test; PASAT). Yet, through the use of measures not traditionally used to evaluate performance on this task, they found that mild TBI participants had higher discontinuation rates compared to controls. Moreover, increasing task complexity in controlled experimental studies can indicate significant cognitive impairment in participants long after mild TBI. For example, while no group differences were found while performing a relatively simple attention task on its own, dividing attention between two concurrently performed tasks decreased information processing speed (Cicerone, 1996; Pare, Rabin, Fogel, & Pepin, 2009), as well as accuracy (Bernstein, 2002; Pare et al., 2009), in mild TBI participants in the post-acute phase compared to controls. Together, these findings provide evidence that long-term attention and working memory impairments can be identified in this population when novel ways of measuring performance on standard neuropsychological tasks are implemented and when task complexity is increased.

When cognitive impairments are observed in the post-acute phase, delayed information processing has been one of the most consistent findings (Bernstein, 2002; Cicerone, 1996; Johansson et al., 2009; Pare et al., 2009; Potter et al., 2002). As previously mentioned, whereas meta-analyses of neuropsychological functioning have found no significant residual effect of mild TBI on cognition (Belanger et al., 2005; Frencham et al., 2005; Rohling et al., 2011), the effect on information processing speed was the largest, though not significant (Frencham et al., 2005). Compared to other neuropsychological measures, information processing speed has been shown to be the only measure to differentiate individuals with moderate-severe TBI from mild TBI participants (Martin, Donders, & Thompson, 2000). Yet, distinguishing individuals with mild TBI from non-head-injured controls has proven to be more difficult and, in line with the

research mentioned above, depends on whether the task measures simple attention and reaction time, or complex information processing speed. Simple reaction time tasks require a button press in response to a single pre-determined target among non-targets; whereas more complex tasks, such as choice- or semantic-reaction time tests, increase information processing demand by requiring participants to press one button for a specific stimulus (or specific category of stimuli) and another button for all other non-target stimuli (or another category of stimuli). In other words, the complex tasks require participants to hold an additional set of rules or information in mind while simultaneously processing target information.

Whereas severe TBI individuals have been shown to perform significantly slower compared to controls and mild TBI participants on three reaction time tasks that ranged from simple to complex (Tombaugh, Rees, Stormer, Harrison, & Smith, 2007), mild TBI participants had longer mean reaction times on only the most complex tasks compared to controls within one month of after injury (Tombaugh et al., 2007) and up to three months post-injury (Hugenholtz, Stuss, Stethem, & Richard, 1988). Taken together, these results suggest that simple measures of processing speed may be sensitive to injury severity within the TBI population, but more complex tasks are required to distinguish a mild TBI population from healthy non-head injured controls, particularly when trying to uncover long-term consequences of mild TBI.

The value of using sensitive response time measures as a clinical tool along with neuropsychological test batteries in the TBI population was recognized long ago (Ferraro, 1996), but this tool has not been widely recognized in research investigating long-term cognitive effects long after a single mild TBI. From the extant mild TBI literature, it still remains difficult to disentangle whether a past mild TBI results in specific deficits in higher level cognitive functioning (decreased accuracy on divided attention tasks; (Bernstein, 2002; Pare et al., 2009), in a general slowing of information processing (largest effect size in meta-analysis; Frencham et al., 2005), in both (slowing observed only on cognitive demanding tasks; Cicerone, 1996; Hugenholtz et al., 1988; Martin et al., 2000; Pare et al., 2009) or neither of the two (no neuropsychological deficits reported in meta-analyses; Belanger et al., 2005; Binder et al., 1997; Frencham et al., 2005; Rohling et al., 2011). To better define these potentially long-lasting, but subtle deficits, it is essential to obtain both sensitive response time measures and accuracy rates

in low- and highly-demanding cognitive task conditions in order to better define lasting changes in information processing following a single mild TBI. The employment of such rigorous methodology may also help to disentangle whether mild TBI results in a deficit in a specific cognitive domain, such as working memory, or a more general slowing of information processing speed, which then contributes to deficits in specific cognitive domains (Chiaravalloti, Christodoulou, Demaree, & DeLuca, 2003).

Increasing Task Complexity: What does it mean?

Bernstein (2002) stated that task difficulty seems to moderate some of the inconsistency in the mild TBI literature. Task complexity can be manipulated in many ways. In this section, I will review how past studies have varied task complexity in the mild TBI population with the goal of specifying cognitive domains and processes most sensitive to the long-term effects of mild TBI. One commonality in the methodologies is that tasks that found slowing or attention deficits long after mild TBI all required participants to process a relatively large amount of information to successfully complete each trial. As previously mentioned, Hugenholtz et al. (1988) reported slowed information processing speed 3 months post- mild TBI on a "complex reaction time task," one that could be differentiated from a simple reaction time task by requiring participants to hold an additional set of rules, or information, in mind while simultaneously processing target information. Also, the aforementioned studies which examined the effect of divided attention on performance (Bernstein, 2002; Cicerone, 1996; Pare et al., 2009) found no residual effects of mild TBI on accuracy or slowing on simple selective attention tasks, but did find performance decrements when participants were required to hold and manipulate additional information while concurrently controlling response outputs.

For example, Cicerone (1996) administered a selective attention task in which participants were instructed to cross out the digits "2" and "7" embedded among other digits. Participants were asked to either complete this selective attention task on its own, while listening to a segment of an irrelevant talk radio show or while solving simple math problems aloud that were presented on a tape at a rate of one every 5 seconds. Compared to controls, mild TBI participants showed no deficits on the task when performed alone or with irrelevant background

information, but showed slowing when they had to process and respond to a secondary task (i. e., solve math problems) simultaneously. The authors suggested that individuals with mild TBI perform normally on tasks which are relatively automatic or less demanding, yet are unable to sustain effective processing when controlled allocation of attention is required for adequate performance on tasks that increase demand place on available resources.

Segalowitz, Bernstein and Lawson (2001) and Bernstein (2002) showed similar findings in that dual-, but not single- task demands impaired performance in mild TBI participants. In these studies, mild TBI participants performed at control levels on two separate tasks performed one at a time: a simple oddball task that required discriminating between two different tone *amplitudes* and on a relatively more difficult oddball task (differentiating tone *durations*). When the difficult oddball task, not the simple task, was paired with a visual working memory task however, mild TBI participants' accuracy dropped below control levels. Pare and colleagues (2008) also reported that mild TBI participants had poorer performance on a digit span forward task compared to controls when paired with a visual oddball task, with no differences observed between groups on the oddball task when performed alone. In line with Cicerone (1996), the authors suggested that the extent to which processing demands are manipulated in mild TBI research is critical when investigating residual cognitive impairment.

There is an important commonality across these studies. Mild TBI participants may not experience impairment when a single task increases in complexity (e. g., tone discrimination) or when they are distracted by relatively simple dual-task demands, but rather when task demands increase the amount of information that must be processed. While often classified as deficiencies in the ability to divide attention or handle heavy processing loads, in the post-acute phase, a more inclusive term to describe these deficits is a difficulty with working memory. In fact, McAllister and colleagues (2004) suggested that "the typical profile of attention and memory deficits [observed after TBI] could be reasonably subsumed under the construct of working memory, the ability to hold information in mind and manipulate that information in light of incoming information." Along with the prevalent memory and attention complaints in the literature (Alves, 1993; Meares et al., 2011; Vanderploeg et al., 2007; Villemure et al., 2011), evidence from these empirical studies suggests working memory deficits in the post-acute phase of mild TBI.

While working memory deficits have been documented long after moderate to severe TBI (Azouvi et al., 1996; Brooks, 1976; Christodoulou et al., 2001; Haut et al., 1990; McDowell et al., 1997), the aforementioned studies have not characterized the long-term cognitive deficits in mild TBI population as deficits in working memory. The next section will provide an overview of working memory in order to better define its specific components and associated processes, as well as to provide a framework for the processes examined in the current thesis that are predicted to be affected post-acutely in individuals who suffered a mild TBI.

Working Memory and Attentional Control

The most common model of working memory used for decades by cognitive psychologists is Alan Baddeley's multi-component working memory model. In its earliest days and in its simplest form, Baddeley and Hitch (1974) proposed that working memory is composed of three separate components: a phonological loop, a visuospatial sketch pad and a central executive. The phonological loop and visuospatial sketchpad were posited to be storage systems responsible for maintaining verbal information and visual/spatial information, respectively. The central executive was defined as an attentional control system with a limited capacity responsible for manipulating information within working memory and for controlling the two secondary storage systems. Years later, Baddeley (2001) added a fourth component to his multi-component working memory model: the episodic buffer, which was also conceptualized as a limited capacity storage system that allowed the binding of information to create integrated episodes. While early research rigorously tested the storage components, the functions of the central executive were relatively much less understood, even though it was deemed the most important out of the three (Repovs & Baddeley, 2006). Specifically, it was unknown as to how the central executive interacted with the slave subsystems and how other cognitive functions may rely on the central executive.

In an attempt to better understand the functions of the central executive, Baddeley (1986) adopted Norman and Shallice's (1986) model of attentional control. In their model, Norman and Shallice proposed that human action is controlled by two basic processes: contention scheduling and the supervisory attentional system. Most of our everyday actions are made up of routine

tasks that are controlled by habits and schemata by making use of environment cues. These different cues are not always congruent and often contradict one another. Yet, using fairly automatic conflict-resolution processes, called *contention scheduling*, these conflicts are often easily resolved. Not all conflicts however, can be resolved using automatic processes based on prior experiences. Novel problems and situations require planning and following through of new solutions based on the active combination of existing stimuli and information stored in long-term memory. Normal and Shallice (1987) assumed that such processes depended on a limited capacity attention component called the *supervisory attentional system* (SAS). William James (1890), often referred to as the father of American psychology, defined attention as:

> Taking possession of the mind in clear and vivid form, of what seems several simultaneously possible objects or trains of thought. Focalization, or concentration, of consciousness is of its essence; it implies withdrawal from some things in order to deal more effectively with others (James, 1890; pp. 403-404).

At the core of this definition are the very components of Norman and Shallice's attentional control model. While the contention scheduling system is sufficient at activating and inhibiting conflicting schemes during relatively simple, automatic, well-learned acts, it is not adequate to support the demands of non-routine, novel situations. Here, it is the role of the SAS to bring about conscious attention in order to make decisions, troubleshoot, execute novel sequences of actions and overcome habit. Norman and Shallice (1986) posited that the SAS requires additional processing resources, such as a mechanism that modulates the selection process by adding activation or inhibition. Early research showed that functions that required SAS were related to prefrontal regions of the brain involved in various executive processes, such as planning, novel learning, and inhibition of distracting information (see Norman & Shallice, 1986).

Baddeley's (1986) adoption of the SAS did not replace the central executive in his original multi-component working memory model, but instead offered a framework for further specifying the processes and capacities required by this attentional controller during working memory operations. From this, Baddeley (1996) proposed and explored four basic executive

capacities: the ability to focus attention, divide attention, switch attention, and relate content of working memory to long-term memory. Various experimental paradigms since then have supported these propositions and have shown that the central executive is implicated in a range of complex cognitive tasks requiring focused attention (see Repovs & Baddeley, 2006). Research also demonstrated a separable executive capacity to divide attention and to switch attention, as well to integrate and maintain information within the episodic buffer. Other researchers have used different, but related terms to describe the processes critical to the operation of working memory, such as executive attention, inhibition, task management and set shifting (Engle, 2002; Posner & Petersen, 1990). Thus many processes have been recognized to play a crucial role in working memory functioning, especially in the executive component.

As a way to make sense of extensive research on the various components and their associated processes involved in working memory functioning, the term has been concisely summed up by Reuter-Lorenz and Sylvester (2005). They posited that all tasks requiring the online, short-term storage of limited amounts of information are measures of working memory. The only difference in various working memory tasks lies in the demands they place on executive processing operations. This view puts working memory tasks along a continuum and it is the level of involvement of executive processing operations that varies for each task. At one extreme are maintenance tasks which place minimal demand on executive processes and at the opposite end are those that place considerable demands on executive processes, such as simultaneously dividing attention between difficult tasks, and selectively attending to relevant information while inhibiting distracting/irrelevant information temporarily held in mind. Importantly, research has also shown that the separable executive functions are not only involved in both the functioning of the phonological and visuospatial storage components of working memory, but also involved in several other general cognitive processes:

> Working memory has proved to be an important part of the cognitive system, providing the ability to maintain and manipulate information in the process of guiding and executing cognitive tasks… Working memory can be usefully described as a multi-component system guided by an executive component consisting of a number of

processes that provide attentional control over other components of working memory as well as other cognitive abilities (Repovs & Baddeley, 2006).

Just as the amount of executive processing varies in working memory depending on task demands, attention tasks with little, or no, memory requirements also vary in the extent to which they draw on executive processes. In fact, the few tasks that have identified attention deficits in the post-acute phase of mild TBI, required executive processes, while requiring little, if any, memory storage.

In addition to the long-term working memory deficits detected through divided attention paradigms, attention tasks rely on other executive components have also been identified in the mild TBI post-acute phase. As mentioned, meta-analyses assessing neuropsychological functioning at least 3 months post-mild TBI have failed to identify significant deficits (Frencham et al., 2005; Rohling et al., 2011; Vanderploeg, Curtiss, & Belanger, 2005). Yet, Binder and colleagues (1997) found a small effect of mild TBI on attention and the few empirical studies that have found deficits have been in the domains of attention (Chan, 2002; Potter et al., 2002; Solbakk et al., 1999). Specifically, impairments were found in selective attention on the incongruent condition of the Stroop task (Chan, 2002; Potter et al., 2002; Solbakk et al., 1999). In this task, participants are instructed to name colors of presented items, and in the incongruent condition, the items are color words that conflict with the correct naming response (e. g., the word *green* presented in red color). The authors suggest that mild TBI results in a specific executive deficit of inhibiting automatic response processes (reading the printed word, *green*, instead of the item color, red). Impairments in sustained attention on the sustained attention to response task (SART), and task switching on the trail making B neuropsychological task (Chan, 2002) have also been documented in the post-acute phase and are well-known to require inhibitory processes and cognitive flexibility, respectively. These results suggest that attention and working memory deficits can be detected long after mild TBI using tasks that require executive processes.

One goal of the current thesis was to further specify long-term cognitive deficits after mild TBI by manipulating executive processing requirements in a working memory task (Experiment 2a) and an action sequence learning task (Experiment 2b), both of which use non-

standard, sensitive measures, and are novel to this population. Next, I will describe a cognitive neuroscience technique I implemented in Experiment 3 to obtain yet more precise measures of information processing changes long after mild TBI.

Brain-based Evidence for Information Processing Changes: Event-Related Potentials

In addition to the difficulties in determining cognitive problems through standard assessments, another main challenge in studying mild TBI is that any permanent neural damage (e. g., diffuse axonal injury) cannot be detected using standard imaging techniques (Bigler, 2004; Ichise et al., 1994). While functional magnetic resonance imaging (fMRI) has recently started to reveal functional changes in the acute phase of injury (McAllister et al., 1999; McAllister et al., 2001; Zhang et al., 2010), event-related potentials (ERPs) offer a unique advantage especially relevant in studying mild TBI individuals in the post-acute phase. For a group suggested to have deficiencies in processing capacity based on behavioral data, ERPs assess functional brain activity and provide an extremely sensitive measure of the subtle changes in information processing resulting from diffuse axonal injury (Gaetz & Bernstein, 2001). Specifically, ERPs allow for noninvasive and real-time recording of the neural events that accompany task performance, thus can complement more traditional reaction time measures (Duncan, Kosmidis, & Mirsky, 2005).

ERPs are typically elicited in oddball tasks whereby participants are instructed to identify infrequent targets (oddballs) among frequent non-targets (Duncan et al., 2005). The components that make up the ERP reflect various aspects of information processing. The P300 component has been most frequently studied in the mild TBI population as it reflects a basic cognitive process by which incoming information is categorized and is related to updating the context of working memory (Donchin & Coles, 1988; Duncan-Johnson & Donchin, 1977). The P300 is considered a late positive component that peaks at approximately 300 ms post-stimulus. This component is elicited after early sensory components (e. g., N100 and P200 elicited by simple stimuli feature registration) and after later conscious detection of deviance (N200 elicited when attention is directed to oddball stimuli; Naatanen, 1992). The P300 component is an index of neural activities that underlie the revision of mental representation induced by incoming stimuli

(Donchin, 1981) and has been shown to increase in magnitude from frontal to parietal electrode sites (Johnson, 1993). Following early sensory processing of stimuli, an attention-driven comparison process evaluates the previous event held in working memory (Heslenfeld, 2003). If no change in stimulus feature is identified (i. e., no oddball), the current mental model of the stimulus context is maintained and sensory ERPs are elicited (N100, P200, N200). However, if a new stimulus is detected (the oddball), attentional processes identify a change or an update of the stimulus representation that is associated with the P300. Examining ERPs in the mild TBI population recently became a popular measurement used by researchers: ERPs are as reliable as clinical tests, are effective at assessing cognitive capability, and are relatively inexpensive to record (Polich & Herbst, 2000).

In addition to using sophisticated electrophysiological techniques to identify the neural substrates of information processing changes long after mild TBI, we studied a group of individuals that could be informative regarding the impact of a remote TBI on the brain. The effects of healthy aging on the brain are well researched and understood by the cognitive neuroscience community. The next section provides a review of the overlaps observed in TBI- and healthy age-related cognitive changes due to their similar effects on the brain. Such a review is also important for understanding the chronic effects of TBI and the potential confounding effects the injury may have on cognitive functioning in older adults.

Similarities in TBI- and Age-related Cognitive Decline

As in the TBI literature, performance differences between older and younger adults become larger with increasing task complexity (Salthouse & Babcock, 1991). Overlapping working memory deficits have also been identified in the post-acute phase of TBI and as a result of healthy aging. Specifically, several studies show performance decrements on working memory tasks that tap into executive processes in young to middle aged TBI participants (Azouvi et al., 1996; Bublak, Schubert, Matthes-von Cramon, & von Cramon, 2000; Christodoulou et al., 2001; Haut et al., 1990; McDowell et al., 1997) and in healthy older adult participants compared to young controls (Bopp & Verhaeghen, 2007; Dobbs & Rule, 1989; Park et al., 2002; Salthouse & Babcock, 1991). For instance, dual-task paradigms have been useful in

detecting impairments after a remote TBI (Leclercq et al., 2000; McDowell et al., 1997; Park et al., 1999) and in healthy older adults (Glass et al., 2000; Kramer, Hahn, & Gopher, 1999; Madden, Pierce, & Allen, 1996; Mayr, 2001; Plude & Hoyer, 1986). On the other hand, relatively simple working memory tasks that involve short-term storage with small manipulation demands have been shown to be spared in both individuals with TBI (Brooks, 1976; Haut et al., 1990) and healthy older adults (Dobbs & Rule, 1989). As such, the authors suggest that memory functions requiring executive processes are more susceptible to age (Dobbs & Rule, 1989) and TBI (Levine, Dawson, Boutet, Schwartz, & Stuss, 2000; Seignourel, Robins, Larson, Demery, Cole, & Perlstein, 2005) compared to components responsible for storage.

At the brain level, these similar executive dysfunctions are likely linked to the frontal lobes, as these are the regions most affected by the natural aging process (Prull, Gabrieli, & Bunge, 2000; Raz et al., 1997; West, 1996) and most susceptible to changes following TBI (Adams, 1975; McDonald, Flashman, & Saykin, 2002). Moreover, a common feature among executive control processes is that they are particularly susceptible to disruption by damage to prefrontal cortical regions (Duncan, Johnson, Swales, & Freer, 1997). The vulnerability of this 'executive brain area' to both TBI and aging is of critical importance as recent studies reported executive processing deficits in working memory in individuals an average of 16 years (range of 2 to 30 years; Anderson & Knight, 2010) and 30 years post-TBI (range: 2 to 63 years; Himanen et al., 2009). These findings provide basis to predict that the effects of a TBI on executive processes sustained in young to middle adulthood may persist and compound executive-related cognitive decline during healthy aging.

Purpose of Thesis

As mentioned, memory and concentration problems are frequent complaints reported long after experiencing a mild TBI, though these conflict with null findings of deficits on standard neuropsychological tests. Experimental research shows that these inconsistencies are, in part, due to the simplicity of neuropsychological tests and while persistent deficits are most often not detected on simple selective attention tasks, they have been more consistently revealed under dual-task demands. As reviewed, there is strong evidence to suggest that these divided attention

deficits are likely a result of heavily taxing the executive processes involved in working memory. Past research also suggests that when neuropsychological deficits are occasionally detected within this population, they could be influenced by diagnosis threat.

The main goal of this thesis was to specify the long-term cognitive effects of mild TBI, with the prediction that, while cognitive complaints may be over-reported due to diagnosis threat, significant deficits can be detected using sensitive measures in experimental paradigms that tap into executive processes. As such, Experiment 1 was designed to test the prediction that diagnosis threat increases reports of everyday attention and memory problems, as well as decreases neuropsychological task performance in young adults with a remote history of mild TBI. In an attempt to further specify persistent cognitive deficits, we designed two different experimental paradigms that uniquely manipulate the amount of executive processing requirements to test young adults with and without a remote TBI, while also minimizing the influence diagnosis threat. Specifically, in Experiment 2a we manipulate processing load on a visual working-memory task across two conditions with the prediction that individuals with a remote mild TBI will show slowing and/or accuracy decrements in the condition that places a higher demand on executive processes compared to controls. In Experiment 2b we examined whether manipulating executive processing requirements on a task would differentiate mild TBI participants from controls, this time during a well-learned action sequence. While differences were not expected during relatively automatic movement sequences, we expected individuals with a mild TBI may perform more slowly or commit more errors during unexpected movement trials, an action that requires executive processes. To more precisely identify the brain basis of information processing long after mild TBI, we administered a working-memory task with varying conditions that systematically increased in processing load requirements, while recording event-related potentials (ERP). Based on previous research, we predicted an attenuated P300 amplitude in mild TBI participants that would undergo larger decreases as a function of increasing processing demands compared to controls. Lastly, in Experiment 4 we examined whether TBI-related deficits persist into older adulthood, and compound the negative effect of aging on cognition. We predicted that, if deficits were observed in older adults with remote TBI, that they would be limited to tasks that measure executive capabilities, as these are also the

functions known to undergo age-related decline in healthy older adults. Together, these thesis experiments will help specify the measures that best detect long lasting cognitive changes following mild TBI, as well as the specific processes affected and how long they may persist.

Chapter 2: The Effect of Diagnosis Threat on Cognitive and Affective Measures

2.1 Introduction

Though neuropsychological tasks most often fail to detect residual impairment after mild TBI, persistent memory and concentration complaints are often documented using self-report measures (Alves, 1993; Meares et al., 2011; Vanderploeg et al., 2007; Villemure et al., 2011). As mentioned, when neuropsychological impairments are detected, research has shown that they may be confounded by 'diagnosis threat'. Specifically, Suhr and Gunstad (2002; 2005) demonstrated that individuals exposed to 'diagnosis threat', were told that they may be experiencing cognitive problems post-injury, had lower performance on tests of general intellect, memory, and attention, as well as slower average psychomotor speed compared to 'neutral' mild TBI participants.

Reports also show that the mere *expectation* that an individual may experience symptoms following a mild TBI is enough to confound the extent of cognitive symptoms. Mittenberg, DiGiulio, Perrin and Bass (1992) initially reported this 'expectation bias' and found that mild TBI patients consistently underestimated the prevalence of affective, somatic, and memory symptoms they experienced prior to being injured, as compared to a base rate of symptoms reported in control participants. This finding has more recently been replicated and termed the 'good-old-days' bias. Specifically, individuals who have sustained a mild TBI in their past report experiencing significantly fewer symptoms pre-injury compared to the reported base rate of symptoms in controls, resulting in an overestimation of the actual degree of change that occurred (Davis, 2002; Gunstad & Suhr, 2001; 2004; Iverson, Lange, Brooks, & Rennison, 2010; Lange, Iverson, & Rose, 2010). The influence of expectation on self-reported symptoms has largely been ignored in the mild TBI literature, but is a critical variable to be considered, as most, if not all, participants/patients are aware that they are being examined because of their mild TBI. As a result, the effects of the 'expectation/good-old-days' bias on cognitive functioning cannot be teased apart from the long-term effects of the injury itself. Together, these studies demonstrate

that negative expectations are substantial enough to result in overestimations of symptom change pre- to post-mild TBI and to result in cognitive impairment.

The goal of the current study was to examine the effect of diagnosis threat on self-reported everyday cognitive errors and affective functioning, as well as on behavioural measures of cognitive functioning, in individuals with a history of a remote mild TBI. To our knowledge, this is the first study to compare everyday cognitive errors (not mild TBI-related symptom severity) between individuals with and without a past mild TBI, in an experimentally controlled study. Also, unlike previous diagnosis threat studies, which investigated the effect by only comparing mild TBI participants across two conditions (i. e., 'diagnosis threat' versus 'neutral'), we recruited additional non head-injured controls, yielding two conditions each with two groups (control and mild TBI). In 'diagnosis threat' condition, we examined cognitive and affective functioning in undergraduate students with and without a self-reported mild TBI. All participants were informed, prior to data collection, of their specific group membership and were told that the purpose of the study was to investigate the potential long-lasting negative effects of a mild TBI on memory and attention. In the 'neutral' condition, we similarly examined individuals with and without a mild TBI on cognitive and affective measures. Here, however, participants were told the purpose of the study was to merely examine memory and attention in young adults. No mention was made of group membership, or of the possibility of long-term negative effects of a past mild TBI.

In each condition, a battery of questionnaires and neuropsychological tests were administered to acquire self-report and behavioural measures of memory and attention. Unique to this study, I administered self-report scales that provide separate measures of attention and memory failures in everyday life: the Attention-related Cognitive Error Scale (ARCES; (Carriere, Cheyne, & Smilek, 2008) and the Memory Failures Scale (MFS; Carriere et al., 2008), respectively. The more commonly used self-report measure of everyday cognitive failures is the Cognitive Failures Scale (CFQ; Broadbent, Cooper, FitzGerald, & Parkes, 1982). The CFQ, however, includes errors due to action, attention and memory failures; thus memory- and attention-related errors cannot be distinguished from one another. The use of the ARCES and MFS allowed the recording of separate measures of everyday errors due to two different types of

cognitive failures: attentional lapses and memory lapses, respectively. Given previous research (Suhr & Gunstad, 2002; 2005), I hypothesized the 'diagnosis threat' mild TBI group would report more everyday failures of memory and/or attention on average, and would also show performance impairments on measures of neuropsychological functioning, compared to the 'neutral' mild TBI group and compared to the non-head injured control groups.

2.2 Methods

Participants

Undergraduate participants were recruited from the University of Waterloo's Research Experience Group, and received course credit for participating. The study was approved by the University of Waterloo's Office of Research Ethics. Students were prescreened for mild TBI, demographic and health status via a generic online questionnaire completed by all students taking Psychology courses at the beginning of the semester (see Appendix A). A mild TBI was defined as any strike to the head or any acceleration/deceleration force (i. e., whiplash; (Kay et al., 1993) that resulted in a loss of consciousness. TBI severity was determined by duration of loss of consciousness (LOC), post-traumatic amnesia (PTA), and disorientation and/or confusion. Participants who had reported experiencing a mild TBI, classified by a LOC not exceeding 30 minutes, were invited to participate in our study. Participants could have also experienced PTA, disorientation, and/or confusion, all not exceeding 24 hours (Kay et al., 1993); see Table 1). Table 1 also indicates if individuals sought medical attention ('doc visit'). The majority of mild TBI participants did not undergo brain imaging following their injury, and of those who did, all reported that no brain abnormalities were detected.

Participants were recruited from a group of 5325 undergraduate students who completed an online prescreen questionnaire at the beginning of either the winter, spring or fall 2009 semester. Of those students, 567 (10.6%) reported experiencing a TBI in the past and 475 (8.9%) fit the study criteria for mild TBI (period of unconsciousness less than 30 min, at least 6 months prior to testing). A total of 43 undergraduates with a self-reported mild TBI (21 females) and 44 with no history of a previous mild TBI (25 females) signed up to participate in this experiment. All participants completed another demographic/head injury questionnaire at the time of testing to confirm details reported in the online prescreen. All participants were fluent English speakers,

and had normal or corrected-to-normal hearing and vision. Participants also reported that they had never been clinically diagnosed with a psychological disorder, neurological disorder, depression or anxiety.

Table 1. *Experiment 1; Head Injury Characteristics for Participants the in 'Diagnosis Threat' and 'Neutral' Conditions.*

'DIAGNOSIS THREAT' MILD TBI GROUP							'NEUTRAL' MILD TBI GROUP						
Cause of Injury	TSI	LOC	PTA	Conf.	Disor.	Doc Visit	**Cause of Injury**	TSI	LOC	PTA	Conf.	Disor.	Doc Visit
Head hit into hockey boards	1.3	2.0	*	*	*	*	*Fell & hit head on door hinge*	13	0.5				*
Fell off bike & hit head on rock	13	6.0			*		*Hit head running into someone*	12	0.3		*	*	*
Tire swing fastener fell on head	9.0	15	*		*	*	*Hit in head with ice block*	16	0.5		*		
Hit water head first after jump	0.7	1.0		*	*		*Hit head on football goal post*	5.0	0.8		*	*	
Head hit ground during rugby	1.0	1.0	*	*	*		*Hit in head with a discus*	9.2	3.0			*	
Biking accident	3.0	1.0				*	*Fell & hit head snowboarding*	0.5	0.2	*	*	*	*
Head hit into hockey boards	8.0	0.08				*	*Fell & hit head on table*	1.0	2.0	*		*	*
Pushed & head hit bookshelf	10	0.1			*		*Hit in head with tire swing*	10	3.0			*	
Dove & hit head into wall	9.0	1.0			*		*Hit heads playing baseball*	4.0	2.0		*		*
Kicked in head during Rugby	0.8	1.0			*		*Rode bike into wall*	10	5.0	*			*
Hit in head during hockey	0.6	1.0			*		*Fell & hit head snowboarding*	9.0	3.0	*	*		*
Hit head against pole skiing	2.0	2.0	*		*		*Fell and hit head on ground*	10	0.5			*	
Head punched in martial arts	1.6	0.03	*		*		*Pushed into hockey boards*	2.0	1.0		*	*	
Fell off bike & hit head	0.5	0.02					*Hit head on ice in hockey*	4.0	0.3			*	*
Pushed & head hit ground	8.5	5.0			*		*Fell & hit head snowboarding*	7.0	1.0				
Head hit bolt on trampoline	5.0	1.0					*Car accident-head hit door*	5.0	0.3	*			*
Fell out of tree	1.3	5.0	*	*		*	*Fell climbing-head hit ground*	9.0	0.2				
Pushed & hit head on ice	5.0	1.0	*		*	*	*Hit in head by baseball*	4.0	1.0		*	*	*
Fell down stairs	2.0	2.0		*	*		*Fell climbing-head hit ground*	12	0.3	*		*	*
Dropped on head wrestling	8.0	1.0			*		*Pushed & hit head on bench*	13	15	*	*		*
Tire swing rail fell on head	18	2.0	*	*	*	*	*Hit in head by lacrosse stick*	2.0	0.5		*	*	
Pushed & hit head on ground	3.0	1.0	*	*	*								
MEAN	**5.1**	**2.2**						**7.5**	**1.9**				
SD	**4.8**	**3.3**						**4.5**	**3.3**				

Note. TSI = time since injury in years; LOC = duration of loss of consciousness in minutes; PTA = post-traumatic amnesia; Conf. = confusion; Disor. = disorientation. Means and SDs bolded for TSI & LOC. Asterisks indicates that participant experienced the specific side effect (< 24hrs) listed in column header.

The experiment title and instructions were manipulated across conditions. Twenty one participants with no history of head injury (11 females) and 22 participants (9 females), who had reported a past mild TBI, signed up to take part in a study that we entitled, "Working memory in young adults who have experienced a head injury compared to young adults who have not experienced a head injury." This condition was labeled the 'diagnosis threat' condition, as all participants were explicitly informed in the Information letter that the experiment was being conducted to examine the potential negative effects of head injury on cognitive functioning. For our 'Neutral' condition, 23 participants (14 female) with no history of head injury and 21 participants (12 females), who had reported a past history of mild TBI, signed up to participate in a study we entitled "Working memory and Attention in Young Adults"; thus participants in this condition were unaware we were investigating the effects of past mild TBI on cognitive functioning.

Materials

Self-report Questionnaires

Participants in both conditions filled out the Beck Depression Inventory (BDI; Beck, Steer, & Brown, 1996), State-Trait Anxiety Inventory (STAI; Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1970), the Attention-related Cognitive Error Scale and the Memory Failures Scale (ARCES and MFS; Carriere et al., 2008). The latter two scales are composed of 12 questions that ask participants to respond by choosing one of five responses on a Likert scale ranging from "Never" to "Very Often" (see Appendix B). Items on this scale were selected from the cognitive failures scale (Broadbent et al., 1982), Reason's diary studies (Reason & Mycielska, 1982) in which participants recorded descriptions of slips of action in their daily lives, and from the authors' own experiences, based on personal diaries of attention and memory lapses. Both the ARCES and MFS have been shown to have good distributional and psychometric properties: good range of scores, no significant deviations from normality in skewness or kurtosis, good internal consistency, and good item-total correlations (Carriere et al., 2008).

Cognitive Measures

Attention span and working memory were assessed using the Digit-span forward and backwards tasks, respectively (Wechsler, 1997). The Trail-making A and B tests (Reitan & Wolfson, 1985) were used to examine processing speed and cognitive flexibility, respectively. Performance on Trial 1 of List 1 of the California Verbal Learning Test (CVLT; Delis, Kramer, Kaplan, & Ober, 1987) was examined to obtain a measure of immediate verbal memory.

Participants also completed a computerized version of the Stroop task. Participants were informed that a string of letters ("xxxx", "red", or "green"; presented in Courier New font, with 18 point size) would appear one at a time on the computer screen, and to press the "z" key, on a standard keyboard, if the font color was red and "m" if the font color was green (counterbalanced). The task was made up of 138 trials: 46 of which were neutral ("xxxx" shown in red or green), 46 congruent (the word, "red" in red font and the word, "green" in green font), and 46 incongruent (the word, "red" in green font and the word, "green" in red font). Trials were presented in random order. Each trial began with a white fixation cross displayed on a black screen for 500 ms, followed by a blank screen for 100 ms. Next the stimulus was presented on the screen until the participant made a "z" or "m" response, which ended the trail with a 1000 ms-blank screen. Participants were instructed to respond as quickly and accurately as possible. Accuracy and response time in each condition were recorded.

Procedure

In the 'diagnosis threat' condition, all participants received an Information/Consent letter informing them that they were participating in a study entitled "Working memory in young adults who have experienced a head injury compared to young adults who have not experienced a head injury" (see Appendix C). After signing the Consent form, participants were asked for demographic and health information. On this form mild TBI participants were asked for additional details regarding their prior head injury (to supplement the information reported on the online prescreen questionnaire). Next, participants completed the neuropsychological tests and questionnaires in the following order: Digit-Span forward and backward, Trail-making A & B, CVLT, Computerized Stroop task, BDI, STAI, ARCES, and the MFS.

In the ‘neutral’ condition, all participants received an Information/Consent letter at the beginning of the experiment informing them that they were participating in a study entitled “Working Memory and Attention in Young Adults” (see Appendix C). Unlike those in the ‘diagnosis threat’ condition, in which participants filled out the demographic and health questionnaire immediately after signing the Consent form, participants in the ‘neutral’ condition first completed the neuropsychological tests and questionnaires. The demographic and health questionnaire was administered only at the very end of the test session as we did not want participants to be aware during testing that we were investigating effects of head injury. All participants were tested during the second and third months of term, and not during the final exam period, to ensure that any group differences were not related to final exam period stressors.

2.3 Results

All data were analyzed using a 2 X 2 analysis of variance (ANOVA) with Group (control and mild TBI) and Instruction condition (‘diagnosis threat’ and ‘neutral’) as the independent variables. Planned independent samples t-tests were administered to determine group differences when a significant interaction was detected.

Demographics

There were no significant main effects of Group, Instruction condition, or a Group X Instruction condition interaction on mean age or mean years of participants’ education (see Table 2 for means and SDs). Independent t-tests showed that there were also no differences between ‘diagnosis threat’ mild TBI and ‘neutral’ mild TBI participants on time since injury, t (41) = -1.74, $p > 0.05$, or duration of unconsciousness, t (41) = 0.32, $p > 0.05$ (see Table 2).

Table 2. *Experiment 1; Demographic Characteristics. Mean Values with Standard Deviations in Parentheses.*

	DIAGNOSIS THREAT CONDITION		NEUTRAL CONDITION	
	Control N = 21	Mild TBI N = 22	Control N = 23	Mild TBI N = 21
Age	19.5 (3.5)	19.3 (1.1)	20.0 (1.2)	20.3 (2.1)
Education	13.9 (1.2)	13.5 (0.8)	13.8 (0.9)	13.7 (1.3)
% Female	52	41	61	57
TSI (years)	N/A	5.1 (4.8)	N/A	7.5 (4.5)
LOC (minutes)	N/A	2.2 (3.3)	N/A	1.9 (3.3)

Note. TSI = time since injury; LOC = duration of loss of consciousness.

Self-report Measures

Table 3 shows the means for each measure across participant grouping.

Table 3. *Experiment 1; Neuropsychological Task and Self-Report Questionnaire Results. Mean Values with Standard Deviations in Parentheses.*

Neuropsychological Test/Questionnaire	Diagnosis Threat Controls	Diagnosis Threat Mild TBI	Neutral Controls	Neutral Mild TBI	Interaction *F*-value	Interaction *P*-value
Digit span forward	9.90(2.17)	8.41(2.22**)**	8.78(2.37)	8.48(1.54)	1.73	0.19
Digit span backward	7.24(1.30)	7.10(2.11)	7.30(2.14)	7.33(2.18)	0.04	0.84
Trail Making A	20.28(7.39)	18.12(4.20)	17.36(5.00)	18.84(4.60)	2.46	0.12
Trail Making B	44.19(18.74)	41.94(16.57)	39.93(12.69)	35.96(9.39)	0.07	0.79
CVLT Trial 1	7.38(2.01)	8.09(2.35)	8.00(1.80	7.29(1.42)	2.96	0.09
ARCES	32.95(5.15)	38.00(7.74)	35.30(7.90)	33.57(7.73)	5.12	**0.03**
MFS[1]	25.30(5.25)	32.67(6.28)	28.78(7.00)	27.95(6.37)	3.94	**0.05**
STAI (state)	32.67(6.84)	30.55(6.50)	30.82(9.06)	36.67(9.26)	5.34	**0.02**
STAI (trait)	37.71(8.00)	35.64(10.80)	35.35(8.29)	40.81(9.86)	3.57	0.06
BDI	7.43(4.86)	10.95(7.33)	8.83(8.11)	10.62(7.88)	0.32	0.58

Notes. Values represented are mean group scores (standard deviations in parentheses). Bold items indicate significant interactions. CVLT = California Verbal Learning Test; ARCES = Attention-related Cognitive Error Scale; MFS = Memory Failures Scale; STAI = State Trait Anxiety Inventory; BDI = Beck Depression Inventory.

1 Once all participants completed the 'diagnosis threat' condition, they were emailed and asked to fill out an additional online questionnaire (the MFS). Only a subset of participants responded (MHI = 6; controls = 10). All participants in the 'neutral' condition completed the MFS.

Although the main effects of Group and Instruction condition were not significant for responses to statements on the ARCES, a significant Group X Instruction condition interaction emerged, F (1, 83) = 5.12, p = 0.03. In the 'diagnosis threat' condition, mild TBI participants complained of more everyday attention failures compared to controls, t (15) = -2.37, p = 0.02 (see Figure 1). Mild TBI participants in the 'diagnosis threat' condition also reported more attention failures compared to mild TBI participants in the 'neutral' condition, t (41) = 2.01, p = 0.05. No other group differences emerged.

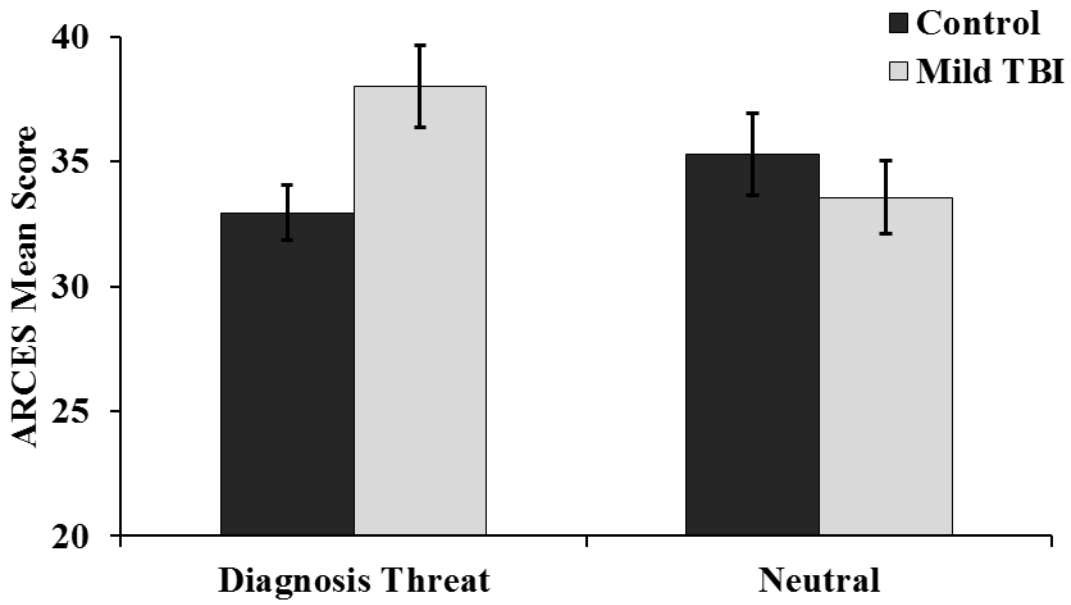

Figure 1. Experiment 1; Mean ARCES score for control and mild TBI participants in the Diagnosis Threat and Neutral conditions. Error bars are standard errors of their respective means.

Similarly, scores on the MFS revealed a significant Group X Instruction condition interaction, F (1, 57) = 3.94, p = 0.05. Mild TBI participants reported higher numbers of everyday errors due to memory lapses compared to controls, and this difference was limited to those in the 'diagnosis threat' condition, t (15) = -2.37, p = 0.03 (see Figure 2). No other group differences emerged, and the main effects were non-significant.

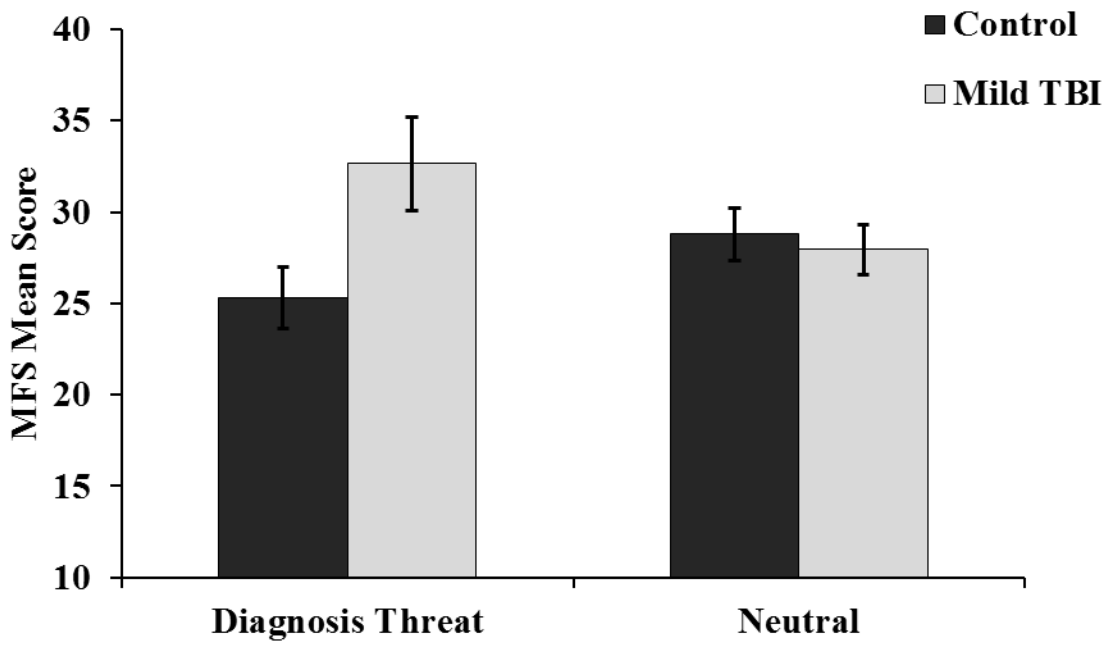

Figure 2. Experiment 1; Mean MFS scores for control and mild TBI participants in the Diagnosis Threat and Neutral conditions. Error bars are standard errors of their respective means.

A significant Group X Instruction condition interaction was also detected on self-reported state anxiety levels, F (1, 83) = 5.34, p = 0.02. Specifically, the 'neutral' mild TBI group reported higher mean state anxiety scores compared to the 'neutral' control group, t (42) = -2.11, p = 0.04 and compared to the 'diagnosis threat' mild TBI group, t (41) = -2.52, p = 0.02 (see Figure 3). No other group differences emerged, and the main effects were non-significant. For the measure of trait anxiety, the interaction trended in the same direction, F (1, 83) = 3.57, p = 0.06. Specifically, 'neutral' mild TBI participants tended to report higher levels of trait anxiety compared to 'neutral' controls, t (42) = -2.00, p = 0.05. There were no significant main effects or an interaction on BDI questionnaire responses.

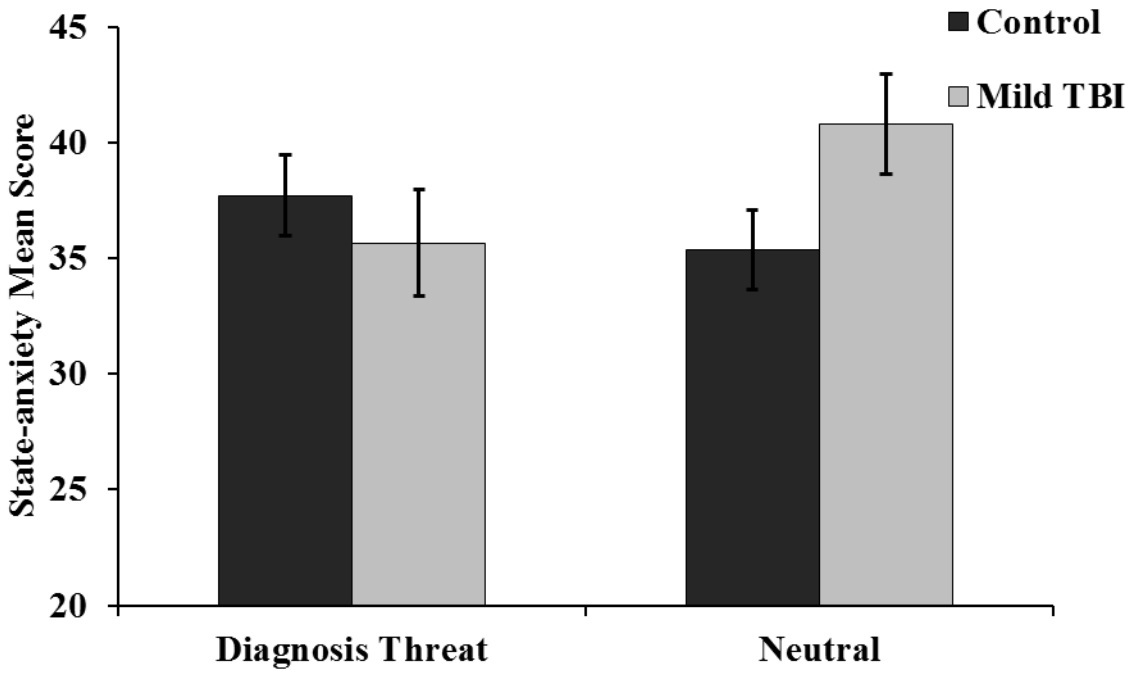

Figure 3. Experiment 1; Mean state-anxiety score as measured by the STAI for control and mild TBI participants in the Diagnosis Threat and Neutral conditions. Error bars are standard errors of their respective means.

Neuropsychological Task Measures

Table 3 (above) shows the group means for each neuropsychological measure. There was a main effect of Group on digit span forward performance, F (1, 83) = 3.97, p = 0.05, such that, regardless of Instruction Type, control participants outperformed mild TBI participants (see Figure 4). Although the Group X Instruction condition interaction was not significant, F (1, 83) = 1.73, p = 0.19, planned comparisons showed that controls outperformed mild TBI participants, t (41) = 2.24, p = 0.03, but only in the 'diagnosis threat' condition.

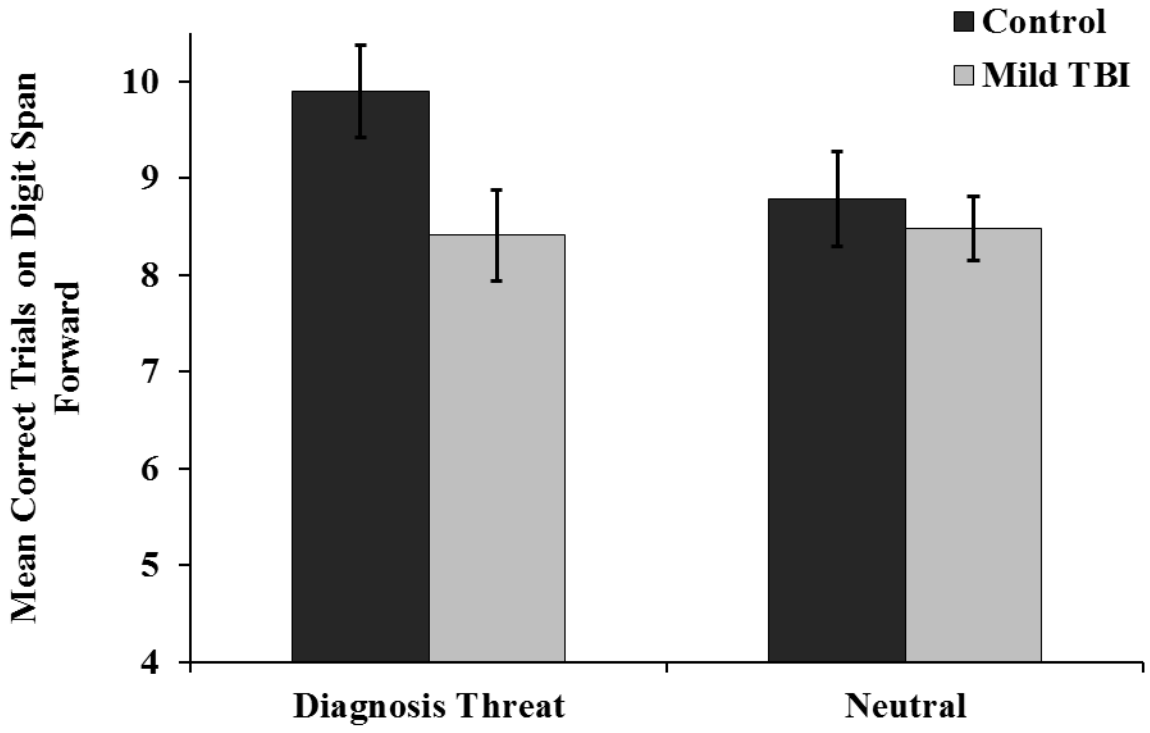

Figure 4. Experiment 1; Mean Digit-span Forward scores for control and mild TBI participants in the Diagnosis Threat and Neutral conditions. Error bars are standard errors of their respective means.

ANOVAs using data from the digit span backwards, Trail making tests, and CVLT did not reveal any significant main effects or interactions.

Two separate 2 X 2 X 3 repeated measures ANOVAs were conducted to examine Stroop accuracy and median RT, with Group (control and mild TBI) and Instruction Condition ('diagnosis threat' and 'neutral') as the between variables, and Trial Type (congruent, incongruent, and neutral) as the within variable. Using accuracy as the dependent variable, there were no significant main effects, and no 2-way or 3-way interactions. Using median RT as the dependent variable, the main effects and 3-way interaction did not even approach significance, though the 2-way Group X Instruction interaction was suggestive, F (1, 83) = 1.07, p = 0.21. Specifically, mild TBI participants in the 'diagnosis threat' condition had slower median RTs (M = 496.84 sec, SD = 97.73) compared to mild TBI participants in the 'neutral' condition (M = 448.49 sec, SD = 84.10), t (41) = 1.74, $p < 0.01$.

2.4 Discussion

The key finding in this study is that the initial information provided to participants regarding the study's purpose influenced cognitive and affective self-report measures in individuals who sustained a mild TBI in their distant past. In line with our hypotheses, when informed that a mild TBI may result in persistent, but subtle, cognitive weaknesses ('diagnosis threat' instruction condition), individuals who sustained a past mild TBI reported significantly more attention-related errors in everyday life compared to non-head injured controls, and compared to mild TBI participants who were not exposed to the 'diagnosis threat' instructions ('neutral' mild TBI group). Similarly, 'diagnosis threat' mild TBI participants reported experiencing significantly more everyday memory failures compared to 'diagnosis threat' controls. In contrast, no differences between mild TBI participants and controls emerged on these self-report measures, or on behavioral measures, when the study's purpose made no mention of mild TBI ('neutral' instruction condition). Importantly, there were no significant differences between the two control groups on any of the self-report or behavioural measures, confirming that both mild TBI groups were being compared to a similar control base rate. Notably, we found differences between control and mild TBI participants in the 'neutral'

condition in terms of anxiety levels: mild TBI participants reported experiencing higher levels of anxiety at the time of testing. 'Neutral' mild TBI participants also reported higher state anxiety levels compared to 'diagnosis threat' mild TBI participants.

With regard to cognitive performance, controls outperformed mild TBI participants on digit span forward performance, regardless of instruction type. No other measure of neuropsychological functioning distinguished group performance, although digit span forward and Stroop test performance showed trends suggesting that diagnosis threat may also impair attention span and slow information processing speed in mild TBI participants, respectively. Taken together, these results suggest that self-reports of everyday attention and memory functioning may be more susceptible to 'diagnosis threat' than standard neuropsychological tests of memory and attention functioning. A novel aspect of the current study is that we not only examined the effect of diagnosis threat by manipulating instructions provided to mild TBI participants, but also compared these groups to their own age-, education-, and gender-matched controls. The addition of non-head injured controls was essential as prior studies have found that even control performance may be negatively impacted by stereotype threat effects even though they are part of the 'non-stereotyped' group (for a review, see Wheeler & Petty, 2001). To our knowledge, this is the first study to show that non-head injured control performance was not negatively impacted by exposure to a mild TBI 'diagnosis threat'.

The effect of 'diagnosis threat' on self-reported attention- and memory-related cognitive errors in the present study is in line with past research demonstrating an underestimation of pre-injury symptoms by mild TBI participants compared to control base rates (Davis, 2002; Gunstad & Suhr, 2001; Iverson et al., 2010; Lange et al., 2010; Mittenberg et al., 1992). We suggest that individuals who have sustained a mild TBI may attribute their present day cognitive errors to their past head injury, unlike non-head injured individuals, who perceive the same errors as normal everyday cognitive foibles. This 'expectation' phenomenon is not unique to mild TBI, but rather is akin to the more general and widely-researched term, 'suggestibility'. Suggestibility is an individual's proneness to accept new information while inhibiting critical judgment and has long been shown to have the power to both accelerate recovery, and worsen serious medical conditions (see Spiegel, 1997 for review). We have shown that 'suggestibility', long after mild

TBI, contributes to an increase in the frequency of self-report cognitive complaints. To our knowledge, the current study is the first to show that mild TBI individuals have higher levels of self-reported everyday attention and memory difficulties at least 6 months after the injury compared to non-head injured controls, but only when they were informed of the possible negative effects head injury may have on cognitive performance.

The lack of significant differences between control and mild TBI participants on the majority of neuropsychological tests in this study is consistent with past reports. Standard neuropsychological tests often fail to detect deficits which distinguish individuals with a past mild TBI from non head-injured controls (for meta-analyses, see Belanger et al., 2005; Binder et al., 1997; Vanderploeg et al., 2005). We did, however, find that mild TBI participants had lower digit span forward scores, a measure of attention span, compared to controls, which is in line with some other studies reporting neuropsychological deficits on attention tasks at least three months after mild TBI (Chan, 2002; Potter et al., 2002; Solbakk et al., 1999; Vanderploeg et al., 2005). It is unclear, however, whether these are affected by diagnosis threat. Suhr and Gunstad (2002; 2005) found that mild TBI participants exposed to the 'diagnosis threat' had larger decrements in attention and psychomotor speed compared to mild TBI participants in their 'neutral' condition. Psychomotor speed in our study was slower in 'diagnosis threat' mild TBI participants than 'neutral' mild TBI participants on the Stroop Task, and they also showed lower digit span scores than their controls, though our conclusions are limited by our relatively small sample size. Inconsistencies in detection of neuropsychological deficits following mild TBI, in the extant literature, may be a result of the heterogeneity of the mild TBI population being examined across studies, including, but not limited to, individual differences in time since injury, cause of injury, and mild TBI criteria used by researchers. It is important to keep in mind that we relied on self-report measures of mild TBIs in university students. Thus, we tested high-functioning young adults with head injuries that are arguably on the very mild end of the severity scale (i. e., average duration of LOC was approximately 2 minutes; see Table 1), which may have contributed to the lack of significant neuropsychological test findings.

A finding unique to this study was that state anxiety measures were heightened in 'neutral' mild TBI participants compared to their matched 'neutral' controls, but no such

differences were found between mild TBI and control groups in the 'diagnosis threat' condition. As well, 'neutral' mild TBI participants reported higher levels of state anxiety compared to 'diagnosis threat' mild TBI participants. Prior studies have also found increased levels of self-reported anxiety (Dischinger et al., 2009; Westcott & Alfano, 2005) and increased prevalence of anxiety-related disorders (Mooney & Speed, 2001) long after mild TBI. This study adds to that literature in that higher anxiety levels were reported by high-functioning undergraduate students with a mild TBI following the completion of a neuropsychological test battery, but only when they were *unaware* the effects of their head injury were being investigated. Other research shows that mild TBI may interrupt neural pathways important for regulating emotional states. For example, brain areas implicated in post traumatic stress disorder (PTSD) have shown to overlap with those affected by mild TBI; the orbitofrontal and dorsolateral cortex and hippocampus (Stein & McAllister, 2009).

Our study suggests that 'diagnosis threat' may differentially affect emotional and cognitive processing. Group differences in self-report anxiety levels may have been undetected in the 'diagnosis threat' condition because the 'diagnosis threat' Information letter acted as justification for participants' perceived poor performance. Feelings of anxiety may have been obscured by the expectation, for mild TBI participants, to show cognitive weaknesses. In other words, if individuals are explicitly reassured that they may show subtle cognitive deficits on these specific tasks due to their previous head injury, anxiety may be temporarily decreased. On the other hand, if mild TBI individuals are not provided with reassurance prior to cognitive task completion ('neutral' mild TBI group), reported anxiety levels may be elevated, and more representative of everyday levels, compared to the 'diagnosis threat' mild TBI group and non-head injured 'neutral' controls.

In conclusion, although persistent neuropsychological deficits may be present after sustaining a single mild TBI (Bernstein, 2002; Chan, 2002; Potter et al., 2002; Solbakk et al., 1999; Vanderploeg et al., 2005) they may be less frequent and more subtle than subjective reports of lasting concentration and memory problems. Consequently, these subtle cognitive weaknesses may only be detected by experimental paradigms that heavily tax cognitive resources (Bernstein, 2002; Cicerone, 1996; Pare et al., 2009). Thus in experiments 2a and b, I

implemented two different experimental paradigms, each of which varied the demand placed on executive processing resources, in an attempt to uncover lingering, but subtle cognitive changes after mild TBI. Specifically, I compared mild TBI performance to non head-injured controls on a working memory task and on a task designed to induce action slips during a well-learned movement sequence; both of which are novel to this population and known to tax executive processing resources to different extents. Moreover, to decrease the influence of diagnosis threat, participants were not informed that the study's purpose was to examine the effects of head injury on cognition until completion of the experiment.

Chapter 3: Examining Long-term Cognitive Impairments after Mild TBI through the use of Novel and Sensitive Empirical Measures

Experiment 2a: The Effects of Mild TBI on Working Memory Functioning

3.1 Introduction

As previously reviewed, while neuropsychological tasks most often fail to identify lingering impairments after mild TBI, research using non-standard, more sensitive and complex measures of cognitive functioning, has started to provide empirical evidence for such complaints. For instance, Vanderploeg and colleagues (2005) reported no residual deficits in individuals who sustained a mild TBI using standard accuracy measures on the PASAT, but found that mild TBI participants had higher discontinuation rates (a non-standard measure) compared to controls. Moreover, increasing task complexity in controlled experimental studies can indicate significant cognitive impairment in participants long after mild TBI. For example, while no group differences were found while performing a relatively simple attention task on its own, dividing attention between two concurrently performed tasks decreased information processing speed (Cicerone, 1996; Pare et al., 2009), as well as accuracy (Bernstein, 2002; Pare et al., 2009), in mild TBI participants in the post-acute phase compared to controls. The authors suggested that individuals with mild TBI perform normally on tasks which are relatively automatic or less demanding, yet are unable to sustain effective processing when controlled allocation of attention is required for adequate performance on tasks that increase demand place on available resources. In other words, deficits were found during working memory functioning, such that participants were required to hold and manipulate additional information while concurrently controlling response outputs. These findings provide evidence that long-term working memory can be identified in the mild TBI population when novel ways of measuring performance on standard neuropsychological tasks are implemented and when task complexity is increased.

When cognitive impairments are observed in the post-acute phase, delayed information processing has been one of the most consistent findings (Bernstein, 2002; Cicerone, 1996;

Johansson et al., 2009; Pare et al., 2009; Potter et al., 2002). Whereas severe TBI individuals have been shown to perform significantly slower compared to controls and mild TBI participants on three reaction time tasks that ranged from simple to complex (Tombaugh et al., 2007), mild TBI had longer mean reaction times on only the most complex tasks compared to controls within one month of after injury (Tombaugh et al., 2007) and up to three months post-injury (Hugenholtz et al., 1988). Taken together, these results suggest that simple measures of processing speed may be sensitive to injury severity within the TBI population, but more complex tasks are required to distinguish a mild TBI population from healthy non-head injured controls, particularly when trying to uncover long-term consequences of mild TBI. To better define these potentially long-lasting, but subtle deficits, it is essential to obtain both sensitive response time measures and accuracy rates in low- and highly-demanding cognitive task conditions in order to better define lasting changes in information processing following a single mild TBI. The employment of such rigorous methodology may also help to disentangle whether mild TBI results in a deficit in a specific cognitive domain, such as working memory, or a more general slowing of information processing speed, which then contributes to deficits in specific cognitive domains (Chiaravalloti et al., 2003).

The purpose of the present study was to examine the possible long-term residual effects of one mild TBI on accuracy and information processing speed on a working memory task with varying levels of executive processing load. Specifically, I administered a modified version of the Repetition Detection working memory task (Bopp & Verhaeghen, 2007) in which participants were asked to identify a repeated digit in both low- and high-processing load conditions. In the low-load condition, participants were instructed to identify a visually-presented repeated digit within a string of random digits. Such a working memory task requires storage (holding a string of digits in mind) and simultaneous manipulation of information (determining if the presentation of a new digit matches one of the digits held in mind). In the high-load condition, executive processing load was increased by asking participants to identify a repeated digit, but only when it was enclosed by a square of the same color. Thus, participants were still required to simultaneously store and manipulate information, but also to monitor (selectively attend to color) and control output (identify target digits that repeat in same color

and ignore distracter digits that repeat in two different colors). The design of this task permitted the recording of hit rates and sensitive response time measures, including the average time to accurately respond to a target per trial, and the position of accurate and distracter responses relative to the target within each trial. Keeping in mind previous research suggesting a lasting impairment in information processing speed following a mild TBI, we lifted response time restrictions in this task and, instead, permitted participants an unlimited response time window (see methods for more detail). The use of sensitive response time measures in two different conditions that vary in executive processing requirements may allow for the detection of more subtle changes associated with a remote mild TBI.

In addition, standard neuropsychological tasks were administered to measure cognitive functioning and simple information processing speed within various cognitive domains. Moreover, I obtained self-report measures of cognitive and affective functioning. Two questionnaires, The Attention-Related Cognitive Error Scale (ARCES) and The Memory Failures Scale (MFS), were used to document frequency and type of participants' everyday lapses in attention, and memory failures, respectively (Carriere et al., 2008). The State-Trait Anxiety inventory (STAI) and the Beck Depression Inventory (BDI) were also administered to assess potential long-lasting effects of a mild TBI on affective functioning.

Studying the mild TBI population has not only shown to be difficult due to the subtlety of deficits, but, as previously mentioned, also due to various confounding variables. In addition to screening for common extraneous variables such as neuropsychiatric, neurological and affective problems, this study was designed reduce the influence "diagnosis threat". Based on Experiment 1 results and previous findings in the literature (Suhr & Gunstad, 2002; 2005), control and mild TBI participants were not informed of the purpose of the current study until after task completion in an attempt to mitigate the effects of "diagnosis threat" on self-report measures and neuropsychological performance; the same protocol used in "neutral" condition of Experiment 1.

We hypothesized that regardless of group membership, all participants would be less accurate and slower to identify a repeated digit in the high verses low processing load condition on our Repetition Detection working memory task. Moreover, if group differences were detected in the low processing load condition, we anticipated that mild TBI participants would perform

more slowly than controls. With the additional increase in demand placed on executive processing in the high-load condition, we expected that mild TBI participants would perform more slowly and/or less accurately, compared to controls. Similar to the majority of previous reports, we did not expect any group differences to emerge on the neuropsychological tasks, nor on our cognitive self-report measures. We did anticipate, however, that mild TBI participants may report higher levels of anxiety compared to controls, a result previously reported in the mild TBI literature (Dischinger et al., 2009; Westcott & Alfano, 2005) and in participants who were not exposed to "diagnosis threat" in Experiment 1.

3.2 Methods

Classification of Mild TBI

Participants were recruited from the University of Waterloo's Research Experience Group, which consists of undergraduate students enrolled in psychology courses who receive course credit for participating in research. As in Experiment 1, we embedded five questions in the 90-item prescreen questionnaire completed by students at the beginning of the semester in order to obtain information about head injury history and severity (see Appendix A). Because our head injury questions were among many other questions, it is very unlikely that participants anticipated that we were examining the effects of head injury on cognition when they later signed up for our specific study. Moreover, the prescreen questionnaire was filled out anywhere from one to three months prior to participation in our study, which, depending on study length, was only one in up to 10 experiments per course that each student was required to complete for course credits.

In order to group participants based on head injury status, two studies with identical titles were posted on the University of Waterloo's Research Experience Group website: one that was only visible to undergraduate students who had indicated never experiencing a prior head injury and one that was only visible to students who reported sustaining a past mild TBI (the experiment management computer system makes this procedure possible based on answers provided by students to head injury questions on prescreen questionnaire). If participants were interested in this study, they would then voluntarily sign up for a specific time slot posted online.

A mild TBI was defined as any strike to the head or any acceleration/deceleration force (i. e., whiplash) that resulted in a loss of consciousness (LOC) lasting at least a couple of seconds and no longer than 30 minutes (Kay et al., 1993). Participants could also report experiencing memory loss (brief amnesia), confusion (inability to focus attention) and/or disorientation (loss of physical bearings), all not exceeding 24 hours (as in Kay et al., 1993); in addition to LOC (see Table 4). We only included participants in our study if they fit the criteria of a mild TBI, and if they sustained their mild TBI at least 6 months prior to testing.

Table 4. *Experiment 2a; Demographic and Head Injury Characteristics for Mild TBI Participants*

Gender	Age	Education	TSI	LOC	Memory Loss	Confusion	Disorientation	Cause of Injury
F	19	13.5	13.0	0 > 1 min				*Tripped and hit head on door*
M	23	13.5	16.0	0 > 1 min		*		*Hit on head with an ice block*
M	23	14.0	5.00	0 > 1 min		*	*	*Hit head on goal post playing football*
F	25	16.0	9.00	1 > 5 min			*	*Hit on head with a discus*
F	23	15.5	0.83	0 > 1 min	*	*	*	*Fell snowboarding & hit back of head*
M	19	13.5	1.17	1 > 5 min	*		*	*Tripped & hit head on table*
F	19	13.5	10.0	1 > 5 min			*	*Hit on head with tire swing*
F	19	13.0	4.00	1 > 5 min		*		*Hit heads with another player during baseball*
M	19	13.0	10.0	1 > 5 min	*			*Rode into wall while riding bike*
M	22	16.0	9.00	1 > 5 min	*	*		*Fell & hit head on ice during hockey*
F	18	12.0	10.0	0 > 1 min			*	*Fell during red rover & hit head on ground*
F	19	13.0	2.00	1 > 5 min		*	*	*Hit head against boards during hockey*
M	18	12.0	4.00	0 > 1 min			*	*Pushed into boards, fell & hit head on ice*
F	22	15.5	2.25	0 > 5 min	*	*	*	*Fell from tree branch & hit head on ground*
F	21	14.5	5.00	0 > 1 min	*			*Car accident – hit head on door frame*
F	22	14.0	9.00	0 > 1 min				*Fell rock climbing & hit head on ground*
F	18	12.0	4.00	1 > 5 min		*	*	*Hit on head with baseball*
M	19	13.0	12.0	0 > 1 min	*		*	*Fell off ladder & hit head on ground*
M	21	13.5	13.0	1 > 5 min	*	*		*Pushed & hit head on bench*
M	18	12.0	2.00	0 > 1 min		*	*	*Hit on head with lacrosse stick*
M	19	12.5	7.00	1 > 5 min		*	*	*Hit head on goal post playing football*
M	20	13.5	7.00	0 > 1 min			*	*Hit head on wall playing handball*
F	26	22.0	10.0	0 > 1 min		*	*	*Hit on head with discus*
M	20	13.5	4.00	0 > 1 min		*		*Hit by car while walking across the street*
F	22	15.5	2.00	1 > 5 min	*	*	*	*Fell & hit head on ice while skating*
M	22	15.0	6.00	0 > 1 min		*	*	*Hit on head with soccer ball*
Mean	**20.62**	**13.96**	**6.82**					
SD	**2.23**	**1.74**	**4.19**					

Note. TSI = time since injury in years; LOC = duration of loss of consciousness. Means and standard deviations bolded for age, education and TSI. Asterisks indicates that participant experienced the specific side effect (< 24hr) listed in column header.

Exclusion Criteria

In order to confirm the responses provided by participants on the online prescreen questionnaire, participants were asked the same demographic- and health-related questions in person, by the researcher, at the end of the experiment. If inconsistencies were found between the two questionnaires, participants were excluded from the study, as group membership could not be reliably established. This resulted in three control participants being excluded: all three reported, in person, experiencing a mild TBI in the past. Five mild TBI participants were excluded: three reported that they did not lose consciousness following their head injury and two hit their head as a result of fainting for an unknown reason (we excluded such participants as a pre-existing condition may have caused them to faint and may have affected cognition prior to the head injury).

Participants

Fifty-seven undergraduate students signed up online to participate in this experiment for course credit; 26 participants who experienced a prior mild TBI (13 female) and 31 had no history of head injury (17 female). The mean age of control participants was 20.48 (SD = 1.59) and 20.62 (SD = 2.23) for mild TBI participants, which did not significantly differ, t (55) = -0.26, $p > 0.05$. Similarly, the mean education level did not significantly differ, t (55) = 0.20, $p > 0.05$, between control (M = 14.03 yrs, SD = 0.94) and mild TBI groups (M =13.96, SD = 1.74). All participants were fluent English speakers and if English was not their first language, it had to be learned before age five for inclusion in the study. Moreover, all participants had to report that they were free from any psychological (including clinical anxiety and depression) or neurological disorders at the time of testing to be included in the study (questions included in prescreen questionnaire). Participants were also required to have normal or corrected-to-normal hearing and vision, according to self-report, and were right handed. All procedures were performed in compliance with University of Waterloo's ethics laws and guidelines for human research and were approved by the University's Office of Research Ethics.

Working Memory Task

Materials

The Repetition Detection working memory task from (Bopp & Verhaeghen, 2007) was adapted for use in our study. The task was administered with a computer, using E-Prime version 1.2 (Psychology Software Tools Inc., Pittsburgh, PA), and was composed of two conditions: low-load and high-load. Target stimuli in each condition were identical, but task instructions were varied. Digits (1 to 9) were presented in 100-point Arial font and enclosed by a 10.63 cm X 10 cm red- or blue-colored square. For both load conditions, a trial consisted of 8 single digits (each presented within a red or blue-colored square), one at a time in the center of the computer screen, on a white background (see Figure 5).

Procedure

Each condition consisted of 20 trials, plus 5 practice trials. Participants sat at a comfortable distance from the computer screen. Each trial began with a fixation cross displayed for 1000 ms, followed by the stimulus onset for 1750 ms. There was an inter-stimulus-interval (white blank screen) of 250 ms. After the offset of the last stimulus was an inter-trial-interval (blank screen) of 1000 ms, followed by another fixation cross, with “Press spacebar to continue” [the next trial] written below.

Figure 5. Experiment 2a; Schematic representation of a trial in the low- and high-load conditions of the Repetition Detection working memory task.

In the low-load condition, one of the eight digits was repeated in each trial. Participants were instructed to press the corresponding number on the keypad when they identified the repeated digit as quickly and accurately as possible. In the high-load condition, participants were also required to identify the repeated digit, but only if it was enclosed by the *same* colored square (e. g., two number '3's enclosed in red squares or two number '3's enclosed in blue squares, but not one '3' enclosed in a red square and one '3' enclosed in a blue square). Participants were warned that a digit may repeat in two *different* colored squares (one in red and one in blue), but that these were distracters and a response should not be made. In the low-load condition, the digits were also presented in alternating red and blue squares, but no mention of color was made by the experimenter until the high-load condition when color was relevant to task performance (see Figure 5).

Participants were instructed to press the corresponding number as soon as they identified the repeated target, although they could make their response anytime following the target (even during the blank screens or presentation of other digits). They were told that their response would be recorded, but that each trial would continue until all stimuli had been presented. If, by the end of the presentation of the eight digits, they were unsure of which one was repeated, they could respond by pressing the "0" key. Even though they had until the end of each trial to respond, participants were told at the beginning of each condition that they should respond as quickly and accurately as possible, and to attempt to respond during the presentation of the repeated stimulus. A lag of three stimuli between target repeats was used in both conditions. A lag of two stimuli between distracter repeats was used in the high-load condition.

Neuropsychological Tests & Self-Report Scales

The same neuropsychological battery and self-report measures were implemented in this experiment as in Experiment 1 (see methods section for description of each measure).

Experimental Procedure

All participants began the experiment by reading the Information Letter, and signing the Consent form. The Letter informed participants that we were studying working memory and attention in young adults using a variety of tasks, but no mention of head injury was made until

the experimental session was complete. The Repetition Detection task was the first to be completed, with the low-load condition always administered prior to high-load. Participants then completed the Digit-Span (Wechsler, 1997), Trail Making (Reitan & Wolfson, 1985), and trial 1 of the CVLT (Delis et al., 1987). Next, the STAI (Spielberger et al., 1970) and BDI (Beck et al., 1996) were administered, followed by the Stroop task, the ARCES and the MFS (Carriere et al., 2008). The researcher then asked all participants questions from the demographic/health questionnaire to obtain additional details about their head injury, should they have had one, and to confirm answers on the prescreen questionnaire. Finally, the researcher provided participants with feedback sheets and debriefed them on the actual purpose of the study: to investigate the residual effects of a mild TBI on cognitive functioning. Participants were also informed of their group membership (control or mild TBI) and that group membership was determined by answers to head injury questions on the prescreen questionnaire completed online.

3.3 Results

Working Memory Task

Two repeated-measure analysis of variance (ANOVAs) with Working Memory Load as the within-subject variable (low- and high-load) and Group as the between-subject variable (control and mild TBI) were used to examine accuracy and response times on the working memory task. Participants whose median response times were 2.5 standard deviations (SD) above or below the group mean were tagged as outliers and subsequently removed from the working memory analyses. This resulted in the removal of 2 control participants: one had a median response time of 4 SD, and another with 2.5 SD above the control group mean.

Hit Rate

Hit rate was calculated by dividing each participant's total number of accurate responses by 20, the total possible number of accurate responses. These proportions were averaged across participants in each group to yield a control and mild TBI mean group hit rate. As predicted, there was a main effect of Working Memory Load, F (1, 53) = 94.51, $p < 0.001$, $\eta^2 = 0.64$, such that participants' mean hit rate was higher in the low-load, $M = 0.97$, $SD = 0.04$, compared to high-load condition, $M = 0.73$, $SD = 0.19$, regardless of group membership (see Figure 6).

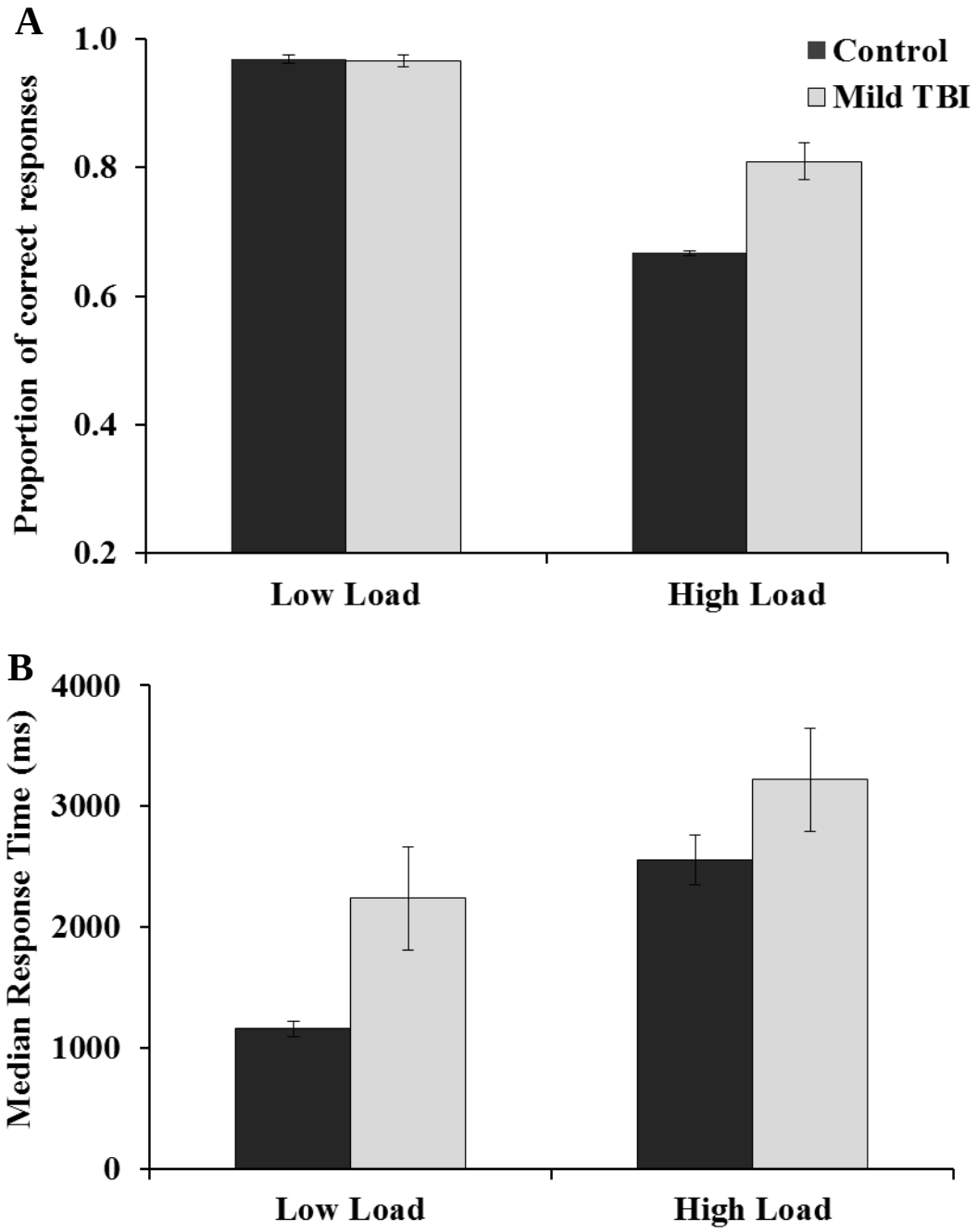

Figure 6. Experiment 2a; Panel A: Mean proportion of correct responses for control and mild TBI participants in the Low Load and High Load conditions. Panel B. Median response times for controls and mild TBI participants in the Low Load and High Load conditions. Error bars are standard errors of their respective means.

A significant 2-way interaction emerged, F (1, 53) = 9.62, $p < 0.004$, $\eta^2 = 0.15$, such that the groups differed only in the high load condition, t (53) = -2.94, $p < 0.006$. Unexpectedly, mild TBI participants had significantly higher hit rates, M = 0.81, SD = 0.15, compared to controls, M =0.67, SD = 0.20. No significant differences in hit rate, t (53) = 0.32, $p > 0.75$, emerged between mild TBI, M = 0.97, SD = 0.04, and control participants, M = 0.97, SD = 0.05, in the low-load condition.

Response Times

For each participant, the median response time was calculated for accurate trials in both the low- and high-load conditions. Following this, group mean response times were calculated by averaging individual median response times in each condition. In line with our hypothesis, participants had significantly slower response times, F (1, 53) = 41.56, $p < 0.001$, $\eta^2 = 0.44$, in the high-load, M = 2703.28 ms, SD = 1626.47, compared to low-load condition, M = 1822.18 ms, SD = 1668.79, regardless of group membership (see Figure 6 above). In addition, a main effect of group emerged, F (1, 53) = 8.18, $p < 0.007$, $\eta^2 = 0.13$, such that mild TBI participants responded significantly slower, M = 2889.52 ms, SD = 2193.28, compared to control participants, M = 1700.78 ms, SD = 979.02. The interaction was not significant, F (1, 53) = 2.34, $p > 0.13$.

Temporal Analysis of Target Identifications

Due to the unexpected higher average hit rate in the mild TBI group compared to the controls in the high-load condition, post-hoc analyses were conducted to determine when, within each trial, participants were making correct repeat identifications. As noted by (Vanderploeg et al., 2005, novel and non-standard measures of task performance (PASAT discontinuation rates in their case) may be more likely to be sensitive to the cognitive approach of mild TBI participants. As extant literature points to slowed cognitive processing in TBI patients, we devised a means of examining how this might be used as a strategy, on our task, in the mild TBI group. We anticipated that a possible explanation for the increased hit rate, in mild TBI participants compared to controls in the high-load condition, was that mild TBI participants were taking

advantage of the unlimited response time window, allowing for more correct responses to be made after the target offset compare to controls.

For each participant, the total number of targets accurately identified was split into two categories: repeats identified *during* the target presentation (During Target), and repeats identified *after* the target offset (After Target). Two repeated-measure ANOVAs with Working Memory Load as the within-subject variable (low- and high-load) and Group as the between-subject variable (control and mild TBI) were used to examine accurate responses made either during the presentation of the target or after the offset of the target. The first ANOVA examined mean number of During Target responses, and the second ANOVA examined mean number of After Target responses.

In the first ANOVA, a main effect of Working Memory Load was identified, F (1, 53) = 104.60, $p < 0.001$, $\eta^2 = 0.66$, such that in the low-load condition participants identified significantly more correct repeats During Target, $M = 15.76$, $SD = 6.62$, compared to when in the high load condition, $M = 10.18$, $SD = 5.59$ (see Figure 7). A significant interaction, F (1, 53) = 23.78, $p < 0.001$, $\eta^2 = 0.31$, revealed group differences in the low load condition, F (1, 53) = 9.06, $p < 0.005$, $\eta^2 = 0.15$, but not the high load condition, F (1, 53) = 0.012, $p > 0.91$, $\eta^2 < 0.001$. Specifically, in the low load condition only, control participants correctly identified more repeats During Target, $M = 18.14$, $SD = 2.79$, compared to mild TBI participants, $M = 13.12$, $SD = 8.50$.

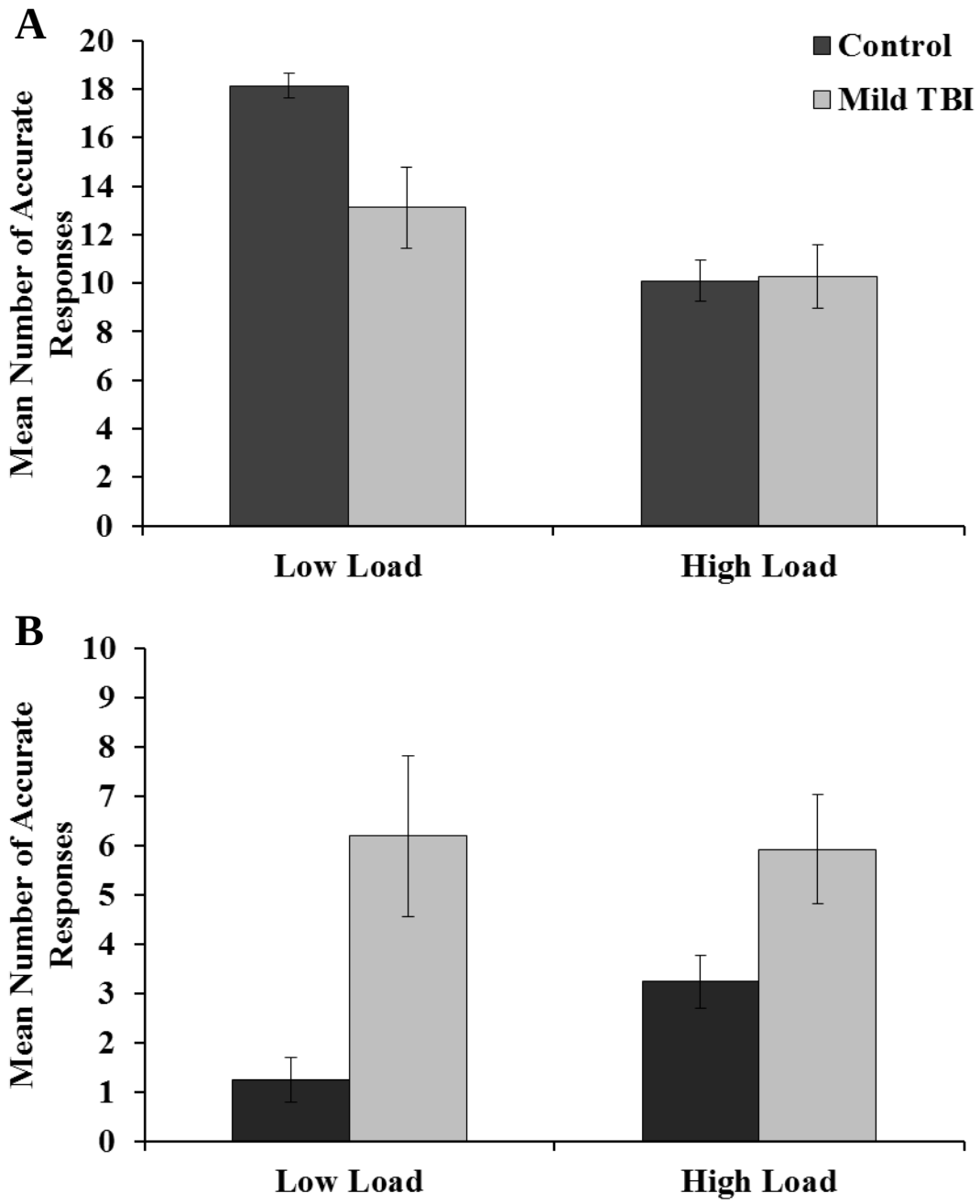

Figure 7. Experiment 2a; Panel A. Mean number of accurate responses made by control and mild TBI participants *during* target presentation in Low Load and High Load conditions. Panel B. Mean number of accurate responses made by control and mild TBI participants *after* target presentation in Low Load and High Load conditions. Error bars represent standard errors of respective means.

In the second ANOVA, the main effects for Condition and Group were non-significant. A significant interaction emerged, F (1, 53) = 6.25, $p < 0.017$, $\eta^2 = 0.11$, such that in the low-load condition, mild TBI participants accurately identified significantly more repeats After Target, M = 6.19, SD = 8.32, compared to control participants, M = 1.24, SD = 2.49, F (1, 53) = 9.34, $p < 0.005$, $\eta^2 = 0.15$ (see Figure 4). The same pattern was seen in the high load condition, (mild TBI; M = 5.92, SD = 5.63, control participants; M =3.24, SD = 2.89; F (1, 53) = 5.10, $p < 0.029$, $\eta^2 = 0.09$ (though the effect size was somewhat smaller). In other words, in the high-load condition, in which the mild TBI group outperformed the controls in terms of hit rate, they made significantly more of their correct responses following the target offset.

Temporal Analysis of Error Responses

In addition to describing the temporal occurrence of accurate responses, we were also interested in examining the timing of different types of error responses, particularly in the high-load condition. Such analyses may provide insight into why the controls had a mean lower hit rate compared to mild TBI participants. The next set of analyses was implemented to investigate where the error responses occurred within each trial in the high-load condition and to determine if the types of errors made in each group differed from one another.

As mentioned in the methods section, in the high-load condition, participants were not only asked to identify repeated targets within the same color, but also to ignore distracters (digit repeated in two different colors). Along with a target repeat presented in each trial, a distracter repeat was presented either prior to (on 50% of trials) or after the presentation of the target (on 50% of trials). Thus, participants could potentially make four different types of errors: distracter responses made before the target (Distracter Before), distracter responses made after the target (Distracter After), an incorrect response that was a number other than a distracter or target (Error), or a "0" response at the end of the trial (Miss). Independent-Samples T – Tests were used to determine if there group differences within these four different types of error responses.

Significant differences were found between groups in the mean number of Distracter Before responses, t (53) = 3.06, $p < 0.004$; see Figure 4. Specifically, controls made significantly more Distracter Before responses, M = 2.69, SD = 2.27, compared to the mild TBI group, M =

1.08, *SD* = 1.52. No other significant differences were found between groups. In sum, the only incorrect response type to distinguish the groups was Distracter Before responses. Given this group difference, we then examined whether the mean number of Distracter Before responses was correlated with the mean number of Target After responses. There was a significant negative correlation between the number of Distracter Before responses and the Target After responses, $r = -0.51$, $p < 0.001$; see scatter plot in Figure 4. In other words, as the number of incorrect responses to distracters prior to target presentation increased, the number of accurate responses to the target after its presentation decreased. This finding may help explain the decreased number of Target After responses in control participants as they had a significantly higher number of Distracter Before responses. The scatter plot in Figure 4 also shows the trend that the majority of Distracter Before responses were made by controls compared to mild TBI participants and that the larger the number of Distracter Before responses, the fewer Target After responses.

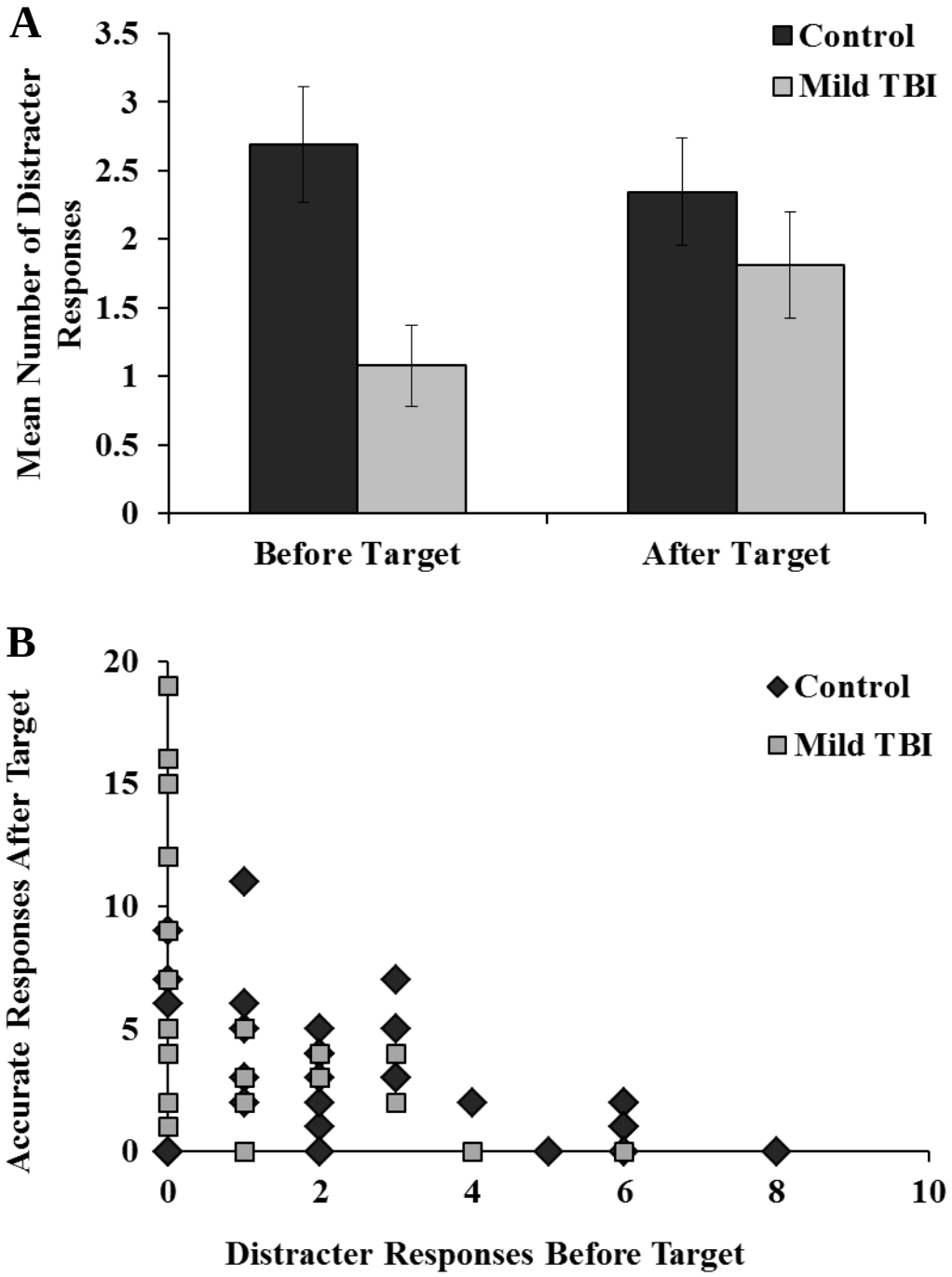

Figure 8. Experiment 2a; Panel A: Mean number of distracter responses made by control and mild TBI participants before and after target presentation. Error bars represent standard errors of respective means. Panel B. Relation between number of distracter responses made before target and accurate responses made after target for controls and mild TBI participants.

Computerized Stroop Task

Stroop accuracy and response times were analyzed using two repeated-measure ANOVAs, with *trial type* as the within-subject variable (congruent, incongruent, and neutral) and *group* as the between-subject variable (control and mild TBI). For the accuracy analysis, there was a main effect of *trial type*, F (2, 54) = 22.77, $p < 0.001$; regardless of group membership, participants had higher mean accuracy on neutral trials ($M = 0.97$, $SD = 0.03$ compared to incongruent trials ($M = 0.94$, $SD = 0.05$); F (1, 55) = 46.20, $p < 0.001$, and higher mean accuracy on congruent trials (M =0.98, $SD = 0.03$) compared to incongruent trials, F (1, 55) = 35.17, $p < 0.001$. A main effect of Group did not emerge, nor did a significant interaction.

For each participant, the median response time was calculated for accurate trials in all three trial types. Following this, group mean response times were calculated by averaging individual median response times in each trial type. Similar to the accuracy results, there was no main effect of Group, nor a significant interaction. There was a main effect of *trial type*, F (2, 54) = 13.8; $p < 0.001$. As expected, participants had longer response times on incongruent (M = 455.45 ms, $SD = 90.88$), compared to neutral ($M = 435.84$, $SD = 73.20$); F (1, 55) = 21.56, $p <$ 0.001, and congruent trials (M = 431.39 ms; $SD = 67.93$), F (1, 55) = 27.90, $p < 0.001$. No other trial differences were significant.

Self-report Questionnaires and Neuropsychological Tests

Independent-samples t tests were used to compare group means on all self-report scales (ARCES, MFS, STAI, and BDI) and neuropsychological tests (Digit Span Forward and Backward, Trail Making A and B, and CVLT trial 1). Significant differences between groups were found on the state anxiety inventory, t (55) = -2.20, $p < 0.04$, such that mild TBI participants reported higher levels of state anxiety at the time of testing, $M = 38.19$, $SD = 8.98$, compared to control participants, $M = 32.94$, $SD = 9.01$ (see Table 5). Similarly, a trend emerged on the trait anxiety inventory, which represents self-reported anxiety level experienced on a daily basis, t (55) = -1.85, $p < 0.08$. Specifically, mild TBI participants reported higher levels of trait anxiety, $M = 41.69$, $SD = 9.54$, compared to controls, $M = 37.29$, $SD = 8.43$. No significant

differences were found on the other self-report scales or on any of the neuropsychological tests (see Table 5).

Table 5. *Experiment 2a; Neuropsychological Task and Self-Report Questionnaire Results. Mean Values with Standard Deviations in Parentheses.*

Task/Questionnaire	Control	Mild TBI	*P*-value
Digit Span Forward	8.58 (2.32)	8.65 (1.50)	0.89
Digit Span Backward	7.35 (2.03)	7.85 (2.42)	0.41
Trail Making A	17.85 (5.05)	18.39 (4.29)	0.67
Trail Making B	40.19 (11.49)	35.50 (9.00)	0.10
CVLT Trial 1	8.06 (1.79)	7.81 (1.96)	0.61
Stroop (mean accuracy)	0.96 (0.04)	0.97 (0.04)	0.29
Stroop (mean RT)	441.88 (77.34)	439.71 (79.72)	0.94
ARCES	34.13 (7.53)	33.19 (6.73)	0.63
MFS	29.16 (6.44)	27.85 (6.63)	0.45
STAI (state)	32.94 (9.01)	38.19 (8.98)	**0.03***
STAI (trait)	37.29 (8.43)	41.69 (9.54)	0.07
BDI	9.19 (7.72)	10.77 (7.32)	0.43

Notes. Bold items indicate significant different between groups. CVLT = California Verbal Learning Test; ARCES = Attention-related Cognitive Error Scale; MFS = Memory Failures Scale; STAI = State Trait Anxiety Inventory; BDI = Beck Depression Inventory.

To ensure that our main finding of slowing during the working memory task was not influenced by state anxiety, it was added as a covariate in the repeated measures ANOVAs for hit rate and response time analyses on the Repetition Detection task. Anxiety did not account for a significant amount of variability in the response time ANOVA, F (1, 52) = 2.61, $p > 0.11$, or the accuracy ANOVA, F (1, 52) = 0.01, $p > 0.93$. Moreover, the addition of state anxiety as a covariate into both analyses did not change the original pattern of results.

3.4 Discussion

The major finding in this study was that young adults who sustained a mild TBI in their distant past took significantly longer, on average, to accurately identify targets on a working memory task, and reported higher levels of anxiety following task completion, compared to non head-injured controls. Moreover, mild TBI participants had identical accuracy performance compared to controls in the low-load working memory condition and, unexpectedly, surpassed control performance in the high-load condition. Post-hoc temporal analyses of responses, conducted to investigate the unpredicted accuracy boost, revealed that, on average, mild TBI participants made significantly more of their accurate repeat identifications following the target offset in both low- and high-load conditions compared to controls.

We suggest that mild TBI participants may have implemented a slowing strategy that resulted in hit rates that were no different from controls in the low-load condition and rates that were significantly higher than controls in the high-load condition. It is likely that a ceiling effect prevented mild TBI participants from successfully applying this slowing strategy, to outperform controls, in the low-load condition. To our knowledge, this is the first study to show significant slowing of information processing speed, with no decrement, but rather a boost in accuracy rates, during a working memory task in young adults who have sustained one mild TBI in the distant past. This slowing down in response time may have also had the unexpected effect of allowing mild TBI individuals to be less susceptible to distracting information, on a working memory task with a heavy executive component. We suggest that slowed information processing, and elevated anxiety levels, may be long-term consequences of a mild TBI.

Slowing of Information Processing long after Mild TBI

These cognitive findings emphasize the importance of using non-standard and sensitive measures when examining long-lasting cognitive changes in the mild TBI population. In this study, mild TBI participants did not differ from controls on simple processing speed measures, Trail Making Tests and Stroop Task, but did significantly differ in average response times on a non-standard assessment of visual working memory, our Repetition Detection Task. The classic Stroop Effect was evident, such that all participants, regardless of group, were significantly slower and less accurate on the incongruent condition compared to the neutral and congruent conditions. That even the incongruent condition, the most complex of the three, did not distinguish mild TBI participants from controls is likely due to the relatively little demand placed on working memory.

The fact that the mild TBI participants were slower to identify targets on the repetition detection task, regardless of the executive processing load, suggests that slowing can be detected during a working memory task even with relatively low executive demands. Instead, delayed processing can be identified long after a mild TBI during a working memory with heavy demands placed on short-term storage requirements (i. e., in order for accurate repetition detection, anywhere from 4-8 digits had to be held in short-term storage). This is the first study to show that in a working memory task that does not restrict when target identifications can be made, long-term delays in information processing can be detected after mild TBI without placing a heavy load on executive components (see general discussion for more detail).

Whereas a few studies have reported slower processing speeds on standard neuropsychological tests in the post-acute phase following one mild TBI (Bernstein, 2002; Potter et al., 2002; Solbakk et al., 1999), the lack of differences between groups on all our standard neuropsychological measures is in line with the majority of reports finding no effect of a single mild TBI on neuropsychological functioning (for meta-analyses, see Belanger et al., 2005; Binder et al., 1997; Frencham et al., 2005; Rohling et al., 2011). At least one meta-analysis has found that compared to all other neuropsychological measures, mild TBI had the largest affect on processing speed (Frencham et al., 2005). However, this effect size was not significant, further emphasizing the need for more sensitive and non-standard measures of performance when

examining long-lasting cognitive deficits, or compensatory cognitive strategies, following a mild TBI, such as the working memory task implemented in this study.

It has more recently been shown that severe TBI participants were slower compared to both mild TBI and control participants on all three reaction time tests that progressively increased in the amount of information to be processed (Tombaugh et al., 2007). However, within one month of injury (Tombaugh et al., 2007) and up to three months post-injury (Hugenholtz et al., 1988), mild TBI participants have been shown to perform slower than controls only on only the most complex of all three reaction time tasks, the one that placed the largest demand on attention and processing resources. Therefore, relatively simple reaction time tasks, which are successful in detecting impairments following moderate to severe TBI, may be too coarse to detect residual deficits, or changes in strategy, long after a mild TBI, necessitating the need for developing alternative ways of assessing performance, such as the temporal analyses of accurate and error responses conducted in the present study.

In so doing, we found that in the low-load condition, the delayed responding observed in the mild TBI group may have helped them maintain hit rates comparable to controls. Temporal analysis of erroneous responses in the high-load processing condition revealed that the control group, on average, made significantly more erroneous responses to distracting stimuli prior to the target onset compared the mild TBI group; moreover, correlations revealed that the higher the average number of Distracter Before responses, the lower number of accurate Target After responses. These analyses suggest that the decreased hit rate in control participants in the high-load condition is due, at least in part, to their increased susceptibility to distracting stimuli before the correct target appeared.

The slowing observed on our working memory task may also help highlight a mechanism by which general everyday self-reported memory problems arise in individuals long after a mild TBI. For example, these individuals may experience slower information processing speeds while completing common daily tasks that tap into working memory with a large storage component (e. g., remembering to select a specific brand of cereal from the shelf that matches the appropriate item in a grocery list currently held in the mind). It is this specific type of slowing that may be captured during one-on-one interviews or self-report questionnaires in the mild TBI

literature, and described as *general* "memory problems" (Alves, 1993; Meares et al., 2011; Vanderploeg et al., 2007; Villemure et al., 2011).

The Boost in Accuracy after Mild TBI

Although information processing speed impairments have been well documented in the mild TBI literature, a boost in accuracy as a result of slowing has not previously been reported. One reason for the novel finding in the current study may lie in the specific design of the Repetition Detection task. Even though participants were instructed to perform as quickly and accurately as possible, they were also told that they could respond any time during the trial following the offset of the target stimulus if they were unsure of the answer (i. e., during the presentation of subsequent stimuli or upon the completion of the trial). As temporal analyses revealed, the unlimited time window permitted mild TBI participants to make significantly more correct responses following the target offset, compared to controls, in both the low- and high-load working memory conditions. In addition, because mild TBI participants took their time while responding, it likely aided their proficiency at ignoring distracting information presented prior to the target on each trial. If time constraints were imposed, in the present study, differences in accuracy, and response time, may not have been observed. The slowing in the current study may be a strategy used by high functioning young adults who have sustained one mild TBI in order to perform optimally in during working memory tasks that place a heavy demand on short-term storage requirements.

In Experiment 2b we also manipulated the demand on executive processing resources, in an attempt to specify the long-term effects of mild TBI on cognitive functioning, but this time during a well-learned action sequence with minimal memory requirements. This study will help to determine how best to "increase task complexity" in order to identify long-term effects of mild TBI. In other words, can a novel movement sequence task that has an executive component, as well as sensitive timing measures, also detect residual changes in information processing after mild TBI, even if there is little, if any, demand placed on working memory?

Experiment 2b: The Effects of Mild TBI on Movements during Learned Action Sequence

3.5 Introduction

Just as the amount of executive processing varies in working memory functioning depending on task demands, attention tasks with little, or no, memory requirements also vary in the extent to which they draw on executive processes. As mentioned, the very few tasks that have identified attention deficits in the post-acute phase of mild TBI, required executive processes, while requiring little, if any, memory storage. Binder and colleagues (1997) found a small effect of mild TBI on attention, in general, and studies by Potter et al. (2002) and Solbakk et al. (1999) suggest that these may be limited to attention components requiring executive processes. Specifically, deficits were found in selective attention on the incongruent, but not congruent or neutral, condition of the Stroop task (Potter et al., 2002; Solbakk et al., 1999), a condition known to require inhibition of automatic response (MacLeod, 1991). The majority of and more recent meta-analyses assessing neuropsychological functioning at least 3 months post-mild TBI, however have failed to identify significant cognitive deficits (Frencham et al., 2005; Rohling et al., 2011; Vanderploeg et al., 2005). While limited, these results suggest that, in addition to working memory impairments, attention deficits may also be detected long after mild TBI using tasks that require executive processes. We suggest that the attention findings may be inconsistent due to the lack of sensitivity and complexity of traditional neuropsychological measures. The goal of this experiment was to test the hypothesis that long-term cognitive deficits could be detected after mild TBI by increasing the amount of executive processing requirements during a series of routine action sequences; another non-standard, sensitive, and task novel to this population.

We specifically sought to determine if long-term cognitive deficits could be identified using a task that has been shown to induce slips of action in healthy controls. Using the Slips Induction Task (SIT) adapted from Clark, Parakh, Smilek, and Roy (2012), we were specifically interested in determining if individuals with a remote mild TBI would perform worse than controls when executive processing was required to make an unexpected movement during a well-learned routine action task. The SIT consists of two conditions varying in processing demands: 1) An unaltered condition where participants carryout a series of well-learned routine

hand movement sequences and 2) An altered condition where a portion of the sequences is altered requiring participants to move to the location indicated by unexpected movement cue. Clark and colleagues (2012) demonstrated that the Slips Induction Task (SIT) was successful at reliably inducing action slips in healthy young adults when an unexpected cue requires a movement to an unexpected target. We also administered the Sustained Attention to Response Task (SART), as a measure of sustained attention. Errors made on the SART have been shown to correlate with SIT errors (Clark et al., 2012) and have been shown to distinguish controls from individuals with severe TBI (Robertson, Manly, Andrade, Baddeley, & Yiend, 1997). The SART requires participants to make a single button press (i. e., the spacebar) to digits presented one at a time on the screen, except when that digit is a "3", where they are required to withhold their response. Compared to healthy controls, severe TBI participants made more incorrect responses to a "3", suggested to be a problem with controlled processing, specifically inhibition difficulties.

As reviewed in the general introduction, Norman and Shallice (1986) proposed that human action is controlled by two basic processes: contention scheduling and the supervisory attentional system. Most of our everyday actions are made up of routine tasks that are controlled by habits and schemata by making use of environment cues. Using a fairly automatic conflict-resolution process, called *contention scheduling*, any inconsistencies that arise during such routine tasks are easily resolved. Not all conflicts however, can be resolved using automatic processes based on prior experiences. Novel problems and situations require planning and following through of new solutions, those of which Normal and Shallice (1986) assumed depended on a limited capacity attention component called the supervisory attentional system (SAS). Here, it is the role of the SAS to bring about conscious attention in order to make decisions, troubleshoot, execute novel sequences of actions and overcome habit. Norman and Shallice (1986) posited that the SAS requires additional processing resources, such as a mechanism that modulates the selection process by adding activation or inhibition. More specifically, early research showed that functions that required SAS were related to prefrontal regions of the brain involved in various executive processes, such as planning, novel learning, and inhibition of distracting information (see Norman & Shallice, 1986).

Based on this model, Clark et al. (2012) suggested that the conflict that arises during the presentation of unexpected movement cues cannot be resolved using the contention scheduling system (i. e., automatic processes based on prior experiences). Instead, additional executive processes are required to accurately inhibit the well-learned action sequence and actively execute a response congruent with an unexpected cue (Clark et al., 2012). In other words, during unexpected changes to the movement routine, the SAS comes online to execute the novel movement in the action sequence and overcome habit. As previously mentioned, a variety of attentionally demanding tasks with a large executive component have been shown to reveal long-term mild TBI-related deficits (Bernstein, 2002; Cicerone, 1996; Pare et al., 2009; Potter et al., 2002; Segalowitz et al., 2001; Solbakk et al., 1999). Thus, due to the extra demand placed on executive resources during altered sequences, we predicted that mild TBI participants would be slower and/or less accurate at executing movements in the presence of unexpected cues, but perform at control levels on the routine unaltered trials.

Due to the subtleties of mild TBI cognitive deficits, and the relatively low demand placed on executive processes, while we expected altered trials of the SIT to differentiate our groups, we did not expect group differences on the SART. The SART can be classified as continuous performance task, which individuals with mild TBI have shown to perform at control levels (oddball task performance; see Duncan et al., 2005). We anticipated that the altered trails of the SIT may reveal deficits that are undetected by the SART, because not only does the SIT require executive processes to inhibit a routine response, as in the SART, but also requires encoding cue information (direction of arrow) and changing the movement goal to accurately execute an infrequent movement (Clark et al., 2012). In other words, while the only responsibility in the SART is inhibit pressing a space bar to the digit "3", the SIT requires inhibition of a well-learned action sequence *plus* executive processing in order to stray from the movement routine and execute a response congruent with an unexpected cue. In addition, the SIT was designed as a truer-to-life measure of well-learned routine actions, most likely making it more difficult to inhibit that well-established routine when an alteration in movement is required. As such, relative to the SART, the SIT, arguably, taxes processing resources more heavily; similar to how it has been suggested that dividing attention reveals mild TBI-related deficits by calling on more

processing resources compared to single sustained/selective attention tasks (Bernstein, 2002; Cicerone, 1996; Pare et al., 2009; Segalowitz et al., 2001).

Also, an important aspect of the SIT is that it can be broken down into micro-movements, yielding incredibly sensitive response time measures. When healthy participants previously avoided slips on this task (Clark et al., 2012), it was at the cost of speed. As previously mentioned, the most consistent, yet often subtle, residual deficit in the mild TBI population is slowing of processing speed (Frencham et al., 2005), especially when processing demands are high (Cicerone, 1996; Pare et al., 2009) making the sensitive timing measures on this task particularly suitable for this population.

3.6 Methods

Participants

A sub-set of participants from Experiment 2a (a total of 39) completed Experiment 2b: 19 controls (12 women) and 20 mild TBI participants (11 women). The mean age was 20.05 (*SD* = 1.08) for control and 20.45 (*SD* = 2.11) for mild TBI participants, which did not significantly differ, t (37) = -0.73, $p > 0.50$. Similarly, the mean education level did not significantly differ, t (37) = 0.04, $p > 0.90$, between control, M = 13.76, SD = 0.92, and mild TBI groups, M = 13.75, SD = 1.31. Just as those included in the Experiment 2a data analysis, all participants in this experiment fit the mild TBI criteria, were right-handed, learned English before age 5, had normal or corrected-to-normal vision and hearing, and reported they were free from any neurological or psychological disorders at the time of testing.

Slip Induction Task

Materials

The SIT was adapted from Clark et al. (2012) in this experiment, whereby participants made movements to target buttons as instructed by arrow cues that appeared on a computer screen. The sequence of arrow stimuli used in this experiment was created using Micro Experiments Laboratory. Each of the arrow cues that were displayed using this program measured 70 mm in length (creating a visual angle of between 11 and 16 degrees) and 50 mm in height (creating a visual angle of between 11 and 16 degrees) and were displayed 125 mm from

the center of the screen in one of four directions. The sequence of arrow stimuli was shown on a 15 inch flat-screen monitor that was inverted to allow the stimuli to be projected onto a mirror that occluded the participants' hands. Situated under the mirror was a 16 x 16 inch button board equipped with five 2-inch diameter buttons, one located centrally with the others located above, below, left and right of the central home button.

Procedure

Prior to commencing, participants were shown the button locations on the response board. Once familiar with the response board and the button locations, participants were informed that a series of arrows were going to appear and that their task was to move as quickly and accurately as possible to the buttons on the response board that corresponded with those arrows. Participants began by completing a "learning phase", in which 120 sequences of seven movement trials, totaling 840 trials, were completed. Each sequence contained a total of seven movements to four target buttons located around a central home button. For each movement in the sequence, a directional arrow appeared above, below, to the right, or to the left of the central button. As such, for each movement, participants received both compatible exogenous (the physical location of the arrow on the screen) and endogenous (the pointed direction of the arrowhead) cuing information about the target location. During the learning phase, the direction of the arrow cues were never altered, and the participants were informed that this was the case.

Following completion of the learning phase, participants began the second phase of the experiment called the "alteration phase". Here participants continued to execute the same sequence of movements for an additional 150 sequences consisting of 7 movements each (150 x 7 = 1050 total trials). However, in 24% of these 150 sequences, one of the seven arrow cues was altered by changing the direction of the arrowhead, while keeping the spatial location constant. This resulted in 36 altered sequences and 114 non-altered sequences. This change of direction, therefore, changed the goal of the movement from what was expected. This meant, for instance, that when participants expected to see an arrow located to the right, indicating a movement to the right target for their third movement, they actually saw an arrow pointed up, down, or to the left but still located to the right of the central home button. In the alteration phase of the experiment,

36 of the sequences contained a directional alteration. Before beginning the alteration phase, all participants were informed that a portion of the sequences would be changed in some way, and it was stressed that their task would be to follow the arrow's instructions. As such, if an arrow appeared that pointed to a new target, they were to move to the new target as quickly and accurately as possible.

In this phase, the sequence of events for each trial (in both the learning and alteration phases) was: a fixation cross appeared in the center of the screen at the beginning of each sequence, and remained for between 500 and 1500 ms to ensure that participants were not able to predict sequence when the sequence of arrow cues was going to begin. Once the fixation cross disappeared, the participant pressed the central home button, which automatically triggered the onset of the first arrow cue. Upon seeing this arrow cue, participants released the home button and quickly moved to the target to which it pointed. Once the target was reached, participants quickly pressed the button, released it, and immediately returned to the central home button. The base sequence of seven movements used in this experiment was *right, down, up, down, right, left*, then *up*.

The Sustained Attention to Response Task

The Sustained Attention to Response Task (SART) was implemented according to methodologies fully outlined in (Robertson et al., 1997). Twenty-five targets, the digit "3", were quasirandomly interspersed with 200 additional digits, 1 through 9. All digits were presented for 250 ms and were followed by a mask with a 900-ms duration. Participants were instructed to press the spacebar on the keyboard each time a digit appeared, except when the digit was 3. As such, participants were asked to inhibit their response to an infrequent target. They were encouraged to complete this task as quickly and as accurately as possible.

Experimental Procedure

All participants went through the exact same experimental procedure as outlined in Experiment 2a, in that they signed the Consent form after reading the Information Letter, and proceeded to complete the Repetition Detection task, the neuropsychological battery and the self-

report questionnaires. Unlike Experiment 2a, however, all participants in the current experiment then completed the SART and SIT, in that order, before answering the demographic/heath questionnaire and being debriefed on the purpose of the study. As all participants were included in Experiment 2a data analyses, only the SART and SIT participant data were analyzed for this part of the experiment. The experiment took a total of 2 hours to complete, for which participants received two course credits (the SART and SIT taking approximately 30 minutes of the total time).

3.7 Results

Slip Induction Task

Four separate repeated-measure analyses of variance (ANOVAs) with Trial Type as the within-subject variable (unaltered and altered trials) and Group as the between-subject variable (control and mild TBI) were used to examine accuracy, initiation times, movement times, and sequence times on the SIT, respectively. Initiation time was calculated for each trial as the time required to release one's hand from the home button when the fixation cross appeared on screen. Movement time was calculated for each trial as the time required to move from the home button, once released, to press an appropriate target button indicated by the arrow cue. Lastly, sequence time was calculated for each trial as the total time required to complete a sequence of seven movements, from the time the home button was released until it was pressed again to finish the sequence.

Exclusion Criteria

Participants whose mean accuracy, altered movement times or sequence times were 2.5 *SD* above or below the group mean were tagged as outliers and subsequently removed from the study. This resulted in removing a total of five controls: two who had mean accuracy rates in the altered condition of 0%, one control who had a mean accuracy rate 3 *SD* above the group mean in unaltered trials, and one control who had an average movement time for altered trials that was 2.5 *SD* above the group mean. One mild TBI participant was also removed from the study due to having an average accuracy rate for unaltered trials 3 *SD* above the group mean. This resulted in

a total of 6 participants whose data were not included in the data analyses, resulting in a total of 19 control and 20 mild TBI participants (as stated in the methods section).

Accuracy

Mean accuracy was calculated separately for each participant in both the unaltered and altered trial conditions. The unaltered condition consisted of a total of 114 sequences of seven movements each, totaling 798 unaltered trials. Accordingly, each participant's total number of accurate responses was divided by the total possible of number of accurate responses (798) in the unaltered condition. For the altered trials, one out of seven movements was altered in 36 sequences, totaling 36 altered trials. As for unaltered trials, each participant's total number of accurate responses was divided by the total proportion of number of accurate responses (36) in the altered condition. The remaining six unaltered movements in each of the 36 altered sequences were not analyzed in the accuracy analyses (but were included in sequence time analyses – see below). These proportions were averaged across participants in each group to yield a control and mild TBI mean group accuracy rate.

As predicted, a main effect of Trial Type emerged, F (1, 37) = 220.90, $p < 0.001$, such that, regardless of group membership, participants had higher mean accuracy rates in the unaltered condition, M = 100.00, SD = 0.01, compared to altered condition, M = 0.51.84, SD = 0.20 (see Figure 9). There was no main effect of Group, F (1, 37) = 0.35, $p > 0.50$, and the Trail Type x Group interaction was not significant, F (1, 37) = 0.37, $p > 0.50$. The identical accuracy rates in the unaltered condition show that both groups successfully learned the movement sequence to nearly perfection.

Initiation Times

For each participant, the mean initiation time was calculated for all trials in both the unaltered and altered conditions. Following this, group mean initiation times were calculated by averaging individual mean initiation times in each condition. Participants had significantly slower initiation times, F (1, 37) = 11.03, p = 0.002, in the unaltered condition, M =146.34 ms, SD = 43.94, compared to the altered condition, M = 128.23, SD = 38.17.

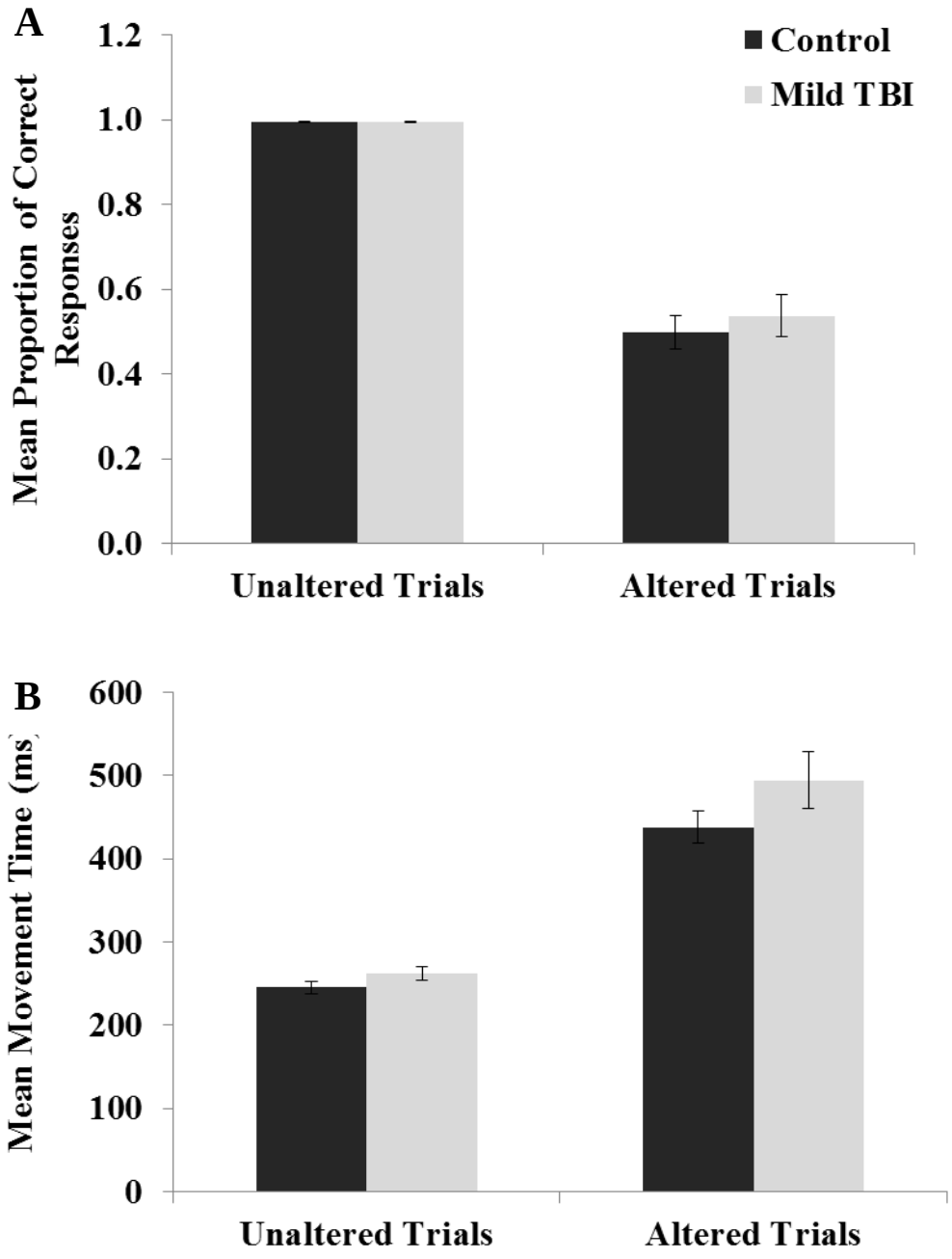

Figure 9. Experiment 2b; Panel A: Mean proportion of correct responses made by control and mild TBI participants for unaltered and altered trials. Panel B: Mean movement time for control and mild TBI participants in unaltered and altered trials. Error bars represent standard error of respective means.

There was no significant main effect of Group, F (1, 37) = 0.09, $p > 0.70$ and no significant Trial Type x Group interaction, F (1, 37) = 1.27, $p > 0.2$ for initiation times.

Movement Times

For each participant, the mean movement time was calculated for all trials in both the unaltered and altered trial type conditions. Following this, group mean movement times were calculated by averaging individual mean movement times in each condition. In line with our hypothesis, participants had significantly slower mean movement times, F (1, 37) = 190.29, $p < 0.001$, in the altered, M = 466.72 ms, SD = 125.21, compared with the unaltered condition, M = 254.01, SD = 46.56, regardless of group membership (see Figure 9 above). There was no main effect of Group, F (1, 37) = 2.55, p = 0.16 and no significant Trial type x Group interaction, F (1, 37) = 3.51, p = 0.21.

Because the altered trials of SIT are designed to induce errors and were successful at doing so, evident by error rate of approximately 50% in this experiment, regardless of group, we conducted further analyses to examine if movement time was influenced by a specific movement type in the altered condition. In other words, was there a difference between groups in the time it took to make an accurate move to an unexpected target cue and to the time it took to make an error in response to an unexpected target cue? To determine this, two independent t – tests were conducted. There was no difference, t (37) = -0.94, $p > 0.30$, between control, M = 205.64 ms, SD = 30.42, and mild TBI participants, M = 215 ms, SD = 33.54, on the time it took to make errors during altered trials. A trend in the data, t (37) = -1.51, p = 0.14, suggests that mild TBI participants responded slightly slower, M = 742.95 ms, SD = 113.33, when making correct movements to the unexpected targets during altered trials compared to controls, M = 689.59, SD = 107.83 (see Figure 10). Retrospective power analyses performed on correct group mean movement times in altered trials showed that d = 0.48 and that, with a power estimate of 0.80, a total of 138 participants (about 70 per group) would need to be tested to obtain a significant difference between groups on this measure; thus we are confident that the effect of mild TBI on movement times during altered trials is small.

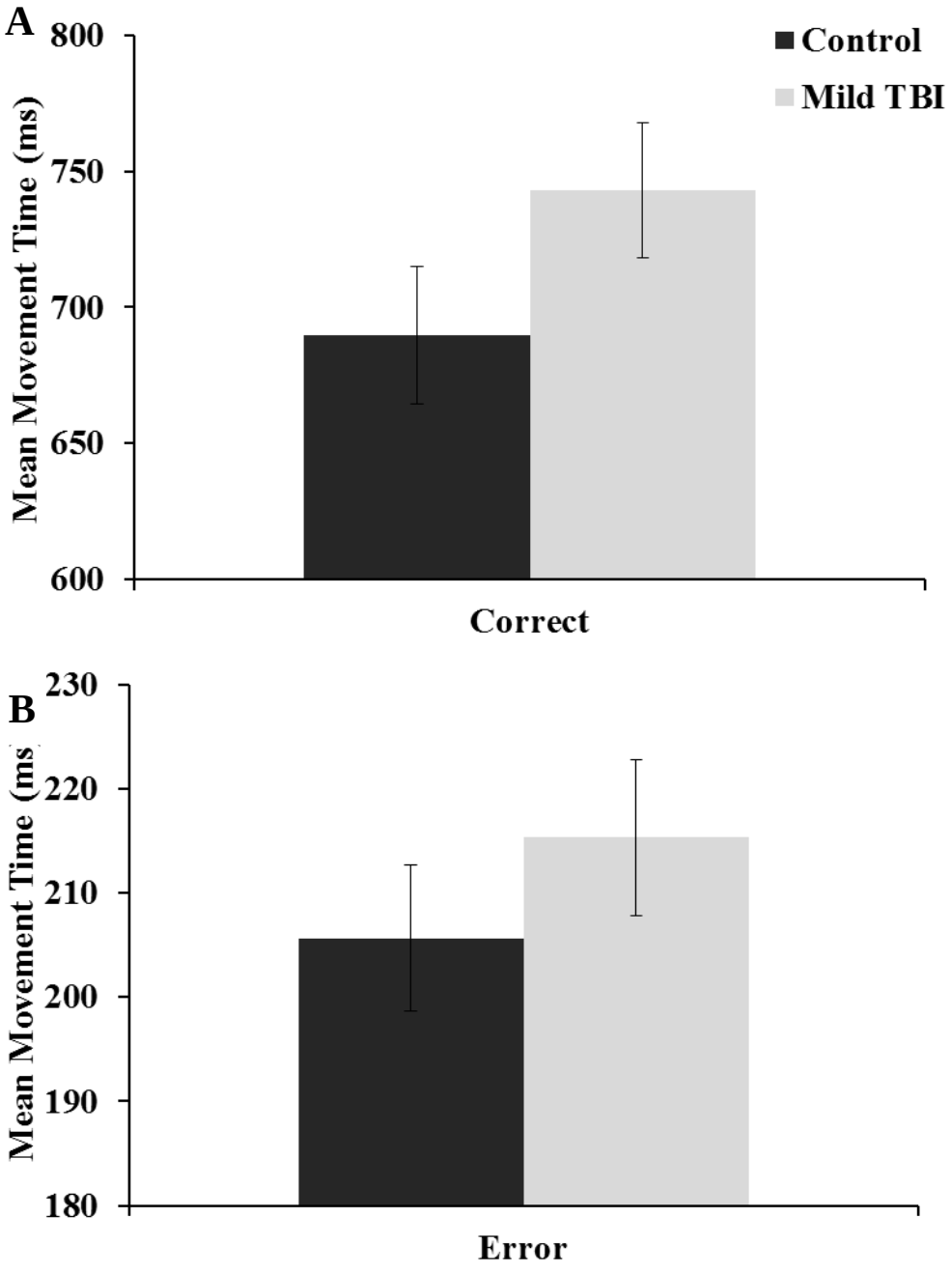

Figure 10. Experiment 2b; Panel A: Mean movement time for controls and mild TBI participants to correctly respond to altered trials. Panel B: Mean movement time for controls and mild TBI participants to make incorrect responses during altered trials. Error bars represent standard errors of respective means.

Sequence Times

For each participant, the mean sequence time was calculated for all sequences in both the unaltered and altered Trial Type conditions. Following this, group sequence movement times were calculated by averaging individual mean sequence times in each condition. There was a main effect of Trial Type, F (1, 37), $p < 0.001$, showing that participants were slowing overall for altered sequences, $M = 7785.32$, $SD = 1171.51$, compared to unaltered sequences, $M = 5060.54$, $SD = 917.07$. There was no main effect of Group, F (1, 37) = 0.001, $p > 0.90$, or significant Trial Type x Group interaction, F (1, 37) = 0.03, $p > 0.80$, for sequence times.

Sustained Attention to Response Task

Independent samples *t*-tests were conducted to compare controls and mild TBI participants on the following variables: hit rates (correctly withholding response to a "3"), false alarm rates (withholding response to a number other than "3"), accurate reaction times (for correct responses to numbers other than a "3") and error reaction times (incorrect reaction times to a "3"). All measures were individually averaged across trials for each participant and then subsequently averaged across participants to make control and mild TBI group means. No differences were found between groups (df = 36) on any of these measures (see Table 6 for more details).

Table 6. *Experiment 2b; Means scores, t-values, and p-values comparing Control and Mild TBI Group Performance on Sustained Attention to Response Task measures. Mean Values with Standard Deviations in Parentheses.*

Measures	Controls	Mild TBI	*t*-value	*p*-value
Hit Rate	0.61 (0.20)	0.62 (0.22)	-0.17	0.87
False Alarm Rate	0.01 (0.02)	0.01 (0.02)	0.39	0.70
Accurate RTs	339.88 (78.53)	346.21 (73.22)	-0.26	0.80
Error RTs	285.38 (48.64)	285.67 (42.97)	-0.02	0.98

3.8 Discussion

The main finding in this study was that, while individuals with a remote mild TBI had identical accuracy rates during both altered and unaltered movements compared to controls, they tended to slow down on altered movements that were correctly executed. While not reaching statistical significance, this pattern is in line with the slowing strategy implemented by mild TBI participants in the Repetition Detection working memory task to maintain control accuracy. The results from the SIT experiment are another testament of the subtle and specific nature of cognitive deficits that may persist following mild TBI. Inducing action slips was successful, as in Clark et al. (2012), shown by the error rate of approximately 50% during altered trials, but this rate did not differ between groups. As predicted, the SART did not differentiate the groups, indicating intact sustained attention long after a mild TBI. Results suggest that the ability to inhibit automatic responses and switch movement goals in accordance with unexpected cue information is not impaired in individuals with a mild TBI.

Even though only a subset of participants was used in Experiment 2b, retrospective power analysis revealed that increasing the sample size to reach that in Experiment 2a would not be sufficient to reveal group differences in correct movement times to unexpected targets (group means would have to be increased to approximately 70 participants per group). Yet, due to the subtle nature of deficits in the mild TBI population, it is important to note that trends should not be overlooked, but rather may serve to direct future research in order better characterize any residual cognitive problems. It is also essential to keep in mind that the groups tested in Experiments 2a and 2b were made up of high-functioning university students with one mild TBI sustained at least a year earlier (with average LOC of less than a minute), who were free from diagnosis threat, neurological and psychological problems. We view this as an advantage of experiments in this thesis in that the persistent mild TBI-related changes are more likely to be organic in nature, relative to the majority of the mild TBI studies that are often confounded with one or more extraneous variables.

Together, findings from Experiment 2a and 2b provide stronger evidence for long-term effects of mild TBI on information processing slowing during correct target detection on a working memory task than during correct altered movements on a well-learned movement

sequence designed to induce action slips. In line with the literature, these studies together provide evidence for mild TBI-related slowing during working memory functioning, but not during relatively less demanding routine action and sustained attention tasks (Cicerone, 1996; Pare et al., 2009). These studies provide a new contribution to the literature such that increasing executive demands (i. e., the amount of attentional control) in a routine action sequence or a working memory task did not negatively affect performance in individuals with mild TBI compared to controls. Instead, a working memory task with a large short-term storage component, with minimal demand placed on executive components, distinguished mild TBI participants from controls by resulting in slower information processing speeds in the former group. We suggest that long-term effects of mild TBI may affect performance when executive processes are called on during tasks that have relatively larger memory component (i. e., working memory), compared to those with limited or no memory requirements (i. e., sustained attention or routine actions). To more precisely identify the neural substrates and precise stage of this cognitive slowing, we administered a working-memory task in Experiment 3 with executive processing load requirements that varied from very low to high, while recording event-related potentials (ERP).

Chapter 4
Experiment 3: Long-term Working Memory Changes after Mild TBI: Electrophysiological Evidence

4.1 Introduction

The high temporal-resolution of ERP recording is extremely suitable for the mild TBI population, known to experience processing speed slowing on cognitively demanding tasks. This technique can be used to help determine the residual effects of a mild TBI on neural substrates of information processing during a working memory task, as well as to help distinguish those from the effects on response processes (i. e., accuracy and response time). Thus, in this experiment, I recorded a specific ERP component (P300) during a working memory task that varied in difficulty, ranging from a condition that had very limited memory storage and executive processing requirements to one that had a higher memory and processing requirements.

The P300 component has been most frequently studied in the mild TBI population as it reflects a basic cognitive process by which incoming information is categorized and is related to updating the context of working memory (Donchin & Coles, 1988; Duncan-Johnson & Donchin, 1977). The P300 is considered a late positive component that peaks at approximately 300 ms post-stimulus. Both *amplitude* and *latency* are measurements that characterize the P300 and are thought to be related to the *amount* of resources involved in stimulus processing and how *quickly* these resources are allocated to stimulus processing, respectively (see Polich, 2007 for review). The magnitude of P300 amplitude has been shown to be maximal when recorded from midline parietal electrode sites (Johnson, 1993). Typically recorded using the oddball paradigm, increases in amplitudes are recorded when the target sequence probability decreases, suggested to reflect more resources engaged in the active processing of infrequent target stimuli. Frequent stimuli can be thought of as more passive processing which elicit smaller amplitudes than active tasks, suggested to be a result of attentional resources being engaged in non-task-related events (see Polich, 2007). Moreover, P300 amplitude is dependent on the amount of attentional resources engaged during dual-task performance. Specifically, decreases in P300 amplitude are

observed during the oddball task when cognitive demands increase on a concurrent task (Isreal, Chesney, Wickens, & Donchin, 1980; Kramer, Wickens, & Donchin, 1985; McEvoy, Smith, & Gevins, 1998; Watter, Geffen, & Geffen, 2001; Wickens, Kramer, Vanasse, & Donchin, 1983), suggesting a re-allocation of attentional resources from the primary to the secondary task.

Mild TBI-related long-term electrophysiological changes have been documented by measuring the P300 component during sustained attention oddball tasks and dual-task paradigms. Individuals with a history of *one* mild TBI sustained at least 6 months prior to testing showed reduced P300 amplitude (Bernstein, 2002; Broglio, Pontifex, O'Connor, & Hillman, 2009; Segalowitz et al., 2001) or increased P300 latency (Sangal & Sangal, 1996) during accurate target detection compared to non head-injured controls, with no measurable performance deficits on standard oddball tasks. Recent research shows a similar pattern in individuals with a history of *multiple* mild TBIs tested at least 6 months since the last injury in that while no performance impairments are observed on standard oddball tasks, decreased P300 amplitudes (De Beaumont, Brisson, Lassonde, & Jolicoeur, 2007; De Beaumont et al., 2009; Gaetz, Goodman, & Weinberg, 2000) (Theriault, De Beaumont, Gosselin, Filipinni, & Lassonde, 2009) and increased P300 latencies (De Beaumont et al., 2009) have been recorded for correctly identified target stimuli compared to controls. The majority of these studies provide evidence for P300 amplitude decreases, suggesting long-term deficits in resource allocation or fewer processing resources (Duncan et al., 2005) available for target classification during simple attention tasks after mild TBI.

These findings show the utility of using the ERP technique long after mild TBI in that, even in the absence of cognitive impairment, neural changes occurring as early as 300 ms post stimulus onset, are apparent. Results from two studies show that while P300 amplitudes are useful in distinguishing mild TBI participants from controls on simple oddball tasks, both P300 amplitudes and performance changes may be used to differentiate the groups during dual-task performance (Bernstein, 2002; Segalowitz et al., 2001). In both studies, decreases in P300 amplitude were recorded with no performance decrements on simple tone discrimination oddball task at least a year post-injury, but when participants were required to concurrently perform the oddball task with a working memory task, accuracy decrements were observed in addition to

P300 changes. The authors suggested that while a limited pool of processing resources may be sufficient to enable performance for mild TBI participants in a single attention task, performance suffers when demands exceed available processing capacity (Bernstein, 2002).

We implemented an *n*-back task in the present experiment as a method by which to systematically investigate the long-term neural and cognitive effects of mild TBI on a working memory task that varies in storage and executive demands. We tested the hypothesis that individuals with a remote history of mild TBI would have inefficient allocation of processing resources during working memory functioning, as suggested by previous research. As well, we wished to test the hypothesis that with increasing working memory demand, individuals with a past mild TBI would be even less efficient at allocating resources compared to controls with no history of head injury. In order to systematically vary working memory demands, we implemented a visual *n*-back task to letters consisting of four loads (0-, 1-, 2-, and 3-back).

In a typical *n*-back task, participants are required to identify a stimulus as a target if it matches a pre-specified stimulus (0-back), or a stimulus presented 1-back, 2-back or 3-back. Additional storage and executive processing is required with each increase in *n*-back load as one more item is added to set of working memory operations of continuous encoding, manipulating, searching and selection. Similar to standard findings on the classic oddball tasks, P300 amplitude has been shown to be larger for infrequent match targets compared to frequent non-match stimuli on the *n*-back task, conceptualized as more effort or processing resources required to identify the match targets (McEvoy et al., 1998; Watter et al., 2001). The *n*-back task is unique in that P300 amplitude can also be measured as a function of processing load and an inverse relationship between the two has been found. Particularly, as processing load increases from 0- to 3-back loads, P300 amplitude decreases along with typical decreases in accuracy and increases in response time (McEvoy et al., 1998; Watter et al., 2001). It has been posited that this inverse relationship between P300 amplitude and working memory load is a result of the attentional resources being reallocated from the demands of matching subtask to the increasing demands of the working memory subtask (McEvoy et al., 1998; Watter et al., 2001).

In the current experiment, depending on the load, participants were asked to indentify target letters on the screen if they matched a pre-determined target (0-back) or a previous letter

shown 1-, 2- or 3-back. As previously reported in mild TBI participants within 3 months post-injury on the *n*-back task, we did not expect group accuracy to differ (McAllister et al., 1999; McAllister et al., 2001), but that mild TBI participants may show longer RTs at the 3-back load. We hypothesized mild TBI participants would show an overall decrease in P300 amplitude compared to controls for accurate identification of targets; in line with previous studies suggesting that mild TBI participants have fewer attentional resources available for accurate oddball detection (Bernstein, 2002; Broglio et al., 2009; Dupuis, Johnston, Lavoie, Lepore, & Lassonde, 2000; Segalowitz et al., 2001). We also expected both groups would show typical decreases in P300 as a function of working memory load, but that greater group differences would emerge at higher loads. We predicted that as working memory load increased, mild TBI participants would have a greater decrease in P300 amplitude compared to controls due to their less efficient attentional resource allocation. We did not hypothesize a significant difference in P300 latency across *n*-back loads, as previously shown in the literature (McEvoy et al., 1998; Watter et al., 2001). If differences did emerge between groups, longer latencies were expected in the mild TBI group compared to controls; although latency differences are less consistently observed (De Beaumont et al., 2009; Sangal & Sangal, 1996).

If supported, our findings would provide electrophysiological evidence for specific changes in cognitive functioning long after mild TBI, which cannot be detected using standard accuracy and RT measures. Results from this experiment will also provide us with a clearer picture of when in the information processing cascade mild TBI-related changes are persisting during working memory: during stimulus classification stages (P300 amplitude and latency measure) or during response stage (response times) and if these changes depend on working memory load. In line with previous studies, we did not expect the groups to differ on our standard neuropsychological measures of attention, working memory, short-term memory, processing speed or cognitive flexibility. We also did not expect differences in affective self-report measures and if differences did emerge between groups on the cognitive self-reports, that mild TBI participants' complaints would be increased compared to controls.

4.2 Methods

Classification of TBI

Participants were recruited via the University of Waterloo's Research Experience Group (REG), and through flyers posted around campus. The REG consists of undergraduate students enrolled in psychology courses who receive course credit for participating in research. At the beginning of every semester, undergraduate students who are enrolled in at least one psychology course complete an online multiple-choice prescreen questionnaire, later used by researchers throughout the semester to recruit participants for their studies. The questions range from those asking about demographic information to medical history to relationship status. Our research group included a question that asked if participants had previously sustained a mild TBI. If participants were interested in this study, they would then voluntarily sign up for a specific time slot posted online. A demographic/health questionnaire was administered to each participant in person at the onset of the study to confirm head injury status and to determine further details about the mild TBI (e. g., time since injury, loss of consciousness duration, etc).

The recruitment flyer posted around campus advertised that we were looking for both individuals who had and had not sustained a mild TBI in their past to participate in a study to examine the effects of mild TBI on cognition and the brain. If individuals were interested in participating, they were instructed to contact the researcher via email. The flyer stated that participants would receive $20 remuneration for participating. The severity, cause, and time elapsed since the mild TBI were all determined prior to participation through questions sent to interested individuals by email. If the mild TBI status fit within our pre-specified criteria (see below), the researcher and participant set up a study time. If mild TBI status did not meet our criteria, participants were thanked for their interest and notified that their mild TBI did not fit into our predefined criteria.

A mild TBI was defined as any strike to the head or any acceleration/deceleration force (i. e., whiplash) that resulted in a loss of consciousness (LOC) lasting no longer than 30 minutes and/or memory loss (brief amnesia), not exceeding 24 hours (Kay et al., 1993). Participants could also report experiencing confusion (inability to focus attention) and/or disorientation (loss of physical bearings), all not exceeding 24 hours (as in Kay et al., 1993); in addition to LOC and memory loss (see Table 7).

Table 7. *Experiment 3; Demographic and Head Injury Details for TBI Participants.*

Gender	Age	Education	TSI	LOC	PTA	Confusion	Disorien.	Cause of Injury
M	22	16	5.5	< 1 min	0.5 hour	0.5 hour	5 mins	*Playing- Hit back of head on floor*
M	18	13	1.5	< 1 min	1 hour	0.5 hour	5 mins	*Floor hockey – hit head on floor*
			3	< 1 min	--	--	--	*Basket ball – elbow to head*
F	22	16	1.33	< 1 min	< 5 min	2 hours	1 week	*Hockey – hit head on boards*
F	20	15	3.33	< 1 min	No	24 hours	0.5 hours	*Rugby – kicked in head*
			4	No	No	No	No	*2 separate accidental hits*
F	22	16	8	< 1 min	< 5 hours	< 5 hours	< 5 hours	*Jumped – hit head on ceiling*
M	21	16	4.42	< 1 min	No	3-4 hours	1.5 hours	*Hit by car – head hit windshield*
			10	< 1 min	No	No	No	*Boating- hit in head by boom*
F	22	17	9	No	No	No	No	*Soccer- hit in head 2x same game*
			1	No	< 5 min	< 5 min	No	*Soccer- head-to-head hit*
M	22	16	12	< 1 min	No	No	No	*Skiing – Fell and hit head*
M	22	16	15	1 > 5 mins	2 hours	1 hour	No	*Playing- Hit back of head on floor*
F	20	14	5	No	No	No	48 hours	*Horse reared up and hit front head*
			4	No	No	No	No	*Biking- fell and hit head*
M	19	14	5	< 1 min	No	10 min	1 hour	*Hockey – hit head on ice*
			Multiple	No	--	--	--	*Hockey- about 10 hits – no LOC*
M	21	15	5	< 1 min	No	No	No	*Fainted – hit back of head*
			Multiple	No	--	--	--	*Sports' hits over time- no LOC*
M	21	16	10	Can't recall	5 hours	24 hours	24 hours	*Rugby- hit in head 3x same game*
M	18	13	1.67	< 1 min	No	No	No	*Hockey- head hit boards, then ice*
M	21	14	4	< 1 min	No	No	2 hours	*Biking- fell off cliff, head hit rock*
M	22	16	7	< 1 min	No	< 1 min	4-5 hours	*Snowboarding – fell and hit head*
F	22	16	5	< 1 min	0.5 min	0.5 hour	0.5 hour	*Fell off cliff, hit head on rock*

Notes. F = Female; M = Male; TSI = Time since injury in years; LOC = Duration of loss of consciousness; PTA = Post-traumatic amnesia;; Conf = Length of Confusion; Disorien = Length of Disorientation. Grey shading indicates those participants experienced 2 or more mild TBIs. "- -" symbol indicates that participants did not answer.

We only included participants in our study if they fit the criteria of a mild TBI, and if they sustained their mild TBI at least 6 months prior to testing.

Participants

A total of 39 individuals completed the study, though data from 5 participants were removed from data analyses. One participant was excluded as she did not fit the time since injury criteria (mild TBI sustained within 6 months prior to study). Another mild TBI participant's data were not included as he was left handed. A further mild TBI participant was removed as his *n*-back task performance was more than 3 standard deviations lower than the mild TBI group mean. The final two participants were excluded due to electrode problems during EGG recording: one mild TBI participant and one control.

Thus a total of 34 participants' data were analyzed: 17 control participants (9 female) and 17 mild TBI participants (6 female). The majority of participants were recruited through REG (14 controls and 10 mild TBI participants) and fewer recruited via flyers (3 controls and 7 mild TBI participants). The mean age was 19.71 (*SD* = 1.21) and 20.88 years (*SD* = 1.41) for control and mild TBI participants, respectively, which differed significantly, t (32) = -2.61, p = 0.01. The mean number of years of education was 14.29 (*SD* = 1.26) for controls and 15.24 (*SD* = 1.20) for mild TBI participants, which also differed significantly, t (32) = -2.23, p = 0.03. While we did not expect that a one year difference between groups would affect our cognitive task performance and ERP findings, we conducted additional correlations to ensure this difference did not affect our main dependent variables (see results section).

All participants reported they were free from any psychological (including clinical anxiety and depression) or neurological disorders at the time of testing (questions included in the prescreen questionnaire). Participants were also required to have normal or corrected-to-normal hearing and vision, according to self-report, and were right handed. All procedures were performed in compliance with University of Waterloo's ethics laws and guidelines for human research and were approved by the University's Office of Research Ethics.

N-Back Task

Stimuli

We used a classic letter variant of the *n*-back task (Braver et al., 1997). Participants were presented with letters on the computer screen, one at a time, using Presentation software (Neurobehavioral Systems, http://www.neurobs.com), which also recorded behavioral responses from a mouse click. Only orthographically distinct uppercase consonants were used in this experiment (B, C, D, F, G, H, J, K, M, Q, R, S, T, V, X, Z; as in Schoning et al., 2009). Participants sat at a comfortable distance from the computer screen. The white-colored letters were presented on a black background in 100-point font. Each trial started with the presentation of a fixation cross lasting 250 ms, then a black screen for 150 ms, followed by the letter stimulus for 500 ms, and ending with a final black screen for a randomized inter-stimulus interval of 1800 - 2200 ms.

Procedure

There were four *n*-back conditions (0-back, 1-back, 2-back and 3-back) that varied in working memory load. Each load condition consisted of 75 trials: 25 match stimuli and 50 non-match stimuli (15 of which were distracters). Distracters were added to ensure that participants were not merely identifying matches regardless of the condition. Each participant completed three fixed-order blocks, each consisting of four different *n*-back load conditions (0 to 3-back). In the lowest load 0-back condition, participants were required to make a left button mouse click when they saw the pre-specified target, "W". In the low load 1-back condition, participants were asked to respond with a left mouse click when the letter on the screen matched the one shown immediately before it. In the moderate load 2-back and highest load 3-back conditions, the target was any letter that matched the one shown two or three trials back, respectively (see Figure 11 for example of 3-back load). Participants were instructed to make a right button click for all letters that did not match the target (non-match condition), depending on *n*-back load, and a left click for match targets (match condition) anytime after the onset of the letter until the completion of the trial. Participants were informed that all responses had to be made prior to completion of

each trial. Responses made after the completion of the trial, and thus made during the subsequent trial, were coded as incorrect.

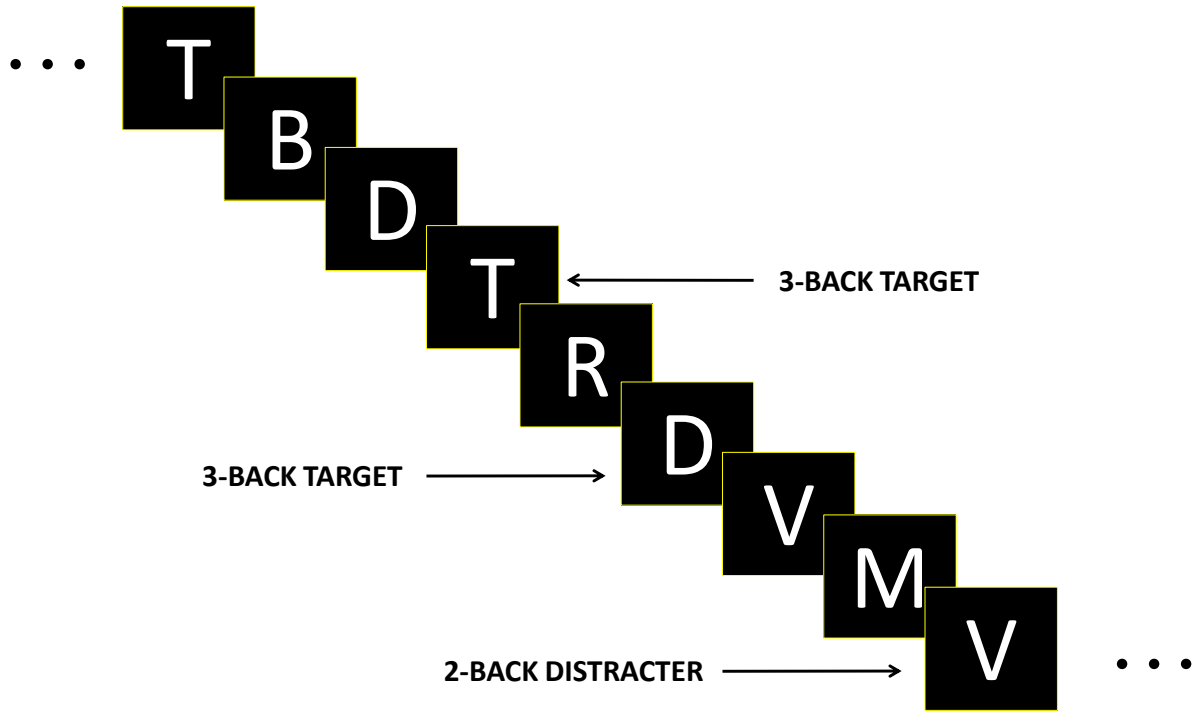

Figure 11. Experiment 3; schematic representation of the 3-back load condition of the *n*-back task.

The *n*-back task started with a practice session, in which all participants completed the 0-, 1-, 2-, and 3-back loads, in that order. The experimenter read aloud the instructions on the screen to the participant prior to each condition. Practice for each load took approximately 1 minute to complete. For each, participants were asked to respond to 6 target and 14 non-target stimuli. In the experimental session, participants completed each of the four *n*-back loads three times; these were presented in three fixed-ordered blocks (block one: 1-0-2-3; block two: 0-2-1-3; block three: 1-3-0-2). While the order of the *n*-back loads within each block was fixed, the order of the blocks was counterbalanced across participants to avoid practice effects (i. e., block three, block one, block two). Participants were told that the *n*-back loads would be presented in a random

order. For the first block, the experimenter read the instructions on the screen aloud to each participant. Participants were notified when they were one-, two- and three-thirds through the experiment. They were also encouraged to take breaks if necessary in between conditions. The experimental session took approximately 45 minutes to complete, plus breaks varying in length between loads/blocks depending on participant.

Neuropsychological Tests

Processing speed, assisted memory recall and free recall were measured using the Digit-Symbol Substitution task. Working memory span was assessed using the Digit-span forward and backward tasks (Wechsler, 1997). The Trail-making A and B tests (Reitan & Wolfson, 1985) were used to examine processing speed and cognitive flexibility, respectively.

Self-Report Scales

All participants completed the demographic/health form, Beck Depression Inventory (BDI; Beck et al., 1996), State-Trait Anxiety Inventory (STAI; Spielberger et al., 1970), the ARCES and MFS (Carriere et al., 2008). All participants also completed the Rivermead Post-Concussion Symptom Checklist, a questionnaire used to determine existence and severity of post-concussive symptoms participants may be experiencing within the last 24 hours. Control participants also filled out this checklist and were told that these are symptoms they may or may not experience in daily life. They were asked to report how often, if ever, they experienced any of the classic mild TBI symptoms.

Experimental Procedure

The experiment began with the participant reading the information letter and signing the consent form. Following this, the researcher asked the participant questions from the Demographic and Head Injury questionnaire. Participants then completed the Digit-Substitution task, followed by the Trail Making and the Digit Span Forward and Backward Tasks. Next, the participant completed the self-report questionnaires in the following order: ARCES, MFS, BDI, STAI, and finally the Rivermead Post Concussion Inventory. Participants were then fitted with

an electrode cap and appropriately prepped for EEG recording. The experimenter sat beside the participant during the *n*-back task to ensure condition-specific instructions were followed and monitor EEG recordings on a computer screen (e. g., frequency and timing of blinks). Following completion of the task, and electrode removal, participants received a feedback letter. The total duration of the study was 2 hours for which participants received 2 course credits or $20 remuneration.

EEG Recording and Data Analysis

EEG data were recorded using 64 Ag/AgCl active electrodes (BioSemi Active Two system, the Netherlands: http://www.biosemi.com) mounted on a flexible cap according to the extended international 10/20 system. A Common Mode Sense (CMS) active electrode and Driven Right Leg (DRL) passive electrode serving as ground were used. Eight additional electrodes were added to the standard montage: four electrodes recorded horizontal and vertical eye movements and were placed at the outer canthus and under the center of each eye. Two additional electrodes were placed on the posterior part of the cap on the left and right sides (CB1 and CB2, respectively) and two more electrodes were placed on the left and right mastoids (TP9 andTP10). EEG was digitized at a sampling rate of 512 Hz.

The data were processed using the EEGLab toolbox (Delorme & Makeig, 2004) and ERPLAB toolbox (http://erpinfo.org/erplab) implemented in Matlab (Mathworks, Inc.). Only correct-response trials were analyzed. EEG was epoched offline using a 100 ms pre-stimulus baseline until 600 ms after letter stimulus onset. Then, trials were digitally band-pass filtered (0.01–30 Hz) and average referenced. Trials containing large artifacts were manually removed through visual inspection. Ocular artifacts were removed using independent component analysis (ICA) decomposition as implemented in EEGLab. On average, 59.17 (*SD* = 4.17; range: 30-75) trials were kept for correct match responses in each *n*-back load (0 to 3-back) and 139.73 (*SD* = 3.97; range: 118-150) were kept for correct non-match responses in each *n*-back load (0 to 3-back) for each participant. Trials were averaged for each group according to *n*-back load (0 to 3-back) and stimulus type (match or non-match), using a 100-ms pre-stimulus baseline. P300 peak amplitude and latencies were measured at the maximum positivity between 300 ms and 400 ms

after stimulus onset at central-parietal (CPz) and parietal (Pz) electrodes; the midline electrodes where P300 amplitude was maximal when averaged across participants in each group. Two separate repeated-measures analyses of variance (ANOVAs) were conducted with *n*-back Load (4), Stimulus Type (2), and Electrode (2) as the within-subject factors and Group (2) as the between-subject factor to examine P300 amplitude and latency.

4.3 Results

Behavioral Data

Two 4 x 2 x 2 repeated-measures ANOVAs were conducted with *n*-back Load (0-, 1-, 2-, 3-back) and Stimulus Type (match and non-match) and the within-subject factors and Group (controls and mild TBI participants) as the between-subject factor to examine hit rates and response times. All ANOVAs used Greenhouse-Geisser adjusted degrees of freedom and planned contrasts used Bonferroni corrections for follow-up analyses.

Hit Rate

Hit rates were calculated by first adding together the total number of accurate match responses and the total number of non-match responses across the three experimental blocks for each *n*-back load. There were 25 match and 50 non-match trials in each *n*-back load per block. Adding these up across the three blocks resulted in a total of 75 possible match responses and 150 possible non-match responses for each *n*-back load. Next, each participant's total number of accurate responses for each stimulus type (match and non-match) was divided by the total possible number of accurate responses for each stimulus type in each *n*-back load. These proportions were averaged across participants within the control and mild TBI group separately to yield eight hit rates: four in the match condition (one for each *n*-back load) and four in the non-match condition (one for each *n*-back condition).

A significant main effect of Stimulus Type, F (1, 32) = 206.91, $p < 0.001$, revealed that participants had higher hit rates in the non-match condition compared to the match condition, regardless of Group (see Table 8 for means). There was also a main effect of *N*-back Load, F (3, 96) = 156.85, $p < 0.001$ (see Figure 12), which was qualified by a significant Stimulus Type x *N*-

back Load interaction, F (3, 96) = 102.53, $p < 0.001$. There was no effect of Group, and Group did not interact with *N*-back Load or Stimulus Type.

Table 8. *Experiment 3; Behavioral Measures: Mean Hit Rates and Response Times for Control and Mild TBI Participants in all N-back Loads across Stimulus Types. Standard Deviations in Parentheses.*

	Control				Mild TBI			
	Match		Non-match		Match		Non-match	
n-back	Hit rate	RT	Hit rate	RT	Hit rate	RT	Hit rate	RT
0	97.3 (0.03)	404.6 (53.4)	98.9 (0.01)	338.5 (30.0)	97.0 (0.03)	397.1 (53.4)	98.8 (0.01)	359.1 (53.4)
1	88.8 (0.89)	416.4 (53.8)	96.6 (0.02)	388.1 (46.1)	88.0 (0.10)	436.9 (84.7)	96.9 (0.02)	432.2 (108.5)
2	76.1 (0.07)	459.0 (126.3)	91.6 (0.02)	451.8 (103.6)	74.7 (0.08)	523.8 (164.1)	89.8 (0.04)	523.2 (181.8)
3	62.6 (0.12)	570.0 (262.7)	92.1 (0.04)	522.2 (155.9)	60.6 (0.12)	689.9 (307.3)	90.1 (0.06)	635.1 (284.2)

Note. Mean hit rates (% correct) and mean RTs (ms).

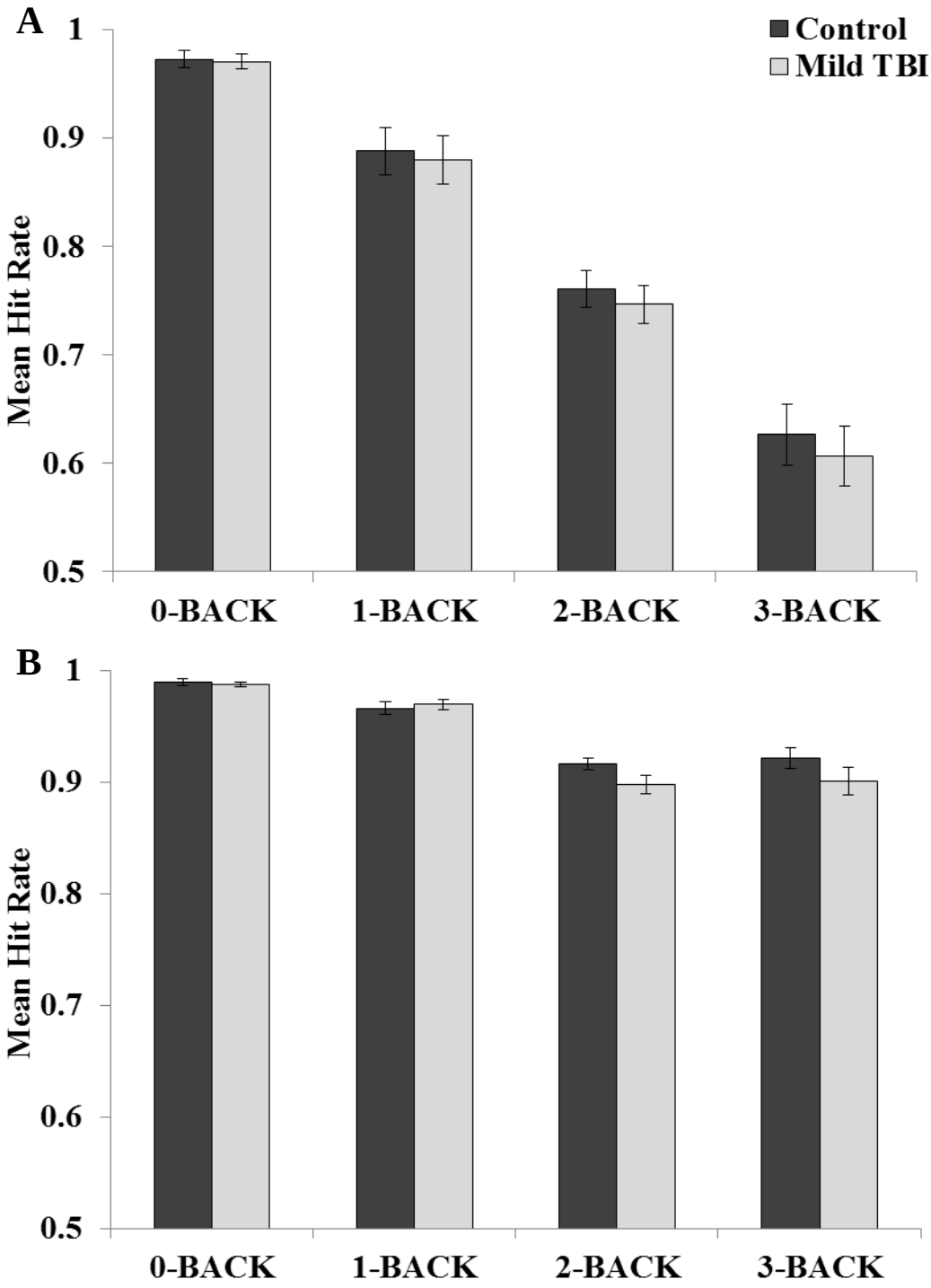

Figure 12. Experiment 3; Panel A: Mean hit rate for control and mild TBI participants in each *n*-back load of the match condition. Panel B: Mean hit rate for control and mild TBI participants in each *n*-back load of the non-match condition. Error bars represent standard error of respective means.

Two follow-up one-way ANOVAs with planned contrasts were conducted to investigate if hit rates varied across *N*-back Loads within each Stimulus Type. For matches, participants had significantly higher hit rates, F (3, 13) = 112.37, $p < 0.001$, in the 0-back compared to the 1-back load, t (132) = 4.23, $p < 0.001$, the 0-back compared to the 2-back load, t (132) = 10.51, $p < 0.001$, and the 0-back compared to the 3-back load, t (132) = 17.17, $p < 0.001$. Similar effects were observed for non-matches, such that participants had higher hit rates F (3, 132) = 58.11, $p < 0.001$, in the 0-back compared to 1-back condition, t (132) = 2.72, $p = 0.007$, and in the 0-back compared to the 2-back condition, t (132) = 10.73, $p < 0.001$, and in the 0-back compared to the 3-back condition, t (132) = 10.25, $p < 0.001$.

Response Times

For each participant, the median RT was calculated for both accurate matches and non-matches in each *n*-back load. These median RTs were then averaged across participants within the control and mild TBI group separately to yield 8 mean RTs: 4 in the match condition (one for each *n*-back load) and 4 in the non-match condition (one for each *n*-back condition).

A significant main effect of Stimulus Type showed that, regardless of Group, RTs were significantly longer for matches than non-matches, F (1, 32) = 6.00, $p = 0.02$ (see Table 8 for means). There was also a significant main effect of *N*-back Load, F (3, 30) = 32.29, $p < 0.001$, such participants took longer to respond accurately in the 2-back compared to 0-back condition, t (132) = -3.16, $p = .002$, and the 3-back compared to the 0-back condition, t (132) = -6.33, $p < 0.001$, but not the 1-back compared to 0-back condition, t (132) = -1.20, $p > 0.20$. The main effect of Group was non-significant, as were interactions between group and the other factors. There was, however, a slight trend towards an interaction of Group X *N*-back Load, such that mild TBI participants performed slightly slower compared to controls as the load in the *n*-back Load increased, F (3, 30) = 1.83, $p = 0.18$ (see Figure 13).

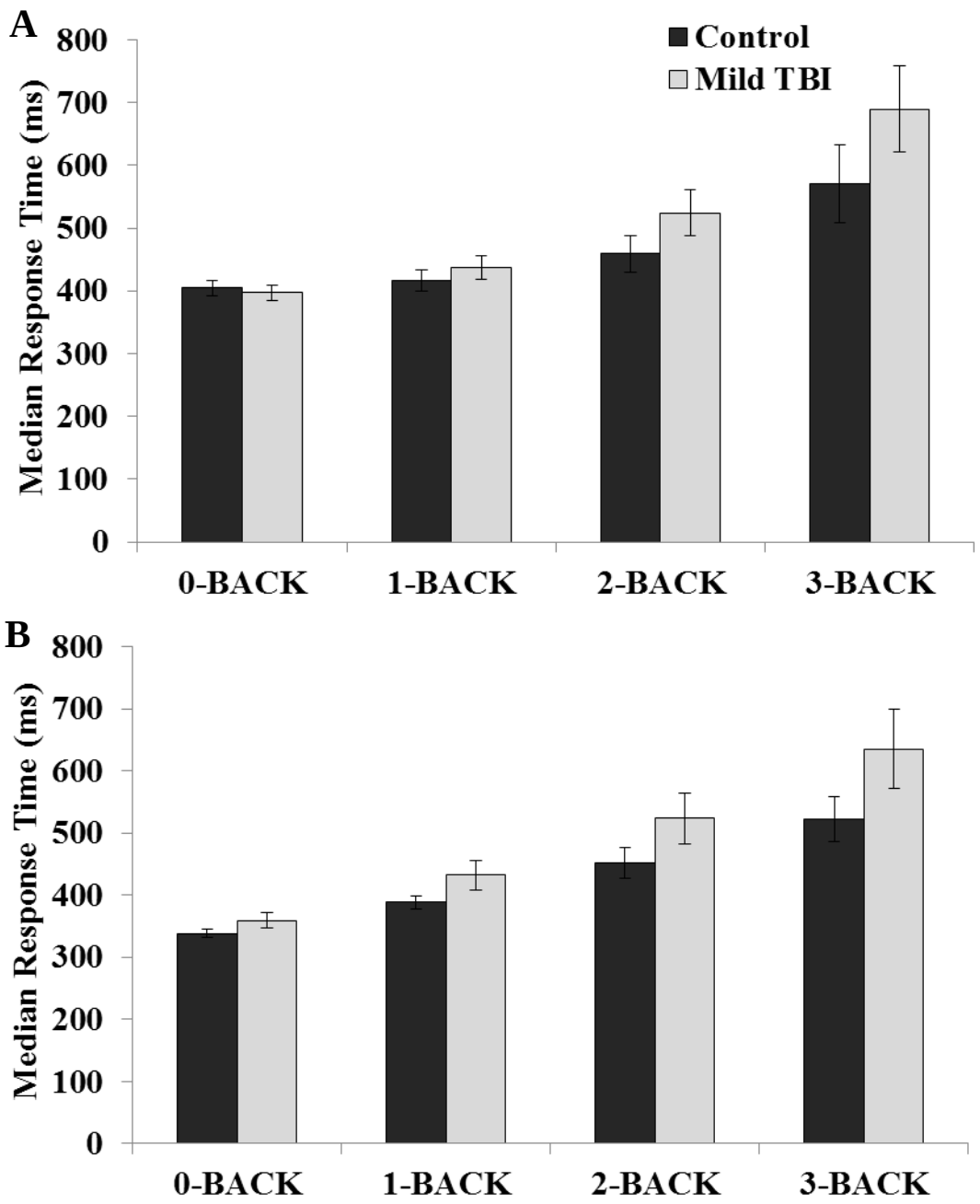

Figure 13. Experiment 3; Panel A: Median response time for control and mild TBI participants in each *n*-back load of the match condition. Panel B: Median response time for control and mild TBI participants in each *n*-back load of the non-match condition. Error bars represent standard error of respective means.

Neuropsychological and Self-report

There were no significant group differences on any neuropsychological task or self-report measure (see Table 9).

Table 9. *Means with Corresponding t-values and p-values for Neuropsychological Task and Self-Report Questionnaires. Standard Deviations in Parentheses.*

Task/Questionnaire	Controls	Mild TBI	*t*-value	*p*-value
Digit-Symbol (DS)	93.1 (13.3)	86.1 (17.3)	1.33	0.19
DS Assisted Recall	7.7 (1.8)	6.8 (2.6)	1.05	0.30
DS Free Recall	8.1 (0.9)	7.5 (1.4)	1.36	0.18
Digit Span Forward	8.9 (1.7)	9.5 (2.4)	-0.84	0.41
Digit Span Backward	8.2 (2.2)	8.8 (1.7)	-0.87	0.39
Trail Making A	15.9 (5.0)	17.0 (6.0)	-0.58	0.57
Trail Making B	38.6 (9.1)	37.9 (17.9)	0.15	0.89
Trail Making Errors B	0.8 (1.6)	0.3 (1.0)	1.17	0.25
ARCES	30.8 (5.0)	33.2 (7.5)	-1.13	0.27
MFS	27.9 (3.8)	30.1 (5.7)	-1.35	0.19
BDI	6.4 (4.1)	8.5 (5.3)	-1.27	0.21
STAI_State	29.5 (7.3)	30.8 (7.2)	-0.52	0.61
STAI_Trait	34.7 (7.8)	34.7 (7.8)	0.00	1.00
Rivermead Checklist	10.6 (6.0)	12.3 (8.5)	-0.64	0.53

Notes. ARCES = Attention-related Cognitive Error Scale; MFS = Memory Failures Scale; BDI = Beck Depression Inventory; STAI = State-Trait Anxiety Inventory.

Electrophysiological Analysis

Two 4 x 2 x 2 x 2 repeated-measures ANOVAs were conducted with *n*-back Load (0-, 1-, 2-, 3-back), Stimulus Type (match and non-match) and Electrode (CPz and Pz) as the within-subject factors and Group (controls and mild TBI participants) as the between-subject factor to examine P300 amplitude and latency. All ANOVAs used Greenhouse-Geisser adjusted degrees of freedom and planned contrasts used Bonferroni corrections for follow-up analyses.

P300 Peak Amplitude

A significant main effect of Stimulus Type revealed that participants had higher mean P300 amplitudes for match compared to non-match trials, F (1, 32) = 398.27, $p < 0.001$ (see Table 10). There was also a main effect of Group which showed that mild TBI participants had significantly lower mean P300 amplitudes compared to controls, F (1, 32) = 286.99, $p = 0.04$. These results were qualified by a Stimulus Type x Group interaction, which showed that mild TBI participants had significantly lower P300 amplitudes only for match trials, t (32) = 2.48, $p = 0.02$, but showed no difference relative to controls on non-match trials, t (32) = 1.64, $p > 0.10$ (see Figure 14). Group did not interact with any other variables.

Table 10. *Experiment 3; Mean P300 Peak Amplitude and Latency Measures for each Group in Match and Non-match Conditions, recorded from CPz and Pz Electrodes. Standard Deviations in Parentheses.*

	P300 peak amplitude							
	Control				Mild TBI			
	Match		Non-match		Match		Non-match	
n-back	CPz	Pz	CPz	Pz	CPz	Pz	CPz	Pz
0	9.64 (3.1)	10.31 (2.8)	4.63 (1.8)	4.87 (1.7)	7.75 (3.5)	8.91 (3.0)	3.39 (2.6)	4.06 (2.4)
1	9.15 (2.6)	10.10 (2.4)	3.98 (2.0)	4.87 (1.4)	6.53 (3.0)	7.89 (2.3)	2.41 (2.0)	3.89 (1.6)
2	7.91 (3.7)	8.29 (3.1)	3.82 (2.3)	4.89 (1.9)	5.71 (3.4)	6.56 (2.8)	2.96 (2.4)	4.63 (2.5)
3	6.88 (2.9)	7.78 (2.7)	2.96 (1.9)	4.10 (1.7)	4.56 (2.5)	5.93 (2.3)	1.96 (1.7)	3.18 (1.5)
	P300 peak latency							
	Control				Mild TBI			
	Match		Non-match		Match		Non-match	
n-back	CPz	Pz	CPz	Pz	CPz	Pz	CPz	Pz
0	366.7 (29.8)	352.4 (31.2)	366.4 (28.6)	354.3 (25.8)	363.9 (30.7)	359.0 (33.7)	374.1 (33.0)	350.6 (36.6)
1	351.5 (27.6)	344.6 (21.1)	362.8 (32.6)	354.4 (31.1)	352.6 (33.3)	345.2 (26.3)	362.5 (44.2)	348.8 (41.1)
2	343.0 (34.3)	341.8 (32.5)	365.4 (25.7)	352.6 (25.3)	358.9 (29.3)	357.3 (26.7)	351.7 (35.1)	348.0 (39.5)
3	348.4 (27.2)	348.1 (25.2)	366.3 (31.3)	348.7 (32.2)	352.3 (29.1)	355.4 (27.7)	359.3 (39.7)	344.6 (35.8)

Note. Mean P300 peak amplitudes (μV) and mean P300 peak latencies (ms).

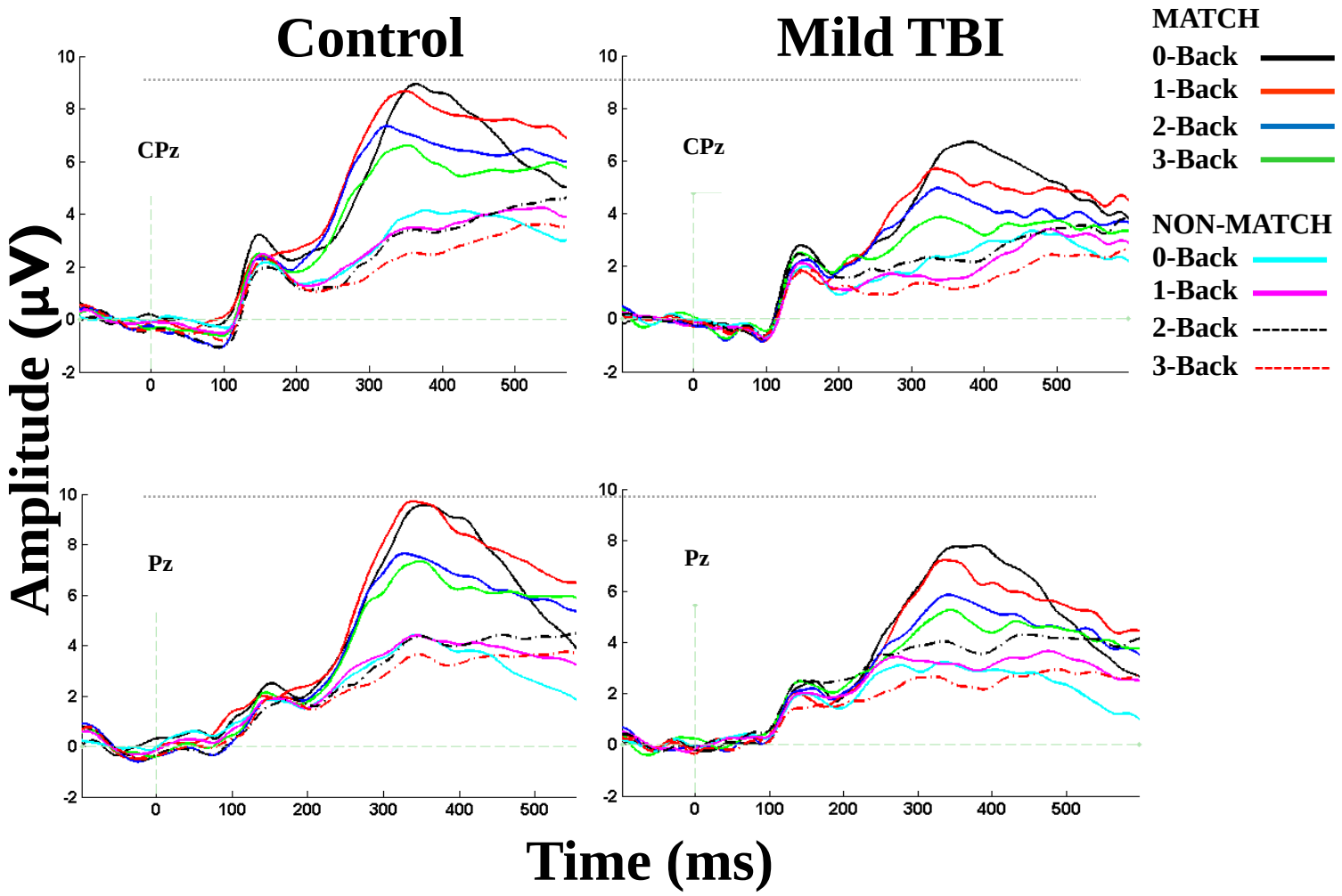

Figure 14. Mean group P300 components for each *n*-back load (0- to 3-back) across trial type conditions (match and non-match) recorded at CPz (top graphs) and Pz electrodes (bottom graphs).

There was a main effect of electrode, F (1, 32) = 25.07, $p < 0.001$, with higher average P300 amplitude recorded from Pz compared to CPz. The main effect of *N*-back Load was significant, F (3, 30) = 16.97, $p < 0.001$, and planned contrasts of interest revealed significant differences in P300 amplitude between 0- and 3-back, t (132) = 3.57, $p < 0.001$, a trend between 0- and 2-back, t (132) = 1.94, $p = 0.055$, and no difference between 0- and 1-back, t (132) = 1.05, $p = 0.30$. There was a significant Electrode x Stimulus Type x *N*-back Load interaction, F (3, 30) = 5.55, $p = 0.002$. Two separate 2 x 4 repeated-measure ANOVAs with Electrode as the within-subject variable, and *N*-back as the between-subject variable were conducted to examine P300 amplitudes separately for match and non-match conditions. There was a significant Electrode x *N*-back interaction for the non-match condition, F (3, 132) = 3.91, $p = 0.01$, but not for the match condition, F (3, 132) = 0.77, $p > 0.50$. Planned contrasts showed that the 3-back load had a lower mean P300 amplitude compared to the 2-back load for non-match stimuli at the Pz electrode, t (66) = 1.80, $p = 0.02$, but no differences were found between 0- and 1-back or 1- and 2-back loads. No significant differences were found across *n*-back loads for non-match stimuli at the CPz electrode.

P300 Peak Latency

A significant main effect of Electrode was found, F (1, 32) = 10.91, $p = 0.002$, such that the CPz electrode had longer latencies compared to the Pz electrode (see Table 10). Moreover, there was a significant Stimulus Type x Electrode interaction, F (1, 32) = 7.65, $p = 0.009$. Planned contrasts of interest were conducted to examine the latency within each electrode between match and non-match conditions and revealed no significant differences. Specifically, average match latency and non-match latency did not differ across groups at CPz, t (66) = -1.25, $p > 0.05$, or at the Pz electrode, t (66) = 0.25, $p > 0.05$. There were no main effects of *n*-back Load or Group and no other interactions were significant.

Correlations

As shown, P300 amplitude was significantly attenuated in mild TBI participants compared to controls during match trials of the repetition detection task, regardless of load. Even though groups did not differ on our behavioral measures, there is an obvious pattern showing that response times tended to increase at higher working memory loads compared to controls.

Moreover, as working memory loads increased to moderate and high loads, both electrophysiological and performance changes were evident compared to the lowest working memory load for control and mild TBI participants. As such, we were interested if P300 amplitude, a neural signature of available processing resources for target identification, was related to response processes (i. e., accuracy and response times).

In order to investigate the relation between P300 amplitude and accuracy rate, as well as P300 and response time, Pearson correlations were conducted separately for each group at every *n*-back load. For controls, significant negative correlations were found between P300 amplitude and response time for the 1-back condition, $r = -0.41$, $p = 0.02$, the 2-back condition, $r = -0.67$, $p = 0.002$, and the 3-back condition, $r = -0.62$, $p = 0.005$, but not the 0-back condition, $r = -0.27$, $p > 0.30$. For mild TBI participants, significant negative correlations were identified between P300 amplitudes and response time for the 2-back condition, $r = -.62$, $p = 0.009$ and the 3-back condition, $r = -0.55$, $p = 0.02$, but not for the 0-back, $r = -0.23$, $p > 0.3$ or 1-back condition, $r = 0.27$, $p > 0.30$. These results imply that 30 to 45% of the variance in participants' response times is accounted for by P300 amplitude during moderate to high working memory loads (2- and 3-back conditions). The relation between P300 amplitude and response time was also significant for controls in the 1-back condition, but this accounted for relatively less variance in response times (17%) compared to higher loads. The correlations between accuracy and P300 were not significant for either group at any of the *n*-back loads.

Due to the significant difference between groups on age and years of education, we correlated these variables with our main dependent variable that dissociated the groups: average P300 amplitude for match trials. Pearson correlations showed that neither age, $r = -0.31$, $p > 0.05$, nor education, $r = -0.22$, $p > 0.05$ correlated significantly with average P300 amplitude on match trials.

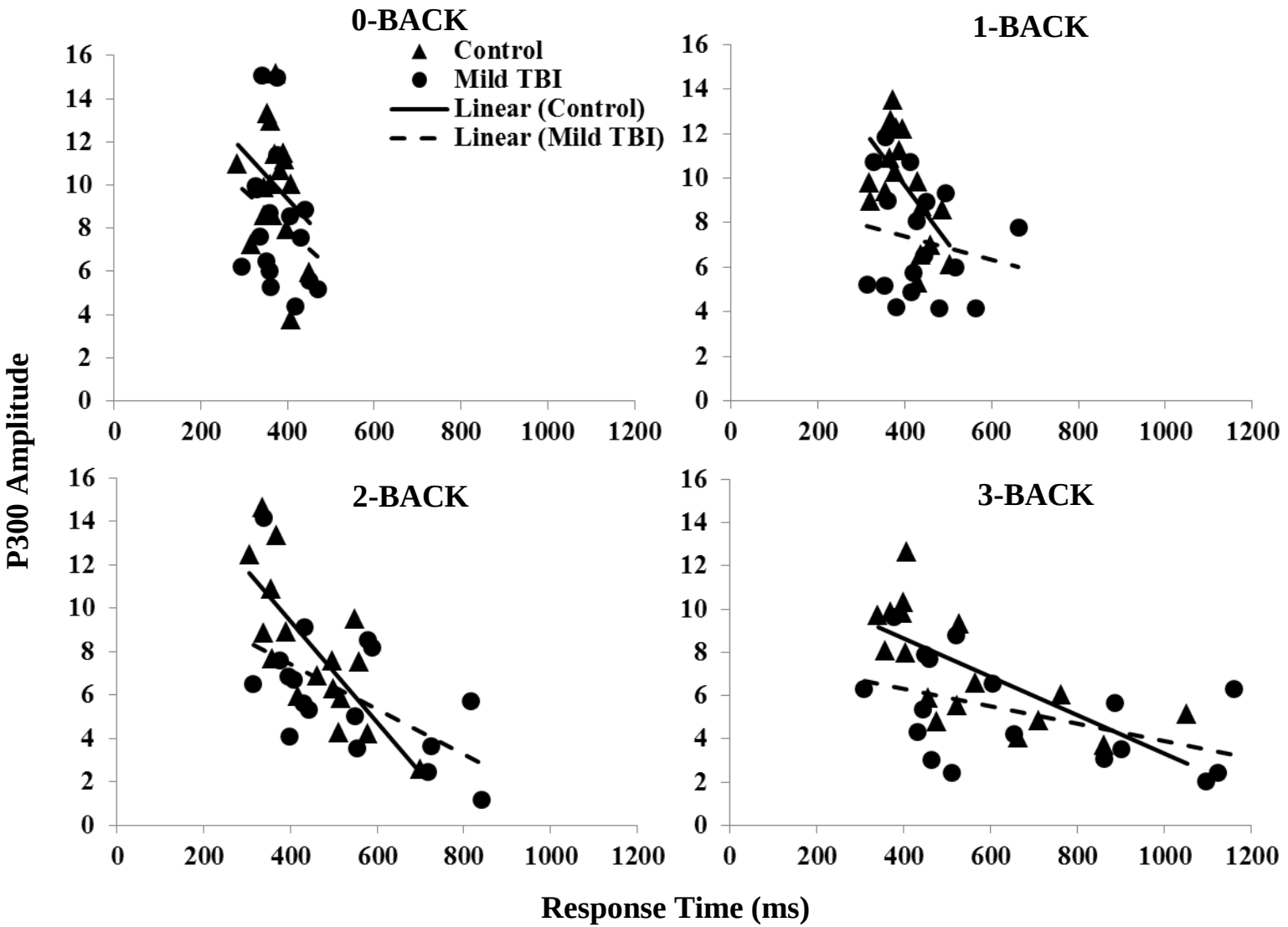

Figure 15. Experiment 3; Relation between P300 amplitude and response time for participants at each *n*-back load.

4.4 Discussion

The main finding in this study was that sensitive electrophysiological measures revealed subtle long-term changes in the time course of information processing during working memory functioning after mild TBI, despite normal performance on the *n*-back task, neuropsychological tests or self-report scales. Specifically, high functioning young adults who sustained their last mild TBI at least a year earlier, showed an average reduction in P300 amplitude during accurate target detection on an *n*-back working memory task compared to controls with no history of mild TBI. While both groups showed typical P300 amplitude decreases with increases in *n*-back load, the smaller average P300 amplitude recorded in mild TBI participants was independent of working memory load. Behaviorally, RT data showed a pattern in that mild TBI participants were slightly slower at responding to match stimuli as *n*-back load increased compared to controls.

To our knowledge, this is the first study to provide a possible neural mechanism for response slowing in that there was an inverse relationship between response times and P300 amplitude: as P300 amplitude decreased, both control and mild TBI participants' response times increased on moderate (2-back), and high (3-back) working memory loads. Pearson's *r* values show that while P300 amplitude only accounted for 17% of the variance in control response times to items 1-back, it accounted for 45% and 38% in control response times and 38% and 30% in mild TBI response times for 2-back and 3-back conditions, respectively. The current findings suggest that response times increase when there are fewer, or less efficient allocation of, processing resources (indexed by reduced P300 amplitude) available for target identification, especially evident during moderate to high working memory loads. Due to the significantly attenuated P300 amplitude in mild TBI participants across *n*-back loads, we suggest that less efficient allocation of processing resources may account for the slowing trends at moderate to high loads. While not significant, the longer average processing speeds in mild TBI participants at 2-back and 3-back loads should not be overlooked considering that slowing is the most consistent finding long after mild TBI (see Frencham et al., 2005).

Neurophysiological Changes after Mild TBI on Oddball Task

To our knowledge, this is the first report of neurophysiological changes during a working memory task in high functioning, asymptomatic university students with a history of 1-2 mild TBIs in their remote past. These findings are in line with reports of smaller P300 amplitudes observed at 6 months following a single mild TBI (Bernstein, 2002; Broglio et al., 2009; Dupuis et al., 2000; Segalowitz et al., 2001) and after multiple mild TBIs (De Beaumont et al., 2007; De Beaumont et al., 2009; Gaetz et al., 2000; Theriault et al., 2009) compared to non head-injured controls on sustained attention during standard oddball tasks. P300 amplitude has been conceptualized as a pool of available processing resources available for attention allocation to on-going tasks (see Polich, 2007 for review). Thus, these results, as well as those reported here, suggest that P300 reductions evident long-after mild TBI are indicative of either fewer available, or abnormal allocation of, processing resources for accurate target identification (see Duncan et al., 2005 for review).

Neurophysiological Changes after Mild TBI on n-back Task

As previously shown in the *n*-back task, as working memory demands increase, the demand on processing resources increases, leaving less available for stimulus classification and evaluation measured by the P300 (McEvoy et al., 1998; Watter et al., 2001). In the current study, we predicted that mild TBI participants may show larger decreases in P300 amplitude as processing loads increased compared to controls due to inefficient allocation of attentional resources. While P300 amplitude decreased in both groups as a function of increasing processing load, mild TBI participants did not show even larger decreases at high loads. Instead, the mild TBI group had average P300 amplitudes that were consistently smaller in amplitude compared to controls for correct target detections at all *n*-back loads. This suggests that mild TBI participants do not reallocate a greater amount of processing resources away from target identification to working memory processing demands when loads are high compared to controls, as indexed by P300 amplitude. Instead, it seems as though a mild TBI results in fewer processing resources available for target detection compared to controls even on simple sustained attention tasks (e. g.,

0-back load), and that these resources, as measured by P300 amplitude, are reallocated to increasing working memory demands to the same extent as controls.

The Long-Term effects of Mild TBI: Neurophysiological and Behavior Measures

Similar to past reports (De Beaumont et al., 2007; 2009; Broglio et al., 2009; Gaetz et al., 2000; Theriault et al., 2009), electrophysiological abnormalities were detected long after mild TBI in the present study without evidence of any observable behavioral deficits. These findings suggests that, although limited or inefficient, the available pool of processing resources is sufficient to accurately detect target stimuli during simple sustained attention tasks, as well as during high working memory demands. This is the first study, to our knowledge, to provide evidence for a relationship between available resources during early cognitive processes and later stage response processes. Indeed, strong negative correlations were found between P300 amplitude and response times 2-back and 3-back loads, in both control and mild TBI participants.

As previously mentioned, a pattern in the data shows that mild TBI participants were increasingly slower than controls at accurately detecting target stimuli as working memory load increased. In lieu of the fact that the P300 amplitudes corresponding to correct target identification were also smaller in the mild TBI group, we suggest that mild TBI-related deficits in cognitive resource allocation may result in response slowing when processing demands are increased. However, in the current study's sample it seems as though these demands did not exceed the processing capacity of the limited or inefficient resource pool in mild TBI participants as their performance was not statistically different from controls. Future research should continue to correlate P300 and response times during working memory tasks as a means to examine the effect of long-term mild TBI-related neural changes on cognitive functioning.

P300 latency differences were not found between mild TBI and control groups in the current study, further specifying the precise changes that occur in the early stages of information processing at least 1 year after mild TBI. We suggest a remote mild TBI results in residual deficits in resource allocation during target classification (P300 amplitude), not in delayed target classification (P300 latency). It is this inefficient allocation of processing resources which leads

to delays further down the information processing cascade, or in other words, leads to delays in accurate target detection. We suggest that P300 amplitude is more closely related to response slowing than accuracy rates as significant correlations were not found between the proportion of correct responses and P300 amplitude at any *n*-back load.

Behavioural and Neurophysiological Changes after Mild TBI using Dual-Tasks

In line with past reports (Belanger et al., 2005; Binder & Rohling, 1996; Frencham et al., 2005; Rohling et al., 2011), the standard neuropsychological tests of attention, working memory, processing speed, and short-term memory used in the present study did not distinguish the mild TBI and control groups. Previous studies have also reported no cognitive impairments when mild TBI participants perform a single oddball task, but show information processing slowing (Cicerone, 1996; Pare et al., 2009) and more working memory errors (Pare et al., 2009) when simultaneously performing a working memory task. Given these non-significant differences on basic neuropsychological and cognitive paradigms, ERP data in our study were used to better elucidate the relationship between processing capacity after mild TBI and the effect of increasing cognitive demand.

P300 amplitude decreases have been recorded in the absence of performance decrements on simple tone discrimination oddball task at least a year post-mild TBI, but when participants were required to concurrently perform a working memory task, behavioral deficits were detected (Bernstein, 2002; Segalowitz et al., 2001). However, similar to the present study, the authors' prediction that increasing task demand would result in an even further decrease in P300 amplitude in mild TBI participants compared to controls were not supported. In fact, despite differences in P300 between groups on the single oddball tasks, the smallest or no differences were evident in the dual-task conditions. It has been suggested that this may be due to a floor effect and that increasing cognitive demands on the secondary task reduces the cognitive resources available for the primary task to floor levels (Bernstein, 2002). The average P300 amplitude in mild TBI participants in the current study may have reach floor, preventing an even further reduction compared to controls on the higher working memory loads. Neuroimaging techniques have also been successful at identifying changes in neural processing due to mild TBI

and several studies have provided compelling evidence for compensatory neural mechanisms underlying cognitive performance when processing demands are exceeded.

Functional Changes after Mild TBI: Neural Imaging

That increasing working memory demand in the *n*-back task did not distinguish mild TBI from control performance is not unique to the current study. Even within the acute stages after mild TBI (< 3 months post-injury), McAllister and colleagues (1999; 2001) reported no differences in accuracy between groups; response time data was not reported. Similar to the present study, this group did show neural processing differences despite behavioral differences. Specifically, using fMRI, they reported a greater extent of activation in bilateral frontal and parietal regions in mild TBI participants at moderate processing load (2-back) compared to controls. They concluded that mild TBI participants may recruit additional processing resources to compensate for processing deficiencies. More recent research has also showed additional brain activation without performance decrements in mild TBI participants 1 month post-injury, not observed in controls, during a spatial navigation working memory task (Zhang et al., 2010). In the current study, the fact that groups did not show performance differences, even though mild TBI participants had smaller average P300 amplitudes, could also be due to recruitment of extra resources in order to compensate for the inefficient processing during target detection.

Given the effect of a remote TBI on the brain, suggested in the current experiment, the following experiment was conducted to examine how such an effect might interact with aging, a natural process also known to compromise brain functioning. The purpose of Experiment 4 was to study a group of older adults at least 20 years post-injury to examine whether a remote history of TBI compounds cognitive functions already known to decline due to healthy aging. Specifically, we compared cognitive performance in a group of older adults with a history of TBI sustained and average of 50 years prior to testing to that of older adults with no history of head injury.

Chapter 5

Experiment 4: Do Long-Term Cognitive Effects of TBI Compound Normal Age-related Declines?

5.1 Introduction

Similar to self-reports of lingering memory problems after TBI (Alves, 1993; Arcia & Gualtieri, 1993; Meares et al., 2011; Oddy et al., 1985; Vanderploeg et al., 2007), healthy older adults frequently report memory difficulties as their #1 cognitive complaint (Bassett & Folstein, 1993; Reid & Maclullich, 2006). A review of the memory literature specific to each population will follow to highlight aspects of memory that are affected by both TBI and healthy aging, as well as those that are spared.

Explicit measures of episodic memory, such as immediate and delayed recall tasks, have revealed both long lasting TBI-related (Baddeley et al., 1987; Bennett-Levy, 1984; Brooker & George, 1984; Brooks, 1976; Hannay et al., 1979; Haut & Shutty, 1992; Kersel et al., 2001; Reid & Maclullich, 2006; Vakil et al., 1992; Zec et al., 2001) and age-related deficits (Craik & McDowd, 1987; La Voie & Light, 1994; Park & Shaw, 1992; Park, Polk, Mikels, Taylor, & Marshuetz, 2001; Rabinowitz, 1984; Rabinowitz, 1986; Schonfield & Robertson, 1966). In contrast, skilled learning and priming effects, measures of implicit memory, have frequently been shown to be unaffected by TBI (Perri et al., 2000; Schmitter-Edgecombe, 1996; Vakil & Tweedy, 1994; Vakil & Oded, 2003; Watt et al., 1999) and healthy aging (Balota & Ferraro, 1996; Howard & Howard, 1992; Light, Singh, & Capps, 1986; Light & Singh, 1978; Moscovitch, Winocur, & McLachlan, 1986). Such findings suggest that individuals with a remote TBI (young to middle-aged) and healthy older adults perform at healthy young control levels on tasks that require little conscious awareness, but experience performance deficits when consciously recollecting past events or information.

As mentioned in the general introduction, just like the differences observed between young adults with and without a past TBI, performance differences between older and younger adults become larger with increasing task complexity (Salthouse & Babcock, 1991). Several

studies provide evidence for performance decrements on working memory tasks that tap into executive processes in young to middle aged TBI participants (Azouvi et al., 1996; Bublak et al., 2000; Christodoulou et al., 2001; Haut et al., 1990; McDowell et al., 1997) and in healthy older adult participants compared to young controls (Bopp & Verhaeghen, 2007; Dobbs & Rule, 1989; Park et al., 2002; Salthouse & Babcock, 1991). For instance, dual-task paradigms have been useful in detecting persistent impairments after TBI (Leclercq et al., 2000; McDowell et al., 1997; Park et al., 1999) and result from natural aging (Glass et al., 2000; Kramer, Hahn, Irwin, & Theeuwes, 1999; Madden et al., 1996; Mayr, 2001; Plude & Hoyer, 1986). On the other hand, relatively simple working memory tasks that involve short-term storage without manipulation have been shown to be spared in both individuals with TBI (Brooks, 1976; Haut et al., 1990) and healthy older adults (Dobbs & Rule, 1989). As such, the authors suggest that memory functions requiring executive processes are more susceptible to age (Dobbs & Rule, 1989) and TBI (Levine et al., 2000; Seignourel, Robins, Larson, Demery, Cole, & Perlstein, 2005) compared to components responsible for storage.

Other memory processes with an executive component have also been shown to be similarly affected by TBI and age. Source memory, for instance, is the ability to monitor and remember contextual details that are secondary to the studied event, such as the temporal order or the modality in which information was viewed (Hashtroudi, Johnson, & Chrosniak, 1989). Previous studies have directly compared the effect of aging and TBI on memory functioning and found that memory for judging the frequency of word occurrence (Tweedy & Vakil, 1988) and the temporal order of words (Vakil & Tweedy, 1994) were equally disrupted at least one year following severe TBI in young and in healthy older adults compared to young controls. Compared to the young controls, both older adults (Kensinger & Schacter, 1999; Norman & Schacter, 1997; Tun, Wingfield, Rosen, & Blanchard, 1998; Watson, Balota, & Sergent-Marshall, 2001; Watson, McDermott, & Balota, 2004) and individuals with TBI (Ries & Marks, 2006) show an increase in both erroneous recall and in false recognition of distracting information. Other research shows an increased false alarm rate, as a function of repetition, compared to young controls (Jacoby, 1999). For example, older adult (Bartlett, Strater, & Fulton, 1991) and TBI participants (Dywan, Segalowitz, Henderson, & Jacoby, 1993) were less able to

discriminate between nonfamous and famous faces when the nonfamous faces were repeatedly presented.

In our recent work, we have directly compared the effects of aging and TBI on the ability to reject highly familiar but distracting information on a recognition test (Ozen, Skinner, & Fernandes, 2010). Here we suggest that older adults and young adults with TBI have overlapping cognitive profiles, such that their ability to correctly recognize target information is intact, yet their ability to reject familiar distracting information is similarly compromised. These results suggest that increased familiarity with distracter items increases memory errors made by older adults and young people with TBI. Moreover, in the same study, neuropsychological assessment showed a similar age- and TBI-related deficit in cognitive flexibility (Trail Making B minus A scores), which was related to increased difficulties in discriminating distracting information from target information. We suggested that both groups may share a common executive dysfunction. Other studies suggest that deficits in executive processes found in older adults may be a cause of memory disruption as these individuals have more *difficulty inhibiting* irrelevant information (Engle, 2002; Hasher & Zacks, 1988; May, Kane, & Hasher, 1995; McDowd & Shaw, 2000).

The evidence that is perhaps the most widely regarded as supporting an age-related decline in inhibition has been obtained from investigations of a non-memory-related measure, the Stroop task. Several experiments have reported that Stroop interference is disproportionately greater for older adults than for younger adults (Brink & McDowd, 1999; Hartley, 1993; Spieler, Balota, & Faust, 1996; Verhaeghen & De Meersman, 1998). Moreover, problems with inhibiting automatic responses have also been shown in a TBI population ranging from mild to severe, at least 3 months post-injury, as participants showed impairments on the incongruent, but not congruent or neutral condition of the Stroop task (Potter et al., 2002; Seignourel et al., 2005; Solbakk et al., 1999). Deficits in inhibitory capacities have recently been reported in healthy retired athletes who sustained 1-5 mild TBIs at least 30 years prior to study participation. Compared to non-concussed retired athletes, those with past head injuries showed decrements in performance on the incongruent condition of the arrow Flanker task (arrow cues are incongruent with position of subsequently presented target), but not on the congruent conditions (De Beaumont et al., 2009). This persisting deficit 30 years after the last mild TBI further supports

the prediction that remote head injuries may compound healthy age-related executive dysfunctions.

In the current study we were specifically interested in testing the hypothesis that a remote TBI in otherwise healthy older adults results in lasting cognitive impairments above and beyond those due to natural age-related decline. To address this question, we compared different aspects of cognitive functioning using tasks with varying levels of executive processing requirements, between older adults who have and have not sustained a remote TBI. Specifically, we manipulated the amount of executive processes necessary for successful working memory performance by administering the same Repetition Detection task from Experiment 2a, as well as a battery of neuropsychological tasks measuring working memory, processing speed and selective attention.

We hypothesized that older adults who sustained a remote TBI would perform worse than non head-injured older adult controls on the repetition detection working memory task. These differences were predicted to be limited to the high-load condition, and manifested in TBI participants as lower accuracy scores compared to controls. We also expected an overall effect of slowing on this task, regardless of condition, as previously shown in young adults who sustained a mild TBI participants (Experiment 2a) and healthy older adults (Bopp & Verhaeghen, 2007) compared to young controls. On the standard neuropsychological test battery, we expected deficits to appear on tasks requiring executive processing, such as Trail Making B, Digit-span Backwards and the incongruent condition of the Stroop task, but not on tasks requiring little or no executive control, such as Digit-span Forward, Trail Making A, or the congruent or neutral conditions of the Stroop task. The Mini-Mental State Exam was also administered as a screening tool for neurological impairment and both of older adults groups were predicted to score within the normal range on this task, as all participants in this study were healthy, independently functioning, volunteers. Lastly, we did not expect groups to differ on our cognitive or affective self-report measures as previous research shows no differences between older adults with and without a past TBI on similar measures (Klein, Houx, & Jolles, 1996).

5.2 Methods

Participants

Participants were recruited from the Waterloo Research Aging Pool (WRAP) and received token monetary remuneration for their participation. WRAP is a database of healthy seniors in the Kitchener-Waterloo area recruited by means of newspaper ads, flyers in community centers, and through local television segments featuring research at the University of Waterloo. During the initial WRAP recruitment procedure, the research coordinator administered a 10-minute questionnaire over the phone to gather demographic and health information. Researchers could then use this information as inclusion/exclusion criteria for their cognitive experiments. The current study used the database to screen for neurological disorders, untreated psychological problems and to set specific criteria pertaining to handedness, visual and auditory health, and head injury status.

A total of 24 older adults were included in this study; 9 had sustained a past TBI (6 female; see classification scheme below) and 15 reported no history of head injury (9 female). The mean age was 73.87 (*SD* = 7.61) for control participants and 73.67 (*SD* = 7.71) for TBI participants, which did not differ significantly, t (22) = 0.06, $p > 0.05$. The mean number of years of education was 14.80 (*SD* = 2.0) for control participants and 14.01 (*SD* = 2.24) for TBI participants, which also did not differ significantly, t (22) = 0.84, $p > 0.05$. All participants were fluent English speakers, and had normal or corrected-to-normal hearing and vision, could read and write unassisted, and were right-handed. All participants reported they were free from any neurological disorders or untreated psychological problems at the time of testing. Two TBI participants reported that they were currently on anti-depressant medication and were free from any depressive symptoms. All participants completed the Mini-Mental State Exam (MMSE;(Folstein, Folstein, & McHugh, 1975)) at the beginning of the experimental session in order to screen for gross neurological conditions. Both the control (*M* = 29.33, *SD* = 0.62) and TBI groups (*M* = 28.67, *SD* = 1.00) had scores that were at least 27/30 or above, indicating that they were free from gross neurological impairment (Folstein, Folstein, & McHugh, 1998).

Classification and severity of TBI

A TBI was defined as any strike to the head or any acceleration/deceleration force (i.e., whiplash; Kay et al., 1993) that resulted in a loss of consciousness. Participants who reported brain damage for a reason other than a TBI (e. g., stroke) were not included in the study. Severity of TBI was classified by participants' self-reported duration of loss of consciousness (LOC) and post-traumatic amnesia (PTA). The TBI was labeled as "mild" if LOC did not exceed 30 minutes and PTA was no longer than 24 hours (Kay et al., 1993), "moderate" if LOC was between 30 min and 6 hr or PTA between 1 and 7 days (Seignourel et al., 2005), and "severe" if LOC was more than 6 hr or PTA of more than 6 days (Seignourel et al., 2005). Using these criteria, 3 participants sustained 2 past head injuries, and 6 had a history of 1 head injury. Of all head injuries, 4 were classified as mild, 4 as moderate, and 3 as severe (see Table 11). Time since injury ranged from 23 to 73 years (M = 51.54, SD = 16.32). With the exception of two head injuries, all participants reported that they sought medical attention immediately following the incident. Of these participants, three underwent a brain scan (i. e., Computed Tomography (CT) or MRI (Magnetic Resonance Imaging)), all showing unremarkable results, four did not have brain scans and two do not recall if they did or not.

Table 11. *Experiment 4; Demographic and Head Injury Details for TBI Participants.*

Gender	Age	Education	TSI (yrs)	LOC (min)	PTA (hours)	LOH (days)	Severity	Cause of Injury
M	80	16.0	73[1]	--	--	4 weeks	--	*Run over by car*
			5[2]	1 hour	--	Overnight	moderate	*Fell down stairs*
F	84	17.0	46[1]	5-10 min	Incident	No	mild	*Car accident: landed in ditch*
			37[2]	20 min	Incident	3-4 days	mild	*Car accident: Rear-ended*
F	74	13.0	58	5 days	Incident	2 weeks	severe	*Car accident*
F	66	16.5	49	15 min	No	6 days	mild	*Car accident: T-bone crash*
M	68	16.0	43[1]	1 hour	No	Few hours	moderate	*Assault: Direct hit to head*
			37[2]	1 hour	No	Few hours	moderate	*Assault: Direct hit to head*
M	72	12.0	60	Few min	Appx. 1 hr	Few hours	mild	*Fell out of car and hit head*
F	76	12.0	--	45 min	No	Overnight	moderate	*Fell down stairs head first*
F	82	12.0	67	5 min	No	No	mild	*Riding bike and hit by truck*
F	61	12.0	23	Days	Week prior	Yes –length?	severe	*Head went through windshield*
Mean	***19.83***	***14.17***	***51.54***					
SD	*1.43*	*1.10*	*16.32*					

Note. TSI = Time since Injury; LOC = Length of Unconsciousness; PTA = Post-traumatic Amnesia; LOH = Length of Hospitalization. Superscripts (1 or 2) in TSI column indicate the first and second TBI details: A total of three participants experienced 2 TBIs.

Participant Exclusion

In order to confirm the responses provided by participants during the initial recruitment phone interview, participants were asked a subset of demographic and health-related questions in person, by the researcher, at the start of the experiment. If inconsistencies were found between the two questionnaires, participants' data were excluded from all analyses. This resulted in data from two control participants being excluded from analyses, as they both reported, in person, that they had experienced a hit to the head in the past. Data from a total of four TBI participants were excluded from the study due to answers provided on the in-person-questionnaire: one was left-handed, one did not lose consciousness following the TBI, one had a history of stroke, and one had epilepsy. Thus analyses presented below are from 15 control and 9 TBI participants.

Materials

Repetition Detection Task

The Repetition Detection working memory task from (Bopp & Verhaeghen, 2007) was adapted for use in our study and was the same task that was administered in Experiment 2a.

Neuropsychological Tests

Working memory Span was assessed using the Digit-span forward and backward tasks (Wechsler, 1997). The Trail-making A and B tests (Reitan & Wolfson, 1985) were used to examine processing speed and cognitive flexibility, respectively. Performance on Trial 1 of List 1 of the California Verbal Learning Test (CVLT; Delis et al., 1987) was used to obtain a measure of immediate verbal memory.

Self-Report Scales

All participants completed the demographic/health form, Beck Depression Inventory (BDI; Beck et al., 1996), State-Trait Anxiety Inventory (STAI; Spielberger et al., 1970), the ARCES and MFS (Carriere et al., 2008).

Computer Tasks

Participants completed the Repetition Detection task and a computerized version of the Stroop task (see methods of Experiment 2a for details).

Experiment Procedure

All participants began the experiment by reading the Information Letter, and signing the Consent form. The researcher then asked all participants questions from the demographic/health questionnaire to obtain additional details about their head injury, should they have had one, and to confirm answers on the prescreen questionnaire. Next, participants completed the MMSE followed by the Repetition Detection task, with the low-load condition always administered prior to high-load. Participants then completed the Digit-Span, Trail Making, and trial 1 of the CVLT. Next, the STAI and BDI were administered, followed by the Stroop task, the ARCES and the MFS. Finally, the researcher provided participants with feedback sheets.

5.3 Results

Repetition Detection Task

Two repeated-measure analysis of variance (ANOVAs) with Load as the within-subject variable (low- and high-load) and Group as the between-subject variable (control and TBI) were used to examine accuracy and response times on the repetition detection task.

Hit Rate

Hit rate was calculated by dividing each participant's total number of correct detections by 20, the maximum number of correct responses. These proportions were averaged across participants in each group to yield means for control and TBI groups. As predicted, there was a main effect of Load, F (1, 22) = 186.86, $p < 0.001$, such that participants' mean hit rate was higher in the low-load, $M = 0.90$, $SD = 0.08$, compared to high-load condition, $M = 0.51$, $SD = 0.13$, regardless of group membership (see Figure 16). There was no main effect of group, F (1, 22) = 0.33, $p > 0.50$, and no interaction between Group and Load condition, F (1, 22) = 1.59, $p > 0.20$.

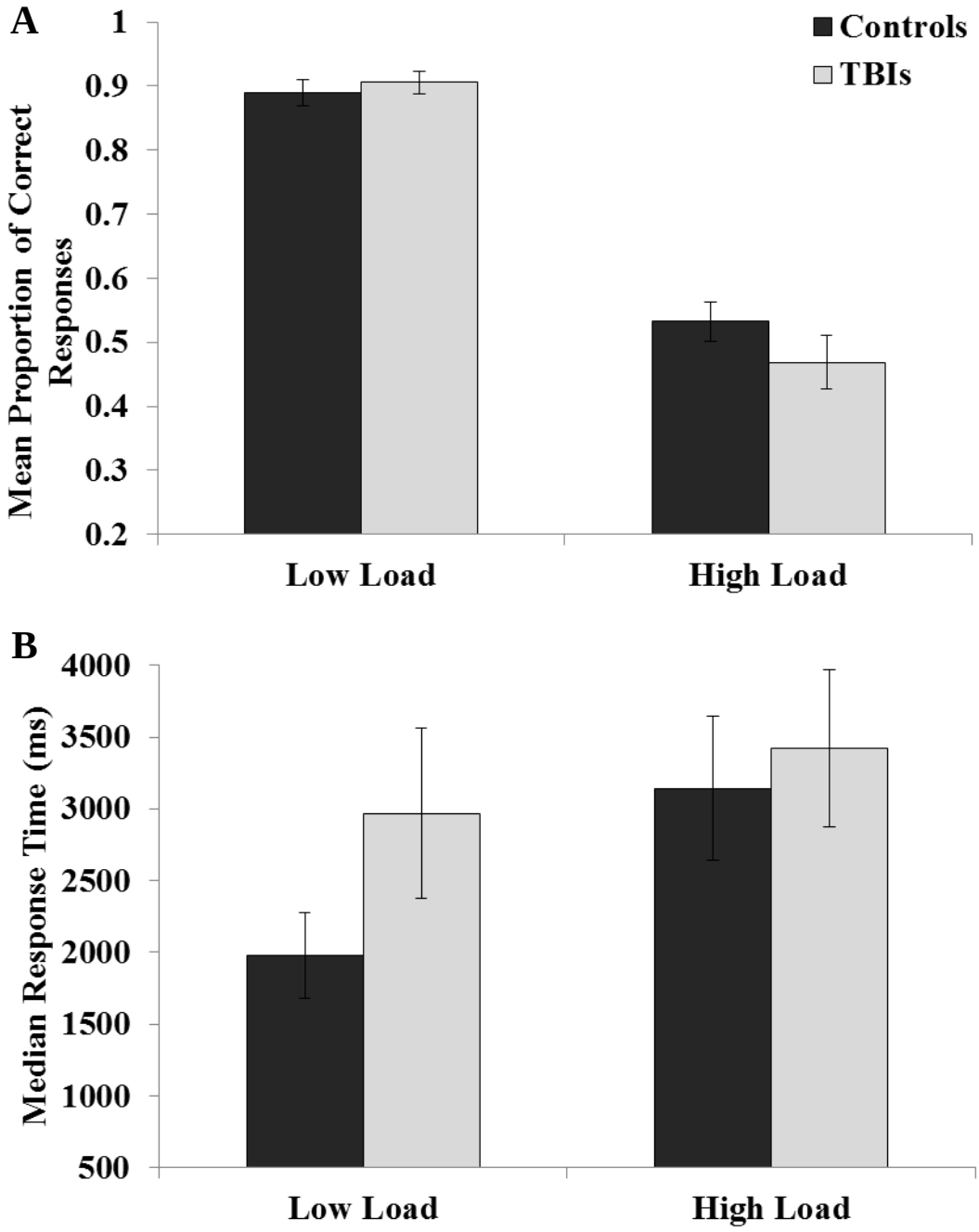

Figure 16. Experiment 4; Panel A: Mean proportion of correct responses made by control and mild TBI participants in the Low Load and High Load conditions. Panel B: Median response times for control and TBI participants in the Low Load and High Load conditions. Error Bars are standard errors for respective means.

Response Times

For each participant, the median response time was calculated for accurate trials in both the low- and high-load conditions. Following this, group mean response times were calculated by averaging individual median response times in each condition. In line with our hypothesis, participants had significantly slower response times, F (1, 22) = 8.65, $p < 0.01$, in the high-load, M = 3243.25 ms, SD = 1951.36, compared to low-load condition, M = 2349.50 ms, SD = 1725.17, regardless of group membership (see Figure 16). There was no main effect of group, F (1, 22), $p > 0.40$, and no group by condition interaction, F (1, 22) = 1.85, p = 0.19.

Computerized Stroop Task

Stroop accuracy and median response times were analyzed using two repeated-measure ANOVAs, with Trial Type as the within-subject variable (congruent, incongruent, and neutral) and Group as the between-subject variable (control and TBI). Greenhouse-Geisser corrections were used for both analyses. For the accuracy analysis, there was a main effect of Trial Type, F (2, 44) = 9.30, $p < 0.01$, regardless of group membership, whereby participants had higher mean accuracy on congruent (M = 0.99, SD = 0.02) compared to incongruent trials (M = 0.97, SD = 0.04), t (23) = 3.31, $p < 0.01$ (see Figure 17). There was also a main effect of Group, F (1, 22) = 7.15, $p < 0.05$, such that control participants had significantly higher average scores (M = 0.99, SD = 0.02) compared to TBI participants (M = 0.97, SD = 0.04), regardless of condition. Moreover, a significant Group x Trial Type interaction emerged, F (2, 44) = 4.72, $p < 0.05$. Follow-up independent t -tests showed that this interaction was due to decreased accuracy performance in TBI participants (M = 0.94, SD = 0.06) only in the incongruent Trial Type compared to controls (M = 0.98, SD = 0.02), t = 2.88, $p < 0.01$.

For response times, a significant main effect of Trial Type was found, F (2, 44) = 10.56, $p < 0.05$). Specifically, participants had slower response times in the incongruent (M = 629.30, SD = 162.29) compared to the congruent (M = 563.30, SD = 121.32), t (22) = 3.42, $p < 0.01$, and neutral condition (M = 572.24, SD = 118.45), t (3.15), $p < 0.01$ (see Figure 17).

No main effect of Group, F (1, 22) = 0.02, p > 0.89, or Group x Condition interaction, F (2, 44) = 0.56, p > 0.50 was found.

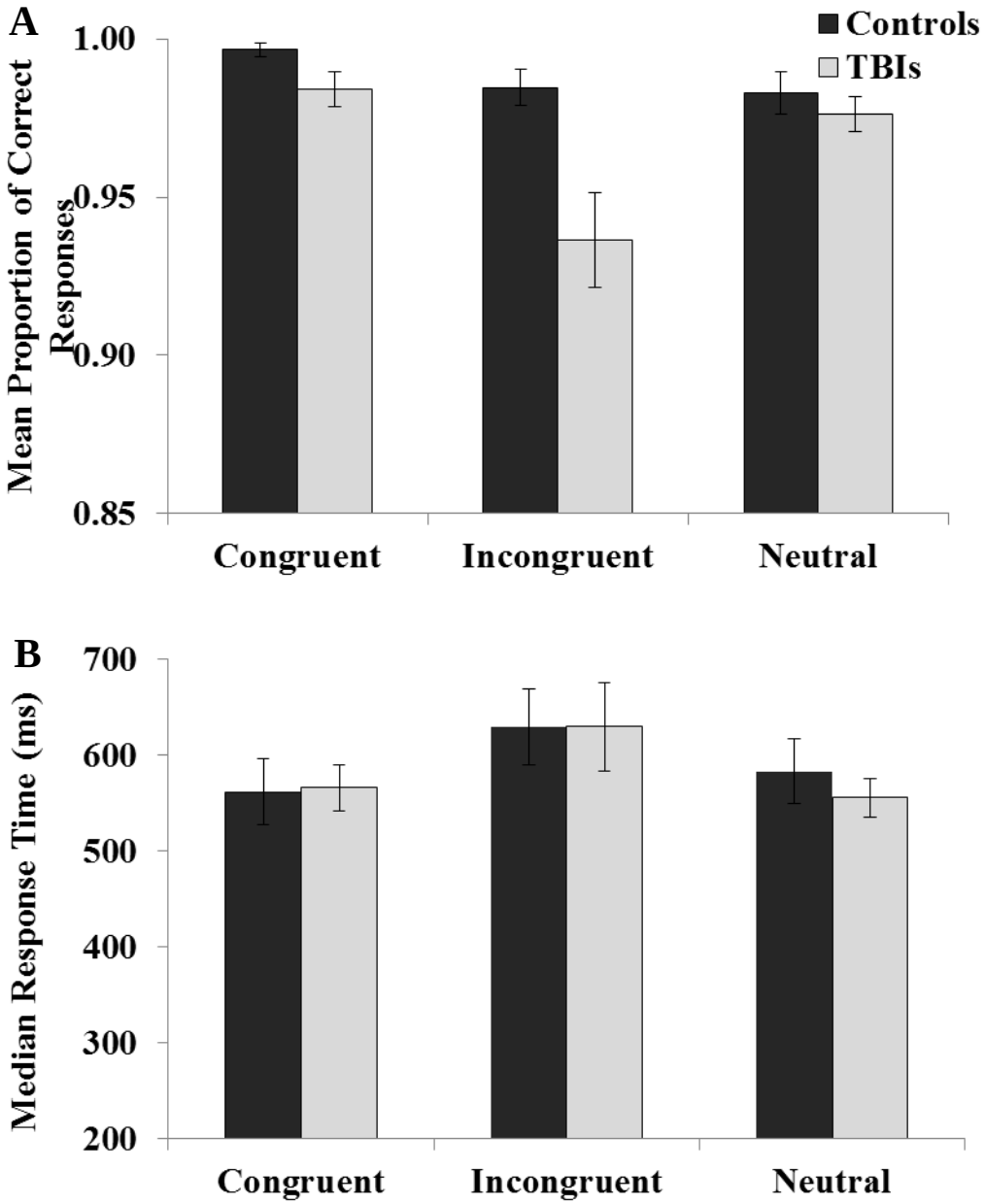

Figure 17. Experiment 4; Panel A: Mean proportion of correct responses made by control and TBI participants in congruent, incongruent and neutral conditions. Panel B: Mean response times for control and TBI participants in the congruent, incongruent and neutral condition. Error bar represent standard error of respective means.

Self-report Questionnaires and Neuropsychological Tests

Independent-samples *t* tests were used to compare group means on all self-report scales (ARCES, MFS, STAI, and BDI) and neuropsychological tests (MMSE, Digit Span Forward and Backward, Trail Making A and B, and CVLT trial 1). Even though both groups scored above 27/30 on the MMSE, suggesting normal neurological functioning, TBI participants scored significantly lower (M = 28.67, SD = 1.00) compared to controls (M = 29.33, SD = 0.61), t (22) = 2.03, p = 0.05. While no significant differences were observed on standard timing measures on the Trail Making task, number of errors on Trails B showed group differences: TBI participants committed significantly more errors (M = 1.44, SD = 1.88) compared to controls (M = 0.20, SD = 0.56), t (22) = -2.42, $p < 0.05$ (see Figure 18).

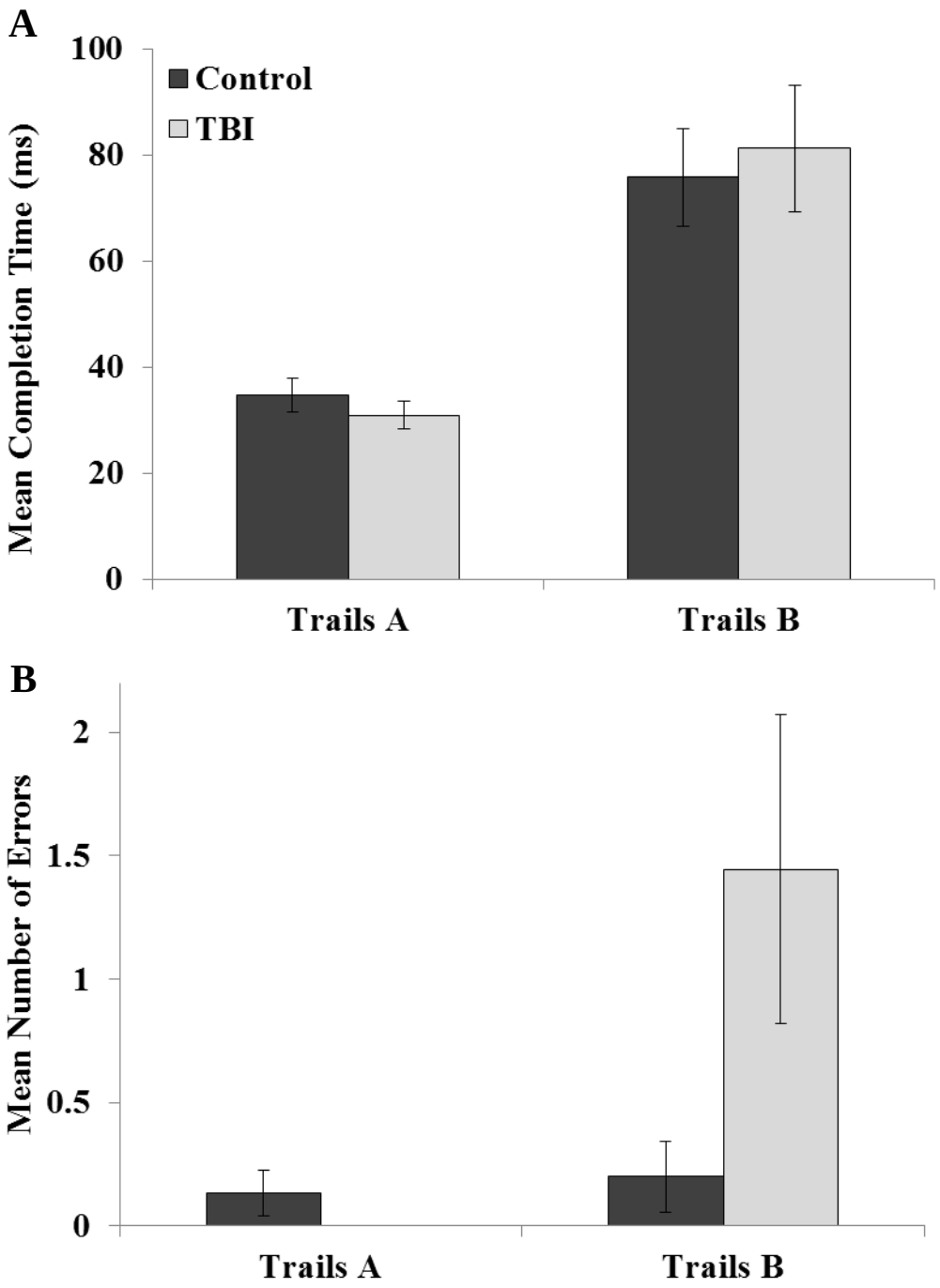

Figure 18. Experiment 4; Panel A: Mean completion time for control and TBI participants to complete Trails A and B. Panel B: Mean number of errors made by controls and TBI participants when completing Trails A and B. Error bars represent standard errors of respective means.

No differences between groups were found on the other neuropsychological tasks or self-report scales used to measure cognitive functioning (see Table 12). However, significant group differences did emerge on the State-trait Anxiety Inventory. Curiously, control participants reported higher levels of state anxiety (M = 34.53, SD = 9.09) compared to TBI participants (M = 27.44, SD = 3.88), t (22) = 2.21, $p < 0.05$. The same pattern was evident for trait anxiety (M = 34.87, SD = 7.01) with controls reporting higher anxiety levels compared to TBI participants (M = 28.89, SD = 4.28), t (22) = 2.30, $p < 0.03$.

Table 12. *Neuropsychological Task and Self-Report Questionnaire Results. Mean Values with Standard Deviations in Parentheses.*

Task/Questionnaire	Control	TBI	*P*-value
Mini-Mental State Exam	29.33 (0.62)	28.67 (1.00)	**0.05***
Digit Span Forward	8.27 (2.28)	7.78 (1.56)	0.58
Digit Span Backward	7.67 (2.16)	6.78 (1.92)	0.32
Trail Making A	34.70 (12.10)	30.85 (7.90)	0.41
Trail Making B	75.79 (35.66)	81.19 (35.73)	0.72
Trail Making A Errors	0.13 (0.35)	0.00 (0.00)	0.27
Trail Making B Errors	0.20 (0.56)	1.44 (1.88)	**0.02***
CVLT Trial 1	7.20 (3.05)	6.56 (2.83)	0.61
ARCES	30.47 (4.16)	31.67 (4.39)	0.51
MFS	29.13 (5.33)	29.44 (3.74)	0.98
STAI (state)	34.53 (9.09)	27.44 (3.88)	**0.04***
STAI (trait)	34.87 (7.00)	28.89 (4.28)	**0.03***
BDI	6.80 (4.86)	6.11 (6.19)	0.76

Notes. Values represented are mean group scores (standard deviations in parentheses). Items in bold indicate significant difference between groups. CVLT = California Verbal Learning Test; ARCES = Attention-related Cognitive Error Scale; MFS = Memory Failures Scale; STAI = State Trait Anxiety Inventory; BDI = Beck Depression Inventory.

5.4 Discussion

The purpose of this study was to investigate whether there were any compounding effects of remote TBI, by examining individuals' cognitive functioning decades later in older adulthood. To our knowledge, this is the first report to document lasting cognitive impairment, limited to attentional processes with executive requirements, in healthy older adults who reported experiencing 1 or 2 TBIs an average of 50 years prior to testing. In particular, older adults with remote TBI performed significantly worse than non head-injured older adult controls on the incongruent condition of a computerized color-word Stroop task, but had comparable accuracy on the congruent and neutral conditions, suggesting a deficit in response inhibition, but not selective attention. TBI older adults also committed significantly more errors than controls on Trail Making B performance, not Trail Making A, suggesting long-term impairment in cognitive flexibility, but not sustained attention. A significant result was found that was not predicted, however, such that while both groups did score in the normal range on the MMSE, TBI participants scored significantly lower than controls. This overall lower score suggests that older adults with a remote TBI may be at a higher risk for age-related cognitive impairment. Results from this experiment provide evidence to suggest that a remote TBI may exacerbate healthy age-related cognitive decline, most evident on cognitively demanding tasks – those that tap into executive processing (i. e., inhibition and cognitive flexibility). It is important to mention, however, that many factors other than the TBI may have contributed to these findings (e.g., diagnosis threat, independent vs. dependent living, personal experience in between the injury and time of testing). We suggest future research continue examining the chronic effects of TBI in otherwise healthy older adults, while also controlling for other TBI- and older adult-related confounding variables known to contribute to cognitive impairment.

While neuropsychological measures of attention with executive components were successful at identifying impairment in older adult participants with a remote TBI compared to controls, significant differences between groups were not observed on our neuropsychological assessment (digit span task) or experimental measures (repetition detection task) of working memory with executive components. A potential explanation for

this lack of group difference may be due to a floor effect in that working memory tasks with a heavy executive component have been shown to be highly sensitive to both TBI- (Azouvi et al., 1996; Bublak et al., 2000; Christodoulou et al., 2001; Haut et al., 1990; McDowell et al., 1997) and age-related changes (Bopp & Verhaeghen, 2007; Dobbs & Rule, 1989; Park et al., 2002; Salthouse & Babcock, 1991). However, it is worth mentioning the overall slowing pattern observed for TBI compared to control participants on the repetition detection task, as well as the TBI groups' lower accuracy in the high processing load.

To ensure that the small sample sizes did not contribute to the null findings on the repetition detection task, retrospective power analyses were conducted separately for accuracy rates and response times. With an effect size (Cohen's *d*) of 0.27 and a power estimate of 0.80, a total of 112 participants (approximately 56 per group) would need to be tested to obtain a significant interaction between group and condition for accuracy. Similarly, with the same power estimate and an effect size of 0.29, 95 participants would be required for the group by condition interaction to reach significance on response time measures. In line with the SIT movement time results from experiment 2b, these calculations suggest that the chronic effect of TBI on accuracy rates and response times during the repetition detection working memory task is also small.

It is of interest that group differences were not observed in information processing speed on the Stroop task or the Trail Making task as cognitive slowing is one of the most well-documented effects of healthy aging (Salthouse, 2000) and very common long after TBI (Frencham et al., 2005). A ceiling effect may be a reason for this lack of difference, and perhaps the confounding effects of TBI on aging are better detected using accuracy measures on attention tasks with executive components.

Impairment of attention-related control processes

This study is the first to show that deficits in attention-related executive processes are evident in otherwise high-functioning healthy older adults who sustained a TBI an average of 50 years ago compared to non head-injured age-matched controls. These findings extend those documenting lasting deficits in response inhibition on the Stroop task a few months to

several years post-mild to severe TBI in young adults (Potter et al., 2002; Seignourel et al., 2005; Solbakk et al., 1999); and show that these deficits persist into older adulthood. It is important to highlight that such problems inhibiting interfering stimuli on the Stroop task have also consistently been shown in the healthy aging population (Brink & McDowd, 1999; Hartley, 1993; Spieler et al., 1996; Verhaeghen & De Meersman, 1998; see MacLeod, 1991 for review), showing that a remote TBI may result in a further impairment of normal age-related declines in executive functioning.

To our knowledge, this is also the first report of increased errors on a test of cognitive flexibility, Trail making B, in the TBI older adult group compared to controls. Error rates are not typically reported on the trail making task, but rather processing speed is used to determine measures of sustained attention (Trail Making A) and cognitive flexibility (Trail Making B; longer times reflecting less cognitive flexibility). Without analyzing error rates in the present study, the differences between TBI and control older adults would have gone unnoticed. Instead, we showed that while the groups took equal amounts of time to complete Trail Making B, TBI participants committed significantly more errors. This finding is in line with Vanderploeg et al. (2005) who showed that long-term impairments on an executive function task could be detected using non-standard measures of neuropsychological task performance. Specifically, they demonstrated that while mild TBI participants had identical performance on a difficult measure of attention and working memory (the PASAT), the mild TBI participants had significantly higher discontinuation levels. Detecting long-term TBI-related impairments in cognitive flexibility using a non-traditional measure of error calculations is also in line with results from Experiment 2a, which found significant response delays in a working memory task through non-standard temporal analyses. Moreover, the current Trail Making results highlight the importance of using sensitive cognitive measures to detect the chronic effects of TBI (Bernstein, 2002; Cicerone, 1996; Pare et al., 2009; Vanderploeg et al., 2005).

Notably, healthy older adults without TBI also show poorer performance on tasks that require cognitive flexibility (Ozen et al., 2010), suggesting that a TBI sustained long ago may further impair the very functions known to decline due to natural aging. Research suggests

that the similar pattern of cognitive impairment observed with advancing age and following TBI is a result of the two processes influencing common neural mechanisms (see Bashore & Ridderinkhof, 2002 for review). Specifically, the comparable TBI- and age-related deficits in executive functioning can be attributed to the fact that the frontal lobes are the brain region most susceptible to changes following TBI (McDonald et al., 2002) and most affected by the natural aging process (for a review, see Prull et al., 2000; Raz et al., 1997). Moreover, these findings are in line with the deficits in executive processes reported long-after one or multiple TBIs in middle to older adults anywhere from 2 to 60 years post-injury (De Beaumont et al., 2009; Himanen et al., 2009; Klein et al., 1996). The current study more specifically delineates the extended duration of TBI effects by showing that attention-related impairments in executive processes are evident at least 23 years post-TBI, with an average of 50 years, in otherwise healthy older adults.

Moreover, the current study showed these deficits can be detected in otherwise healthy older adults with a past TBI, who report no more everyday memory and attention failures in daily life compared to non head-injured controls. Research suggests that this lack of difference in perceived deficits in daily life may be due to coping strategies developed following a TBI (Klein et al., 1996). The neuropsychological findings in this experiment suggest that tasks requiring various aspects of executive processing, such as response inhibition and cognitive flexibility, can be used to detect chronic impairments in healthy older adults who sustained a TBI in their early life. In addition our MMSE results suggest that healthy older adults with a past TBI may be at a higher risk for age-related cognitive impairment compared to older adults with no history of a TBI. We suggest that screening for past TBIs when measuring cognitive functioning in healthy older adult studies may be essential as a remote TBI may exacerbate age-related cognitive decline. Such claims are merely speculative at this point until future research examines the effect of a remote TBI and age on cognitive functioning in the same study by directly comparing younger and older adults with and without TBI (as in Klein et al., 1996).

Chapter 6: General Discussion

The findings from this thesis provide behavioral and electrophysiological data to show significant information processing delays and inefficiencies after a remote mild TBI in an asymptomatic, high-functioning, young adult population. Importantly, results are the first to provide evidence for information processing slowing limited to working memory tasks which had a large short-term storage component and relied on executive processes. Particularly, through sensitive temporal analyses, we demonstrated that university students with a remote mild TBI may implement slowing strategies to maintain, and even boost, accuracy to levels higher than controls during a repetition detection *n*-back working memory task. Moreover, our ERP findings were the first to show that mild TBI results in an inefficient allocation of cognitive processing resources, indexed by an attenuated P300 amplitude, during a working memory *n*-back task, that is independent of load condition. Notably, this is also the first study to provide evidence that response delays are related to smaller P300 amplitudes; a potential mechanism underlying the response slowing observed as function of increasing working memory load. Such a relationship may help explain the trending pattern of slower response times in mild TBI participants compared to controls at higher working memory loads. Together, the experiments in this thesis helped to identify the measures that best detect long lasting cognitive changes following mild TBI.

Importantly, mild TBI-related changes were not detected on tasks that required executive processing, but had no or limited memory requirements. Specifically, our experimental and neuropsychological measures, both of which required minimal short-term memory store, were not sensitive to the effects of mild TBI (i. e., SIT, SART, Stroop, and Trail Making A and B tasks). Instead, only our working memory task that involved manipulating relatively large amounts of information temporarily held in mind identified long-term changes after mild TBI. Such results have important implications for the field, in that they provide a potential explanation for why long-term cognitive deficits are difficult to detect in the mild TBI population: the majority of neuropsychological tests are insensitive to minor changes in information processing speed and, as a result, the execution of slowing

strategies to maintain accuracy may go undetected (i. e., response times not recorded on digit span forward and backward tasks). In contrast, neuropsychological tasks that tapped into executive processes were found to be more sensitive to the chronic effects of sustaining 1-2 TBIs ranging from mild to severe severity. Older adults with a history of remote TBI examined an average of 50 years post-injury showed impairments in inhibitory functions and cognitive flexibility; also known to be susceptible to normal age-related cognitive decline. Findings demonstrate the importance of investigating longer-term effects of TBI, as they may be chronic and impact cognitive task performance in old age, amplifying normal age-related cognitive deficits.

Importance of Reducing Influence of Diagnosis Threat

The first three experiments in the current thesis are important and unique to the field in that deliberate steps were taken to limit the negative effects of expectation on cognitive and affective outcomes. Experiment 1 sought to document whether diagnosis threat influenced self-report of everyday attention and memory problems and neuropsychological task performance in undergraduate university students with a remote history of mild TBI. Mild TBI individuals in the 'diagnosis threat', relative to 'neutral', condition were more likely to report having attention and memory failures in their daily lives. This study highlighted that 'diagnosis threat' is a critical variable to be considered when assessing cognitive status in young adults with a remote mild TBI and call into question the efficacy of using of self-report measures to identify long-term deficits when such expectation biases are not controlled for.

It is important to emphasize that 'diagnosis threat' studies (Suhr & Gunstad, 2002; 2005), including Experiment 1 findings, demonstrate the negative impact of 'diagnosis threat' on cognitive outcomes in high-functioning undergraduate students who self-reported a prior mild TBI, for which the main motivation to participate was extra class credit. Thus, 'diagnosis threat' may be even more apparent in participants examined in the majority of the mild TBI literature, as most are recruited from hospital emergency departments or neuropsychologists' databases. In such situations, the motivation for cognitive testing is more

likely to be affected by various mild TBI-related issues such as workers compensation and litigation. Future research should control for 'diagnosis threat' in addition to the confounds that are more often controlled for in the mild TBI patient population, including pre-existing factors (Vanderploeg et al., 2007), co-morbid psychosocial factors (Chan, 2002; Dischinger et al., 2009; Fann et al., 2001; Rapoport et al., 2005; Stulemeijer et al., 2007), and litigation (for review, see Belanger et al., 2005; Binder & Rohling, 1996; Tsanadis et al., 2008).
In a recent report, Iverson, Zasler, and Lange (2007) compared effect sizes of such common variables from meta-analytic studies that influence neuropsychological functioning and found that mild TBI had the smallest effect size (d = -0.12) on neuropsychological performance, followed by diagnosis threat (d = -0.45), litigation (d = 0.48), depression (d = -0.49), and malingering (d = -1.1). In addition to emphasizing the small effect of mild TBI on cognition, such a comparison helps to further elucidate the confounding variables that complicate research attempting identify organic cognitive impairment after mild TBI.

Thus, in Experiment 2, we continued to test undergraduate university students with a *remote* mild TBI, a non-patient population that would be, if at all, minimally affected by malingering and litigation issues. In addition to screening for affective and neurological problems, we reduced the possible influence of diagnosis threat on self-report, neuropsychological, and experimental measures, by merely informing participants that their cognitive functioning was being examined, with no mention of head injury. As in Experiment 1, participants were screened for head injury status, along with many other health and demographic questions at the beginning of the semester in Experiments 2a and 2b. This prescreening process makes it highly unlikely that participants knew they were involved in a study investigating cognitive effects of mild TBI. Moreover, the sole purpose of participating in Experiments 1 and 2 was to obtain extra course credit for various psychology classes. Studying a group with similar motivations, as well as educational background, arguably makes this a more homogenous mild TBI group compared to the recruiting from patient databases, for example, as done in the majority of studies in the literature. We view this group homogeneity as an advantage of the experiments in this thesis, as it is more likely that any cognitive difference observed between groups are due to head injury status, and less

affected by common patient confounds, including 'diagnosis threat', malingering, litigation, and affective problems. This suggestion is purely speculative and could be confirmed in future research by comparing cognitive performance in a mild TBI undergraduate group to a mild TBI patient group recruited from medical databases, with respective controls.

'Diagnosis threat' and demographic variables could also help explain the main findings in Experiment 2a. Here, we observed a significant increase in delayed responses and accuracy for mild TBI participants compared to controls during the high processing load working memory condition. A potential explanation for this slowing strategy, that has not previously been documented in the literature, is that participants were high functioning university students who were likely unaware of the study's purpose at the time of testing. We suggest that by reducing the risk of expectation bias in this population, our findings of a slowing strategy in mild TBI are more representative of the long-term cognitive effects of sustaining one mild TBI. We also demonstrated, in this experiment, that cognitive slowing can be identified long-after a mild TBI, even in the absence of increased self-reported cognitive complaints (non-significant ARCES and MFS findings). However, while we attempted to reduce the influence of "diagnosis threat" by withholding the study's purpose from participants until experiment completion, we cannot conclude that it was eliminated without including a proper control condition ("diagnosis threat" condition). Future studies should continue to investigate the influence of "diagnosis threat" on cognition by directly manipulating this variable across conditions (i.e., include both a "diagnosis threat" and "neutral" condition).

Increasing Working Memory Demands to Identify Residual effects of Mild TBI

We demonstrated the utility of using sensitive and complex measures, novel to the mild TBI population in Experiment 2a and 2b. In an attempt to further specify persistent significant cognitive deficits, we manipulated executive processing load on a visual working-memory task, across two conditions in Experiment 2a. While self-report and neuropsychological measures of attention and memory did not differentiate the groups, the mild TBI group took significantly longer to accurately detect repeated targets on our working

memory task, regardless of executive processing load. Accuracy was comparable in the low-load condition and, unexpectedly, mild TBI performance surpassed that of controls in the high-load condition.

A novel and sensitive timing measure implemented in the high load condition, temporal analysis of target identification, suggested a strategy difference between groups: mild TBI participants made a significantly greater number of accurate responses following the target's offset, and significantly fewer erroneous distracter responses prior to target onset, compared to controls. Our findings highlight the importance of not limiting analysis to only a single dependent variable when examining the effects of mild TBI (Madigan, DeLuca, Diamond, Tramontano, & Averill, 2000), but instead, to consider how a change in strategy might underlie performance. If we had limited our analyses to standard response time measures (i. e., time to respond to target in milliseconds), we would not have uncovered the significant slowing patterns observed in mild TBI participants in the high load condition (i. e., *when* responses were being made in relation to target position).

Experiment 2a also emphasizes the need to use non-standard tasks and measures of performance in order to detect subtle residual cognitive changes in individuals who have sustained a mild TBI in their remote past. As shown in this study, such changes may be advantageous in that, as long as task design permits, slowing down helps mild TBI participants ignore distracting information, and maintain, or even surpass, performance of controls. Future research should investigate the effects of timing variables on mild TBI performance. For example, if, in the repetition detection task, participants were required to make their response prior to the offset of the target stimulus, the accuracy boost in mild TBI participants may not have been observed (i.e., the task would not have permitted post-target responses).

While using novel and sensitive measures revealed cognitive changes in Experiment 2a, such changes were less evident in Experiment 2b. Here we examined whether manipulating executive processing requirements during a routine action sequence task would differentiate mild TBI from controls. Action slips were induced by presenting unexpected cues during a routine sequence on the SIT, requiring participants to use executive processes

to inhibit the expected movement in order to execute a new move to the unexpected target location. While not significant, there was a trending pattern such that mild TBI participants were slightly slower to re-adjust movements, compared to controls, following an unexpected cue. As mentioned throughout the this thesis, previous research suggests that cognitive deficits only emerge long after mild TBI when the cognitive demands of a task exceed the processing capacity of available cognitive resources (Bernstein, 2002; Cicerone, 1996; Pare et al., 2009; Segalowitz et al., 2001).

As demonstrated in Experiments 2a and 2b, merely increasing executive demand was not sufficient in order to identify long-term deficits after mild TBI, but rather the specific cognitive domain that was requiring executive processing was essential in revealing long-lasting changes. For example, the repetition detection working memory task was more sensitive to mild TBI-related changes than the SIT designed to induce action slips during routine movement sequences. Particularly, information processing delays were evident in mild TBI participants even when minimal demand was placed on executive resources during working memory performance (i. e., on the low load condition of the repetition detection task), but no differences were observed when a relatively high demand was place on executive processes to execute a unexpected movements during the SIT. Based on these findings, we suggest that in order to exceed processing capacity in this population and detect cognitive changes, it is just as, or even more, important to increase the short-term memory load during a working memory task as it is to tap into executive processing.

To successfully complete the low load condition of the repetition detection task, participants were required to store anywhere from 4-8 digits in their phonological loop in order to identify the repeated target. In addition to the storage component, a low demand was placed on executive processes such that individuals also had to focus attention (executive component of working memory) on the most recent digit presented on the screen to determine if it matched one currently in storage to determine the next step of action. If there was no match, the current number would be added to the digit string held on line, if there was a match, participants were required to identify that digit by pressing a corresponding key on the keypad. While mild TBI participants were just as accurate at identifying target stimuli,

they were significantly slower than controls and this difference did not depend on the amount of executive processes required (i. e., main effect of slowing, but no interaction with load condition). Yet, in the SIT task, mild TBI participants implemented a routine action sequence just as quickly as controls, even when faced with altered movement cues.

The comparison of the sensitivity of the repetition detection and SIT task is important as both were experimentally designed to be sensitive to subtle differences in response times and differentially manipulated executive processing demands in different cognitive domains. While it is important to point out that mild TBI participants tended to be slightly slower during correct movements on altered trials, groups did not significantly differ on total initiation, sequence or movement times. From these data, we suggest that long after a mild TBI individuals do not experience general slowing while accurately executing routine actions, but may experience delays when required to inhibit automatic responses and execute unexpected movements. More importantly, mild TBI-related cognitive slowing is more evident when individuals are required to hold multiple pieces of information in mind in order to accurately detect a target. Thus, a remote mild TBI may slow down working memory functioning when one is responsible for remembering large amounts of information, but have less of an effect on more routine, automatic sustained attention tasks.

These findings highlight the importance of implementing tasks with sensitive timing measures in the mild TBI population. For instance, such measures could be employed in standard neuropsychological tasks to increase their sensitivity to subtle mild TBI-related changes. In all of the experiments of this thesis, for example, the digit-span task was administered but did not detect group differences. Yet, these differences could have been in response times, a measure not traditionally recorded with this task. Future research would benefit from recording accuracy and response times (e. g., using a stop watch or computer version of digit-span) during neuropsychological tasks. It may be that mild TBI participants respond at the same speed and accuracy rate as controls on digit span forward, but are slower to manipulate the digits in order to accurately produce the digit string backwards.

Moreover, it may be more important when studying the mild TBI population to manipulate memory load in working memory tasks as a way to increase processing load,

instead of increasing executive demand. For example, our repetition task may not have identified mild TBI-related slowing if participants were only required to hold anywhere from 2 to 6 digits online, instead of 4 to 8. As mentioned in the introduction, Reuter-Lorenz and Sylvester (2005) posited that all tasks requiring the online, short-term storage of limited amounts of information are measures of working memory. The only difference in various WM tasks lies in the demands they place on executive processing operations. This view puts working memory tasks along a continuum and it is the level of involvement of executive processing operations that varies for each task. At one extreme are maintenance tasks which place minimal demand on executive processes and at the opposite end are those that place considerable demands on executive processes, such as simultaneously dividing attention between difficult tasks, and selectively attending to relevant information while inhibiting distracting/irrelevant information temporarily held in mind.

We suggest that in order to detect differences in the mild TBI population, it may be just as important for the working memory task to place heavy demands on the storage component (phonological or visuospatial) with minimal demands on executive processes, as evident in the low load working memory condition. This is in line with past research that has identified deficits on selective attention tasks when, not only executive demand is increased, but when processing load is increased by adding a concurrent short-term memory task (e. g., digit span forward; (Bernstein, 2002; Cicerone, 1996; Pare et al., 2009; Segalowitz et al., 2001). Although we detected slowing on our working memory task, it is imperative to highlight that response delays were observed with no change, and even a boost, in accuracy when executive demand increased. Future research would benefit by increasing processing load through manipulating both short-term memory load and executive demands separately during working memory tasks, while also examining strategy use long after mild TBI.

As demonstrated by Experiment 3, increasing task sensitivity can also be accomplished through electrophysiological recordings as a means to uncover the neural substrates of cognitive performance. To more precisely identify the brain basis of the cognitive slowing observed in Experiment 2, we administered an *n*-back working-memory task while systematically increasing working memory demands, from 0- to 3-item loads,

while recording ERPs. Compared to controls, mild TBI participants showed a reduction in their P300 amplitude, conceptualized in past work as an index of available cognitive resources for stimulus classification; this reduction occurred regardless of load condition. To our knowledge, this is the first study to show neural evidence for inefficient processing long after a mild TBI during a working memory task.

In line with behavioral evidence of slowing on the low load repetition detection condition, this inefficient processing, as indexed by attenuated P300 amplitude, was apparent even during the low load 0-back condition. We suggest that a mild TBI results in a reduced amount, or inefficient recruitment of, processing resources for target detection; a potential neural mechanism for response slowing during working memory tasks. Even the though the groups did not show behavioural differences on any load levels, response times showed a slight increase as P300 decreased only at higher processing loads in mild TBI participants. It may be that behavioural deficits are only observable long after mild TBI if processing demands of the task exceed the capabilities of the available processing resources.

Specifically, P300 amplitude accounted for relatively large amounts of variance in response times, but not accuracy rates, during the 2-back and 3-back loads. With this load increase, both memory storage and executive demands increase. For example, compared to the 1-back load, in the 2-back load, participants are required to hold 3 pieces instead of 2 pieces of information on line. Moreover, in order to accurately detect target stimuli in the 2- and 3-back conditions, participants must *drop* the first of the three or four digits held in short-term storage, *shift* the items forward while *maintaining* sequence order, and *add* the most recent item to the end of the string. Thus, the executive requirements, as well as demand placed on the storage component, of the 2- and 3-back conditions far exceed those of the 0- and 1-back condition. This is an example of increasing working memory processing load through both executive and memory load demand. As mentioned, future research could implement a working memory task designed to manipulate each component separately in order to more specifically measure the long-term effects of mild TBI on short-term storage and executive processes involved in working memory.

Neural Imaging and Mild TBI

Neural imaging studies have provided further evidence to show that a mild TBI may lead to inefficient allocation of processing resources. Examined 1-month post-injury using functional magnetic resonance imaging (fMRI), it has been shown that, in the absence of cognitive performance differences, mild TBI participants show increased bilateral frontal lobe activation compared with controls during working memory *n*-back tasks (McAllister et al., 1999; McAllister et al., 2001; Zhang et al., 2010). It has been posited that the additional neural recruitment observed in individuals after mild TBI is not necessarily a result of deficits in working memory capacity, but rather impairments in the ability to appropriately match processing resources to processing load (McAllister, 1999). Moreover, McAllister (1999) suggested that it may be these matching difficulties that underlie the persistent attention and memory problems reported by individuals long after mild TBI (for example, Alves, 1993; Gaetz et al., 2000; Meares et al., 2011; Vanderploeg et al., 2007; Villemure et al., 2011).

We demonstrated, in the current thesis, that inefficient allocation of processing resources, indexed by an attenuated P300 amplitude, are evident during working memory functioning in a group of young adults with post-injury symptom ratings no different non head-injured controls (i. e., no significant differences between groups on the Rivermead Concussion Inventory, MFS or ARCES). This finding is critical in that, while self-report, neuropsychological and experimental cognitive task performance did not distinguish the groups, ERP recording revealed subtle differences in high-functioning individuals with a remote mild TBI. The use of sensitive neuroscience techniques should continue to be implemented and correlated with behavioural measures to reveal underlying mechanisms of subtle changes in performance (i. e., negative correlation between P300 amplitude and response time in mild TBI participants). While no difference in self-report measures were found between groups in the current study, it is a variable that should be controlled for, or manipulated in future work, as neural processing changes have been related to the extent of symptom severity.

For instance, symptomatic, but not asymptomatic, concussed athletes had reduced P300 amplitudes compared to controls tested on a visual oddball task between 1 month and 2 years (Lavoie, Dupuis, Johnston, Leclerc, & Lassonde, 2004) and at least 2 years post-injury (Dupuis et al., 2000). In the latter study, the symptomatic concussed athletes also had delayed reaction times compared to asymptomatic and control athletes. Functional MRI has shown a relationship between neural processing differences and concussion symptomology, even in the absence of performance differences on a working memory task. Both one week (Pardini et al., 2010) and one month (Smits et al., 2009) post-mild TBI, activation *outside* the working memory network was positively correlated with severity of post-concussion symptoms, with no observable *n*-back performance differences compared to controls.

Also, one to 14 months prior to injury, symptomatic concussed athletes showed decreased activation *within* the working memory network (in the mid-dorsolateral prefrontal cortex) during a working memory tasks compared to controls, and this activation was negatively correlated with self-reported post-concussion symptoms (Chen et al., 2004; Chen, Johnston, Petrides, & Ptito, 2008). Less activation was reported in the same region in low and moderate symptomatic concussed athletes compared to asymptomatic athletes during a working memory task (Chen, Johnston, Collie, McCrory, & Ptito, 2007). Moreover, symptomatic concussed athletes who had reduced activation in the dorsolateral prefrontal cortex compared to controls at 3 months post-injury showed increased activation in this area months later if symptoms resolved, but those who were still symptomatic continued to have decreased activity.

These results provide support for the neural compensation hypothesis after mild TBI, in that symptomology is positively correlated with increased activity outside the working memory network, and decreased brain activation within the working memory network is observed in symptomatic patients compared to asymptomatic and controls. Together the studies show that self-reported symptoms have may an organic brain basis and that symptom severity is related to long-term abnormalities in neural processes. Such changes have been further elucidated through structural imaging techniques.

Diffusion tensor imaging (DTI), used to examine white matter integrity, has shown that the extent of microstructural axonal damage following a single mild TBI has also been related to symptom severity. Messe and colleagues (2011) showed that patients with more post-concussive symptoms 3 months post-injury had a greater extent of axonal damage when imaged earlier at one month post-injury compared to those with fewer symptoms. Moreover, in participants who sustained a mild TBI one month earlier, the extent of microstructural axonal damage positively correlated with slower information processing speeds on a simple attention task (Niogi et al., 2008). Similar results have been found 1 month post-injury, but in asymptomatic mild TBI participants, such that more microstructural damage was noted bilaterally in the dorsal-lateral prefrontal cortex (Zhang et al., 2010). The extent of this damage was positively correlated with amount of brain activation recorded via fMRI during a working memory task in mild TBI participants, but not controls.

Such results provide evidence for neural damage shortly after mild TBI and that the extent of damage is positively related to self-report symptom severity and response times on an attention task. Results from the Experiment 3 add to these findings by showing neural processing changes evident through electrophysiological measures at least one year after mild TBI are related to response slowing on a working memory task in asymptomatic individuals. While these imaging studies provide evidence for the neural changes shortly after mild TBI, future research should be directed at specifically determining the *long-term* effects of mild TBI on the brain and cognition in both symptomatic and asymptomatic individuals.

Applying Slowing Strategies to Increase Performance after Mild TBI

Research has demonstrated that individuals with a moderate to severe TBI performed slower and less accurately compared with controls during an externally paced complex working memory task (PASAT; Madigan et al., 2000). When accuracy was controlled for however, by increasing the duration of the inter-stimulus interval, TBI participants still performed significantly slower than controls, but no longer showed decrements in accuracy performance. It is a reasonable assumption that if adults with a severe TBI are capable of

performing at the level of controls, when provided with more time to make each response, then young adults who have sustained a single mild TBI can surely also use the strategy of slowing to maintain control performance when time restrictions are lifted, as shown in Experiment 2a. Specific to mild TBI, Vanderploeg and colleagues (2005) showed that at least a year post-injury, individuals had higher discontinuation rates compared to controls on the PASAT, a complex working memory task. Future research could investigate the effects of increasing the duration of inter-stimulus intervals on PASAT performance, as well as discontinuation rates long after mild TBI.

The evidence for cognitive slowing in the present thesis and other controlled experimental studies could be used to assist with strategy development programs for individuals who have persistent cognitive complaints after mild TBI. For example, results from Experiment 2a demonstrated that when mild TBI participants have unlimited time to respond, they may use this extra time to outperform controls on a working memory task. Our findings may also have clinical value: cognitive performance may be improved, in young adults who have suffered a mild TBI, by allowing unlimited time to make responses. In daily life, such individuals may experience a boost in performance if they take extra time to complete working memory tasks that place a demand on short-term memory storage and executive components. For instance, lifting time restrictions may be especially beneficial to the undergraduate population with a remote mild TBI during exams; situations where some sort of working memory functioning is most likely necessary.

Individuals who are experiencing mild TBI-related symptomology may benefit from training programs already implemented in populations who also experience cognitive slowing. For example, mental slowing has been a well-documented finding in individuals following severe TBI and stroke. Consequently, Winkens, Van Heugten, Wade, and Fasotti (2009) have developed a Time Pressure Management (TPM) training program that teaches cognitive strategies to individuals with acquired brain injury in order to mitigate disabilities resulting from mental slowness. A recent randomized controlled trial showed that TPM training was effective at improving speed on everyday tasks in stroke patients, while having no effect on their self-report of mental slowness (Winkens, Van Heugten, Wade, Habets, &

Fasotti, 2009). Implementing such strategy training programs may assist individuals who are still experiencing memory or concentration difficulties after mild TBI. Perhaps even more beneficial to a mild TBI population would be to implement educational training programs designed to inform individuals of the most common persistent symptoms. Due to the negative effects of 'diagnosis threat' alone, individuals should be taught about expectation biases and how merely associating cognitive performance with mild TBI can be even more detrimental than any actual effects of the injury itself. Future research would benefit from implementing such training programs in the mild TBI population, while recording pre- and post-cognitive measures, through experimentally controlled pilot studies that may ultimately inform larger randomized controlled clinical trials.

TBI: A Risk Factor for Age-related Dementia?

In addition to specifying long lasting cognitive changes after mild TBI, the current thesis also showed that the effects of TBI (ranging from mild to severe) are chronic. In Experiment 4, we reported that both older adults with and without a past TBI were free from moderate to severe forms of cognitive decline or dementia as measured by the MMSE; the most commonly used cognitive screening tool used by physicians in the USA, Canada and the UK (Shulman et al., 2006). However, even though both groups scored in the normal range, the TBI group scored significantly lower than controls. Although this screening tool has been shown to be less than ideal at detecting mild cognitive impairment (Tombaugh & McIntyre, 1992; van der Cammen, van Harskamp, Stronks, Passchier, & Schudel, 1992) taken together with the neuropsychological deficits detected in this group, we suggest that these significantly lower scores may be evidence of permanent cognitive impairment in older adults with a remote TBI. Furthermore, our neuropsychological findings suggest that a remote TBI may exacerbate healthy age-related cognitive decline, most evident on cognitively demanding tasks – those that tap into executive processing (i. e., inhibition and cognitive flexibility).

Recent studies have started to provide evidence for the similar effects of TBI and age-related dementias on cognitive and the brain. It has been report that within hours and up to

years' post-TBI, there is evidence of abnormal protein accumulation similar to that found in Alzheimer's Disease (AD), suggesting that AD-related neuropathological mechanisms may contribute to cognitive impairments long after TBI (see Sivanandam & Thakur, 2012 for review). Recent research out of Boston University's Center for the Study for Traumatic Encephalopathy has shown that multiple concussions (mild TBIs) lead to similar patterns of neural degeneration and cognitive sequela found in individuals who suffered from AD (McKee et al., 2009). With the increasing aging population, it is urgent that risk factors for dementia, such as a remote TBI, be further understood in order to develop rehabilitation methods to delay potential decline. Such research will also reveal the importance of continuing to inform the public of the cognitive risks associated with TBI in order for preventative measures to be put in place, such as the recent new rules being implemented in the National Hockey League to prevent concussions. Our findings are imperative in that they show that even sustaining 1-2 remote TBIs can cause permanent deficits in higher order cognitive functions during the late stages of life. Research should continue to investigate the effects of single and multiple TBIs at various times since injury, as well as continue to research the potential cumulative effect of a remote TBI on natural age-related cognitive decline.

Limitation of the Current Thesis

We do acknowledge that self-report methods and lack of access to medical records are limitations of the current study that could result in inaccurate reports of head injury history and participant classification. However, that we could document significant effects, even in a high-functioning university sample, shows that a mild TBI experienced long ago can have lasting repercussions on cognitive functioning. We also acknowledge that we did not control for pre-morbid personality characteristics, such as risk-taking tendencies and frequency of sports play; however, we have no reason to believe that our mild TBI and control group would differ significantly on these variables. For example, in Experiments one through three, approximately half of the group sustained mild TBIs due to sports injuries, making the sample sufficiently variable in origin of injury that this variable is unlikely to

have had a systematic effect on the data. We also did not control for the potential effect of other non-TBI injuries on cognitive functioning in the current study, which could influence performance to the same extent as mild TBI, as recently shown in the pediatric population (as in Babikian et al., 2011). Once again, however, because both of our control and mild TBI samples were recruited from a student population during the university semester, we do not believe that non-TBI injuries contributed to our findings.

Conclusions

The findings from this thesis are the first to show, through sensitive temporal analyses, that high-functioning young adults may implement slowing strategies to maintain, and even boost, working memory accuracy to levels higher than controls. Our ERP findings are the first to indicate that the fewer processing resources available for stimulus classification, indexed by P300 amplitude, the slower response times are for accurate target detection, especially under moderate to high working memory loads. The fact that mild TBI participants had significantly reduced P300 amplitude compared to controls warrants future research to investigate inefficient information processing as a potential neural mechanism underlying response delays long after mild TBI. Such results have important implications for the field, in that they provide a potential explanation for why long-term cognitive deficits are difficult to detect in the mild TBI population: the majority of neuropsychological tests are insensitive to minor changes in information processing speed and, as a result, the execution of slowing strategies to maintain accuracy may go undetected. Such results can be used to inform randomized controlled clinical trials designed to examine the utility of time management and mild TBI educational training programs. Our findings also demonstrate the importance of continuing the investigation of longer-term effects of TBI, as they may be chronic and impact cognitive task performance in old age, amplifying normal age-related cognitive deficits.

Appendix A

Prescreen Head Injury Questions

Please choose one option for each question below.

Have you ever had a concussion (a blow to the head)? If so, did you lose **consciousness** for:

- 0 seconds (did not experience loss of consciousness)
- 1-59 seconds
- 1-5 minutes
- 5-15 minutes
- 15-30 minutes
- greater than 30 minutes

When did the concussion occur?

- less than 1 month ago
- 1-3 months ago
- 3-6 months ago
- 6 months to 1 year ago
- over 1 year ago

If you have had a concussion, did you experience loss of **memory** (brief amnesia) for:

- 0 seconds (did not experience)
- 1-59 seconds
- 1-60 minutes
- 1-24 hours
- greater than 24 hours

If you have had a concussion, did you experience **confusion** (inability to focus attention) for:

- 0 seconds (did not experience)
- 1-59 seconds
- 1-60 minutes
- 1-24 hours
- greater than 24 hours

If you have had a concussion, did you experience **disorientation** (difficulty with regard to direction or position/ loss of physical bearings) for:

- 0 seconds (did not experience)
- 1-59 seconds
- 1-60 minutes
- 1-24 hours
- greater than 24 hours

Appendix B

Attention and Memory Error Scales

Attention-related Cognitive Error Scale (ARCES; Carriere et al., 2008)

1. I have gone to the fridge to get one thing (e.g., milk) and taken something else (e.g., juice).
2. I go into a room to do one thing (e.g., brush my teeth) and end up doing something else (e.g., brush my hair).
3. I have lost track of a conversation because I zoned out when someone else was talking.
4. I have absent-mindedly placed things in unintended locations (e.g., putting milk in the pantry or sugar in the fridge).
5. I have gone into a room to get something, got distracted, and left without what I went there for.
6. I begin one task and get distracted into doing something else.
7. When reading I find that I have read several paragraphs without being able to recall what I read.
8. I make mistakes because I am doing one thing and thinking about another
9. I have absent-mindedly mixed up targets of my action (e.g., pouring or putting something into the wrong container).
10. I have to go back to check whether I have done something or not (e.g., turning out lights, locking doors).
11. I have absent-mindedly misplaced frequently used objects, such as keys, pens, glasses, etc.
12. I fail to see what I am looking for even though I am looking right at it.

Everyday Memory Failures Scale (MFS; Carriere et al., 2008)

1. I forget people's names, even though I rehearsed them.
2. I forget people's names immediately after they have introduced themselves.
3. I forget to set my alarm.
4. I double-book myself when scheduling appointments.
5. Even though I put things in a special place I still forget where they are.
6. I remember facts but not where I learned them.
7. I forget what I went to the supermarket to buy.
8. I find I cannot quite remember something though it is on the tip of my tongue.
9. I forget to pass on messages (e. g., phone messages)
10. I forget appointments.
11. I forget important dates like birthdays and anniversaries.
12. I forget passwords.

Appendix C

Information Letters

Diagnosis Threat Experiment: Information Letter

"Working memory in young adults who have experienced a head injury compared to young adults who have not experienced a head injury"

You are invited to participate in a research study to help us learn more about memory performance in individuals who have experienced a head injury in their past (at least 6 months ago) that was a result of any contact forces (i. e., hit or fall) or acceleration/deceleration trauma (i. e., vehicle accident). Past research indicates that some people who have experienced a head injury show mild memory difficulties on some types of tasks, but not others. This can occur for a variable amount of time after the head injury, ranging from days to years. This study will examine whether having experienced a head injury affects aspects of working memory (the ability to store and manipulate information) long after the injury. You will be included as part of the healthy group of young adults who have not experienced a head injury [this would read 'young adults who have experienced a head injury' for the MHI group] and your data will be compared to that of young adults who have experienced a head injury.

This study involves completing one memory task, five questionnaires, two short verbal tasks, and one short visual task. In the memory task, you will be asked to recall a short list of words that you will have listened to. For the verbal tasks, you will be asked to repeat numbers and read some simple words aloud. For the visual task, you will be asked to connect numbers and letters together. For the four questionnaires, you will be asked some questions regarding your demographic and health information, and personality traits. Most tasks are short, and you will be given break time between tasks.

Neutral Experiment: Information Letter

"Working Memory and Attention in Young Adults"

You are invited to participate in a research study to help us learn more about working memory and attention performance young adults. This study involves completing one memory task, four questionnaires, two short verbal tasks, and one short visual task. In the memory task, you will be asked to recall a short list of words that you will have listened to. For the verbal tasks, you will be asked to repeat numbers and read some simple words aloud. For the visual task, you will be asked to connect numbers and letters together. For the four questionnaires, you will be asked some questions regarding your demographic and health information, and personality traits. Most tasks are short, and you will be given break time between tasks.

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