Long-Term Cognitive Impairment Following Mild Traumatic Brain Injury With Loss of Consciousness

by

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Abstract

A small subset of individuals that have experienced mild traumatic brain injury (mTBI) may experience persistent cognitive deficits more than a year following the head injury. Neuroimaging studies reveal structural and functional changes in frontal areas of the brain, exacerbated when loss of consciousness is experienced, and indicate that these changes may be progressive in nature for some people. Social support and social participation have, however, been suggested to confer *cognitive reserve* - neurocognitive protection against cognitive decline. Analyses were run on Canadian Longitudinal Study on Aging (CLSA) neuropsychological data, consisting of individuals who experienced mTBI with loss of consciousness (n = 536 for less than 1 minute, and n = 435 for unconsciousness between 1 and 20 minutes) more than a year prior, and 13,163 no-head injury comparisons. These same individuals were re-assessed three years later.

The results presented in this thesis suggest that at a year or more after a single mTBI with loss of consciousness, a small subset of individuals are more likely to be impaired on prospective memory and other executive functioning tasks, relative to comparisons. In addition, when examined at three-year follow-up, those who experienced mTBI with longer duration of unconsciousness were more likely to exhibit cognitive decline relative to those who experienced less unconsciousness or comparisons. Moreover, greater social participation over the past year, and more perceived social support were predictive of lessened cognitive deterioration in those individuals.

Keywords: mild traumatic brain injury, cognitive impairment, cognitive reserve, CLSA

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Chapter 1: Introduction

1.1 Thesis Overview

Traumatic brain injuries (TBI) are estimated to have an annual incidence of 400 per 100,000 individuals (Bruns & Hauser, 2003; Voss et al., 2015), a figure suggested to be an underestimate of the true number of cases because many are not reported (Dewan et al., 2018; Voss et al., 2015). This therefore presents as an important public health concern because a number of individuals go on to exhibit cognitive dysfunction following TBI (Karr et al., 2014; Voss et al., 2015). The majority of studies of cognitive functioning following TBI have, however, focused on severe cases of TBI (Bruns & Hauser, 2003). This is of particular concern given the estimate that 70% of all traumatic brain injuries may be categorized as mild (Cassidy et al., 2004; Voss et al., 2015).

The past two decades have seen interest in understanding cognitive dysfunction following mild TBIs (mTBI), but findings examining the protracted nature of any impairment have been mixed (Bigler et al., 2013; Binder et al., 1997; Frencham et al., 2005; Iverson, 2010; Pertab et al., 2009; Rohling et al., 2012). It has been suggested that this is likely due to the use of aggregate mean-level analyses, which can obscure cognitive impairment, and a lack of sensitivity in the use of standard neuropsychological instruments (Bigler et al., 2013; Karr et al., 2014; Pertab et al., 2009). Prospective memory has been considered a more naturalistic cognitive function (Ellis & Kvavilashvili, 2000), that I contend provides means by which to detect ongoing cognitive difficulty in mTBI. Moreover, important clinical indicators like loss of consciousness, indicative of brain injury processes (Kraus et al., 2007; Sorg et al., 2014), may help to identify those more apt to experience cognitive dysfunction, and anchor neuropsychological prognoses in the long-term. Considered further, an understanding of any cognitive change (improvement or decline) in

the long-term following mTBI is not clear, leaving in the dark those who may be experiencing protracted difficulties, dubbed the ‘miserable minority’ (Rohling et al., 2012).

Some individuals may similarly be more resilient to cognitive deterioration, protected through a concept referred to as cognitive reserve (Stern, 2002, 2009). Analogues of cognitive reserve, including social support and social participation (Evans et al., 2018; Fleck et al., 2019; Scarmeas et al., 2001; Stern, 2009) have shown promise, serving as a presumed protective factor against cognitive deterioration. The extent that social support or social participation may be associated with reduced likelihood of exhibiting cognitive deterioration has however not previously been examined in mTBI.

This thesis was therefore organized into three sequentially connected articles, all designed to examine long-term cognitive functioning, a year or more after mTBI with loss of consciousness. This thesis discusses findings of: prospective memory impairments (chapter 2), broad-based impairments in executive functioning and declarative memory (chapter 3), and cognitive change, including the buffering effects of social support and social participation against cognitive deterioration (chapter 4). Of note, the first two articles (chapters 2 and 3) have been previously published (Bedard et al., 2018, 2020, respectively), but appear in this thesis as slightly modified versions. These articles were revised in the thesis so that alcohol frequency could be included as a covariate. In addition, the study embedded as chapter 2 was modified from its published version (Bedard et al., 2018) to include a refined sample, so that only those who had experienced a single lifetime mTBI more than a year prior to investigation were included. This same sample was then used across the three articles of this thesis (chapters 2 through 4). This thesis first begins with a succinct literature review covering the requisite background to provide the framework from which this thesis is organized.

1.2 Mild Traumatic Brain Injury

Although many definitions of TBI severity have been used (Saatman et al., 2008), mTBI is commonly defined as involving *at least one of*: loss of consciousness, amnesia following the incident (i.e., posttraumatic amnesia), altered mental state following the incident, or focal neurological deficits due to head trauma (American Congress of Rehabilitation Medicine, 1993). Posttraumatic amnesia, if present, should not have persisted for more than 24 hours, and loss of consciousness (LOC) must not have exceeded 30 minutes. In addition, 30 minutes following the incident, Glasgow Coma Scale scores (Teasdale & Jennett, 1974) should be 13 or higher. The Glasgow Coma Scale, a measure of consciousness administered by medical personnel upon admission to hospital and by paramedics, assesses orientation to self and others, as well as motor responses to simple commands, and has a highest possible score of 15.

Etiologic contributors to mTBI are varied, whether from falls, motor vehicle or sports collisions, concussive blasts, or an impact to the head (Bruns & Hauser, 2003; Dewan et al., 2018; Voss et al., 2015). At the least, mTBI is considered to result from a force that is applied to the brain from impact, or non-impact means (e.g., acceleration or deceleration; Kay et al., 1993; Prins et al., 2013). Principally, the primary injury is the initial blow (i.e., coup; although rotational forces must not be minimized) that causes the brain to be displaced within the skull, usually resulting in the brain hitting the opposite side of the skull in what is referred to as contrecoup. More insidious however are the secondary injuries, which occur as a consequence of ongoing cellular changes, leading to further damage (Namjoshi et al., 2013).

Although not a focus of the current thesis, it is worth considering that secondary injury processes are thought to be complex, and include cellular, neurochemical, metabolic, and inflammatory aberrations (see Namjoshi et al., 2013, and Prins et al., 2013, for reviews). Animal

models have provided insights into the specific secondary changes, including altered brain blood flow, swelling, increased intracranial pressure and blood-brain barrier permeability, cellular excitotoxicity, oxidative damage from heightened free radical production, and increased inflammatory processes - many of which are thought to occur *days to weeks* following the primary injury (Giza & Hovda, 2001; McAllister, 2011; Namjoshi et al., 2013; O'Connell & Littleton-Kearney, 2013; Prins et al., 2013; Werner & Engelhard, 2007). Moreover, the prolonged nature and chronicity of sustained damage may be influenced by continued activity following the brain injury, because the neurometabolic and vascular changes inherent in secondary processes can lead to increased vulnerability to further neuronal stress while the brain is restoring homeostasis and working towards remediation and repair (Asken et al., 2016; Lazzarino et al., 2012).

1.3 mTBI Neuroanatomy

In human studies, neuroimaging has revealed structural and functional brain alterations, particularly to frontal areas and not just immediately following mTBI (Abdel-Dayem et al., 1998; Bottari et al., 2017; Mayer et al., 2011; McDonald et al., 2012; Sorg et al., 2014; Strangman et al., 2010), but also several months and years after mTBI (Hartikainen et al., 2010; Helmich et al., 2015; Mac Donald et al., 2017). Moreover, these alterations have been more pronounced when loss of consciousness is experienced (Kraus et al., 2007; Sorg et al., 2014; Strangman et al., 2010). Neuropathophysiological evidence explaining a link between LOC and mTBI are limited, but suggest that LOC may occur due to shearing strains and stresses resulting in the decoupling of functional tracts impacting ascending pathways of the reticular activating system supporting consciousness (Blyth & Bazarian, 2011; Jang, Kim, & Lee, 2019). In terms of specific pathological processes inherent in mTBI, evidence from diffusion tensor imaging (DTI)

has largely supported a role of diffuse axonal injury (inferred from reduced fractional anisotropy; Asken et al., 2018). This is to say that findings suggest that at least part of the damage inherent in mTBI is consistent with shearing along axons, linking reduced axonal transmission and white matter integrity in frontal brain regions (e.g., anterior corona radiate, inferior longitudinal fasiculus, genu of the corpus callosum, uncinate fasiculus) within a month to a year post-mTBI (Asken et al., 2018).

Among a subset of individuals, chronically reduced white matter integrity has been observed along frontal brain tracts in DTI studies a year or more following the mTBI (Dean et al., 2015; Jorge et al., 2012; Kraus et al., 2007; Sorg et al., 2014; Wada et al., 2012). Of note, it appears that in these long-term intervals, reduced fractional anisotropy was more likely to be observed when LOC was experienced compared to when no LOC was reported (Jorge et al., 2012; Kraus et al., 2007; Sorg et al., 2014). Frontal areas of the brain are instrumental in a wide range of cognitive abilities, with white matter integrity being particularly integral to executive functioning, including working memory, inhibition, and cognitive flexibility, and processes involved in memory encoding and retrieval (Sasson et al., 2013). As such, examination of cognitive functioning following mTBI ought to be considered further.

1.4 Cognitive Functioning in mTBI

Despite greater attention devoted to severe cases of TBI, over the last 10 years there has been increasing interest in examining cognitive outcomes following mTBI. Many of the studies have focused on what has been termed the acute phase, which is to say the first 3 months post-injury, a time when individuals typically present for medical consultation (Binder et al., 1997; Frencham et al., 2005). Given that mTBI is considered a common source of neuropsychological

difficulty (Cassidy et al., 2004; Voss et al., 2015), examination of the protracted nature of any cognitive deficits is of consideration in this thesis.

1.4.1 Sub-Acute Cognitive Functioning Within One Month

In examining emergency department presentations for head injury, cognitive deficits have been noted to occur in executive functioning as compared to non-head injury comparisons (Brewer et al., 2002). At the one-month mark, however, despite mildly reduced performance on a demanding task of executive functioning and working memory (auditory consonant trigrams), cognitive functioning was not found to differ in mTBI, at least as a function of longer posttraumatic amnesia (Tellier et al., 2009). However, it should be noted that the analyses by Tellier et al., (2009) did not involve a normative sample or control group for comparisons. When considering cognitive performance in the first month against comparisons, executive dysfunction has been more pronounced (Brewer et al., 2002; McGowan et al., 2019), particularly when factoring LOC; those who had spent greater time unconscious were more apt to be dysexecutive (Brewer et al., 2002). These studies all seem to suggest a tendency of the executive dysfunction to be associated with a lack of inhibitory control – reduced ability to inhibit prepotent responding.

1.4.2 Cognitive Functioning Within 3 Months

It has been found that, shortly after and up to two months following mTBI, deficits in executive functioning (e.g., attentional control or inhibition) have also been observed, and deficits in episodic memory (particularly verbal recall) have been found when compared to non-head injury comparisons (Karr et al., 2014). However, longitudinal studies have examined the nature of cognitive deficits within the first week post-head injury, and at a three-month follow-up. It has been found that although impaired executive functioning and episodic memory were

observed within the initial week consultation window, people with mTBI were no longer discernible from comparisons at three months (Meares et al., 2008; Ponsford et al., 2012). Findings from longitudinal analyses have however not been overly consistent: global cognitive deficits have been found to linger at three months in one study (Nygren de Boussard et al., 2005), and prolonged verbal memory difficulties were observed in another (Heitger et al., 2006). In mTBI participants who continue to report post-concussive symptoms, executive dysfunction (planning, task-setting, and error detection) was also observed and was related to reduced activation in prefrontal areas (Bottari et al., 2017).

1.4.3 Long-Term Cognitive Dysfunction

The notion of cognitive deficit abatement at 3 months has not been wholly supported in the literature: investigations indicating long-term cognitive deficits have continued to surface over the last decade. For instance, when examined more than 3 months after the mTBI, people have been found to perform worse than healthy comparisons on tasks of divided attention and elevated working memory load (Dean & Sterr, 2013; McHugh et al., 2006; Vanderploeg et al., 2005; Oldenburg et al., 2015), which are highly reliant on executive processes (Tombaugh, 2006). Deficits have also been observed in measures of verbal fluency up to years after mTBI (McHugh et al., 2006; Konrad et al., 2011).

With respect to episodic memory, verbal memory abilities have generally been found to recover within the first year (Blanchet et al., 2009; Heitger et al., 2006; Himanen et al., 2006), at least when attentional capacities are maximized, limiting frontal-executive resources (Blanchet et al., 2009). Instances of prolonged verbal memory deficits have, however, been noted in some cases (Beeckmans et al., 2017; Oldenburg et al., 2015; Tayim et al., 2016).

Deficits have not been consistently supported, with a number of longitudinal and cross-sectional studies in the long-term post-acute period failing to discern cognitive deficits among those who had sustained mTBI (Clarke et al., 2011; Dikmen et al., 2009; Ettenhofer & Abeles, 2009; Sterr et al., 2006), at least in the absence of other affective symptoms (Clarke et al., 2011; Sterr et al., 2006). Indeed, cognitive deficits have been noted to be more apparent if post-concussive symptoms persist (Helmich et al., 2015). Neuropsychological deficits following mTBI are thus heterogeneously observed, and a clear understanding as to the extent of any protracted cognitive impairments is still needed in this population. It is perhaps most fruitful therefore to consider results from meta-analyses.

1.4.4 Meta-Analytic Dissensus

Initial meta-analyses suggested that cognitive deficits remit by 3 months post-injury (Binder et al., 1997; Frencham et al., 2005). However, these earlier meta-analyses have been called into question for a number of reasons. In particular, it has been suggested that they obscure the minority of mTBI cases who may continue to exhibit persistent cognitive impairment beyond three months (Bigler et al., 2013; Iverson, 2010; Pertab et al., 2009; Rohling et al., 2012). Indeed, a more recent review of meta-analytic work has found that a small subset of people exhibit lasting cognitive impairment months or even years after the mTBI (Karr et al., 2014). Those who continued to exhibit affective disturbances as part of a constellation of post-concussive symptomatology, or those who had experienced multiple lifetime mTBIs, were more likely to have persistent cognitive deficits (Belanger et al., 2010; Karr et al., 2014). Heterogeneity between study methodologies and sample idiosyncrasies notwithstanding, it has also been suggested that inconsistent meta-analytic findings may be due to a lack of sensitivity across many neuropsychological measures towards evaluating (ecologically-valid) cognitive

functioning outside of an office setting (Bigler et al., 2013; Karr et al., 2014; Pertab et al., 2009). With regards to this, there has been burgeoning interest in understanding prospective memory functioning, which is considered an ecological cognitive function (Ellis, 1996).

1.5 Prospective Memory

Prospective memory (PM), refers to our ability to "remember to remember" to do something in the future (Ellis & Kvavilashvili, 2000). Over the past two decades, there has been increasing neuropsychological interest in understanding the abilities of individuals to remember to perform an intended action in the future. PM tasks are often differentiated as either being *event-based*, when a planned action is completed in the presence of an external cue (e.g., remembering to refill a prescription while at a medical appointment), or *time-based*, when the planned intention (e.g., remembering to take medication) is carried out following a certain amount of time or at a given time (e.g., every 12 hours). As described by the examples above, PM is a crucial aspect of cognition and a necessity for independent daily functioning (Smith et al., 2000). It is therefore important from a neuropsychological perspective to have an understanding of the specific factors underlying successful PM performance, so as to better understand PM failures when they arise. To this end, an understanding of some of the component processes and neural correlates subserving PM functioning is germane to establishing a case for possible PM deficits following mTBI.

Although it may be misunderstood as a distinct memory system (e.g., from retrospective or declarative memory, which refers to the ability to recall past facts and events), PM is actually a term used to account for the processes involved in the *formation, retention, and retrieval* of an intended action that is to take place at a future moment (Ellis, 1996; Graf & Uttl, 2001; McDaniel & Einstein, 2007). In addition, at the very least, PM can be conceptualized as

involving two fundamental component processes. One of these processes, the *prospective component*, involves remembering to recall a formed intention in the future, and the other, the *retrospective component*, involves remembering the contents, or what it is that must be remembered, and when it needs to be initiated (Ellis, 1996; Ellis & Kvavilashvili, 2000). For instance, if an individual must take medication at a certain time of day, they would have to form that intention (i.e., decide to take the medication), and then later have to remember to recall (prospective component) the specific type of medication (the what) and the specific time (the when) or context (e.g., taken with a meal) to take it. Therefore, in order to remember this content (retrospective component) so that it may be recalled in the future, they would have to first encode it.

1.5.1 Processes of Prospective Memory

1.5.1.1 Memory Encoding. To form the intention, conscious thought, which may be independent of the stimulus, is required not only to identify the need for that future action, but also to formulate future steps and strategies to enact it (Burgess et al., 2007). Neuroimaging studies have implicated what should perhaps best be identified as the anterior prefrontal cortex (PFC), but which is more commonly referred to as the rostral PFC (corresponding to the cytoarchitectonic area of Brodmann area 10; Knowlton et al., 2012), and in particular the rostrolateral PFC (Burgess et al., 2007; Poeppenk et al., 2010), in driving the formation of the intention (Burgess et al., 2011). In this capacity, the rostrolateral PFC plays a role in organizing inputs for further processing (Moscovitch, 1994), including supplying temporal context for the event (Jenkins & Ranganath, 2010), so that the content may be encoded and remembered to be carried out in the future.

To accomplish this, the rostrolateral PFC inputs are sent downstream to the medial temporal lobes (Ketz et al., 2015), where they are then encoded (Okuda et al., 2003; Poppenk et al., 2010). In particular, within the medial temporal lobes, it is thought that the encoding takes place in the hippocampus (Addis & Schacter, 2008; Gordon et al., 2011) and the parahippocampal gyrus (Burgess et al., 2011; Okuda et al., 2003; Poppenk et al., 2010).

1.5.1.2 Maintenance or Retention. Unfortunately, there has not been a lot of investigation into the neural correlates that subserve content retention, as most of the PM literature has instead focused on neural networks underlying retrieval. However, evidence from experimental studies suggests that the PFC again underlies much of the executive processes in the maintenance of PM (Burgess et al., 2003; McDaniel & Einstein, 2011). In this way, the rostrolateral PFC may play a role in maintaining the intention and remembering the intended action (Simons et al., 2006), bringing back up the relevant information into consciousness while engaged in another activity, so that the delayed intention can be retrieved and realized.

1.5.1.3 Retrieval. There has been a great deal of work aimed at understanding the specific retrieval processes and neural correlates underlying these processes. Although not all-encompassing, current understanding indicates that there are two main processes guiding the retrieval of PM, which are described as *strategic monitoring* and *spontaneous retrieval* (McDaniel & Einstein, 2007).

***1.5.1.3.1 Strategic Monitoring*.** Strategic monitoring refers to maintaining the PM intention while searching the environment for a cue or signal for an indication that it is time to complete the intended action (Guynn, 2003; Shallice & Burgess, 1996). For example, if an individual is to take medication at a specific time at night they may need to make conscious efforts to clock-monitor to know when to take it. Not unlike the processes involved in the

retention of an intended action as described above, the PFC has been implicated in the executive processes underlying strategic monitoring (Burgess et al., 2001). Indeed, the rostrolateral PFC has been associated with detecting the cue for action (Poppenk et al., 2010) in addition to maintaining the PM intention (Burgess et al., 2003). However the medial rostral PFC may also play a role in suppressing distracting thoughts from surfacing (Burgess et al., 2003), so as to sustain attention on the ongoing task and therefore work in concert with the rostrolateral PFC to aid in identifying the appropriate time for remembering and realizing the intention (Gilbert et al., 2005; Simons et al., 2006).

The processes underlying strategic monitoring are *very dependent on frontal lobe resources* such that when monitoring has to be engaged to a greater extent to find a cue, performance on any other ongoing task that divides attention will likely suffer (Scullin et al., 2010). However, failures in PM may also arise due to an inability to adequately engage in strategic monitoring (McDaniel & Einstein, 2000; Scullin et al., 2010). In considering the example of the individual that is required to take medicine at a specific time, but in this example may be heavily engaged in completing a challenging puzzle at the same time, it is conceivable that they may quite easily fail to monitor and notice when it is the correct time, and thus fail to take the medication.

To a significant extent, working memory capacity may therefore influence the ability to engage in strategic monitoring, particularly if the ongoing demands are high (Brewer et al., 2010; Wang et al., 2013). However, it must be acknowledged that much of the research on strategic monitoring has been constrained to laboratories and assessed on timescales of tens of minutes to an hour or two (Scullin et al., 2010). In more naturalistic settings involving real-world tasks, the interval between intention formation and execution may be substantially longer, often spanning

days or weeks. In these instances, individuals likely engage in selective monitoring, monitoring when in a context that the cue may be expected to be found (Marsh et al., 2006), and disengaging strategic monitoring when it is not appropriate (Chen et al., 2010). In contexts where individuals selectively remember when to monitor, often based on some salient cue or indicator (e.g., noticing the bathroom where the medication is stored), it has been suggested that another PM retrieval mechanism, *spontaneous retrieval*, may be engaged (Scullin et al., 2013).

1.5.1.3.2 Spontaneous Retrieval. Generally speaking, spontaneous retrieval is defined as an instance in which an individual does not consciously rehearse the intention (which would involve the rostral PFC; Burgess et al., 2001; 2003; Gilbert et al., 2005; Poppenk et al., 2010; Simons et al., 2006), but instead, recalls the intention relatively automatically. Thus, spontaneous retrieval has been suggested to occur in situations when someone may have momentarily forgotten the prospective memory component, or at least was not attending to it (Burgess et al., 2011; McDaniel & Einstein, 2000;). Indeed, participants from research studies often report the retrieval as if it had "popped into mind" (McDaniel & Einstein, 2000).

It has been suggested that the neurocognitive correlates of spontaneous retrieval encompass the hippocampus (Gordon et al., 2011; Moscovitch, 1994), such that the cue that is encountered (e.g., the bathroom) elicits enough of an interaction with the memory trace (e.g., needing to take the medication) to lead to a relatively automatic retrieval of the intention (McDaniel et al., 2004). At present, this finding of hippocampal involvement has only been found for contextually mediated spontaneous retrieval, which is to say only when an individual finds themselves in an environment with the relevant cues (Gordon et al., 2011). Although more research is needed to further corroborate this notion, it is at least in line with the perspective that

the hippocampus and surrounding regions of the medial temporal lobe are integral to spatial aspects of memory retrieval, likely due to place-cell formations (Miller et al., 2013).

In addition to the medial temporal lobe, there have also been suggestions that spontaneous retrieval may be subserved by the rostrolateral PFC (Burgess et al., 2011; Dumontheil et al., 2010). Although the exact mechanisms are unclear, previous work has established that the rostrolateral PFC supports processes during instances when thoughts are spontaneously generated (Christoff et al., 2004), in addition to the executive processes involved when tasks demands are high. Indeed, findings from functional magnetic resonance imaging indicate that activity in the rostrolateral PFC may follow a U-shape (Dumontheil et al., 2010), such that greater activity in the rostrolateral PFC may be observed when demands are low, in the generation of spontaneous thoughts necessary for spontaneous retrieval, but also in situations that place greater demands on executive processes, such as when trying to strategically monitor for a cue (Simons et al., 2006). Despite overlapping neural correlates, the case for strategic monitoring versus spontaneous retrieval is largely driven by the types of cues the individual is thought to be relying on.

1.5.1.3.3 Time- Versus Event-Based Cues. As has been mentioned previously, PM functioning is often differentiated as being time-based when the intended action is to be completed after a set amount of time has passed, or event-based when an external cue drives the intention recall. It has been suggested that time-based PM requires more effortful monitoring and self-initiated retrieval, rather than event-based PM, thought more prone to spontaneous retrieval strategies (McDaniel & Einstein, 2000). Due to greater demands on the executive functioning processes of self-initiated retrieval and strategic monitoring (Einstein et al., 1995), time-based tasks are therefore thought to place more demands on the frontal lobe (Burgess et al., 2001,

2003; Oksanen et al., 2014; Okuda et al., 2007), relative to event-based tasks, which are thought to be recalled more spontaneously and with less effort (McDaniel & Einstein, 2000).

1.5.2 Prospective Memory in mTBI

Despite the extensive evidence of frontal lobe alterations following mTBI (Abdel-Dayem et al., 1998; Bottari et al., 2017; Hartikainen et al., 2010; Helmich et al., 2015; Mac Donald et al., 2017; Mayer et al., 2011; McDonald, et al., 2012; Sorg et al., 2014; Strangman et al., 2010), and the extensive frontal involvement in PM processes as described earlier, at the time of thesis inception, only two studies had investigated prospective memory function in people with mTBI. One found that, compared to a no head injury comparison group, PM deficits were observed shortly after the head injury and in some cases, up to three months following mTBI (Tay et al., 2010). The second found that people over 65 years of age who had experienced mTBI were more likely to have PM deficits compared to no head injury comparisons (Kinsella et al., 2014). Despite these associations, as well as indications that LOC may indicate greater frontal trauma resulting from mTBI, the effects of LOC on PM among those with mTBI had yet to be investigated. Moreover, despite neuroanatomical evidence of alterations in the frontal lobe, even long after mTBI (Dean et al., 2015; Jorge et al., 2012; Kraus et al., 2007; Sorg et al., 2014; Wada et al., 2012), long-term PM functioning in mTBI had not been previously investigated, including differentiation of time- versus event-based deficits.

1.6 mTBI Cognitive Deterioration

A growing body of literature has supported the notion that mTBI may lead to accelerated brain aging (Bigler & Stern, 2015; Cole et al., 2015; Santhanam et al., 2019; Tremblay et al., 2019). Of note, it has been found that in some cases, following initial recovery, decline might be due to secondary neuropathological changes that are initiated by the primary injury (Bigler &

Stern, 2015; Gavett et al., 2011). In this way, the initial injury has been thought to set the stage for secondary injury (Bigler & Stern, 2015), propagating cortical changes. Burgeoning interest into these associations has subsequently uncovered links between mTBI and diffuse white matter cortical thinning, similar in scope to that found in aged brains (Cole et al., 2019; Santhanam et al., 2019, Tremblay et al., 2019), *along frontal brain regions and tracts* (Santhanam et al., 2019; Tremblay et al., 2019). Thus, indications suggest that some of these changes may be progressive in nature, laying way for early onset neurodegeneration (Cole et al., 2015). In fact, current evidence points to earlier-life mTBI as contributing to greater neurological decline in older adulthood as compared to late-life mTBI (Tremblay et al., 2019). In this way, mTBIs are thought to contribute to brain changes that can accelerate neurocognitive decline in some individuals (Bigler & Stern, 2015; Ross et al., 2012; Zhou et al., 2013).

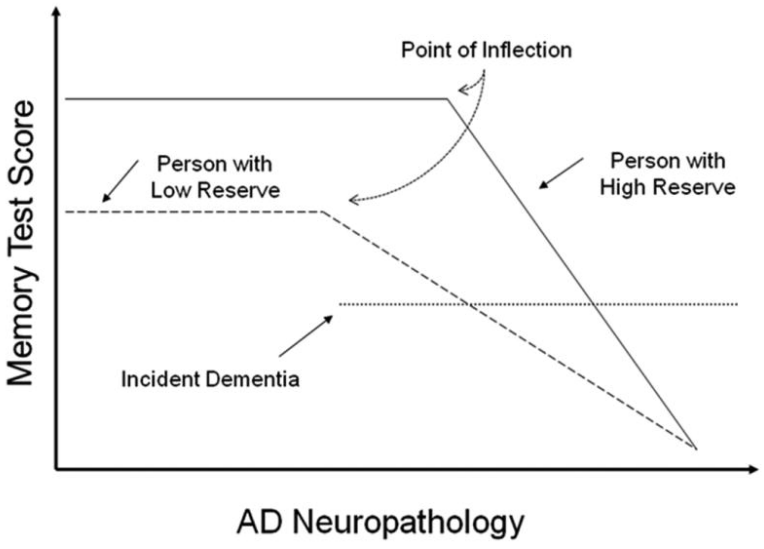
1.7 Cognitive Reserve

Evidence has surfaced to support the notion that the association between mTBI and cognitive outcomes are non-linear as a function of *cognitive reserve* (Mathias & Wheaton, 2015). Cognitive reserve refers to the findings that certain people may be protected from clinical manifestations of brain pathology or damage; it is this protection against cognitive impairment that comprises cognitive reserve (Stern, 2002, 2009). Related, but distinctly different, the overall brain size or neuronal count may also serve as a more passive role against brain injury, a protective factor identified as brain reserve (Steffener & Stern, 2012). In contrast, cognitive reserve typically is construed to denote more active neuronal processes as a buffer to brain damage, thought to occur through pre-existing cognitive processes, or through enlisting compensatory strategies (Stern, 2002, 2009). Thus, varying levels of cognitive reserve may explain that certain individuals are more apt to cope with (i.e., mask) brain damage.

Cognitive reserve is typically assessed through measurable indices, including intelligence, or educational or occupational attainment (Bigler & Stern, 2015); these lifetime exposure indices have for instance been found to be protective against the development of dementia in community samples. Thus, cognitive reserve is thought of as an inherent capability to buffer against neurocognitive changes, protecting against any progressed neurological degeneration contributing to maintenance of intact functioning (Bigler & Stern, 2015). By extension, research has indicated that once disease or brain-aging processes do take hold, the degenerative behavioural manifestations occur at a much quicker pace (Stern 2002, 2009). Those with higher cognitive reserve are therefore thought more able to withstand the accumulation of brain pathology, up to a critical limit leading to an inflection point, after which there is an accelerated deterioration of cognitive abilities to severe function loss, consumed as part of major neurocognitive dementias (Stern, 2009).

Figure 1

Stern (2009) Theoretical Cognitive Reserve Illustration



Note. A conceptualized graphical representation of cognitive performance as a function of cognitive reserve, considered through the lens of memory test scores. Figure from Stern (2009).

In addition to interest in understanding how occupational or educational exposures mitigate cognitive decline, over the last two decades there has been concerted attention to understanding whether other later life exposures may also be protective. For instance, independent of education or occupational attainment, engagement in a diverse set of leisure activities, including those that involve social contact, has been shown to serve as a proxy of cognitive reserve (Scarmeas et al., 2001; Stern, 2009). That is, increased participation in engaging activities in later life may attenuate the effects of neurological changes, providing neurocognitive buffering in the face of neurodegeneration. In a longitudinal study, greater participation in activities, including those that involve social contact but also exposure to greater perceived levels of social support (Evans et al., 2018; Fleck et al., 2019) were found to confer cognitive reserve. Although conventionally different from originally postulated indices of cognitive reserve, these lifetime exposures are not conceptually dissimilar on a neurocognitive level, as environmental enrichment has been shown to prevent or slow the accumulation of brain pathology in animal models (Lazarov et al., 2005), and through imaging studies on humans (Anaturk et al., 2018). However, the neuroprotection from social contact may be limited to a certain point of brain pathology, as among those who were later diagnosed with Alzheimer's disease, greater engagement in diverse leisure activities *even prior* to dementia onset were associated with much more rapid neurocognitive decline (Helzner et al., 2007).

1.7.1 Cognitive Reserve in mTBI

A meta-analysis has found that cognitive reserve, whether indexed based on educational attainment or pre-morbid intelligence (however measured) is associated with better cognitive and

functional outcomes following TBI (Mathias & Wheaton, 2015). Of note, participants were assessed at an average of a year and a half post-injury, and included all levels of TBI severity, from mild to severe. In contextualizing the influence of cognitive reserve in mTBI, individual investigations ought to be examined.

Longitudinal examinations of cognitive dysfunction following mTBI have found that, although people with mTBI exhibited lower performance on tasks of executive functioning than comparisons at 3 months following initial consultation, high levels of cognitive reserve minimized this relationship (Stenberg et al., 2020). It has, however, been suggested that lower cognitive reserve might be associated with proclivity to exhibit other post-concussive symptoms (Oldenburg et al., 2015). Over a 12-month follow-up period post-TBI, individuals with varying levels of severity were found to be protected from cognitive deficits across cognitive domains as a function of cognitive reserve when compared against healthy comparisons (Steward et al., 2018). Although recovery was most apparent for those with severe TBI, remittance of cognitive deficits as a function of greater cognitive reserve was also observed in mTBI. Indeed, a role for cognitive reserve in mitigating executive deficits in abstraction, reasoning, and problem solving following TBI has also been supported when participants are examined cross-sectionally within the first year post head injury (Donders & Stout, 2019).

1.8 Additional Considerations

Beyond these larger associations, this thesis was designed with consideration given to a number of other confounding factors. These variables were either controlled for, or were used to adjust neuropsychological test scores. Previous work has shown that, when investigating deficits in executive functions generally and PM functioning specifically, a number of demographic factors should be considered. For instance, age is an important variable to consider as older

adults (relative to younger adults) tend to be more susceptible to declines in cognitive functioning generally, with deficits often occurring in executive functioning (Murman, 2015); difficulties in prospective memory functioning have similarly been observed (Einstein et al., 1995).

Moreover, with regard to sex, research evidence has been remarkably varied, but suggests that sex differences in cognitive functioning may be related more to specific developmental stages, as opposed to naturally observable differences (Grissom & Reyes, 2019) and so sex has been controlled for in all studies presented in this thesis. Higher levels of educational attainment are associated with greater cognitive abilities (Wilson et al., 2009), and educational levels can be informative if considering cognitive reserve in research findings (Stern, 2009, 2011), and so education was controlled for in all studies included in this thesis.

From a neuropsychological perspective, language of administration may also affect results (Lorentz et al., 2002), perhaps due to a lack of psychometric equivalence on language-based tasks (Pekkala, 2012). It has also been established that more regular and heavier alcohol consumption is associated with lower levels of executive functioning (Day et al., 2015). In cases where individuals are experiencing cognitive deficits, alcohol consumption has been associated with higher risk of cognitive decline (Koch et al., 2019). Lower cognitive functioning following TBI has also been evidenced in cases where alcohol is being consumed (Ponsford et al., 2013), and has been linked to poorer cognitive outcomes in the rehabilitation from TBI (Weil et al., 2018). Alcohol consumption and testing language were therefore both controlled for in this thesis.

In considering clinical characteristics, executive functions subserved by the frontal lobe tend to be more sensitive to multiple mTBIs (Karr et al., 2014). Although it is not wholly clear

whether the effects of multiple mTBIs are additive or multiplicative, cognitive functioning tends to be lower in the case of multiple versus single lifetime mTBIs (Karr et al., 2014). In the present set of investigations, we included only individuals who had experienced a single life-time mTBI. Lastly, executive dysfunction and reduced PM performance have been found in those who are depressed relative to comparisons (Altgassen et al., 2009; Rock et al., 2014), and we controlled for depressive symptomatology in these studies.

1.9 Thesis Rationale

Given that frontal neural circuitry subserves executive functioning (Stuss, 2011), it is not surprising that executive dysfunction has been evident following mTBI. However, it remains unclear the extent to which mTBI affects executive function in the long term, particularly with respect to potential influences due to differing durations of experienced LOC. Although LOC has been found to exacerbate the neural effects of mTBI on the frontal lobe (Kraus et al., 2007; Sorg et al., 2014; Strangman et al., 2010), little is known concerning cognitive functioning following mTBI with LOC a year or more after the incident injury. This is particularly the case when considering prospective memory functioning, which is highly reliant on executive processes and frontal brain regions, particularly in time-based PM tasks as opposed to event-based tasks (Burgess et al., 2001, 2003; Oksanen et al., 2014; Okuda et al., 2007). A central goal of this thesis was to understand the extent of neuropsychological dysfunction in the long-term following mTBI with varied durations of LOC.

Moreover, despite indications of progressive frontal cortical loss following mTBI (Cole et al., 2019; Santhanam et al., 2019, Tremblay et al., 2019), little is known concerning the rate of cognitive deterioration in the long-term. Despite evidence suggesting that cognitive reserve may be imparted by participation in diverse engaging social activities (Scarmeas et al., 2001; Stern,

2009), and possibly through socially supportive resources (Evans et al., 2018; Fleck et al., 2019), these possibly-protective influences on cognitive deterioration in mTBI are less clear. The present investigation therefore sought to identify the rate of cognitive decline in the long-term following mTBI, and to examine for the predictive influence of social participation and social support against cognitive decline.

Chapter 2: Prospective Memory Impairment (Bedard et al., 2018)

2.1 Background and Hypotheses

Prospective memory functioning is reliant on frontal brain regions (Burgess et al., 2001, 2003; McFarland & Glisky, 2009), particularly in the involvement of executive processes including planning, strategic monitoring, and self-initiated retrieval (Gilbert et al., 2009; McDaniel & Einstein, 2011), which are engaged to a greater capacity in time-based relative to event-based PM tasks (Burgess et al., 2001, 2003; Oksanen et al., 2014; Okuda et al., 2007). A growing body of research has supported the prevailing view that structural and functional alterations to frontal brain areas are observed following mTBI (Abdel-Dayem et al., 1998; Mayer et al., 2011; Mcdonald et al., 2012; Sorg et al., 2014; Strangman et al., 2008), changes that are more pronounced when LOC is experienced (Kraus et al., 2007; Sorg et al., 2014; Strangman et al., 2008).

Despite evidence of reduce white matter integrity (Mac Donald et al., 2017), and lasting cognitive impairment in a minority of cases (Karr et al., 2014; McInnes et al., 2017) years after mTBI, only two studies had investigated PM functioning in those with mTBI. Of those, compared to comparisons, deficits were reported within a month of the head injury (Tay et al., 2010), and at 3 months among older adults (Kinsella et al., 2014). Published findings indicate that those who experienced varying LOC may exhibit PM deficits in the long-term following mTBI (Bedard et al., 2018), but it is unclear whether this is due to the number of lifetime mTBIs experienced. Consequently, the present study investigated for prospective memory impairments a year or more following *a single mTBI*, and examined whether time spent unconscious may influence reported findings.

2.1.1 Hypotheses

1. Based on available evidence from investigations of PM among those with mTBI (Kinsella et al., 2014; Tay et al., 2010), and of findings indicating that neuropsychological impairments may persist in those with mTBI (Karr et al., 2014; Mayer, Quinn, & Master, 2017), PM functioning will be lower in those with mTBI than in no head injury comparison participants.
2. Given that frontal lobe dysfunction has been found in long-term survivors of mTBI (Hartikainen et al., 2010; Mac Donald et al., 2017; Matsushita et al., 2011), and that time-based PM tasks are more dependent on the frontal lobe (e.g., Burgess et al., 2001), those who experienced mTBI with LOC should exhibit greater deficits in time-based than event-based PM tasks.
3. Given that the executive processes underlying PM are subserved by the frontal lobes (Burgess et al., 2001, 2003; Oksanen et al., 2014; Okuda et al., 2007), failures in PM will more likely be due to executive dysfunction, rather than a failure to recall the content of PM (i.e., retrospective memory).
4. Those who experienced mTBI with LOC will be more likely to be impaired in PM relative to no head injury comparisons. Moreover, PM impairment rates should increase with increasing length of LOC.

2.2 Methods

2.2.1 Sample

The CLSA consists of a national stratified random sample of over 50,000 male and female permanent Canadian residents aged 45 to 85 (Raina et al., 2009, 2019). This particular age range was decided on so that the study could capture mid-life experiences and transitions to

older age. For instance, those who were 45 at recruitment will be 65 at study conclusion, which is the age of demarcation for classifying individuals as older adults. In addition, the upper limit of recruitment was selected so that health and wellness could be assessed into the final years of the lifespan.

Participants were recruited into two separate cohorts. 30,097 participants (the Comprehensive Cohort) were recruited through postal mail-outs using contact information from Provincial Health Registration databases, and also through random digit dialing. As will be clarified below, individuals were only considered for the Comprehensive Cohort if they lived within a 50-kilometer radius of one of 11 data collection sites across the country. The initial sampling frame had prospective participants stratified based on age, and allowed for approximately 160,000 individuals to be considered for study inclusion. Of these, approximately 70,000 had agreed to be contacted. The final sampling frame for the Comprehensive Cohort consisted of stratified cluster sampling from consenting individuals to attain pre-determined quotas consistent with the relative age and sex distributions across each of the 10 Canadian provinces.

The other 21,241 CLSA participants (Tracking Cohort) were considered for recruitment if they had participated in the Canadian Community Health Survey and had consented to future contact. In addition, the sampling frame included individuals recruited from the Provincial Health Registration databases and through random digit dialing, as with the Comprehensive Cohort. These individuals were recruited through stratified cluster sampling in a manner similar to the Comprehensive Cohort, to attain age- and sex-distributed quotas.

2.2.1.1 Exclusion Criteria. Although a rationale is not provided, individuals were excluded from the CLSA if they resided in the three territories, lived on federal First Nations

reserves, or were full-time members of the Canadian Armed Forces. Moreover, individuals living in long-term care institutions were also excluded from the sampling frame. Participants were required to be fluent in English and/or French.

2.2.1.2 Study Specific Inclusion and Exclusionary Criteria. For the current investigation, only individuals who participated in the Comprehensive Cohort were included, because prospective memory was not evaluated in the Tracking Cohort, and the Comprehensive Cohort includes more extensive testing of executive functioning. Individuals will be excluded from the current analyses if they were ever diagnosed with a neurological disorder (e.g., Alzheimer's disease, multiple sclerosis, etc.), reported ever having had a stroke or transient ischemic attack, if they had experienced more than one brain injury, or if they had experienced a brain injury or extra-cranial injury in the past 12 months. Although it is important to consider more proximal time courses of executive dysfunction following mTBI, those who had experienced any of these injuries in the past 12 months were excluded because the CLSA does not capture any information on when the injury may have occurred. Thus, it would not be clear whether those individuals were in the acute phase (within three months post-injury) or not. Therefore, our mTBI sample consisted of those who had self-reported a single head injury, co-occurring with LOC, and experienced more than 12 months prior to study recruitment.

Per the CLSA protocol, participants were further divided based on length of LOC, including those who experienced LOC for less than one minute, and those who experienced LOC for 1-20 minutes. Although the CLSA also includes data on individuals who were unconscious for more than 20 minutes, they did not measure what the upper limit of unconsciousness was. The proposed study aims to examine executive functioning, including PM functioning in those with mTBI, and those with LOC greater than 20 minutes were therefore be excluded, because it

could not be determined which of those individuals have mTBI, and which have moderate to severe TBI (i.e., LOC greater than 30 minutes; American Congress of Rehabilitation Medicine, 1993). In addition to the mTBI groups, a comparison group consisting of individuals who had never experienced a brain or extra-cranial injury were included. Lastly, for the present investigation, only participants for whom data on all the variables detailed below were included.

2.2.2 Procedure

Prior to CLSA participant recruitment and assessment, ethical review of the CLSA protocol was conducted by the Ethical, Legal, and Social Issues Committee of the Canadian Institutes of Health Research (CIHR). Further institutional research ethics board approval was acquired for each individual research site prior to data collection.

Those in the Comprehensive Cohort were evaluated through 90-minute in-home interviews in addition to more in-depth physical and cognitive assessments conducted at one of 11 data collection sites across Canada. As mentioned previously, they were recruited from within a 25-kilometer radius of the data collection sites, and were assessed within 2-3 weeks of the in-home interview. For the proposed study, baseline data from participants in the Comprehensive Cohort have already been acquired. Given that the other 20,000 participants in the Tracking cohort participants did not complete PM testing, they are not included here. The present investigation was approved by research ethics boards at the Bruyère Research Institute and the University of Ottawa.

2.2.3 Measures

Demographic and clinical information, including age, education level, sex, marital status, alcohol consumption frequency, and previous injury (i.e., TBI) within the past 12 months were self-reported by participants using questionnaires that were administered through structured in-

person interviews. With respect to alcohol consumption, a 7-item frequency of use (from never to almost everyday) questionnaire was adapted from the Ontario Health Survey, originally sourced from the Canadian Health Measures Survey. All participants provided informed consent prior to completing the questionnaires and the neuropsychological assessments described below.

2.2.3.1 Traumatic Brain Injury. The Brief Traumatic Brain Injury Screen (BTBIS; Schwab et al., 2007) is a quick self-report screening tool of TBI for use with large numbers of individuals. It collects data on the number of lifetime TBIs, and length of unconsciousness following TBI (longest duration in the case of multiple TBIs) measured on a 3-point Likert scale. Reported LOC is recorded as either having been less than 1 minute, between 1 and 20 minutes, or greater than 20 minutes. The BTBIS has demonstrated good test-retest reliability (Van Dyke et al., 2010), construct validity (Ivins et al., 2009), and excellent concurrent validity with structured interviews in identifying mTBI, consistent with the criteria defined by the American Congress of Rehabilitation Medicine (1993).

2.2.3.2 Depression. Depressive symptomatology was assessed using the Center for Epidemiologic Studies Short Depression Scale (CES-D10; Andresen et al., 1994), a 10-item self-report measure with items rated on a 4-point Likert scale. Total scores range from 0-30, with higher scores indicating greater depressive symptomatology; a score of 10 or more is suggestive of clinically significant depressive symptomatology. The CES-D has demonstrated good test-retest reliability and internal consistency in community samples (Mohebbi et al., 2018), and also in older adults with and without cognitive impairment (Ros et al., 2011). Given associations between depressive symptomatology and PM (Altgassen et al., 2009), this measure has been included as a covariate in subsequent analyses.

2.2.3.3 Prospective Memory. The Miami Prospective Memory Test (MPMT; Hernandez Cardenache et al., 2014; Lowenstein & Acevedo, 2004), a 30-minute test, was used to evaluate PM functioning. The MPMT consists of 1 event-based trial, in which, after hearing a timer ring after 15 minutes, the participant is asked to select a $5 bill from a number of other denominations, and to hand it to the examiner, as well as to take a $10 bill and keep it. For the time-based task, a clock placed on the wall behind the examiner and in view of the participant is initially set to 08:00. At 08:15, the participant is to ask for an envelope from the examiner, which has five numbered cards (28, 14, 17, 13, and 11), as they are to give card number 17 to the examiner. There is a second time-based task at 30 minutes, but this second trial was not administered in the CLSA protocol.

The MPMT trials are scored based on intention to perform (i.e., whether the participant performed the action or the degree that they did not) scored from 0-3; accuracy (i.e., extent that the participant recalled the content of the intention, or substitutes the response with another) scored from 0-3; and their need for reminders, scored from 0-3. Reminders are provided after 4 minutes without response during the time-based trials, or during the event-based trial if the participant has not initiated a response within 60 seconds of the timer. Scores for intention to perform, accuracy, and need for reminders are summed for each trial, with trial scores ranging from 0-9. Higher scores indicate better performance.

As a relatively new measure of PM, the MPMT has only been used in a small number of published studies. Regardless, it has demonstrated adequate test-retest reliability, and good convergent validity with measures of executive functioning and episodic memory in identifying mild cognitive impairment (Hernandez Cardenache et al., 2014). However, data do not yet exist

to identify the convergent or discriminant validity of the MPMT relative to other published measures of PM.

2.2.3.4 Letter Fluency Test. The Controlled Oral Word Association Test (COWAT; Lezak et al., 2004), uses the three letters *F*, *A*, and *S* to assess letter fluency. Participants name as many words as possible within 1 minute, with separate trials for each letter. Participants are instructed not to provide proper names and not to provide different forms of the same word (e.g., loved, loving, lover). The score derived is the sum of the total number of admissible words provided for each letter. The COWAT has demonstrated good internal consistency across trials ($\alpha = .83$), and test-retest reliability even after 5-years follow-up (.74) (Tombaugh et al., 1999).

2.2.3.5 Animal Fluency Test. The Animal Fluency Test (AFT; Rosen, 1980) is a measure of semantic (i.e., category) fluency, in which individuals are to list as many animals as they can within 1 minute. Credit may be given for general categories (e.g., cat), but also for specific descriptions (e.g., hound) when both are provided. Two AFT scores are calculated, one being strict and one lenient. In the case of calculating strict AFT scores, if participants provided the category of animal but also specified subordinate speciation, the category was not counted in the score. For example, if a participant reported “dog, border terrier, great dane,” then “dog” would not be counted as it is the category to which the other responses belong. For the lenient AFT scores, broader inclusion criteria allowed for points to be awarded for breed and sub-speciation of animals. For this investigation, the lenient AFT scores were considered, and the total score was derived by summing the total number of admissible responses. The AFT has demonstrated good test-retest reliability of over .70 (Strauss et al., 2006), and convergent validity with the COWAT (.52; Tombaugh et al., 1999).

2.2.3.6 Mental Alternation Test. The Mental Alternation Test (MAT; Teng, 1994) is a set-shifting task, wherein participants count aloud, alternating between numbers and letters in ascending order (i.e., "1-A, 2-B, 3-C") as quickly as possible for 30 seconds. The correct number of alternations, consisting of each correct number-letter sequence, determines the total score. The MAT has demonstrated good test-retest reliability (.80; Jones et al., 1993), and is sensitive to detecting cognitive decline (Billick et al., 2001).

2.2.3.7 Victoria Stroop Test. The Victoria Stroop Test (Stroop; Regard, 1981) measures inhibition, mental speed, and mental control. The test consists of three parts. First, participants read a list of words printed in different ink colours (Word trial). In the second condition (Dot trial), participants are asked to name the printed ink colour of dots. In the third condition, participants name the colour of ink in which colour words are printed (Color-Word trial; e.g., to say "red" for the word "blue" printed in red ink). Scoring is based on the time to complete the 100 items in each trial. From this an interference score was derived by dividing task time of the Color-Word trial by the completion time of the Dot trial, to account for the influence of cognitive slowing (Strauss et al., 2006). The Victoria Stroop has demonstrated excellent test-retest reliability across the Word, Dot, and Color-Word trials (.83, .90, and .91, respectively; Troyer et al., 2006), and moderate convergent validity with other measures of inhibitory control (Strauss et al., 2006).

2.2.3.8 Rey Auditory Verbal Learning Test. The Rey Auditory Verbal Learning Test (RAVLT; Rey, 1964) is a measure of verbal learning and retention. Fifteen nouns are read out to participants at a rate of one word per second, after which participants are asked to immediately recall as many of the words as they can, in any order (immediate recall). Participants are prompted to recall the words again 5 minutes later (delayed recall). The number of correctly

recalled words constitutes scores for the immediate and delayed trials, respectively. The RAVLT has exhibited good internal consistency ($\alpha = 0.80$), and moderate test-re-test reliability (de Sousa Magalhaes et al., 2012; Strauss et al., 2006).

2.2.4 Statistical Analyses

Statistical analyses were performed using SPSS version 26 (Armonk, NY, USA: IBM Corp.). All continuous variables were checked for normality with the use of Q-Q plots, and through determining whether skew statistics remain between -2 and 2 (Curran et al., 1996), as is indicated for use with large datasets (Tabachnik & Fidell, 2013). Normalization of skewed variables was addressed following recommended procedures by Tabachnik & Fidell (2013). For all subsequent analyses, a significance level of $p < .05$ was used.

Group differences on continuous demographic and clinical data were analyzed with univariate analysis of variance (ANOVA), with Bonferroni-corrected pairwise comparisons. Categorical data were examined with Kruskal-Wallis tests and pairwise comparisons followed by Mann-Whitney U tests with Bonferroni corrections. To identify group differences on each neuropsychological test, univariate analyses of covariance (ANCOVAs) were performed, while controlling for age, education, sex, depressive levels, alcohol use frequency, and testing language. Pairwise comparisons included Bonferroni correction.

To investigate for a differential deficit in time-based or event-based PM among those that sustained a mTBI with LOC relative to comparisons, a repeated-measures analysis of covariance (ANCOVA) using group as the between-subjects factor (i.e., each of comparison, and the two mTBI groups) and PM cue type (i.e., time- vs. event-based) as the within-subjects factor was conducted, which included testing language (French or English), age, education, sex, depressive

symptomatology, and alcohol frequency, as covariates. Pairwise comparisons were performed with Bonferroni correction.

Following this, to determine the percentage of PM impairment, Z-scores were calculated on age and education adjusted time- and event-based functioning for each participant, using the mean and standard deviation of the comparison group's data. Using standard conventions to determine single test impairment (Strauss et al., 2006), impairment on time- and event-based functioning were defined as scoring more than 2 standard deviations (i.e., $Z < -2$) below the comparison group mean time- and event-based performance, respectively. Kruskal-Wallis tests were used to compare between-group rates of impairment in time- and event-based conditions; pairwise comparisons were completed with Mann-Whitney U tests with Bonferroni corrections, to adjust for the number of comparisons made within each impairment cue type (i.e., time- and event-based).

An additional aim of the study was to examine for differential functioning on intention to perform, accuracy, and the need for reminders, which were performed by first combining each of those domain scores across the event- and time-based tasks. Subsequently, a 4 x 3 parametric repeated-measures ANCOVA was run, in which the between-subjects factor was group and the within-subjects factor was domain type (i.e., inverse transformed intention to perform, accuracy, and need for reminders); the same covariates were entered as in the ANCOVA described above.

Finally, logistic regression analyses were conducted to examine the distinctive contributions of executive functioning and retrospective memory on PM impairment, conducted separately for each mTBI group. Raw scores of these neuropsychological measures were examined in the logistic regression, and the same covariates that were entered in the previous ANCOVAs were also included.

2.3 Results

2.3.1 Demographic and Clinical Characteristics

Table 1 details demographic and clinical characteristics of our sample. There were a total of 14,134 participants included in the study for whom data was available on all variables of interest. 13,163 were comparisons, and the remaining 971 belonged to the mTBI groups, consisting of those who experienced LOC for less than 1 minute (n = 536), and those between 1 and 20 minutes (n = 435). All three groups were found to be comparable in terms of education (p = .61), marital status (p = .39), and age (p = .25), but differed with respect to sex (p < .01). Specifically, comparisons were found to have a larger proportion of females relative to males, compared to those with LOC < 1 min, p < .01, OR = 0.70, 95% CI = 0.59-0.82, and those with LOC 1-20 min, p < .01, OR = 0.67, 95% CI = 0.56-0.81. The mTBI groups had a similar proportion of females to males (p = .75).

Levels of depressive symptomatology differed between the groups (p = .01). Comparisons had lower depression scores than those with LOC 1-20 min (p < .01), but not those with LOC < 1 min (p = 1.0), and those with LOC 1-20 min did not differ from those with LOC < 1 min (p = .21).

Table 1

Participant Demographic and Clinical Characteristics

	Comparisons (*n* = 13163)	LOC < 1 min (*n* = 536)	LOC 1-20 min (*n* = 435)
Age, mean (SD)	61.8 (9.9)	61.0 (9.3)	61.6 (10.14)
Age, range	45-86	45-86	45-85
Sex			
Female (%)	54.0	44.1	44.0
Male (%)	46.0	54.9	55.9
Education			
< High school (%)	2.5	2.2	2.3
High school (%)	7.5	7.5	8.7
College diploma (%)	34.4	34.0	32.4
University degree (%)	29.0	28.2	26.4
Graduate degree (%)	26.6	28.2	30.3
Marital status			
Married (%)	71.6	74.4	73.3
Widowed (%)	7.3	7.3	9.4
Divorced (%)	9.8	6.3	6.0
Separated (%)	2.6	3.2	2.1
Single (%)	8.5	8.8	9.2
Depression, mean (SD)	4.7 (4.3)	4.8 (4.4)	5.3 (4.7)
Alcohol frequency			
Never (%)	9.6	9.0	7.8
< once a month (%)	16.6	19.0	17.9
About once a month (%)	11.2	10.4	11.5
2-3 times a month (%)	22.5	26.9	26.2
Once a week (%)	11.8	11.4	8.5
2-3 a week (%)	10.3	10.1	11.3
4-5 a week (%)	6.7	5.2	4.8
Almost every day (%)	11.3	8.0	12.0

Note. LOC = loss of consciousness.

2.3.2 Prospective Memory Functioning

Means and standard deviations by group on the MPMT are presented in Table 2. A repeated measures ANCOVA revealed a significant main effect of cue type, $F(1, 14121) = 85.25$, $p < .01$, $\eta 2 = 0.006$) with lower event- versus time-based performance, and a significant interaction between group and cue type, $F(2, 14121) = 7.41$, $p < .01$, $\eta 2 = 0.001$). Pairwise comparisons revealed that in time-based PM, both mTBI groups performed more poorly than the comparisons ($M = 8.76$; ps $< .01$), and that those with LOC < 1 minute ($M = 8.69$) did not differ from those with LOC 1-20 minutes ($M = 8.71$; $p = 1.0$). In event-based PM, those with LOC < 1 minute ($M = 8.71$) were found to perform better than comparisons ($M = 8.54$; $p < .01$) and those with LOC 1-20 minutes ($M = 8.52$; $p < .01$), and comparisons did not differ from those with LOC 1-20 minutes ($p = .50$).

2.3.2.1 Comparisons of Error Types. To investigate between-group differences on intention to perform, accuracy, and need for prompts, an additional repeated measures ANCOVA was conducted. It revealed a marginally significant main effect of group $F(2, 14121) = 2.83$, $p = .06$), a main effect of measurement type (intention, accuracy, and reminder), $F(2, 14121) = 8.48$, $p < .01$, $\eta 2 = 0.001$), and a significant interaction between group and measurement type, $F(2, 14121) = 7.52$, $p < .01$, $\eta 2 = 0.001$). Pairwise comparisons indicated that none of the groups differed on accuracy or need for reminders (ps $> .05$). For intention to perform, those with LOC 1-20 minutes had lower scores than comparisons ($p = .04$), but not those with LOC < 1 min ($p = .82$). Those with LOC < 1 min did not differ from comparisons on intention to perform ($p = .88$).

2.3.2.2 Time- and Event-Based Impairment. After applying the impairment criteria (i.e., scoring below the 5th percentile cut-off of the comparison group), 4.6% of comparisons,

5.5% for those with LOC < 1 min, and 7.1% of those with LOC 1-20 min were impaired on time-based PM, χ^2 (2) = 7.56, p = .02. Pairwise comparisons revealed that those with LOC 1-20 min had a higher rate of impairment on time-based PM than comparisons (p < .01), but not those with LOC < 1 min (p = .32). Comparisons did not differ from those with LOC < 1 min (p = .38). In event-based functioning, impairment rates were 7.2% for comparisons, 5.2% for those with LOC < 1 min, and 6.2% for those with LOC 1-20 min, rates that did not differ between groups χ^2 (2) = 3.43, p = .18.

Table 2

Prospective Memory and Cognitive Test Performance in the Study Samples

			Mild Traumatic Brain Injury			
	Comparison (n = 13163)		LOC < 1 minute (n = 536)		LOC 1-20 minutes (n = 435)	
Test	*M*	*SD*	*M*	*SD*	*M*	*SD*
Prospective memory						
Time-based (0-9)	8.76	0.78	8.69	0.87	8.71	0.88
Event-based (0-9)	8.54	1.27	8.71	0.98	8.52	1.29
Impairment rates						
Time-based (%)	4.6		5.5		7.1	
Event-based (%)	7.2		5.2		6.2	
MPMT Errors						
Intention to perform (0-6)	5.56	1.03	5.58	0.94	5.53	1.08
Reminder (0-6)	5.83	0.49	5.88	0.34	5.82	0.51
Accuracy (0-6)	5.91	0.40	5.93	0.29	5.88	0.46
Executive functioning						
COWAT	40.76	12.42	41.27	11.98	40.94	12.55
Stroop Interference	2.10	0.73	2.07	0.56	2.13	0.88
MAT	27.54	8.30	28.00	8.14	27.69	8.41
Declarative Memory						
RAVLT immediate	6.10	1.86	6.19	1.88	6.05	1.88
RAVLT delayed	4.29	2.15	4.41	2.15	4.14	2.12

Note. LOC = loss of consciousness; MPMT = Miami Prospective Memory Test; COWAT = Controlled Oral Word Association Test; MAT = Mental Alternation Test; RAVLT = Rey Auditory Verbal Learning Test

2.3.3 Predictors of PM impairment

2.3.3.1 Time-Based Impairment. To identify the unique contributions of retrospective memory (RAVLT immediate and delayed) and executive functioning (COWAT, AFT, Stroop, and MAT) to time-based PM impairments for each of the mTBI groups, logistic regressions were run, separately for each group, including the raw retrospective memory and executive function scores entered as predictors in addition to the demographic and clinical characteristics from the ANCOVA. For those with LOC of < 1 min, a test of the full model against a constant-only model was statistically significant, χ^2 (10) = 25.23, $p < .01$, Nagelkerke $R^2 = 0.10$. As shown in Table 3, an increase of one year of age (OR = 1.044, 95% CI = 1.02-1.07) was associated with a 4.4% increase in the odds of being classified as impaired. Among those with LOC of 1–20 min, χ^2 (13) = 30.765, $p < .01$, Nagelkerke $R^2 = 0.12$, a single point decrease on the MAT (OR = 0.90, 95% CI = 0.82-0.99), and a single year increase of age (OR = 1.04, 95% CI = 1.01-1.07), were associated with a 10% and 4% increase in odds of being classified as impaired on time-based performance, respectively.

2.3.3.2 Event-Based Impairment. As was done previously, logistic regressions were run, separately for each group, to investigate the unique predictors of event-based impairment, by including the raw retrospective memory and executive function scores and the demographic and clinical characteristics as predictors. As displayed in Table 4, results from logistic regressions to investigate the predictors of event-based impairment indicated that none of the variables entered into the model significantly predicted impairment status for those with LOC < 1 min ($p > .05$). However, for those with LOC 1-20 min, χ^2 (13) = 28.78, $p < .01$, Nagelkerke $R^2 = 0.12$, a single point increase of age (OR = 1.05, 95% CI = 1.01-1.08) was associated with a 5% increase in odds of being identified as impaired on event-based PM functioning.

Table 3

Logistic Regression Model for Predictors of Time-Based Prospective Memory Impairment Among the Participants

	LOC < 1 minute		LOC 1-20 minutes	
	OR	95% C.I.	OR	95% C.I.
Executive functioning				
COWAT	0.997	0.976, 1.020	1.006	0.982, 1.030
Stroop Interference	0.923	0.593, 1.436	1.060	0.780, 1.441
MAT	0.994	0.964, 1.025	**0.904**	**0.821, 0.987**
Declarative memory				
RAVLT immediate	1.037	0.861, 1.249	0.916	0.741, 1.133
RAVLT delayed	0.883	0.753, 1.036	0.967	0.804, 1.164
Testing language				
English (reference)	1.00		1.00	
French	1.170	0.531, 2.578	0.468	0.195, 1.122
Depression scores	1.034	0.981, 1.090	1.011	0.955, 1.070
Age	**1.044**	**1.016, 1.074**	**1.037**	**1.007, 1.069**
Sex				
Male (reference)	1.00		1.00	
Female	0.994	0.601, 1.658	1.127	0.606, 2.097
Education				
< High school (reference)	1.00		1.00	
High school	0.312	0.430, 14.076	0.317	0.057, 1.743
College	0.699	0.270, 7.046	0.729	0.164, 3.247
University degree	0.846	0.221, 6.305	0.624	0.137, 2.853
Graduate degree	0.713	0.258, 7.276	0.291	0.061, 1.382

Note. LOC = loss of consciousness; COWAT = Controlled Oral Word Association Test; MAT = Mental Alternation Test; RAVLT = Rey Auditory Verbal Learning Test; OR = Odds Ratio. Odds ratios that are significant ($p < .05$) have been bolded. Odds ratios greater than 1 indicate increased odds of being classified as impaired on time-based functioning, whereas odds ratios of less than 1 indicate decreased odds of impairment.

Table 4

Logistic Regression Model for Predictors of Event-Based Prospective Memory Impairment Among the Participants

	LOC < 1 minute		LOC 1-20 minutes	
	OR	95% C.I.	OR	95% C.I.
Executive functioning				
COWAT	1.007	0.976, 1.039	0.989	0.962, 1.017
Stroop Interference	1.163	0.662, 2.044	0.954	0.581, 1.568
MAT	1.002	0.959, 1.048	0.969	0.933, 1.006
Declarative memory				
RAVLT immediate	**0.675**	**0.505, 0.905**	0.903	0.712, 1.146
RAVLT delayed	1.064	0.824, 1.372	0.946	0.766, 1.168
Testing language				
English (reference)	1.00		1.00	
French	0.996	0.356, 2.824	0.311	0.103, 0.937
Depression scores	0.903	0.815, 1.001	1.000	0.937, 1.066
Age	**1.072**	**1.09, 1.053**	**1.046**	**1.011, 1.082**
Sex				
Male (reference)	1.00		1.00	
Female	1.125	0.545, 2.323	0.617	0.312, 1.222
Education				
< High school (reference)	1.00		1.00	
High school	0.454	0.059, 3.510	1.439	0.139, 14.932
College	0.448	0.078, 2.556	1.883	0.209, 16.994
University degree	0.409	0.067, 2.501	1.391	0.148, 13.051
Graduate degree	0.264	0.041, 1.685	2.126	0.229, 19.707

Note. LOC = loss of consciousness; COWAT = Controlled Oral Word Association Test; MAT = Mental Alternation Test; RAVLT = Rey Auditory Verbal Learning Test; OR = Odds Ratio. Odds ratios that are significant ($p < .05$) have been bolded. Odds ratios greater than 1 indicate increased odds of being classified as impaired on time-based functioning, whereas odds ratios of less than 1 indicate decreased odds of impairment.

2.4 Discussion

Prior research has indicated that frontal areas of the brain may be compromised in those that have experienced even mild TBI (Abdel-Dayem et al., 1998; Mayer et al., 2011; McDonald et al., 2012; Sorg et al., 2014; Strangman et al., 2008), particularly in those who had experienced LOC (Kraus et al., 2007; Sorg et al., 2014; Strangman et al., 2008). Moreover, there is growing concern that, at least in a subset of those who have experienced mTBI, alterations to frontal regions may persist many years after the TBI (Faber et al., 2016; Mac Donald et al., 2017; Matsushita et al., 2011). In addition, it has been recognized that time-based tasks relative to event-based tasks may place more demands on executive processes (McDaniel & Einstein, 2000) that are subserved by the frontal lobe (Burgess et al., 2001, 2003; Oksanen et al., 2014; Okuda et al., 2007). However, to the best of our knowledge, no studies have investigated whether length of LOC influences PM functioning in mild TBI. The present study thus had two principal goals: first, to evaluate performance of time- and event-based PM tasks among those who have experienced mTBI with LOC, and second, to assess the association between PM performance, executive function, and retrospective memory performance in people with a history of mTBI.

Contrary to our hypotheses, initial findings from the present study did not find evidence for a disproportionate deficit on time-based relative to event-based PM performance for those that experienced a mTBI with LOC. However, a small difference, with lower time-based performance was observed among both mTBI groups compared to comparison participants. Given that sex, age, education level, depressive symptoms, language of test completion, and alcohol frequency were controlled for, these findings do not seem to be accounted for by between-group variations in these factors. At first blush the present data indicate very subtle (and none for most participants) PM deficits, similar in magnitude to those observed in metanalyses of

neuropsychological deficits in the post-acute phase (i.e., 3 or more months post-TBI) (Binder et al., 1997; Frencham et al., 2005; Scretlen, & Shapiro, 2003).

However, after applying impairment criteria, a higher proportion of people in the mTBI groups exhibited time-based PM impairments (5.5-7.1%) than in the comparison group (4.6%). Our results therefore seem to align with the perspective that although a large proportion of those who experience mTBI may not develop significant dysfunction, a small minority may go on to exhibit cognitive impairment (Iverson, 2010; Bigler et al., 2013; Pertab et al., 2009; Rohling et al., 2012). Furthermore, as hypothesized, impairment in time-based PM was found to be more likely in those who were unconscious any length of time compared to comparisons. Furthermore, we did not observe differences in the rates of event-based impairment between the mTBI groups and the comparisons, with the exception of those who were unconscious for less than 1 minute, who had a lower rate of impairment relative to comparisons.

Importantly, we found evidence for a differential pattern of time- and event-based impairment in those who lost consciousness following TBI. While rates of event-based impairment did not differ between the mTBI groups and the comparisons, as indicated previously, we found that those who experienced a single mTBI with LOC of any length were more likely to exhibit time-based impairment than those with no history of TBI. This finding therefore suggests that the amount of time spent unconscious may be a useful indicator of the likelihood of exhibiting PM impairments, at least in time-based tasks, which are thought to be more reliant on the frontal lobe (Burgess et al., 2001, 2003; Oksanen et al., 2014; Okuda et al., 2007).

An additional aim of the present study was to evaluate the cognitive processes that may be involved in the PM impairments observed in those with TBI. Error analyses suggested that

PM deficits were associated with executive dysfunction (e.g., self-initiated retrieval or strategic monitoring), rather than a failure to recall the content of the PM task (i.e., retrospective component). Logistic regression analyses indicated that a single-point increase on the Mental Alternation Test was associated with decreased odds of time-based impairment for those who were unconscious for longer (1-20 minutes). These findings are consistent with previous work indicating that PM deficits following TBI may be driven by declines in the executive processes underlying PM (Fleming et al., 2008), as opposed to a failure of retrospective memory (Henry et al., 2007).

Chapter 3: Cognitive Impairment in mTBI (Bedard et al., 2020)

Some meta-analyses examining cognitive functioning following mTBI have found that cognitive deficits observed shortly after head injury remit by three months post-injury (Binder et al., 1997; Frencham et al., 2005). However, it is thought that the use of meta-analysis may have concealed the small subset of individuals who do experience persistent cognitive impairment following mTBI (Bigler et al., 2013; Iverson, 2010; Pertab et al., 2009; Rohling et al., 2012), and extant more than a year following mTBI (Karr et al., 2014; McInnes et al., 2017).

Previous research has found impairments in prospective memory among those who experienced any number of mTBI with varying time spent unconscious a year or more ago (Bedard et al., 2018), and has shown that prospective memory is largely reliant on executive processes (McDaniel & Einstein, 2011), However, the long-term effects of a single mTBI with loss of consciousness on executive functioning has not been examined previously. Because few studies have examined long-term neuropsychological outcomes from mTBI, particularly in the case of those who had spent time unconscious, this second study aimed to identify the proportion of individuals who experience cognitive impairment more than a year following mTBI with LOC.

3.1 Hypotheses

1. Given that those who experienced mTBI may exhibit alterations to frontal lobes years after head injury (Hartikainen et al., 2010; Mac Donald et al., 2017), it is predicted that those who experienced mTBI will be impaired on measures of executive functioning relative to no head injury comparisons.
2. Longer LOC has been found to predict greater frontal lobe disturbances (Kraus et al., 2007; Sorg et al., 2014; Strangman et al., 2010). We therefore predict that those who

spent more time unconscious will be more likely to have executive functioning impairments.

3.2 Methods

As with the first study presented in Chapter 2, the data for the present study came from the Canadian Longitudinal Study on Aging (CLSA) baseline comprehensive dataset. Our institutional research ethics boards provided approval for the present study.

3.2.1 Participants

For the present investigation, detailed inclusion and exclusionary criteria are provided in Bedard et al., (2020). Being the same as those in the first article described in Chapter 2 of this thesis, participants were excluded if they were ever diagnosed with a neurological disorder, had a cerebrovascular accident, or had likely experienced a brain injury in the past 12 months, as were those who had experienced multiple brain injuries, leaving only those who reported having lost consciousness as a result of a head injury that occurred more than 12 months prior to assessment. Those who failed to meet these inclusionary criteria within the T1 to T2 interval were excluded from the present study. mTBI participants were divided based on length of LOC: less than one minute (LOC < 1 min), one to 20 minutes (LOC 1-20 min), and individuals who had never experienced a brain injury served as the comparison group. Only participants for whom data were available for all the analytic variables were included. Thus, the people used in the Chapter 2 article are the same as in this study.

3.2.2 Measures

Demographic and clinical information, including age, education level, sex, marital status, and relative date of brain injury (i.e., more than 12 months ago) were self-reported by participants using questionnaires administered through structured in-person interviews. All

participants provided informed consent prior to completing the questionnaires and neuropsychological assessments described below. As is described to a greater extent in Chapter 2, categorization of the mTBI sample was done with the Brief Traumatic Brain Injury Screen (BTBIS; Schwab et al., 2007), and the Center for Epidemiologic Studies Short Depression Scale (CES-D10; Andresen et al., 1994), served to measure depressive symptomatology.

3.2.2.1 Neuropsychological Assessment. The same neuropsychological battery described in Chapter 2 was employed for the analyses in this present study. That is, neuropsychological measures included the: Animal Fluency Test (Rosen, 1980), Controlled Oral Word Association Test (COWAT; Lezak et al., 2004), Mental Alternation Test (MAT; Teng, 1994), the same abbreviated Rey Auditory Verbal Learning Test (RAVLT; Rey, 1964), and the Victoria Stroop Test (Spreen, & Strauss, 1998). The Stroop interference score was again derived by dividing task time of the Color-Word trial by the completion time of the Dot trial (Stroop; Strauss et al., 2006). As is described in greater detail in Bedard et al. (2018), prospective memory was assessed with the Miami Prospective Memory Test (MPMT; Hernandez Cardenache et al., 2014), with specific focus on the time-based (range: 0-9), and event-based (range: 0-9) subscales for the present study.

3.2.3 Statistical Analyses

Statistical analyses were performed using SPSS version 26 (Armonk, NY, USA: IBM Corp.). All continuous variables were normally distributed as checked with Q-Q plots and skew statistics, with the exception of the Stroop Interference scores, which were positively skewed and subsequently transformed using a logarithmic function.

Group differences on continuous demographic and clinical data were analyzed with univariate analysis of variance (ANOVA), coupled with Bonferroni corrected pairwise

comparisons. Categorical data were analyzed with Kruskal-Wallis tests and pairwise comparisons were conducted using Mann-Whitney U tests with Bonferroni corrections. Multivariate analyses of covariance (MANCOVA) were conducted including neuropsychological test scores, age, and depression scores as dependent variables, and education, sex, and language of testing as covariates. Follow-up univariate tests were then conducted with Bonferroni-corrected pairwise comparisons.

To determine the percentage of individuals experiencing cognitive impairment, Z-scores were calculated for each neuropsychological measure for each participant, using the mean and standard deviation of the comparison group's data. Using standard conventions (Schinka et al., 2010; Strauss et al., 2006), impairment was defined as a score 1.5 or more standard deviations below age- and education-adjusted comparison group means. Impairment rates were summed separately for tests of declarative memory (RAVLT immediate and delayed) and executive functioning (COWAT, AFT, MAT, and Stroop). Two-test within-domain impairment (i.e., impairment on two tests of declarative memory, or two or more tests of executive functioning) was then calculated using a 1.5 standard deviation cut-off. Kruskal-Wallis tests were used to compare between-group rates of impairment; pairwise comparisons included Bonferroni corrected Mann-Whitney U tests.

3.3 Results

3.3.1 Group Differences on Neuropsychological Measures

Means and standard deviations for the measures of neuropsychological functioning are duplicated in Table 5. The MANCOVA revealed significant group differences, $F(7, 14126) = 2.28$, $p < .01$, $\eta_p^2 = .001$. Follow-up univariate tests showed that this was due to group differences on the AFT, $F(2, 14134) = 6.0$, $p < 1 .01$, $\eta_p^2 = 0.001$. Those with LOC < 1 minute

scored higher on the AFT than comparisons, $p < .01$, $\eta_p^2 = 0.001$, and those with LOC 1-20 minutes, $p = .03$, $\eta_p^2 = 0.004$, but those with LOC 1-20 minutes did not differ from comparisons on the AFT, $p = 1.0$. Group differences were not observed on the COWAT, Stroop, MAT, nor on the RAVLT immediate or delayed (ps > .05).

Due to small effect size estimates obtained, the MANCOVA was re-run using a randomly selected subset of the sample, in order to generate more interpretable comparisons. In line with power analyses using G*Power 3.1.9.3, 279 participants were randomly selected for each of the three groups in order in order to detect small size effects, with Cohen's f of 0.14, with a power of 0.80. This MANCOVA was not significant, $F(6, 826) = 1.16$, $p = .33$.

3.3.2 Neuropsychological Impairment

3.3.2.1 Single-Test Impairment. As described above, the comparison group had fewer men relative to women when compared to the mTBI groups, and so a random sample of women equal in number to men (6233 participants of each sex) were selected to develop impairment rates. Groups remained similar with respect to age and education, ps > .05. Rates of impairment on the neuropsychological measures are presented in Table 1. Impairment rates differed across groups on the MAT, χ^2 (2) = 8.61, $p = .01$. Pairwise comparisons indicated that people with LOC 1-20 mins ($p = .01$, OR = 1.48, 95% CI = 1.09-2.03) were more likely than comparisons to be impaired, but not more likely than those with LOC < 1 min ($p = .53$). Those with LOC < 1 min did not differ from comparisons on the MAT ($p = .12$).

Group differences also emerged on the COWAT, χ^2 (2) = 12.17, $p < .01$: people with LOC 1-20 min were more likely to be impaired than comparisons ($p < .01$, OR = 1.65, 95% CI = 1.24-2.19) and people with LOC < 1 min ($p = .01$, OR = 1.69, 95% CI = 1.11-2.56), while those

with LOC < 1 min did not differ from comparisons (p = .89). Any LOC was associated with COWAT impairment across the sample, (OR = 1.28, 95% CI = 1.04-1.59).

Similar results were found for RAVLT immediate and delayed (χ^2 (2) = 12.37, ps < .01): people with LOC 1-20 were more impaired than comparisons (ps < .01, OR = 1.73, 95% CI = 1.14-2.63) and people with LOC < 1 min (ps = .01, OR = 1.65, 95% CI = 1.24-2.). People with LOC < 1 min did not differ from comparisons on the RAVLT immediate or delayed (ps = .78).

3.3.2.2 Two-Test Impairment. Rates of impairment on two or more within-domain tests (i.e., two declarative memory tests, or two or more 2 executive function tests) are presented in Table 5. Groups differed on two-test 1.5 SD impairment for both declarative memory, χ^2 (2) = 12.37, p < .01, and executive functioning, χ^2 (2) = 6.23, p = .04. People with LOC of 1-20 mins were more likely to be impaired on declarative memory (13.1% vs. 8.4%) than comparisons (p < .01, OR = 1.65, 95% CI = 1.24-2.20) and people with LOC < 1 min (p = .01, OR = 1.73, 95% CI = 1.14-2.63), while comparisons did not differ from people with LOC < 1 min, p = .78. A larger proportion of people with LOC 1-20 mins were impaired than comparisons on ≥2 executive functions (9.5% vs. 6.5%, p = .02, OR = 1.49, 95% CI = 1.06-2.09); people with LOC < 1 min did not differ from comparisons or those with LOC 1-20 mins (ps > .10).

Table 5

Neuropsychological Test Scores and Impairment Rates Across Study Groups

			Mild Traumatic Brain Injury				
	Comparison (n = 13163)		LOC < 1 min (n = 536)		LOC 1-20 min (n = 435)		p-value
Test	M	SD	M	SD	M	SD	
Declarative memory raw scores							
RAVLT immediate	6.10	1.86	6.19	1.88	6.05	1.88	.29
RAVLT delayed	4.29	2.15	4.41	2.15	4.14	2.12	.14
Impairment rates							
RAVLT immediate (%)	8.4		8.0		13.1		**.01**
RAVLT delayed (%)	8.4		8.0		13.1		**.01**
Executive functioning raw scores							
Stroop interference	2.10	0.73	2.07	0.56	2.13	0.87	.52
Mental Alternation Test	27.54	8.30	28.00	8.14	27.70	8.41	.69
COWAT	40.76	12.42	41.27	11.98	40.94	12.55	.42
Animal Fluency Test	20.30	5.56	21.30	5.59	20.41	5.56	**.01**
Impairment rates							
Stroop Interference (%)	4.0		3.4		6.0		.07
Mental Alternation Test (%)	7.8		9.0		11.4		**.01**
COWAT (%)	8.4		8.2		13.1		**.01**
Animal Fluency Test (%)	9.5		6.5		7.8		.07
Two-test impairment							
Declarative memory	8.4		8.0		13.1		**.01**
Executive functioning	6.5		9.0		9.5		**.04**

Note. LOC = loss of consciousness; RAVLT = Rey Auditory Verbal Learning Test; COWAT = Controlled Oral Word Association Test; neuropsychological raw scores are presented and rates of impairment based upon scoring 1.5 SD below the comparison group (n = 13163) mean and standard deviations (i.e., Z-scores); p-values considered significant (p < .05) have been bolded.

3.4 Discussion

Previous research examining long-term cognitive impairment after mTBI has provided mixed evidence, with studies generally finding persistent cognitive deficits among 4% to 10% of individuals (Karr et al., 2014), although it has recently been argued that these figures may be vast underestimates (McInnes et al., 2017). The understanding of persistent cognitive impairment following mTBI has unfortunately been limited by varied definitions of impairment across studies (Karr et al., 2014; McInnes et al., 2017). From this perspective, has been argued that adopting guidelines commonly used to identify mild cognitive impairment (Schinka et al., 2010) would provide a consistent definition for identifying impairment, particularly when examining impairment across cognitive domains.

The present data reveal that those with greater duration of unconsciousness (i.e., LOC 1-20 minutes) were more likely to be impaired than comparisons on the MAT (11.6% vs. 7.7%) and the COWAT (12.9% vs. 8.5%), which assess mental set-shifting, inhibitory comparison, and verbal initiation. Moreover, people with LOC 1-20 minutes had higher impairment rates than comparison participants on the RAVLT immediate and delayed declarative memory tasks (15.2% vs. 10.6%).

These group impairment rate differences were also found when two-test impairment criteria were used: a larger proportion of people with LOC 1-20 min were impaired on two or more tests of executive functioning (8.2% vs. 5.5%) and on the two tests of declarative memory (15.2% vs. 10.6%) compared to comparisons. It is also notable that those who reported LOC < 1 min were not more likely be impaired than comparisons when using two-test criteria. That is, consistent with findings from recent meta-analyses (Karr et al., 2014; McInnes et al., 2017), these data suggest that a small proportion (8.2% to 15.2%) of people may experience persistent

mild executive and declarative memory impairment following a single mTBI with loss of consciousness. Our findings indicate that most people who experience a single mTBI with LOC do not go on to exhibit long-term cognitive impairment, but support the prevailing view that a small minority of individuals may experience persistent cognitive dysfunction. These deficits were most apparent among those who reported having spent a longer time unconscious.

While the large sample size of the CLSA is a significant strength of the present study, a couple of limitations pertinent to this article must be taken into account. Although these data suggest that people who experienced mTBI with LOC of 1-20 minutes are more likely to be cognitively impaired than people who report mTBI with shorter periods of unconsciousness or no head injury comparisons, the data may also support the notion of greater score variability as opposed to greater impairment. There was a large sample size and sex imbalance, particularly between comparisons and the mTBI groups, which may have influenced reported findings. However, steps were taken to alleviate these biases both in parametric and non-parametric analyses. We also do not report ethnicity or cultural background, which is an important limitation when considering clinical translation of these findings. Finally, information regarding premorbid functioning (e.g., occupational attainment or estimates of intellectual ability) is not available. Differences in premorbid functioning may account in part for the unexpected findings for performance on the AFT.

Research has shown lower processing speed in people with mTBI compared to comparison participants with no history of head injury (Karr et al., 2014). The current study focused on memory and executive function exclusively; future research should investigate whether processing speed impairments may be implicated in the observed deficits. Similarly, the testing battery relied solely on verbal output, and so we cannot comment on, or extend findings

to other cognitive functions such as motor output, or visual memory. This will limit clinical inferences that can be drawn from these data.

3.4.1 Conclusions

The current study provides evidence that people who self-reported mTBI with LOC more than 12 months ago are more likely to present with executive and declarative memory impairment than people who have not experienced head injury. More time spent unconscious increased the likelihood of impairment, suggesting that length of time spent unconscious may be a relevant factor in considering long-term outcomes in mTBI. Future work will aim to identify specific predictors that may differentiate those who experience ongoing impairment from those who fully recover.

Chapter 4: Long-term Cognitive Decline Following mTBI

Although cognitive dysfunction following mild traumatic brain injury (mTBI) has long been believed to remit within the acute period (i.e., the first three months post-injury), a growing body of literature has indicated that some individuals continue to experience cognitive impairment long after the head injury (Karr et al., 2014; McInnes et al., 2017). Using a large sample from the Canadian Longitudinal Study on Aging (CLSA), we recently reported that people who had experienced mTBI with loss of consciousness (LOC) *more than a year* prior were more likely to be cognitively impaired on measures of executive functioning and verbal memory (Bedard et al., 2018, 2020).

Recent research has suggested that mTBI may lead to accelerated brain aging in some cases (Bigler & Stern, 2015; Cole et al., 2015; Santhanam et al., 2019; Tremblay et al., 2019), possibly due to secondary neuropathological changes that are initiated by the primary injury (Bigler & Stern, 2015; Gavett et al., 2011). Interestingly, links have been made between mTBI and associated diffuse white matter cortical thinning in frontal brain regions (Ross et al., 2012; Santhanam et al., 2019; Zhou et al., 2013) and tracts (Tremblay et al., 2019), similar to that found in aged brains (Cole et al., 2019; Santhanam et al., 2019, Tremblay et al., 2019). These findings open the possibility that some of the brain changes following mTBI may be progressive, increasing the risk of early-onset neurodegeneration (Cole et al., 2015). Current evidence indeed indicates that early-life mTBI contributes to greater neurological decline in older adulthood compared to late-life mTBI (Tremblay et al., 2019).

However, evidence has surfaced to support the notion that cognitive outcomes from mTBI are likely to differ as a function of *cognitive reserve* (Mathias & Wheaton, 2015). Cognitive reserve is typically indexed by measures of intelligence, educational or occupational

attainment (Bigler & Stern, 2015), and cognitive reserve theories hold that the brain can withstand brain damage either through the use of pre-existing cognitive processes, or through enlisting compensatory strategies (Stern, 2002, 2009). Thus, varying levels of cognitive reserve may explain findings indicating that some people exhibit greater cognitive decline than others after experiencing brain damage. Cognitive reserve has been associated with reduced extent of executive dysfunction at 3-months post mTBI when examined longitudinally (Oldenburg et al., 2015; Stenberg et al., 2020). Similar findings were also reported over a 12 month follow-up period post-TBI in an investigation involving mTBI participants (Steward et al., 2018); although recovery was most apparent for people with severe TBI, lower cognitive deficits as a function of greater cognitive reserve was also observed in mTBI. Similarly, in a cross-sectional study, cognitive reserve was found to be related to deficits in abstraction, reasoning, and problem solving following TBI, within the first year following head injury (Donders & Stout, 2019).

In addition to the most common measures of cognitive reserve such as pre-morbid intelligence, educational and occupational attainment, a role has been proposed for other later life exposures, including engagement in a diverse set of leisure activities (Scarmeas et al., 2001; Stern, 2009). Activities that involve not only social contact but also exposure to greater perceived levels of social support (Evans et al., 2018; Fleck et al., 2019) have been suggested to contribute to cognitive reserve relevant to neurodegeneration. Although social participation has been shown to be a possible protective factor long after more severe cases of TBI (Levi et al., 2013; Rassovsky et al., 2015), to date these links have, to our knowledge, not been examined in people with mTBI.

The present study therefore extended previous investigations (Bedard et al., 2018, 2020) by re-examining cognitive outcomes three years later in people who had reported experiencing a

single mTBI with varying levels of loss of consciousness, experienced more than a year prior to initial testing. We used data from the Canadian Longitudinal Study on Aging (CLSA, Raina et al., 2009, 2019), a large population-stratified study of aging. The extent to which mTBI may be associated with cognitive decline longitudinally is not readily clear, and much less so when loss of consciousness was experienced. This was therefore the focus of the present investigation, as was the assessment of the possible protective influence from social engagement and social support against cognitive decline in mTBI.

4.1 Hypotheses

1. Driven by findings that mTBI may lead to accelerated brain aging (Bigler & Stern, 2015; Cole et al., 2015; Santhanam et al., 2019; Tremblay et al., 2019), particularly in frontal brain regions (Ross et al., 2013; Santhanam et al., 2019; Tremblay et al., 2019; Zhou et al., 2013), it is thought that those with mTBI will be more likely to exhibit cognitive decline relative to comparisons. We believe that this will be more pronounced on measures of executive functioning, and for those who spent more time unconscious.
2. Findings in the cognitive reserve literature have supported a possible buffering to cognitive dysfunction in cases of brain pathology (Bigler & Stern, 2015), found to occur in cases of mTBI (Oldenburg et al., 2015; Stenberg et al., 2020; Steward et al., 2018). Stemming from the associated notion that engaging in diverse activities involving social contact (Scarmeas et al., 2001; Stern, 2009), and of perceiving greater social support (Evans et al., 2018; Fleck et al., 2019) may be an index of cognitive reserve, it is thought that greater time spent in leisure activities, and of perceiving having more social supportive resources, will each be predictive of a lower likelihood of exhibiting cognitive decline.

4.2 Methods

The data used for the present study were from the Canadian Longitudinal Study on Aging (CLSA), a large ongoing 20-year study examining health transitions and trajectories in a national stratified random sample of over 50,000 male and female Canadian residents aged 45 to 85 (Raina et al., 2009, 2019). Ethical review of the CLSA protocol was conducted by the Ethical, Legal, and Social Issues Committee, falling under the jurisdiction of the Canadian Institutes of Health Research (CIHR), and additional research ethics board approval was received for each research site prior to data collection. Baseline (T1) and the first 3-year follow-up (T2) wave of information, including demographic and clinical information, had been collected for all participants, with an initial sample of 30,097 (Comprehensive Cohort) evaluated through 90-minute in-home interviews, including more in-depth physical and cognitive assessments conducted at one of 11 data collection sites across Canada. The remaining 21, 241 participants (Tracking Cohort) were evaluated through phone interviews. The present study uses baseline (T1) and follow-up (T2) data from participants in the Comprehensive Cohort only, because participants in the Tracking Cohort were not asked to report prior TBI. Our institutional research ethics boards provided approval for the present study.

4.2.1 Participants

Detailed information on the sampling frame is provided in Raina et al. (2009, 2019). Briefly, CLSA participants include adults between the ages of 45 and 85 years who are fluent in English and/or French. For the present investigation, detailed inclusion and exclusionary criteria are provided in Bedard et al., (2020). Briefly, participants were excluded if they were ever diagnosed with a neurological disorder, had a cerebrovascular accident, or had likely experienced a brain injury in the past 12 months, as were those who had experienced multiple brain injuries, leaving

only those who reported having lost consciousness as a result of a head injury that occurred more than 12 months prior to T1 assessment. Those who failed to meet these inclusionary criteria within the T1 to T2 interval were excluded from the present study. mTBI participants were further divided based on length of LOC: less than one minute (LOC < 1 min), one to 20 minutes (LOC 1-20 min), or greater than 20 minutes (LOC > 20 min). In keeping with guidelines of classifying mTBI (i.e., LOC less than 30 minutes; American Congress of Rehabilitation Medicine, 1993), and as we have done previously (Bedard et al., 2018, 2020) participants who reported losing consciousness for more than 20 minutes were excluded from our analyses.

It should be noted that the CLSA does not examine posttraumatic amnesia or information for the calculation of a Glasgow Coma Scale score, and the specific date of brain injury is not known: the date of brain injury is recorded as having occurred more than 12 months ago. Finally, in addition to the mTBI groups, we included people who had never experienced a brain injury as our comparison group. Only participants for whom data were available for all the variables of analysis were included.

4.2.2 Measures

Demographic and clinical information, including age, education level, sex, marital status, and relative date of brain injury (i.e., more than 12 months ago) were self-reported by participants using questionnaires administered through structured in-person interviews. All participants provided informed consent prior to completing the questionnaires and neuropsychological assessments described below.

4.2.2.1 Traumatic Brain Injury. Identification and categorization of the mTBI sample was carried out with the Brief Traumatic Brain Injury Screen (BTBIS; Schwab et al., 2007), a short self-report TBI screening tool. The BTBIS records loss of consciousness as having

occurred for less than one minute (LOC < 1 min), between one and 20 minutes (LOC 1-20 min), or greater than 20 minutes, in addition to the number of lifetime TBIs. The BTBIS has demonstrated good test-retest reliability (Van Dyke et al., 2010), construct validity (Ivins et al., 2009), and excellent concurrent validity with structured interviews in identifying mTBI, consistent

4.2.2.2 Depression. The Center for Epidemiologic Studies Short Depression Scale (CES-D10; Andresen et al., 1994), a 10-item 4-point Likert rating scale was used to assess depressive symptoms. Items are summed, with a total range from 0-30, higher scores indicating greater depressive symptomatology. Clinically, a score of 10 or more suggests significant depressive symptomatology. The CES-D has demonstrated good test-retest reliability and internal consistency in community samples (Mohebbi et al., 2018), and also in older adults with and without cognitive impairment (Ros et al., 2011).

4.2.2.3 Social Participation. Social engagement was measured by having participants report the frequency of involvement in community-related social activities over the previous 12 months, including: 1) activities with family or friends outside the home; 2) church or religious activities; 3) sports or physical activities; 4) educational or cultural social activities; 5) service clubs or fraternal organizations; 6) neighbourhood, community or professional association activities; 7) volunteer or charitable work; and 8) other recreational social activities (e.g., hobbies, playing cards, gardening). Items were recorded using a 5-point Likert scale with scores corresponding to temporal frequency spans: 1 (daily), 2 (weekly), 3 (monthly), 4 (yearly), and 5 (never). The total social participation scale score was then calculated by separating out participants who first reported any daily participation across the social engagement variables, and then of those remaining, any of those who reported weekly participation were parsed,

followed by monthly, and yearly social engagement. *The total social participation score therefore ranged from 0 (never) to 4 (daily), denoting the greatest social involvement that a participant had engaged in over the previous year*. This measure of social participation was adopted from the Canadian Community Health Survey – Healthy Aging, and the English Longitudinal Study on Aging.

4.2.2.4 Social Support. The MOS Social Support Survey (Sherbourne & Stewart, 1991) was used to assess levels of perceived social support. The measure is a 19-item instrument that involves a 5-point Likert scale, rated from 1 (none of the time) to 5 (all of the time), comprising a total score range from 19 to 95, with higher scores indicative of greater appraised levels of social support. Items are also divided into several subscales, including: 1) emotional support (e.g., positive affect expressions and empathic understanding); 2) informational support (e.g., advisory, guidance, or commentary); 3) tangible support (e.g., providing instrumental aid whether material or behavioural); 4) positive social interaction (e.g., having others available to engage with); and 5) affectionate support (e.g., expressing love and admiration). Internal consistency of the MOS Social Support Survey is good across component scales (α = .72-90; Sherbourne & Stewart, 1991), and it has adequate test-retest reliability (Giangrasso & Casale, 2014).

4.2.2.5 Neuropsychological Assessment. A standardized neuropsychological battery was completed by participants, consisting of the: Animal Fluency Test (Rosen, 1980), Controlled Oral Word Association Test (COWAT; Lezak et al., 2004), Mental Alternation Test (MAT; Teng, 1994), and the Victoria Stroop Test (Spreen, & Strauss, 1998). The Stroop interference score was derived by dividing task time of the Color-Word trial by the completion time of the Dot trial (Stroop; Strauss, Sherman, & Spreen, 2006). An abbreviated Rey Auditory Verbal

Learning Test (RAVLT; Rey, 1964) was administered, consisting of one immediate trial and one delayed recall trial. As is described in greater detail in Bedard et al. (2018), prospective memory was assessed with the Miami Prospective Memory Test (MPMT; Hernandez Cardenache et al., 2014), which allows for the calculation of a prospective memory score (range: 0-18), as well as a time-based (range: 0-9), and event-based (range: 0-9) subscales, with higher scores indicative of greater prospective memory functioning.

4.2.3 Statistical Analyses

Statistical analyses were performed using SPSS version 26 (Armonk, NY, USA: IBM Corp.). All continuous variables were normally distributed as checked with Q-Q plots and skew statistics, with the exception of the Stroop interference and MPMT scores, which were positively skewed and subsequently transformed using logarithmic and inverse functions, respectively.

Group differences on continuous demographic and clinical data were analyzed with univariate analysis of variance (ANOVA), contrasts corrected with Bonferroni procedure. Categorical data were analyzed with Kruskal-Wallis tests and pairwise comparisons were conducted using Mann-Whitney U tests with Bonferroni corrections. Repeated measures analyses of covariance (ANCOVA) were run, with time-point (T1 and T2) and neuropsychological test scores as within-subjects factors, and group (LOC < 1 min, 1-20 min, and comparisons) as the between-subjects factor, while holding age, education, sex, and testing language and depression scores at T2 as covariates. Follow-up univariate tests were then conducted with Bonferroni-corrected pairwise comparisons.

Neuropsychological test scores were then adjusted by age and education. Reliable change indices (RCI) were then calculated by subtracting adjusted discrepancy test scores (i.e., T2-T1) by the comparison group adjusted mean discrepancy test scores (i.e., T2 mean – T1 mean). This

allows for further score adjustment based upon comparison group practice effects. This subtracted term then serves as the numerator, being divided by the standard error the difference of the comparison group age- and adjusted mean test score differences. A more detailed explanation with visual mathematical terms can be seen in Duff (2012) when RCI with practice effects are discussed. To then identify cognitive decline versus no change, a z-score cutoff of ± 1.645 was used; those scoring ≤ -1.645 were considered as having declined, those with RCI scores of ≥ 1.645 were identified as improved, and those between -1.645 and + 1.645 were regarded as having exhibited no change. Bonferroni corrected Kruskal-Wallis tests were used to identify group differences on the dichotomized declined vs. collapsed no change/improved RCIs across individual tests, as well as the reverse (improved vs. collapsed no change/declined). Similar sets of analyses were run collapsing RCIs across the test scores, but with decline being identified as deteriorating on two or more tests. This was done to identify global cognitive decline.

Finally, binary logistic regression analyses were conducted to examine the distinctive influences of social participation, and social support on cognitive decline vs. no change on the mTBI group with LOC 1-20 min. A significance level of $p < .05$ was used for all analyses.

4.3 Results

4.3.1 Demographic and Clinical Characteristics

The sample in the present study included 11,502 participants: 10,712 no head injury comparisons, 440 mTBI participants with LOC < 1 min, and 350 mTBI participants with LOC of 1-20 min. Demographic and clinical data are presented in Table 6. All three groups were similar in terms of age (p = .29) and education ($p = .29$), depression scores at T1 ($p = .32$) and T2 ($p = .53$), and marital status at T1 ($p = .37$) and T2 ($p = .13$). A Time x Group interaction was not

significant for depression ($p = .06$) nor marital status ($p = .60$). Participants differed on sex ($p < .01$), with the comparison group having a smaller proportion of males to females compared to people with LOC < 1 min ($p < .01$, OR = 0.63, 95% CI = 0.53-0.76) and people with LOC 1-20 min ($p < .01$, OR = 0.60, 95% CI = 0.49-0.74). The two mTBI groups had a similar proportion of females to males ($p = .73$).

Total social support levels were similar between groups at T1 ($p = .69$) and T2 ($p = .72$), and the Time x Group interaction was not significant ($p = .95$). When social support subscales were examined separately, no between-group differences were observed at T1 or T2 on any subscale (ps > .1), none of the Time x Group interactions on the social support subscales were significant, nor were there main effects of Time (ps >.1). Likewise, the Time x Group interaction for social participation was not significant ($p = .57$), nor were the main effects of Time ($p = .93$), or Group ($p = .06$). In examining social participation over the past year, Kruskal-Wallis revealed a group difference at baseline ($p = .03$), which Mann-Whitney U tests indicated was due to comparison participants reporting more frequent social participation relative to people with LOC < 1 min (p = .03). People with LOC 1-20 min did not differ from comparisons ($p = .15$), nor people with LOC < 1 min ($p = .70$). Social participation over the previous year did not differ between groups at T1 ($p = .22$).

Table 6

Participant Demographic and Clinical Characteristics

	Comparisons (*n* = 10712)		LOC < 1 min (*n* = 440)		LOC 1-20 min (*n* = 350)	
	T1	T2	T1	T2	T1	T2
Age, mean (SD)		64.6 (9.6)		64.5 (9.2)		63.8 (9.9)
Age, range		47-89		47-88		47-88
Sex						
Female (%)		54.7		43.0		41.7
Male (%)		45.3		57.1		58.3
Education						
< High school (%)		2.8		3.2		2.0
High school (%)		10.4		7.3		8.6
College diploma (%)		347.8		39.5		38.9
University degree (%)		25.5		26.4		22.6
Graduate degree (%)		23.6		23.6		28.0
Marital status						
Married (%)	72.6	71.3	76.4	75.9	74.3	73.7
Widowed (%)	7.3	8.5	6.1	6.6	6.3	6.9
Divorced (%)	9.6	9.3	8.0	7.5	7.7	7.4
Separated (%)	2.5	2.5	3.0	3.4	2.6	2.0
Single (%)	8.0	8.3	6.6	6.4	9.1	10.0
Depression, mean (SD)	8.9 (3.1)	8.7 (3.0)	8.8 (3.0)	8.8 (3.0)	9.1 (3.4)	8.6 (2.9)
Alcohol frequency						
Never (%)	9.8	8.0	8.6	7.5	9.4	7.7
< once a month (%)	11.4	11.2	9.8	8.2	10.9	11.1
About once a month (%)	6.5	7.0	5.2	5.5	6.6	6.9
2-3 times a month (%)	10.6	10.6	10.5	10.2	8.6	9.7
Once a week (%)	11.7	12.3	13.2	12.3	9.7	11.1
2-3 times a week (%)	22.8	22.1	22.0	21.1	25.1	22.0
4-5 times a week (%)	11.1	11.0	11.6	12.0	12.3	10.6
Almost everyday (%)	16.1	16.6	19.1	21.6	17.4	22.0
Social Support Total	82.1 (12.1)	82.5 (12.3)	82.5 (12.3)	82.5 (12.2)	81.73 (12.6)	81.8 (12.8)
Tangible	17.1 (3.2)	17.3 (3.2)	17.4 (3.1)	17.5 (3.1)	17.1 (3.1)	17.3 (3.1)
Affection	13.6 (2.2)	13.5 (2.2)	13.6 (2.2)	13.6 (2.2)	13.5 (2.3)	13.4 (2.3)
Positive Interaction	13.1 (2.1)	13.1 (2.1)	13.1 (2.1)	13.2 (2.0)	13.1 (2.2)	13.0 (2.2)
Emotional	34.3 (5.6)	34.3 (5.7)	34.2 (5.7)	34.1 (5.7)	34.1 (5.8)	34.0 (6.0)
Annual Social Participation						
None (%)	0.1	0.1	0.0	0.0	0.0	0.0
Yearly (%)	1.1	1.3	1.1	0.9	0.9	1.7
Monthly (%)	11.8	12.2	15.0	15.9	16.6	15.4
Weekly (%)	69.8	69.9	69.5	68.2	65.4	63.4
Daily (%)	17.2	16.6	14.3	15.0	17.1	19.4

Note. LOC = loss of consciousness.

4.3.2 Longitudinal Neuropsychological Functioning

Neuropsychological and impairment score data are presented in Table 7. A Greenhouse-Geisser corrected repeated measures analysis of covariance (ANCOVA) did not reveal a significant three-way Group by Neuropsychological Test Scores by Time-Point interaction, $F(5.79, 27724.28) = 0.86$, $p = .52$, and the Group by Neuropsychological Test Scores interaction was not significant, $F(4, 27724.28) = 0.81$, $p = .52$. However, there was a significant interaction between Time-Point and Neuropsychological Test, $F(2.90, 27724.28) = 10.84$, $p < .01$, which Bonferroni corrected pairwise-comparisons indicated was due to elevated performance on the RAVLT immediate and delayed at T2 compared to T1, ps $< .05$. The main effect of Group was not significant, $F(2, 9569) = 0.92$, $p = .40$.

4.3.3 Reliable Change Indices

4.3.3.1 Individual-Test Reliable Deterioration. When considering the relative dichotomized frequency of deterioration vs. no change/improvement between participants, Bonferroni corrected Kruskal Wallis analyses found significant group differences on the AFT, $\chi^2 (2) = 6.37$, $p = .04$, and the MAT, $\chi^2 (2) = 6.2$, $p = .04$, with no group differences in the other neuropsychological measures (ps $> .05$). Compared to comparisons, the LOC 1-20 min group included a greater proportion of people exhibiting cognitive deterioration from T1 to T2 on the MAT ($p = .02$, OR = 1.60, 95% CI = 1.09-2.37), and the AFT ($p = .01$, OR = 1.70, 95% CI = 1.12-2.58). People with LOC 1-20 min were similarly more likely to have deteriorated on the MAT ($p = .04$, OR = 1.82, 95% CI = 1.02-3.26), but not on the AFT ($p = .08$), compared to those with LOC < 1 min. No differences were observed between comparison participants and people with LOC < 1 min on the AFT or MAT (ps $> .05$). Notably, groups did not differ on dichotomized improvement rates (improved vs. no change/deterioration), or when omnibus

group level differences across the three RCI categorizations (improved vs. no change vs. deterioration) were examined, all *p*s > .10.

4.3.3.2 Global Reliable Deterioration. Omnibus level group differences emerged when further examining reliable decline on at least two cognitive measures, χ^2 (2) = 6.93, p = .03. Mann-Whitney U test pairwise comparisons indicated that people with LOC 1-20 min were more likely to have declined on two or more tests than comparisons, (p < .01, OR = 1.60, 95% CI = 1.23-2.28). People with LOC < 1 min exhibited a trend towards lower decline compared to people with LOC 1-20 min (p = .06), and no difference from comparison participants (p = .93). Reliable improvement on at least two cognitive measures was not found to differ between groups, *p*s > .10.

Table 7

Neuropsychological test and impairment rates across study groups

	Comparison (n = 10712)		Mild Traumatic Brain Injury LOC < 1 min (n = 440)		LOC 1-20 min (n = 350)	
Test, mean (SD)	T1	T2	T1	T2	T1	T2
Declarative memory raw scores						
RAVLT immediate	6.08 (1.84)	6.85 (2.12)	6.14 (1.92)	6.94 (2.23)	6.00 (1.85)	6.84 (2.15)
RAVLT delayed	4.30 (2.12)	4.97 (2.36)	4.28 (2.16)	4.97 (2.48)	4.21 (2.13)	4.89 (2.37)
RCI Deterioration/Improvement						
RAVLT immediate (%)		6.2 / 1.7		5.7 / 1.6		7.1 / 1.7
RAVLT delayed (%)		6.4 / 2.1		5.9 / 1.8		5.1 / 2.0
Executive functioning raw scores						
Stroop interference	2.12 (0.70)	2.10 (0.70)	2.07 (0.50)	2.04 (0.59)	2.19 (1.01)	2.10 (0.52)
Mental Alternation Test	27.62 (8.30)	27.11 (7.36)	27.96 (8.47)	27.03 (7.95)	27.53 (7.94)	26.69 (7.23)
COWAT	40.32 (12.45)	41.13 (12.27)	40.39 (11.97)	41.28 (11.68)	39.83 (12.47)	40.70 (13.02)
Animal Fluency Test	20.32 (5.50)	20.08 (5.13)	20.89 (5.51)	20.60 (5.19)	20.42 (5.10)	20.79 (4.88)
Event-based PM	8.58 (1.19)	8.68 (1.06)	8.68 (1.06)	8.75 (0.92)	8.64 (1.09)	8.69 (0.97)
Time-based PM	8.79 (0.70)	8.70 (0.88)	8.73 (0.73)	8.66 (0.97)	8.77 (0.72)	8.64 (0.96)
RCI Deterioration/Improvement						
Stroop Interference (%)		3.8 / 6.2		3.2 / 5.0		4.6 / 2.6
Mental Alternation Test (%)		5.4 / 2.6		4.8 / 2.5		8.3 / 3.4
COWAT (%)		6.6 / 2.9		5.5 / 3.6		8.6 / 4.3
Animal Fluency Test (%)		4.3 / 4.6		4.3 / 4.3		7.1 / 4.6
Event-based PM (%)		3.8 / 7.3		2.3 / 6.6		2.9 / 6.3
Time-based PM (%)		6.8 / 2.0		5.2 / 1.8		7.4 / 2.6
Global RCI Decline/Improvement						
Two or more tests (%)		6.7 / 6.4		6.6 / 6.1		10.3 / 6.6

Note. LOC = loss of consciousness; RAVLT = Rey Auditory Verbal Learning Test; COWAT = Controlled Oral Word Association Test; RCI = reliable change index; neuropsychological raw scores are presented and RCI rates represent those calculated on age- and education-adjusted test scores. Deterioration, presented before the forward slash is indexed as an RCI value of ≤ -1.645, and improvement, presented after the forward slash identifies the percentage of RCI values ≥ 1.645.

4.3.4 Predictors of Cognitive Deterioration

For each group, logistic regressions were run on dichotomized cognitive decline, including the social support subscales and the social participation scale as predictors, along with sex, testing language, depression and marital status at T2. The logistic regressions are presented in Table 8. The initial model, χ^2 (13) = 55.81, $p < .001$, was further refined with the removal of depression, marital status, and the affection subscale due to low predictive discriminability (Wald = 0.05, 0.02, and 0.3, respectively). The final logistic regression was statistically significant against a constant only model, χ^2 (5) = 24.89, $p < .001$, Nagelkerke $R^2 = 0.14$. For those with LOC 1-20 minutes, an increase of one point on the emotional support (OR = 0.86, 95% CI = 0.78 to 0.96) and positive social interaction scales (OR = 0.67, 95% CI = -0.46 to 0.88) were each associated with a 14% and 33% decrease in odds of cognitive deterioration. Moreover, a level increase in social participation over the previous year amounted to a 21% decrease (OR = 0.79, 95% CI = 0.67 to 0.91) in likelihood of cognitive deterioration. Over and above these, identifying as male came with a 461% increased odds of exhibiting cognitive deterioration (OR = 4.61, 95% CI = 1.77-11.98). For those who reported LOC < 1 min (χ^2 (5) = 13.24, p =.03, Nagelkerke $R^2 = 0.05$), a single point increase in emotional support came with a 10% decrease in odds of cognitive decline (OR = 0.90, 95% CI = 0.82 to 0.99), and being male was associated with a 194% increase in odds of cognitively declining (OR = 1.94, 95% CI = 1.29 to 2.58). A single point increase in emotional support was associated with a 5% decrease in exhibiting cognitive decline among comparisons (OR = 0.95, 95% CI = 0.93 to 0.97), χ^2 (5) = 87.48, $p < .001$, Nagelkerke $R^2 = 0.02$. For comparisons, being male came with a 182% increase in odds (OR = 1.82, 95% CI = 1.56 to 2.13), and a level increase in social participation was linked with a 17% increase (OR = 1.17, 95% CI = 1.11 to 1.23), in odds of cognitive deterioration.

Table 8

Logistic Regression Model for Predictors of Cognitive Deterioration on Two or More Tests

	Comparisons		LOC < 1 minute		LOC 1-20 minutes	
	OR	95% C.I.	OR	95% CI	OR	95% C.I.
MOS Social Support						
Tangible	0.98	0.95, 1.02	1.01	0.85, 1.20	0.892	0.76, 1.05
Positive Interactions	1.03	0.97, 1.09	1.18	0.87, 1.49	**0.67**	**0.46, 0.88**
Emotional	**0.95**	**0.93, 0.97**	**0.90**	**0.82, 0.99**	**0.86**	**0.78, 0.96**
Social Participation	**1.17**	**1.11, 1.23**	0.71	0.37, 1.37	**0.79**	**0.67, 0.91**
Sex						
Female (reference)	1.00		1.00		1.00	
Male	**1.82**	**1.56, 2.13**	**1.94**	**1.29, 2.58**	**4.61**	**1.77, 11.98**

Note. LOC = loss of consciousness; OR = odds ratio; p-values < .05 have been bolded.

4.4 Discussion

Increasing research interest has focused on understanding long-term neuropsychological function following mTBI. Although the literature has largely supported the prevailing view that cognitive dysfunction, if present, remits by three months following head injury, a subset of people with mTBI experience ongoing cognitive impairment (Bedard et al., 2018, 2020; Karr et al., 2014; McInnes et al., 2017). Beyond cross-sectional findings, little work has been devoted to longitudinal analyses in the post-acute period. However, preliminary indications suggest that mTBI may propagate accelerated brain aging (Bigler & Stern, 2015; Cole et al., 2015; Santhanam et al., 2019; Tremblay et al., 2019).

The present study reports on the first follow-up wave from the Canadian Longitudinal Study on Aging (CLSA); baseline data have been published previously (Bedard et al., 2018, 2020). We found that at three-year follow-up, people who had experienced mTBI with 1-20 minutes unconsciousness were 60% more likely to exhibit cognitive decline on the MAT (8.3% vs. 5.4%) and 70% more likely to decline on animal fluency (7.1% vs. 4.3%) when compared to people who had never experienced a TBI. A similar level of relative decline (82%) was found on the MAT when those with LOC of 1-20 minutes were compared to those who reported LOC of less than one minute (8.3% vs. 4.8%). When considering global cognitive decline, indexed as having declined on two or more neuropsychological measures, people with LOC 1-20 minutes were 60% more likely to experience cognitive decline (10.3% vs. 6.7%) compared to comparison participants. Notably, none of the groups differed with respect to rates of reliable improvement.

These data therefore provide neuropsychological evidence that is in line with the notion supported by imaging studies that mTBI is associated with accelerated neurocognitive decline (Bigler & Stern, 2015; Cole et al., 2015; Santhanam et al., 2019; Tremblay et al., 2019), and

provide evidence for the importance of loss of consciousness as a clinical consideration. Consistent with prior findings of diffuse axonal thinning and anisotropy within the frontal lobe (Ross et al., 2012; Santhanam et al., 2019; Tremblay et al., 2019; Zhou et al., 2013), the cognitive decline observed among people who have experienced mTBI with LOC between 1-20 minutes was apparent on measures of executive functioning. This occurred on tasks assumed to require executive control, set-shifting, and inhibition, highly reliant on working memory and processing speed – processes that are subserved by frontal tracts (Sasson et al., 2013). The present data indicate that these associations were stronger in people who experienced unconsciousness for a longer period of time (i.e., one to 20 minutes).

We also found an effect of social support and social participation on cognitive deterioration in mTBI: in people who experienced mTBI with LOC 1-20 minutes, a single-point increases on emotional support (which ranges from 0-40) and positive social interaction (0-15 range) were associated with 14% and 33% decreases in the likelihood of exhibiting cognitive decline, respectively. Moreover, we observed a 21% decrease in odds of cognitive deterioration with each level increase in social participation (i.e., increasing engagement from none to yearly, yearly to monthly, monthly to weekly, or weekly to daily). These data therefore suggest that social participation, particularly engaging in social activities that involve connecting with others, is associated with a lower long-term likelihood of experiencing cognitive decline following mTBI. These findings thus fit with the proliferating evidence suggesting that socially engaging leisure activities and perceived levels of social support buffer against cognitive dysfunction (Evans et al., 2018; Fleck et al., 2019; Scarmeas et al., 2001; Stern, 2009). Previous research has indicated that social participation can have protective neurocognitive influences in people with severe TBI (Rassovsky et al., 2015; Levi et al., 2013), and the current paper extends these

findings to people with mTBI. Note too that, whereas social participation was seemingly a positive protective factor against cognitive deterioration in people who reported mTBI with LOC of 1-20 minutes, it was associated with a 17% increase in odds of exhibiting cognitive decline in comparison participants. Although seemingly discrepant, these findings may be supported by the cognitive reserve literature: cognitive reserve is thought to impart a buffering effect up to an inflection point (Stern, 2009), and increased social participation has been associated with more rapid neurocognitive decline in some cases (Helzner et al., 2007). However, this discrepancy may also be driven by a subset of older participants experiencing cognitive decline among comparisons.

The present investigation takes advantage of the large sample size of the Canadian Longitudinal Study on Aging (CLSA) to assess long-term cognitive functioning following mTBI with LOC. It should be noted that analyses aiming to identify cognitive decline in the present study were conducted on age- and education-adjusted raw scores, and that the reliable change indices were calculated by using the standard error of the difference of mean comparison group performance, accounting for practice effects on repeat testing (Duff, 2012). This is a unique strength of the present paper, allowing for a more robust substantiation that cognitive declines are in fact *reliable*.

We also note a few limitations unique to the present study within the larger thesis. Although these data suggest that people who experienced mTBI with LOC of 1-20 minutes are more likely to experience cognitive decline at three-year follow-up relative to comparisons, it is also possible that what is observed is due to greater score variability as opposed to definite impairment. However, we contend that if this were the case, the variability should be weighted toward lower scores at follow-up, particularly given that group differences did not emerge when

looking at rates of reliable improvement. Given that the specific date or time since the mTBI is not known, it is not possible to make any definitive assertion with respect to temporality of findings – we know that the initial mTBI occurred more than 12 months before T1 testing, but how long before remains unknown.

4.4.1 Conclusions

We found that self-reported mTBI with loss of consciousness that occurred more than a year prior is associated with a greater likelihood of exhibiting cognitive decline relative to healthy comparison participants over a three-year follow-up period. It is notable that these associations occurred in the context of greater time spent unconscious (i.e., 1-20 minutes), indicating that length of unconsciousness is an important factor in guiding long-term outcomes. Moreover, in people who exhibited cognitive decline, greater social participation over the previous year and higher social support, were each associated with a lower likelihood of cognitive decline.

Chapter 5: General Discussion

The present thesis had three principal goals: 1) to identify the extent of differential impairments in time- versus event-based prospective memory functioning a year or more after mTBI with differing lengths of unconsciousness; 2) to clarify the rate of any impairments across executive functioning tasks; 3) to ascertain the extent to which these same mTBI participants exhibit cognitive decline over time; and 4) understand whether social participation and social support confer cognitive reserve against cognitive decline.

The first research article (Chapter 2) reexamined findings from a published paper (see Bedard et al., 2018) that had assessed prospective memory (PM) impairments long after mTBI with varying levels of loss of consciousness (LOC; i.e., LOC < 1 minute and LOC 1-20 minutes). As was mentioned previously, the sample in the first research article was reduced from the published manuscript (Bedard et al., 2018) in order to focus on individuals who had experienced only one lifetime mTBI, and so that alcohol consumption frequency could be included as a covariate in analyses. This first article found that people who had experienced mTBI with LOC of any length were more likely to experience PM impairment than comparisons more than a year later, with impairment categorized as scoring two or more standard deviations below age- and education-adjusted comparison group mean levels. Interestingly, this paper also identified that the impairments were differentially isolated to time-based PM functioning (i.e., not event-based PM), and that the proportion of being classed as impaired was much greater in those who spent more time unconscious. Indeed, 7.6% of those with LOC between 1-20 minutes exhibited impaired time-based PM, proportionally greater than in comparisons (4.6%), although not significantly greater than those with LOC < 1 minute (5.5%). Given that mean level prospective memory performance was no different between groups, and that group differences

emerged when examining impairment rates, these results therefore seemed to align with the growing view that most people who experience mTBI likely recover cognitively, but that a minority experience prolonged dysfunction (Bigler et al., 2013; Iverson, 2010; Pertab et al., 2009; Rohling et al., 2012).

Given that the impairments were most evident in time-based PM, which are conceptually thought to involve tasks that place greater demands on the frontal lobe relative to event-based PM (Burgess et al., 2001, 2003; Oksanen et al., 2014; Okuda et al., 2007), the finding that LOC 1-20 minutes was associated with greater likelihood of time-based impairment is also consistent with neuroimaging evidence suggesting greater frontal alterations as occurring in those who experienced longer unconsciousness following mTBI (Kraus et al., 2007; Sorg et al., 2014; Strangman et al., 2008). This link is also tentatively and indirectly supported by the neuropsychological data in the first study, as examination of error types across groups revealed PM deficits as being driven by a breakdown in executive processes (e.g., self-initiated retrieval or strategic monitoring), rather than an ability to recall the PM task content. Further binary logistic evidence highlighted co-occurring deficits on the Mental Alternation Test with increased likelihood of time-based PM impairments among those who had LOC of 1-20 minutes, therefore further indicating a role for declines in the executive processes as underlying the PM impairment (Fleming et al., 2008).

Findings in the first paper therefore motivated further inquiry into executive functioning within these same mTBI participants. In breaking down executive functioning by more component processes, the second paper (see Bedard et al., 2020) was able to examine for unique deficits across various tasks of executive functioning associated with mental set-shifting, inhibitory control, and sustained attention (Stuss, 2011). Accordingly, the second paper

reaffirmed findings from the first study that impairments in executive functioning are identifiable long after mTBI with loss of consciousness. This is of importance because deficits in the long-term following mTBI have been purportedly obscured in many other research studies given widespread efforts to examine mean level group-differences, and heterogeneous application of impairment definitions when used in examining multiple tests (Bigler et al., 2013; Iverson, 2010; Pertab et al., 2009; Rohling et al., 2012).

The second paper defined impairment as scoring 1.5 standard deviations below mean age- and education-adjusted comparison group test scores. As a number of different tests were examined, two-test within-domain (executive functioning and declarative memory) impairment criteria were used to identify cognitive impairment. We found evidence for impairment on individual tests of executive functioning (Mental Alternation Test and the Controlled Oral Word Association Test) among those with greater duration of unconsciousness (LOC 1-20 minutes) relative to comparisons. Given the associated correlated deficits between the Mental Alternation Test and time-based PM functioning in the first article, the impairments in the Mental Alternation Test among those who experienced mTBI with LOC 1-20 minutes in the second article is somewhat expected. However, as executive impairments still surfaced among those with LOC 1-20 minutes relative to comparisons, when impairment was classified as scoring impaired on two or more tests of executive functioning, the notion of long-term executive deficits following mTBI with unconsciousness appears further substantiated.

Furthermore, those with LOC 1-20 minutes were also found to exhibit impaired declarative memory, both on immediate and delayed recall as well as two-test declarative memory (combine immediate and delayed) impairment (15.2%) as compared to comparisons (10.6%) and those with LOC < 1 minute (10.4%). Taken together, these findings of impairments

in declarative memory and executive functioning are therefore consistent with findings from contemporary meta-analyses indicating that although most people recover from mTBI, a small subgroup appears to exhibit protracted cognitive dysfunction (Karr et al., 2014; McInnes et al., 2017). Although the specific mechanisms driving these neuropsychological findings in the long-term following single mTBI with unconsciousness are unclear, these behavioural data are indirectly supported by neuroimaging findings of reduced regional blood flow and fractional anisotropy within frontal brain regions (Dean et al., 2015; Hartikainen et al., 2010; Helmich et al., 2015; Jorge et al., 2012; Kraus et al., 2007; Mac Donald et al., 2017; Sorg et al., 2014; Wada et al., 2012). Loss of consciousness is also regarded as an index of brain injury severity, and is associated with neuroanatomical changes (Kraus et al., 2007; Sorg et al., 2014), with alterations to the frontal lobe being more likely to occur when loss of consciousness is reported (Jorge et al., 2012; Kraus et al., 2007; Sorg et al., 2014; Strangman et al., 2010). Evidence suggests that in cases when LOC is experienced, greater cortical shearing strains were likely to have occurred, with downstream consequences to cortical tracts supporting consciousness (i.e., ascending reticular activating system; Blyth & Bazarian, 2011; Jang, Kim, & Lee, 2019). Impairments in declarative memory and executive functioning in the present investigations among those with LOC 1-20 minutes are therefore consistent with these other data.

Recent neuroimaging findings indicate that mTBI is associated with accelerated brain aging (Bigler & Stern, 2015; Cole et al., 2015; Santhanam et al., 2019; Tremblay et al., 2019), thought to be a result of secondary neuropathological changes that are initiated by the primary injury (Bigler & Stern, 2015; Gavett et al., 2011). The white matter diffusivity noted in neuroimaging studies described above has similarly been compared to those found in aged brains (Cole et al., 2019; Santhanam et al., 2019; Tremblay et al., 2019), particularly when mTBI was

experienced earlier in life as compared to in later life (Tremblay et al., 2019). The analyses contained in the third paper of this thesis were therefore conducted to determine the extent that the same mTBI participants may be more likely to exhibit cognitive decline at follow-up.

At the three-year follow-up interval of CLSA data collection, the third paper (Chapter 4) reports that those who experienced mTBI with 1-20 minutes unconsciousness were 60% more likely to exhibit cognitive decline on the MAT (8.3% vs. 5.4%) and 70% more likely to decline on animal fluency (7.1% vs. 4.3%) when compared to comparison participants. A similar level of relative decline (82%) was found on the MAT when those with LOC of 1-20 minutes were compared to those who reported LOC of less than one minute (8.3% vs. 4.8%). When considering global cognitive decline, indexed as having declined on two or more neuropsychological measures, people with LOC 1-20 minutes were 60% more likely to experience cognitive decline (10.3% vs. 6.7%) compared to comparison participants.

These data therefore provide initial neuropsychological evidence that is in line with imaging data suggesting that mTBI is associated with accelerated neurocognitive decline (Bigler & Stern, 2015; Cole et al., 2015; Santhanam et al., 2019; Tremblay et al., 2019), and provide evidence for the importance of loss of consciousness as a clinical consideration. Consistent with prior findings of diffuse axonal thinning and anisotropy within the frontal lobe (Ross et al., 2012; Santhanam et al., 2019; Tremblay et al., 2019; Zhou et al., 2013), the cognitive decline observed among people who have experienced mTBI with LOC between 1-20 minutes was apparent on measures of executive functioning. This occurred on tasks assumed to require executive control, set-shifting, and inhibition, highly reliant on working memory and processing speed – processes that are subserved by frontal tracts (Sasson et al., 2013). The present data indicate that these

associations were stronger in people who experienced unconsciousness for a longer period of time (i.e., one to 20 minutes).

A secondary aim of the third paper was to assess whether social support and social participation may protect against some of the cognitive deterioration observed in those who experienced mTBI. We also found a relationship of social support and social participation on cognitive deterioration in mTBI: in people who experienced mTBI with LOC 1-20 minutes, a single-point increases on emotional support (which ranges from 0-40) and positive social interaction (0-15 range) were associated with 14% and 33% decreases in the likelihood of exhibiting cognitive decline, respectively. Moreover, we observed a 21% decrease in odds of cognitive deterioration with each level increase in social participation (i.e., increasing engagement from none to yearly, yearly to monthly, monthly to weekly, or weekly to daily).

These data therefore suggest that social participation, particularly engaging in social activities that involve connecting with others, is associated with a lower long-term likelihood of experiencing cognitive decline following mTBI. These findings thus fit with the proliferating evidence suggesting that socially engaging leisure activities and perceived levels of social support buffer against cognitive dysfunction (Evans et al., 2018; Fleck et al., 2019; Scarmeas et al., 2001; Stern, 2009). Previous research has indicated that social participation can have protective neurocognitive influences in people with severe TBI (Levi et al., 2013; Rassovsky et al., 2015), and the current paper extends these findings to people with mTBI. Note too that, whereas social participation was seemingly a positive protective factor against cognitive deterioration in people who reported mTBI with LOC of 1-20 minutes, it was associated with a 17% increase in odds of exhibiting cognitive decline in comparison participants. Although seemingly discrepant, these findings are supported by the cognitive reserve literature: cognitive

reserve is thought to impart a buffering effect up to an inflection point (Stern, 2009), and greater reported social participation prior to clinical manifestations of cognitive impairment have been associated with greater decline at follow-up (Helzner et al., 2007). In the case of those who experienced mTBI with LOC 1-20 minutes, increased social participation was suggestive of protection against cognitive decline. More research is required to replicate and understand this further. It may well be indicative of an inflection point to surface at subsequent follow-up intervals.

5.1 Limitations

The studies in this thesis are subject to a number of limitations. With respect to the specific sample used, data on mTBI were self-reported and are therefore biased by retrospective recall, which may have limited the ability to discern which individuals may have experienced LOC between 1-20 minutes from those who lost consciousness for less than 1 minute. Participants may have also perceived questions related to head injury and concussion differently than intended, and thus some people who experienced a head injury with or without LOC within the past year may have gone undetected. In addition, it is acknowledged that data were not available for post-traumatic amnesia, or Glasgow Coma Scale scores. Similarly, an acknowledged limitation is a lack of data on the exact time since injury. Given the prevalence of mTBI in younger adults, and that this study included individuals between the ages of 45-85, it is not exactly clear what the relationship between time since injury, nor the impact of temporal span among those who experienced multiple brain injuries.

Moreover, there was a large sample size and sex imbalance, particularly between comparisons and the mTBI groups, which may have influenced the findings. However, steps were taken to alleviate these biases both in parametric and non-parametric analyses. We also do not

report ethnicity or cultural background, which is an important limitation when considering clinical translation of these findings. Finally, information regarding premorbid functioning (e.g., occupational attainment or estimates of intellectual ability) is not available. Pre-mTBI cognitive assessments would be useful for identifying the factors (e.g., pre-mTBI executive dysfunction, emotional distress, or old age) that predispose someone to long-term PM impairments resulting from a mTBI.

Although these data suggest that people who experienced mTBI with LOC of 1-20 minutes are more likely to be cognitively impaired than people who report mTBI with shorter periods of unconsciousness or no head injury comparisons, the data may also support the notion of greater score variability as opposed to greater impairment. However, we contend that if this is the case, the variability is seemingly weighed toward lower scores. This appears most clearly in the third article, where greater extent of reliable decline relative to improvement was observed among those who experienced mTBI with LOC of 1-20 minutes compared to comparisons.

A limitation in the present study also has to do with family-wise error within impairment analyses; when uncorrected, proclivity for false-positive errors is increased (see Huizenga et al., 2016). Even in the presence of highly correlated tests, family-wise error may be unfavourably elevated. Therefore, caution is advised in interpreting the odds ratios attributed to significant impairment analyses, as they may be slightly elevated. However, the testing battery also made use of two tests of declarative memory and four measures of executive functioning, which in the second and third article of this thesis, were examined within a two-test impairment framework as another index of impairment (Schinka et al., 2010). This does protect against family-wise error rate violations to a certain extent, as deviation on multiple tests to infer impairment would better satisfy family-wise errors (Axelrod & Wall, 2007; Huizenga et al., 2016). In the second article,

there is however an inherent discrepancy in psychometric equivalence for between-domain impairment analyses, notwithstanding that the same verbal information is used for both measures of declarative memory. The two-test impairment analyses that were run should be weighed with this in mind, and considered as a way to characterize within-domain impairment as opposed to elucidating differential impairment.

Moreover, in considering the odds ratios attributed to varying levels of LOC across the three articles, it should be noted that odds of impairment attributed to any experienced unconsciousness (i.e., agnostic to head injury status) is not discernible. The current data set only included information related to unconsciousness relevant to a head injury, used for the analyses, and data concerning any other experienced unconsciousness is not reported. Therefore, although comparison participants did not include those who had reported experiencing a concussion or brain injury, it should be noted that the odds ratios cannot inform cognitive impairment as a function of any unconsciousness experienced. The only unconsciousness data available has to do with that experienced as a result of the head injuries.

5.2 Future Directions

Research has shown lower processing speed in people with mTBI compared to comparison participants with no history of head injury (Karr et al., 2014), which is of note given that the present studies focused on memory and executive functioning exclusively. Future research should investigate whether processing speed impairments may be implicated in the observed deficits, this is notable given that particularly in the case of measuring executive functioning, processing speed is intricately implicated (Stuss, 2011).

Cognitive reserve is thought to help withstand the accumulation of brain pathology to a point of inflection, after which the deterioration of cognitive abilities is thought to be accelerated

(Stern 2009). For example, greater neurological decline was for found even prior to the diagnosis of dementia in those who reported more social participation (Helzner et al., 2007). Insofar as social support and social participation were predictive of less cognitive impairment in the LOC 1-20 minutes group, it could be that these same individuals exhibit more pronounced decline at the next three-year follow-up interval. This can be examined once the next wave of CLSA data is made available. In the interim, it is possible that the mTBI participants who were impaired at baseline may have exhibited greater neurocognitive decline in the face of elevated social support or social participation at this first follow-up interval. A follow-up study to this thesis can involve identifying whether the mTBI participants who were impaired at baseline are more likely to decline further as a function of social support and social participation at the same T2 period.

In extending some of the limitations of the present investigations, although use of large data from the CLSA has been helpful in understanding cognitive impairment following long-term mTBI, future investigations involving more stringent mTBI criteria would be helpful to confirm the findings from the present investigations. Future investigations could include data on post-traumatic amnesia, specific length of time spent unconscious, and Glasgow Coma Scale scores.

5.3 Clinical Implications

The findings from this thesis support a growing perspective that a small minority of individuals exhibit cognitive impairment following mTBI, and suggest that LOC should be an important clinical consideration, guiding both assessment and rehabilitative efforts.

Promising work has provided evidence toward efficacy in the use of transcranial magnetic stimulation in alleviating persistent post-concussive symptoms and in improving bilateral frontal brain activation (Ansado et al., 2019; Koski et al., 2015). Similar work may

explore rehabilitation in people who experience persistent neuropsychological difficulties in mTBI, years after the incident head injury. When cognitive impairments are identified, evidence has supported the utility of cognitive retraining, wherein impaired cognitive functions may be restored or ameliorated, typically through repetitive practice and by gradually increasing cognitive-difficulty in a stepwise manner (Ponsford, Sloan, & Snow, 2013). Findings from his thesis would suggest that cognitive retraining for people following mTBI may be most beneficial if it is to focus on attentional set-shifting and inhibitory control. Evidence supports the use of 10-weeks of attention process training as being helpful toward improving difficulties with cognitive control in people who have experienced acquired brain injuries (Sohlberg et al., 2000).

An alternative approach may be to implement compensatory strategies to reduce the cognitive demands and automate processes that may otherwise be dependent on deficient cognitive functions (Nowell et al., 2019). With regards to assisting deficits in executive functioning, the use of external compensatory approaches (Fleming, Shum, Strong, & Lightbody, 2005) (e.g., Google calendar on mobile phones; Baldwin & Powell, 2015; McDonald et al., 2011) could prove beneficial for tasks encountered in daily life. This would not only reduce general demands placed on executive functions, but also to bypass any impaired self-initiated retrieval processes that can be encountered during time- or event-based prospective memory functioning. In cases where deficits appear in prospective memory functioning, implementation intentions, which are if-then conditions between an event and an intended action, may provide improvements in intention retrieval (Smith, McConnell Rogers, McVay, Lopez, & Loft, 2014). Moreover, visual imagery, an internal memory strategy, has been shown to strengthen retrieval by increasing the automaticity of recall (Thöne-Otto & Walther, 2008), and may be of benefit to

increase time- and event-based memory functioning in patients with traumatic brain injury (Potvin, Rouleau, Sénéchal, & Giguère, 2011).

Relatedly, this thesis suggests that rehabilitation efforts should consider the effectiveness of social support and social participation in possibly protecting against cognitive decline following mTBI. Consistent with findings found in this thesis, increased levels of social support, particularly emotional support have predicted better cognitive performance in older adults (Seeman et al., 2001). Among those who have experienced mTBI, increased levels of social support have been associated with reduced levels of mental fatigue, particularly if social support was experienced shortly after the mTBI (Zheng et al., 2016). In the case of people receiving cognitive rehabilitation following traumatic brain injury, people who perceive having more social support have experienced greater cognitive improvement while completing cognitive-rehabilitative programs (Nowell et al., 2019). Therefore, it could be inferred from the results of this thesis that rehabilitation that is holistic in approach, by involving social supportive networks would be helpful in limiting the extent of any cognitive dysfunction experienced into the long-term following mTBI.

5.4 Conclusions

This thesis provides evidence to support the notion that a small group of individuals are likely to experience cognitive impairments a year or more following mTBI that was experienced with loss of consciousness. In the present thesis, this was found most notably in tasks assessing executive functioning processes. The first article, focusing on PM deficits indicated that the impairments were localized to time-based PM, particularly among those who spent a longer time unconscious (i.e., LOC 1-20 minutes). Given the presumed increased demands on frontal areas of the brain when engaging in executive processes subserving time-based functioning (like

strategic monitoring and retrieval), the findings of impaired time-based PM among those with LOC of 1-20 minutes was interestingly predicted by lower scores on the Mental Alternation Test, a measure thought to involve executive control, set-shifting, and sustained attention.

Evidence for impaired executive functions in the long term following mTBI with LOC were further supported in the second paper, again identifying that unique impairments were observed on the Mental Alternation Test and the Controlled Oral Word Association test in those who reported LOC of 1-20 minutes relative to comparisons. This was also notably found to co-occur with deficits in immediate and delayed declarative memory, and the impairments on those unique tests were further supported by impaired performance when two-test within domain (declarative memory and executive functioning) was delineated.

At three-years follow-up those with LOC 1-20 minutes were found to be more likely to exhibit cognitive decline as measured through age- and education-adjusted reliable cognitive indices, further adjusted to account for practice effects. Therefore, the decline observed in those participants are thought to be *reliable*, and suggest that mTBI with longer duration of unconsciousness is associated with cognitive deterioration. Further analyses revealed that perceiving more socially supportive resources, and of reporting spending time engaged in more frequent social activities over the previous year were both associated with decreased likelihood of exhibiting cognitive decline in those with LOC 1-20 minutes.

In summary, this thesis provides evidence to show that a subset of individuals who have experienced mTBI with loss of consciousness are more likely to exhibit cognitive impairment on measures of executive functioning (including prospective memory) and declarative memory when compared to individuals who have not reported a head injury. Moreover, those who

experienced mTBI with longer time spent unconscious were more likely to exhibit cognitive deterioration over a three-year follow-up period.

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Appendix A

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Long-term prospective memory impairment following mild traumatic brain injury with loss of consciousness: findings from the Canadian Longitudinal Study on Aging

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ABSTRACT

Objective: We aimed to examine the extent to which loss of consciousness (LOC) following mild traumatic brain injury (mTBI) may be associated with impairments in time- and event-based prospective memory (PM). PM is thought to involve executive processes and be subserved by prefrontal regions. Neuroimaging research suggests alterations to these areas of the brain several years after mTBI, particularly if LOC was experienced. However, it remains unclear whether impairments in time- or event-based functioning may persist more than a year after mTBI, and what the link with duration of LOC may be. **Method:** Analyses were run on data from the Canadian Longitudinal Study on Aging, a nationwide study on health and aging involving individuals between the ages of 45–85. The present study consisted of 1937 participants who experienced mTBI more than 12 months prior, of whom 1146 reported spending less than 1 min unconscious, and 791 had LOC between 1 and 20 min, and 13,525 cognitively healthy adults. Participants were administered the Miami Prospective Memory Test, and tests of retrospective memory and executive functioning. **Results:** Both mTBI groups were impaired in time-based PM relative to people with no history of TBI. Time- and event-based impairments were predicted by older age, and executive dysfunction among those who spent more time unconscious. **Conclusions:** Those with mTBI with LOC may experience impairments in PM, particularly in conditions of high demand on executive processes (time-based PM). Implications for interventions aimed at ameliorating PM among those who have experienced mTBI are discussed.

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Introduction

Traumatic brain injuries (TBI) are a common source of neurological disability, estimated to have an annual incidence of 400 per 100,000 individuals (Bruns, Jr. & Hauser, 2003; Voss, Connolly, Schwab, & Scher, 2015), although this figure is thought to be an underestimate, because many brain injuries go unreported (Voss et al., 2015). Most reported cases would be classified as mild traumatic brain injury (mTBI), which is thought to comprise around 70%

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of all TBI (Cassidy et al., 2004; Voss et al., 2015). Although there is a great deal of heterogeneity in definitions of TBI severity (Saatman et al., 2008), mTBIs are commonly defined based on the presence of any one of the following: loss of consciousness (LOC), amnesia surrounding the incident, altered mental state following the incident, or focal neurological deficits (American Congress of Rehabilitation Medicine, 1993). In addition, any LOC must not exceed 30 min, posttraumatic amnesia should not have persisted for more than 24 h, and Glasgow Coma Scale scores should be 13 or higher 30 min following the incident.

Despite the fact that 70% of TBIs are classified as mild, much of the research literature has focused on those who have sustained moderate-to-severe TBIs (those exceeding the previous criteria; American Congress of Rehabilitation Medicine, 1993). There is, however, burgeoning concern surrounding the nature of post-concussive symptoms following mTBI, most notably cognitive problems. Studies suggest that deficits in executive functioning and episodic memory may be most evident immediately after the brain injury and for up to two months afterwards (Karr, Areshenkoff, & Garcia-Barrera, 2014), and are thought to remit in a majority of individuals with mTBI by 3 months post-injury (Karr et al., 2014; Mayer, Quinn, & Master, 2017). However, neuropsychological deficits may persist in a minority of patients several months or even years after the mTBI (Karr et al., 2014; Mayer et al., 2017). For those that do exhibit ongoing cognitive dysfunction following brain injury, studies have found that a variety of variables, including individual factors (although not exhaustive), such as: increased age, lower levels of education, emotional distress prior to and after injury, and sleep difficulties may be implicated (Segev et al., 2016; van der Naalt et al., 2017).

Common among those that have experienced moderate or severe TBI are prospective memory (PM) deficits (Shum, Fleming, & Neulinger, 2002). PM is an aspect of episodic memory, but unlike conventional episodic memory, which involves retrospective memory – the ability to recall past facts and events – PM comprises our ability to 'remember to remember' to do something at a future time (Ellis & Kvavilashvili, 2000). For example, PM tasks may include remembering to take medication at specific times, or to attend medical appointments in the future. As such, PM is a crucial aspect of cognition and a necessity for independent daily functioning (Smith, Della Sala, Logie, & Maylor, 2000).

Neural correlates of PM

Mounting evidence from neuroimaging studies and electrophysiological recordings indicates that frontal lobe regions, particularly the rostral prefrontal cortex (i.e. Brodmann's area 10) subserve PM (Burgess, Gonen-Yaacovi, & Volle, 2011; Burgess, Quayle, & Frith, 2001; Burgess, Scott, & Frith, 2003; McFarland & Glisky, 2009). In addition, co-activations within parietal (Burgess et al., 2001, 2011; Gilbert, Gollwitzer, Cohen, Burgess, & Oettingen, 2009) and medial temporal lobes (Gordon, Shelton, Bugg, McDaniel, & Head, 2011; Moscovitch, 1994) are commonly found to support encoding, maintenance, and processes associated with spontaneous retrieval. There is also evidence for a role of the anterior cingulate cortex in processes implicated in preparatory attention toward fulfilling a prospective intention (Hashimoto, Umeda, & Kojima, 2011). Notwithstanding those associations, PM is mostly reliant on the executive processes underlying PM, including the following list of: planning, self-initiated retrieval, and strategic monitoring, which are subserved by frontal systems (Gilbert et al., 2009; McDaniel & Einstein, 2011).

Neuroimaging in mTBI

Neuroimaging studies have revealed structural and functional alterations to frontal areas of the brain following mTBI (Abdel-Dayem et al., 1998; Mayer, Mannell, Ling, Gasparovic, & Yeo, 2011; McDonald, Saykin, & McAllister, 2012; Sorg et al., 2014; Strangman et al., 2010), found also in those with persistent cognitive dysfunction (Hartikainen et al., 2010; Mac Donald et al., 2017). Moreover, these alterations may be more pronounced when LOC is experienced (Kraus et al., 2007; Sorg et al., 2014; Strangman et al., 2010). Despite these associations, only two studies have investigated PM function in those with mTBI. Of these, it has been reported that compared to controls, adults with mTBI may exhibit deficits on PM within a month of the incident, which may persist three months following the mTBI (Tay, Ang, Lau, Meyyappan, & Collinson, 2010). In addition, those over the age of 65 may exhibit deficits relative to controls on PM three months following the mTBI (Kinsella, Olver, Ong, Gruen, & Hammersley, 2014). Given the paucity of research in these areas, there is clearly a need for more extensive research into the impact on PM of mild forms of TBI, particularly in the long term (beyond 3 months post-injury), but also with older samples generally (Thompson, McCormick, & Kagan, 2006; although see Kinsella et al., 2014). Moreover, although LOC has been found to exacerbate the effects of mTBI on the frontal lobe, little is known about the effects of LOC on PM function.

It has been suggested that the relative requirements for strategic monitoring and self-initiated retrieval during the execution of PM may vary depending on whether the PM cue is event-based or time-based (McDaniel & Einstein, 2000). Whereas an event-based PM task is completed based on the presence of an external cue (e.g. remembering to refill a prescription at a medical appointment), a time-based PM task involves the execution of a planned intention following a certain amount of time or at a given time (e.g. remembering to take medication at a certain time). Due to increased demands for self-initiated retrieval and monitoring (Einstein, McDaniel, Richardson, Guynn, & Cunfer, 1995), time-based tasks have been posited to place more demands on the frontal lobe (Burgess et al., 2001, 2003; Oksanen, Waldum, McDaniel, & Braver, 2014; Okuda et al., 2007). Thus, given that frontal lobe dysfunction has been found in long-term survivors of mTBI (Hartikainen et al., 2010; Mac Donald et al., 2017; Matsushita, Hosoda, Naitoh, Yamashita, & Kohmura, 2011), we hypothesize that, compared to controls, those who experienced mTBI with LOC will exhibit greater deficits in time-based than event-based PM tasks. We also hypothesize that greater time spent unconscious will be associated with lower PM performance.

The present study reports data from a large population-based study of aging, the Canadian Longitudinal Study on Aging (CLSA), which evaluated PM using the Miami Prospective Memory Test (MPMT; Lowenstein & Acevedo, 2004). The MPMT consists of one event-based and two time-based tasks (only one is administered in the CLSA protocol), which are scored to allow for the assessment of the relative contribution of the memory intention (i.e., the extent to which the participant remembers that they are supposed to do something), accuracy (i.e., their ability to remember what it is that they are to do), and the need for reminders or prompting, with regard to PM performance. This coding system may allow for an evaluation of whether PM deficits may be due to a retrospective memory failure, as indicated by lower accuracy scores, or whether PM dysfunction may be driven by deficits in executive processes (Hernandez Cardenache, Burguera, Acevedo, Curiel, & Loewenstein, 2014). Finally, as mentioned above, PM may be associated with executive functioning (e.g., planning,

strategic monitoring, or even impulsivity) and retrospective memory abilities (to remember the content of the intention); we thus examined these associations among CLSA participants with mTBI.

Materials and procedures

We used data from the CLSA, an ongoing long-term study consisting of a national stratified random sample of over 50,000 male and female Canadians aged 45–85 (Raina et al., 2009). Ethical review of the CLSA protocol was conducted by the Ethical, Legal, and Social Issues Committee, which falls under the jurisdiction of the Canadian Institutes of Health Research (CIHR). Further institutional research ethics board approval was acquired from each individual research site prior to data collection. Participant data will be collected at 3-year intervals for a span of at least 20 years to examine health transitions and trajectories. Baseline information, including demographic and clinical information has been collected for all participants, with approximately 30,000 (Comprehensive Cohort) evaluated through 90-min in-home interviews, in addition to more in-depth physical and cognitive assessments conducted at one of 11 data collection sites across Canada. Participants in the Comprehensive Cohort were recruited from within a 25-km radius of the data collection sites, and were assessed within 2–3 weeks of the in-home interview (see Raina et al., 2009 for more detailed sampling frame information). The present study uses baseline data from participants in the Comprehensive Cohort. The other 20,000 participants in the Tracking cohort participants did not complete PM testing. The present study was approved by the research ethics boards at our institutions, responsible for reviewing studies including human participants.

Participants

Although detailed information on the sampling frame is provided in Raina et al. (2009), briefly, CLSA participants include adults between the ages of 45–85 years who are fluent in English and/or French. For the present investigation, individuals were excluded from the current analyses if they were ever diagnosed with a neurological disorder (e.g. Alzheimer's or Parkinson's diseases, multiple sclerosis), had ever had a cerebral vascular accident or transient ischemic attack, or those that experienced a brain injury or received multiple injuries (which may include brain injury) in the past 12 months. Thus, those that had self-reported having lost consciousness as a result of a head injury that occurred more than 12 months prior to study recruitment were included for our mTBI sample. They were further divided based on length of LOC, as captured in the CLSA protocol, for which we have data on those who experienced LOC for less than 1 min, and those who experienced LOC for between 1 and 20 min. Although the CLSA also includes those who lost consciousness for more than 20 min, as the present study sought to examine PM functioning in those with mTBI, those with LOC greater than 20 min were excluded, as it is not possible to ascertain whether they are all mild cases, or include moderate-to-severe TBI based on established conventions (i.e. LOC greater than 30 min; American Congress of Rehabilitation Medicine, 1993). However, it should be noted that the CLSA does not include data on posttraumatic amnesia, information for the calculation of a Glasgow Coma Scale score, nor date of brain injury. Finally, in addition to the mTBI groups, we included those that had never experienced a brain injury as our control group. We further only included participants for which we had data on all the variables detailed below.

Measures

Demographic and clinical information, including age, education level, sex, marital status, and previous injury within the past 12 months were self-reported by participants using questionnaires that were administered through structured in-person interviews. All participants provided informed consent prior to completing the questionnaires and the neuropsychological assessments described below.

Traumatic brain injury

Data pertaining to participant TBI(s) were recorded with the use of the Brief Traumatic Brain Injury Screen (BTBIS; Schwab et al., 2007), which was designed as a quick self-report screening tool of TBI for use with large numbers of individuals. This measure collects data on the number of lifetime TBIs, and length of unconsciousness following TBI (longest duration in the case of multiple TBIs), measured on a three-point Likert scale, with LOC reported as having been less than 1 min, between 1 and 20 min, or greater than 20 min.

Depression

Depressive symptoms were assessed with the Center for Epidemiologic Studies Short Depression Scale (CES-D10; Andresen, Malmgren, Carter, & Patrick, 1994), which comprises 10 questions rated on a four-point Likert scale. Total scores range from 0 to 30, with higher scores indicating greater depressive symptomatology (Cronbach's $\alpha = 0.79$). A score of 10 or more is indicative of clinically significant depressive symptomatology.

Prospective memory

PM was evaluated with the Miami Prospective Memory Test (MPMT; Hernandez Cardenache et al., 2014; Lowenstein & Acevedo, 2004), a 30-min test. See Hernandez Cardenache et al. (2014) for a complete description of the administration and scoring procedures. The MPMT is composed of 1 event-based trial, in which the participant is asked to select (from a number of different denominations of bills and change) a $5 bill, to be handed to the examiner, and a $10 bill that is to be taken and kept by the participant, after hearing a loud timer that is set for 30 min. For the time-based task, a clock placed on the wall behind the examiner and in view of the participant is initially set to 08:00. At 08:15 (and 08:30 for Trial 2), the participant is to request from the examiner an envelope, which has five numbered cards (28, 14, 17, 13, and 11), and to give card number 17 to the examiner. There is another similar time-based task at 30 min, but this second trial was not administered in the CLSA protocol.

Each of the MPMT trials are scored based on intention to perform (i.e. whether the participant performed the action, or their relative degree of failure to acknowledge the cue) scored from 0 to 3; accuracy (i.e. degree to which the participant correctly recalls the content, or substitutes the content of the response) scored from 0 to 3; and need for reminders, scored from 0 to 3. Reminders are provided in a hierarchical order after 4 min without response during the time-based trials, or if the participant has not initiated a response within 60 s of the timer going off in the event-based trial. Scores for intention to perform, accuracy, and need for reminders are summed for each trial, with trial scores ranging from 0 to 9, with higher scores indicating fewer errors.

Neuropsychological assessment

Additional measures of episodic memory and executive functions were completed by participants, including the Rey Auditory Verbal Learning Test (RAVLT; Rey, 1964) immediate and delayed recall, the F-A-S Controlled Oral Word Association Test (COWAT; Spreen & Benton, 1977), the Mental Alternation Test (MAT; Teng, 1994), and the Victoria Stroop Test (VST; Regard, 1981; although for a description see Strauss, Sherman, & Spreen, 2006), which was used to generate an interference score, calculated by dividing the completion time of the Color-Word trial by the Dot trial, to correct for the influence of cognitive slowing (Strauss et al., 2006).

Statistical analyses

Statistical analyses were performed using SPSS version 24 (Armonk, NY, USA: IBM Corp.). All continuous variables were checked for normality with the use of Q-Q plots, and through determining whether skew statistics remained between −2 and 2 (Curran, West, & Finch, 1996). Most variables were normally distributed, with the exception of all MPMT variables, which were negatively skewed, and the VST interference scores, which were positively skewed. Following recommended procedures (Tabachnick & Fidell, 2013), normality was achieved using inverse transformations on the MPMT variables and the VST interference scores were normalized with the use of logarithmic transformations; subsequent parametric analyses used these transformed variables.

Group differences on continuous demographic and clinical data, including age and depression were analyzed with univariate analysis of variance (ANOVA), with Bonferroni-corrected pairwise comparisons. Kruskal-Wallis tests were done to examine between-group differences on the categorical demographic data of education and marital status. Mann-Whitney U tests with Bonferroni corrections were used for pairwise comparisons on the categorical demographic data, and to examine for group sex differences.

To investigate for a differential deficit in time-based or event-based PM among those that sustained a mTBI with LOC relative to those who have not had a brain injury, a parametric repeated-measures analysis of covariance (ANCOVA) using group as the between-subjects factor (control and each of the TBI groups) and PM cue type (time- vs. event-based) as the within-subjects factor was conducted, which included testing language (French or English), age, education, sex, depressive symptomatology, and number of lifetime TBIs as covariates. Pairwise comparisons were conducted with Bonferroni correction.

Following this, impairment on time- and event-based functioning were defined as scoring below the 5th percentile of control group time- and event-based performance, respectively. Kruskal-Wallis tests were used to compare between-group rates of impairment in time- and event-based conditions; pairwise comparisons were completed with Mann-Whitney U tests with Bonferroni corrections, to adjust for the number of comparisons made within each impairment cue type (i.e., time- and event-based).

An additional aim of the present study was to determine whether differential functioning was observed on intention to perform, accuracy, and the need for reminders. This analysis was performed by first combining each domain score across the event- and time-based tasks to get composite error scores. We conducted a 3 x 3 parametric repeated-measures ANCOVA in which the between-subjects factor was group and the within-subjects factor was domain

type (i.e. inverse transformed intention to perform, accuracy, and need for reminders); the same covariates were entered as in the ANCOVA described above.

Finally, logistic regression analyses were conducted to examine the distinctive contributions of a priori selected measures of executive functioning and retrospective memory on PM impairment, conducted separately for each TBI group. Raw scores of these neuropsychological measures were examined in the logistic regression, and the same covariates that were entered in the previous ANCOVAs were also included. A significance level of $p < .05$ was used for all analyses.

Results

Demographic characteristics

Table 1 details demographic and clinical characteristics. There were a total of 15,462 participants included in the study for which data were available on all variables of interest. 13,525 were controls, and the remaining 1937 belonged to the mTBI groups, consisting of those who experienced LOC for less than 1 min ($n = 1146$), and those between 1 and 20 min ($n = 791$). The three groups were comparable in terms of education ($p = .936$) and marital status ($p = .162$), but differed with respect to age ($p < .001$), and sex ($p < .001$). Specifically, control participants were older than the two mTBI groups ($ps < .05$), which did not differ ($p = .130$). The control group contained a higher proportion of women compared to the mTBI groups ($p < .001$), which did not differ ($p = .352$).

Clinical characteristics

Levels of depressive symptoms were found to differ between the groups ($p < .001$). Bonferroni-corrected pairwise comparisons indicated that the control group had lower

Table 1. Demographic and clinical characteristics of the mild traumatic brain injury groups and controls.

		Mild traumatic brain injury	
	Controls ($n = 13,525$)	LOC < 1 min ($n = 1146$)	LOC 1–20 min ($n = 791$)
Age, mean (SD)	61.76 (9.90)	60.03 (9.10)	60.88 (9.78)
Sex			
Female (%)	54.3	38.7	40.3
Male (%)	45.7	61.3	59.7
Education			
< High school (%)	2.5	2.6	2.9
High school (%)	7.5	8.1	7.5
College (%)	34.5	34.0	36.0
University degree (%)	29.0	28.1	25.4
Graduate degree (%)	26.6	27.1	28.2
Marital status			
Married (%)	71.6	75.5	72.6
Widowed (%)	7.5	4.6	6.8
Divorced (%)	9.7	9.3	9.1
Separated (%)	2.6	3.1	2.0
Single (%)	8.5	7.5	9.5
Depression, mean (SD)	4.73 (4.30)	5.46 (4.62)	5.56 (4.78)
Number of TBIs, mean (SD)	0	2.36 (2.29)	2.03 (2.01)

Note: TBI = traumatic brain injury; LOC = loss of consciousness. In individuals that experienced more than one TBI, LOC refers to the longest period of unconsciousness experienced.

depression scores than either of the mTBI groups (*p*s < .001), while no differences were observed between the mTBI groups ($p = 1.0$). Moreover, participants with LOC < 1 min were found to have experienced more TBIs in their lifetime compared to those with LOC of 1–20 min ($p < .001$).

Prospective memory functioning

Means and standard deviations by group on the MPMT are presented in Table 2. A repeated measures ANCOVA revealed a significant main effect of group $F(2, 15454) = 4.18$, $p = .015$, $\eta^2 = 0.001$), a significant main effect of cue type, $F(1, 15454) = 71.71$, $p < .001$, $\eta^2 = 0.005$) with lower event- vs. time-based performance, and a significant interaction between group and cue type, $F(3, 15454) = 18.60$, $p < .031$, $\eta^2 = 0.002$. Pairwise comparisons revealed that in time-based PM, both mTBI groups performed more poorly than the controls (*p*s < .001), and that those with LOC < 1 min did not differ from those with LOC 1–20 min ($p = 1.0$). In event-based PM, those with LOC < 1 min were found to perform better than controls ($p = .005$) and those with LOC 1–20 min ($p = .044$), and controls did not differ from those with LOC 1-20 min ($p = 1.0$).

Comparisons of error types

To investigate between-group differences on intention to perform, accuracy, and need for prompts, an additional repeated measures ANCOVA was conducted. It revealed a marginally significant main effect of group $F(2, 15454) = 2.947$, $p = .053$, $\eta^2 = 0.000$, a main effect of measurement type (intention, accuracy, and reminder), $F(2, 15454) = 9.46$, $p = .002$, $\eta^2 = 0.001$, and a significant interaction between group and measurement type, $F(2, 15454) = 8.99$, $p < .001$, $\eta^2 = 0.001$. Pairwise comparisons indicated that none of the groups differed on

Table 2. Prospective memory and cognitive test performance in the study samples.

			Mild traumatic brain injury			
	Control (*n* = 13,525)		LOC < 1 min (*n* = 1146)		LOC 1-20 min (*n* = 791)	
Test	*M*	*SD*	*M*	*SD*	*M*	*SD*
Prospective memory						
Time-based (0–9)	8.76	0.78	8.66	0.92	8.65	0.97
Event-based (0–9)	8.53	1.27	8.71	0.977	8.56	1.20
Impairment rates						
Time-based (%)	4.6		7.2		6.9	
Event-based (%)	1.6		0.4		1.3	
MPMT Errors						
Intention to perform (0–6)	5.55	1.03	5.57	0.97	5.49	1.10
Reminder (0–6)	5.83	0.49	5.87	0.37	5.82	0.47
Accuracy (0–6)	5.91	0.41	5.93	0.30	5.90	0.40
Executive functioning						
COWAT	40.73	12.43	41.67	12.12	41.11	12.79
VST Interference	2.11	0.73	2.08	0.54	2.11	0.74
MAT	27.49	8.30	28.24	8.31	27.77	8.50
Declarative Memory						
RAVLT immediate	6.10	1.86	6.14	1.81	6.07	1.92
RAVLT delayed	4.29	2.15	4.36	2.10	4.20	2.15

Note: LOC = loss of consciousness; MPMT = Miami Prospective Memory Test; COWAT = Controlled Oral Word Association Test; VST = Victoria Stroop Test; MAT = Mental Alternation Test; RAVLT = Rey Auditory Verbal Learning Test.

accuracy or need for reminders (*p*s > .05). For intention to perform, those with LOC 1–20 min were found to score lower than controls ($p = .023$), while those with LOC < 1 min did not differ from the LOC 1–20 min group ($p = .969$), nor from the control group ($p = .274$).

Time- and event-based impairment

After applying the impairment criteria (i.e. scoring below the 5th percentile cut-off of the control group), 4.6% of controls, 7.2% for those with LOC < 1 min, and 6.9%, of those with LOC 1–20 min were impaired on time-based PM, χ^2 (2) = 22.39, $p < .001$. Pairwise comparisons revealed that both mTBI groups had a higher rate of time-based PM impairment than controls (*p*s < 0.01), and those with LOC < 1 min were not found to differ from those with LOC 1–20 min ($p = 1.0$). In event-based functioning, impairment rates were 1.6% for controls and 0.4% for those with LOC < 1 min, and 1.3%, for those with LOC 1–20 min, χ^2 (2) = 19.55, $p = .006$. Pairwise comparisons indicated that those with LOC < 1 min were less likely to be classified as impaired on event-based performance than the other groups (*p*s < .05), which did not differ ($p = 1.0$).

Predictors of PM impairment

Time-based impairment

Descriptive data on the other neuropsychological tasks are provided in Table 2. To identify the unique contributions of retrospective memory (RAVLT immediate and delayed) and executive functioning (COWAT and MAT) to time-based PM impairments for each of the mTBI groups, logistic regressions were run, separately for each group, including the raw retrospective memory and executive function scores entered as predictors in addition to the demographic and clinical characteristics from the ANCOVA. For those with LOC of < 1 min, a test of the full model against a constant-only model was statistically significant, χ^2 (14) = 55.38, $p < .001$, Nagelkerke $R^2 = 0.12$. As shown in Table 3, an increase of one year of age (OR = 1.050, 95% CI = 1.022–1.080) was associated with a 5% increase in the odds of being classified as impaired, while a single-point increase in the RAVLT delayed score (OR = 0.815, 95% CI = 0.700–0.948) was associated with a 19% decrease in the odds of being classified as impaired. Among those with LOC of 1–20 min, χ^2 (14) = 37.84, $p < .001$, Nagelkerke $R^2 = 0.12$, an increase of one year of age (OR = 1.063, 95% CI = 1.029–1.099) was associated with a 6.3% increase in odds, and an increase in one lifetime mTBI experienced (OR = 1.183, 95% CI = 1.058–1.322) was associated with an 18.3% increase in odds of being classified as impaired. In addition, of the variables entered into the analyses, it was found that a single point increase on the CES-D10 was associated with a 6% increase (OR = 1.062, 95% CI = 1.013–1.113) in the odds of being classified as impaired among those with LOC < 1 min. Among those with LOC 1–20 min, χ^2 (14) = 37.93, $p < .001$, Nagelkerke $R^2 = 0.12$, a single point increase in MAT scores was associated with a 3.1% decrease in odds of being impaired in time-based functioning (OR = 0.969, 95% CI = 0.948–0.991).

Event-based impairment

As was done previously, logistic regressions were run, separately for each group, to investigate the unique predictors of event-based impairment, by including the raw retrospective memory and executive function scores and the demographic and clinical characteristics as

Table 3. Logistic regression model for predictors of time-based prospective memory impairment among the mild traumatic brain injury participants.

	LOC < 1 min		LOC 1–20 min	
	OR	95% C.I.	OR	95% C.I.
Executive functioning				
COWAT	0.996	0.976, 1.018	1.009	0.983, 1.035
VST Interference	1.071	0.715, 1.604	1.121	0.845, 1.487
MAT	0.975	0.947, 1.005	**0.969**	**0.948, 0.991**
Declarative memory				
RAVLT immediate	1.128	0.943, 1.348	0.906	0.725, 1.134
RAVLT delayed	**0.815**	**0.700, 0.948**	1.051	0.858, 1.286
Testing language				
English (reference)	1.00		1.00	
French	0.527	0.203, 1.367	0.422	0.145, 1.226
Number of TBIs	1.035	0.940, 1.139	**1.183**	**1.058, 1.322**
Depression scores	**1.062**	**1.013, 1.113**	1.039	0.981, 1.099
Age	**1.050**	**1.022, 1.080**	**1.063**	**1.029, 1.099**
Sex				
Male (reference)	1.00		1.00	
Female	0.674	0.393, 1.157	1.692	0.898, 3.187
Education				
< High school (reference)	1.00		1.00	
High school	2.386	0.442, 12.871	0.153	0.019, 1.202
College	2.518	0.529, 11.978	0.689	0.175, 2.717
University degree	1.198	0.234, 6.122	0.504	0.120, 2.116
Graduate degree	1.656	0.330, 8.309	0.647	0.153, 2.729

Note: LOC = loss of consciousness; COWAT = Controlled Oral Word Association Test; VST = Victoria Stroop Test; MAT = Mental Alternation Test; RAVLT = Rey Auditory Verbal Learning Test; TBI = traumatic brain injury; OR = Odds Ratio. Odds ratios that are significant ($p < .05$) have been bolded. Odds ratios greater than 1 indicate increased odds of being classified as impaired on time-based functioning, whereas odds ratios of less than 1 indicate decreased odds of impairment. For those with LOC < 1 min, $n = 1146$, and those with LOC 1–20 min, $n = 791$.

predictors. However, given the low number of individuals with mTBI that were classified as impaired, the education variable was excluded as a predictor in these analyses. As displayed in Table 4, results from logistic regressions to investigate the predictors of event-based impairment indicated that none of the variables entered into the model significantly predicted impairment status for either those with LOC < 1 min or those with LOC 1–20 min ($ps > .05$). However, marginal significance was found for an increase of one year of age being associated with a 7.6% (OR = 1.076, 95% CI = 0.999–1.159) increase in odds of impairment among those with LOC 1–20 min.

Unplanned post hoc analyses were conducted to investigate possible contributions to the counterintuitive finding of lower event-based impairment among those unconscious for less than one minute compared to controls. A binary logistic regression was run, collapsing the two groups, and by including the demographic and clinical characteristics (those covariates included in the earlier ANCOVA) as predictors of event-based impairment, χ^2 (9) = 260.48, $p < .001$, Nagelkerke $R^2 = 0.099$. This analysis indicated that age (OR = 1.100, 95% CI = 1.086–1.115) and depression scores (OR = 1.05, 95% CI = 1.024–1.078) were significant predictors of event-based impairment.

Table 4. Logistic regression model for predictors of event-based prospective memory impairment among the mild traumatic brain injury participants.

	LOC < 1 min		LOC 1-20 min	
	OR	95% C.I.	OR	95% C.I.
Executive functioning				
COWAT	1.001	0.907 1.105	0.945	0.891 1.003
VST Interference	1.609	0.562, 4.606	0.881	0.302, 2.574
MAT	0.915	0.824, 1.017	0.967	0.884, 1.058
Declarative memory				
RAVLT immediate	0.592	0.235, 1.491	0.796	0.493, 1.286
RAVLT delayed	1.371	0.587, 3.204	0.845	0.523, 1.364
Testing language				
English (reference)	1.00		1.00	
French	1.670	0.132, 21.184	0.454	0.053, 3.896
Number of TBIs	0.556	0.160, 1.926	1.042	0.826, 1.313
Depression scores	1.060	0.892, 1.260	0.979	0.857, 1.119
Age	0.949	0.837, 1.077	1.076	0.999, 1.159
Sex				
Male (reference)	1.00		1.00	
Female	0.656	0.076, 5.683	0.324	0.083, 1.260

Note: LOC = loss of consciousness; COWAT = Controlled Oral Word Association Test; VST = Victoria Stroop Test; MAT = Mental Alternation Test; RAVLT = Rey Auditory Verbal Learning Test; TBI = traumatic brain injury; OR = Odds Ratio. Odds ratios that are significant ($p < .05$) have been bolded. Odds ratios greater than 1 indicate increased odds of being classified as impaired on time-based functioning, whereas odds ratios of less than 1 indicate decreased odds of impairment. For those with LOC < 1 min, $n = 1146$, and those with LOC 1–20 min, $n = 791$.

Discussion

Prior research has indicated that frontal areas of the brain may be compromised in people who have experienced even mild TBI (Abdel-Dayem et al., 1998; Mayer et al., 2011; McDonald et al., 2012; Sorg et al., 2014; Strangman et al., 2010), particularly in those who have experienced LOC (Kraus et al., 2007; Sorg et al., 2014; Strangman et al., 2010). Moreover, there is growing concern that, at least in a subset of those who have experienced a mTBI, alterations to frontal regions may persist many years after the brain injury (Hartikainen et al., 2010; Mac Donald et al., 2017; Matsushita et al., 2011). In addition, it has been recognized that time-based tasks may place more demands on executive processes than event-based tasks (McDaniel & Einstein, 2000), which are subserved by the frontal lobe (Burgess et al., 2001, 2003, 2011; Oksanen et al., 2014; Okuda et al., 2007). However, to the best of our knowledge, no studies have investigated whether PM deficits may persist into the long-term (i.e. beyond 3-months post-injury), and if length of LOC may influence PM functioning in mTBI. The present study thus had two goals: first, to evaluate performance of time- and event-based PM tasks among those who have experienced mTBI with LOC, more than 12 months ago, and second, to assess the relative contributions of executive function, and retrospective memory performance in predicting PM impairments among people with a longstanding history of mTBI.

Initial findings from the present study of a nationally representative sample of adults aged 45–85 provides evidence for a disproportionate deficit on time-based PM performance for those that experienced a mTBI with LOC less than 1 min and for those with LOC between 1 and 20 min. At first blush, the present data indicate subtle time-based PM deficits among those who experienced mTBI with LOC, similar in magnitude to those observed in meta-analyses of neuropsychological deficits 3 or more months post-TBI (Binder, Rohling, & Larrabee, 1997; Frencham, Fox, & Maybery, 2005; Schretlen & Shapiro, 2003). However, after applying

impairment criteria, a higher proportion of people in the mTBI groups exhibited time-based PM impairments (7.2 and 6.9%) than in the control group (4.6%). Our results, therefore, seem to align with the perspective that although a large proportion of those who experience mTBI may not develop persistent dysfunction, a small subset may continue to exhibit cognitive impairment (Bigler et al., 2013; Iverson, 2010; Karr et al., 2014; Mayer et al., 2017; Pertab, James, & Bigler, 2009; Rohling, Larrabee, & Millis, 2012).

Performance on the event-based task was found to be more nuanced, with controls not differing from those with LOC between 1 and 20 min, while those with LOC < 1 min were actually found to outperform the former groups. This was an unexpected finding because previous studies have observed deficits in event-based functioning following mTBI, relative to controls (Kinsella et al., 2014; Tay et al., 2010). Thus, this counterintuitive finding in the present study was explored through post hoc logistic regression analyses, which found age and depressive symptomatology to be significant predictors of event-based impairment among those who were unconscious for less than a minute as well as controls. This, therefore, suggests that these discrepant results may have been a function of the lower age found among those unconscious for less than a minute, which is consistent with the notion that performance on event-based PM tasks may decrease with advancing age (Kleigel, Jäger, & Phillips, 2008; Maylor, 1996; Smith & Bayen, 2006).

Importantly, we found evidence for a differential pattern of time- and event-based impairment in individuals 12 months after they had lost consciousness following mTBI. While performance on the event-based task was not sensitive to mTBI, people who experienced mTBI with LOC of any length were more likely to exhibit time-based impairment than those with no history of mTBI. This finding, therefore, suggests that spending any amount of time unconscious may be a useful indicator of the likelihood of exhibiting PM impairments in time-based tasks, which are thought to be more reliant on the frontal lobe (Burgess et al., 2001, 2003, 2011; Oksanen et al., 2014; Okuda et al., 2007).

An additional aim of the present study was to evaluate the cognitive functions associated with PM impairments in people with mTBI with LOC. Given that the data reported here show similar rates of PM impairments in people with LOC < 1 min and those with LOC of 1–20 min, it may be argued that those groups should be considered together. However, error analysis suggested that PM deficits were associated with executive dysfunction (e.g., self-initiated retrieval or strategic monitoring), rather than a failure to recall the content of the PM task (i.e., retrospective component), only among those who reported LOC between 1 and 20 min. Logistic regression analyses supported this finding of executive dysfunction: a single-point increase on the Mental Alternation Test was associated with decreased odds of time-based impairment for those who reported unconsciousness between 1 and 20 min. Among those with LOC of less than 1 min, PM impairments generally seemed to emerge with lower retrospective memory ability, which appears to be consistent with imaging data indicating smaller medial temporal lobe volumes in those who had a mTBI decades prior to evaluation (Monti et al., 2013). These findings, therefore, seems to parallel previous work indicating that more time spent unconscious may be associated with greater frontal lobe and executive dysfunction (Kraus et al., 2007; Sorg et al., 2014; Strangman et al., 2010), and thus LOC may serve as an important variable to consider in outcomes from mTBI.

A number of limitations to the present study must be noted. First, the data on mTBI were self-reported and are, therefore, biased by retrospective recall, which may have limited our ability to distinguish individuals that may have experienced LOC between 1 and 20 min from

those who lost consciousness for less than 1 min. In addition, it is acknowledged that data were not available for post-traumatic amnesia, nor were Glasgow Coma Scale scores. Similarly, an acknowledged limitation is a lack of data on the exact time since injury. Given the prevalence of mTBI in younger adults, and that this study included individuals between the ages of 45–85, it is not exactly clear what the contribution of time since injury is, nor the impact of temporal span between brain injuries among those who experienced multiple brain injuries. Moreover, these findings are based on cross-sectional data and information about premorbid function is not available. Pre-mTBI cognitive assessments would be useful for identifying the factors (e.g., pre-mTBI executive dysfunction, emotional distress, or old age) that predispose someone to long-term PM impairments resulting from a mTBI. For instance, the present study suggests that age may be an important factor: age was a predictor of time-based PM impairment in all groups. Future CLSA data will allow us to address some of these questions.

Clinical implications

As mentioned, future research should evaluate who may be particularly predisposed to PM impairments following mTBI, and investigate the utility of early interventions in these individuals. For instance, as the present study found evidence of executive dysfunction underlying time-based impairments, there has been work to suggest that implementation intentions, which are if-then conditions between an event and an intended action, may provide improvements in intention retrieval (Smith, McConnell Rogers, McVay, Lopez, & Loft, 2014). Moreover, visual imagery, an internal memory strategy, has been shown to strengthen retrieval by increasing the automaticity of recall (Thöne-Otto & Walther, 2008), and may be of benefit to increase time- and event-based memory functioning in patients with traumatic brain injury (Potvin, Rouleau, Sénéchal, & Giguère, 2011). In addition, future research may wish to examine external compensatory approaches (Fleming, Shum, Strong, & Lightbody, 2005) (e.g., Google calendar on mobile phones; Baldwin & Powell, 2015; McDonald et al., 2011) to bypass the impaired self-initiated retrieval processes could prove beneficial for both time- and event-based tasks encountered in daily life.

Conclusions

The present investigation provides evidence that those who have experienced mTBI with LOC more than 12 months ago are more likely to exhibit deficits in time-based than event-based PM tasks, and that these impairments appear to be associated with executive dysfunction in those with more time spent unconscious. As PM is essential to everyday functioning, the findings from this study are relevant in terms of developing cognitive rehabilitation strategies aimed at ameliorating PM among long-term survivors of mTBI.

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Appendix B

Bedard, M., Steffener, J., & Taler, V. (2020). Long-term cognitive impairment following single mild traumatic brain injury with loss of consciousness: Findings from the Canadian Longitudinal study on Aging. *Journal of Clinical and Experimental Neuropsychology, 42*(4), 344-351.

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Long-term cognitive impairment following single mild traumatic brain injury with loss of consciousness: Findings from the Canadian Longitudinal Study on Aging

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ABSTRACT

Objective: We examined the extent to which loss of consciousness (LOC) following mild traumatic brain injury (mTBI) may be associated with impairments in executive functions and declarative memory more than a year after brain injury.
Method: Analyses were run on 548 participants who had self-reported LOC of <1 min, 441 with LOC of 1–20 min, and 13,609 no brain injury comparison participants, taken from the Canadian Longitudinal Study on Aging (CLSA), a nationwide study on health and aging.
Results: Those that had mTBI with LOC of 1–20 min were more likely than no head injury comparisons to be impaired on measures of executive functioning and declarative memory. Impairments were evident when examining for single- and two-test impairment rates on measures of executive functioning and declarative memory.
Conclusions: A subset of people that had reported a single mTBI with LOC more than 12 months ago may experience impairments in executive functioning and declarative memory, particularly those who spent more time unconscious.

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Traumatic brain injury; loss of consciousness; cognitive impairment; executive functions; CLSA

Over the last 2 decades there has been mounting interest in cognitive impairments following traumatic brain injury (TBI). TBIs are a common public health concern, and are estimated to occur in more than 400 per 100,000 people on an annual basis (Voss, Connolly, Schwab, & Scher, 2015). The majority of reported cases (70%) are considered mild TBI (mTBI) (Voss et al., 2015); commonly-accepted criteria for mTBI have been published by the American Congress of Rehabilitation Medicine, Mild Traumatic Brain Injury Committee of the Interdisciplinary Special Interest Group (1993).

Despite the higher incidence of mTBI relative to more severe cases, a large proportion of studies have focused on moderate to severe TBI. However, the last 10 years have seen increased interest in cognitive dysfunction following mTBI. Deficits in declarative memory, attention, processing speed, and executive functioning have been observed up to three months following mTBI (Karr, Areshenkoff, & Garcia-Barrera, 2014). Meta-analyses and reviews reveal that a large majority of studies show remission of cognitive deficits by three months post-injury, which has been considered the end of the acute phase of injury (Binder, Rohling, & Larrabee, 1997; Frencham, Fox, & Maybery, 2005; Godbolt et al., 2014; Larabee, 2014). Cognitive deficits have also not been found following mTBI when non-credible performance is considered, as may occur in the case of litigation (Larabee, 2014). However, it is suggested that meta-analyses may have obscured a minority of mTBI cases where cognitive impairment persists beyond three months (Iverson, 2010; Pertab, James, & Bigler, 2009). Research has suggested that a minority of people exhibit lasting cognitive impairment even more than a year after mTBI (Karr et al., 2014; McInnes, Friesen, MacKenzie, Westwood, & Boe, 2017), although the absence of validity testing should be noted. Nevertheless, very few studies have centered on long-term outcomes, and thus the long-term effect of mTBI on cognitive function remains unclear (McInnes et al., 2017).

Neuroimaging studies have found altered white matter function and structure (i.e., diffuse axonal injury; DAI), particularly in frontal regions, immediately following mTBI (McDonald, Saykin, & McAllister, 2012; Sorg et al., 2014), and in some cases, years after mTBI (Mac Donald et al., 2017). Alterations to frontal brain areas may be more pronounced when loss of consciousness is experienced (Sorg et al., 2014). Given that frontal neural circuitry subserves executive functioning, it is not surprising that

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executive dysfunction has been evident following mTBI. However, the extent to which mTBI affects executive functions in the long term remains unknown.

The present study evaluated cognitive outcome in people who had reported experiencing a single mTBI at least a year previously, and who had reported varying levels of loss of consciousness. We used data from the Canadian Longitudinal Study on Aging (CLSA, Raina et al., 2009), a large population-stratified study of aging. We have previously reported impairments in prospective memory in this group (Bedard, Taler, & Steffener, 2018). Although prospective memory is thought to be largely reliant on executive processes (McDaniel & Einstein, 2011), long-term effects of mTBI with loss of consciousness on executive functioning have, to our knowledge, not been examined previously.

Materials and procedures

The data used for the present study was from the Canadian Longitudinal Study on Aging (CLSA), a large ongoing 20-year study examining health transitions and trajectories in a national stratified random sample of over 50,000 male and female Canadian residents aged 45 to 85 (Raina et al., 2009). Ethical review of the CLSA protocol was conducted by the Ethical, Legal, and Social Issues Committee, falling under the jurisdiction of the Canadian Institutes of Health Research (CIHR), and additional research ethics board approval was received for each research site prior to data collection. Baseline information, including demographic and clinical information, has been collected for all participants, with approximately 30,000 (Comprehensive Cohort) evaluated through 90-minute in-home interviews, in addition to more in-depth physical and cognitive assessments conducted at one of 11 data collection sites across Canada. The remaining 20,000 participants (Tracking Cohort) were evaluated through phone interviews. The present study uses baseline data from participants in the Comprehensive Cohort only, because participants in the Tracking Cohort were not asked to report prior TBI. Our institutional research ethics boards provided approval for the present study.

Participants

Detailed information on the sampling frame is provided in Raina et al. (2009). Briefly, CLSA participants include adults between the ages of 45 and 85 years who are fluent in English and/or French. For the present investigation, participants were excluded from the analyses if they were ever diagnosed with a neurological disorder (e.g., Alzheimer's or Parkinson's diseases, multiple sclerosis), had ever had a cerebrovascular accident or transient ischemic attack, or had experienced a concussion or other brain injury, or received multiple injuries (which may include brain injury) in the past 12 months. Moreover, those who reported experiencing multiple head injuries were excluded. Thus, only people who reported having lost consciousness as a result of a head injury that occurred more than 12 months prior to study recruitment, and who had experienced only one lifetime head injury, were included for our mTBI sample. Participants were further divided based on length of LOC: less than one minute (LOC <1 min), one to 20 minutes (LOC 1–20 min), or greater than 20 minutes (LOC >20 min). In keeping with guidelines of classifying mTBI (i.e., LOC less than 30 minutes; American Congress of Rehabilitation Medicine, Mild Traumatic Brain Injury Committee of the Interdisciplinary Special Interest Group, 1993), participants who reported losing consciousness for more than 20 minutes were excluded from our analyses.

It should be noted that the CLSA does not include data on posttraumatic amnesia or information for the calculation of a Glasgow Coma Scale score, and the specific date of brain injury is not known: the date of brain injury is recorded as having occurred more or less than 12 months ago. Finally, in addition to the TBI groups, we included people who had never experienced a brain injury as our comparison group. Analyses included only participants for whom data were available for all the variables detailed below.

Measures

Demographic and clinical information, including age, education level, sex, marital status, and relative date of brain injury (i.e., more or less than 12 months ago) were self-reported by participants using questionnaires administered through structured in-person interviews. All participants provided informed consent prior to completing the questionnaires and neuropsychological assessments described below.

Traumatic brain injury

The Brief Traumatic Brain Injury Screen (BTBIS; Schwab et al., 2007) is a short self-report TBI screening tool. It collects data on the number of lifetime TBIs; length of unconsciousness following TBI is measured on a three-point Likert scale. Reported LOC is recorded as less than one minute (LOC <1 min), between one and 20 minutes (LOC 1–20 min), or greater than 20 minutes.

Depression

Depressive symptomatology was assessed using the Center for Epidemiologic Studies Short Depression Scale

(CES-D10; Andresen, Malmgren, Carter, & Patrick, 1994), a 10-item self-report measure where items are rated on a four-point Likert scale. Total scores range from 0–30, with higher scores indicating greater depressive symptomatology; a score of 10 or more is suggestive of clinically significant depressive symptomatology.

Neuropsychological assessment

Participants completed the Animal Fluency Test (Rosen, 1980), Controlled Oral Word Association Test (COWAT; Lezak, Howieson, & Loring, 2004), the Mental Alternation Test (MAT; Teng, 1994), and the Stroop task, from which an interference score was derived by dividing task time of the Color-Word trial by the completion time of the Dot trial from the Victoria Stroop Test (Stroop; Strauss, Sherman, & Spreen, 2006). An abbreviated version of the Rey Auditory Verbal Learning Test (RAVLT; Rey, 1964) was administered, consisting of one immediate trial and one delayed recall trial. Non-credible performance was deemed using a raw cutoff of ≤4 for the immediate trial, necessary to identify probably malingering (Binder, Kelly, Villanueva, & Winslow, 2003; Suhr & Gunstad, 2000), and ≤2 for the delayed trial (Boone, Lu, & Wen, 2005), which allow for specificity of ≥90%.

Statistical analyses

Statistical analyses were performed using SPSS version 24 (Armonk, NY, USA: IBM Corp.). All continuous variables were normally distributed as checked with Q-Q plots and skew statistics, with the exception of the Stroop Interference scores, which were positively skewed and subsequently transformed using a logarithmic function.

Group differences on continuous demographic and clinical data were analyzed with univariate analysis of variance (ANOVA), coupled with Bonferroni corrected pairwise comparisons. Categorical data were analyzed with Kruskal-Wallis tests and pairwise comparisons were conducted using Mann-Whitney U tests with Bonferroni corrections. Multivariate analyses of covariance (MANCOVA) were conducted including neuropsychological test scores, age, and depression scores as dependent variables, and education, sex, and language of testing as covariates. Follow-up univariate tests were then conducted with Bonferroni-corrected pairwise comparisons.

To determine the percentage of individuals experiencing cognitive impairment, Z-scores were calculated for each neuropsychological measure for each participant, using the mean and standard deviation of the comparison group's data. Using standard conventions (Schinka et al., 2010; Strauss et al., 2006), impairment was defined as a score 1.5 or more standard deviations below age- and education-adjusted comparison group means. Impairment rates were summed separately for tests of declarative memory (RAVLT immediate and delayed) and executive functioning (COWAT, AFT, MAT, and Stroop). Two-test within-domain impairment (i.e., impairment on two tests of declarative memory, or two or more tests of executive functioning) was then calculated using a 1.5 standard deviation cutoff. Kruskal-Wallis tests were used to compare between-group rates of impairment; pairwise comparisons included Bonferroni corrected Mann-Whitney U tests.

Results

Demographic and clinical characteristics

The sample in the present study included 14,598 participants: 13,609 no head injury comparison participants (comparisons), 548 mTBI participants with LOC <1 min (prevalence: 3.75%), and 441 mTBI participants with LOC of 1–20 min (prevalence: 3.02%). Demographic and clinical data are presented in Table 1. All three groups in the present dataset were comparable in terms of education (p = .64), marital status (p = .40), and age (p = .24), but differed with respect to sex (p < .01). Specifically, the comparison participant group had a smaller proportion of males relative to females compared to those with LOC <1 min, p < .01, OR = 0.70, 95% CI = 0.59–0.82, and those with LOC 1–20 min, p < .01, OR = 0.67, 95% CI = 0.56–0.81. The mTBI groups had a similar proportion of females to males (p = .78).

Levels of depressive symptomatology differed between the groups (p = .02). Comparison participants

Table 1. Participant demographic and clinical characteristics.

	Controls (n = 13609)	LOC < 1 min (n = 548)	LOC 1-20 min (n = 441)
Age, mean (SD)	61.8 (9.9)	61.1 (9.4)	61.5 (10.15)
Age, range	45-86	45-86	45-85
Sex			
Female (%)	54.2	44.9	44.0
Male (%)	45.8	55.1	56.0
Education			
< High school (%)	2.5	2.2	2.3
High school (%)	7.4	7.7	8.8
College diploma (%)	34.5	33.6	32.4
University degree (%)	29.0	27.9	26.6
Graduate degree (%)	26.6	28.6	29.9
Marital status			
Married (%)	71.6	74.6	73.2
Widowed (%)	7.5	7.3	9.5
Divorced (%)	9.8	6.2	6.1
Separated (%)	2.6	3.1	2.0
Single (%)	8.5	8.8	9.2
Depression, mean (SD)	4.7 (4.3)	4.8 (4.4)	5.3 (4.7)

LOC = loss of consciousness.

had lower depression scores than those with LOC 1–20 min ($p < .01$, $\eta^2 = 0.001$), but not those with LOC <1 min ($p = .64$), and those with LOC 1–20 min did not differ from those with LOC <1 min ($p = .06$).

Group differences on neuropsychological measures

Means and standard deviations for the measures of neuropsychological functioning are presented in Table 2. When examining for possible non-credible performance, groups did not differ on RAVLT immediate χ^2 (2) = 2.06, $p = .37$, or RAVLT delayed, χ^2 (2) = 1.52, $p = .47$, cutoffs when assessed individually. Two-test invalid performance beyond cutoffs on both the RAVLT immediate and delayed, more indicative of non-credible performance, reveal that controls (10.2%), those with LOC <1 minute (9.1%), or those with LOC 1–20 minutes (11.6%), did not differ, χ^2 (2) = 2.69, $p = .26$.

The MANCOVA revealed significant group differences, $F(6, 14592) = 2.18$, $p < .01$, $\eta_p^2 = .001$. Follow-up univariate tests showed that this was due to group differences on the AFT, $F(2, 14592) = 8.49$, $p < .01$, $\eta_p^2 = 0.001$. Those with LOC <1 minute scored higher on the AFT than comparisons, $p < .01$, $\eta_p^2 = 0.001$, and those with LOC 1–20 minutes, $p = .03$, $\eta_p^2 = 0.004$, but those with LOC 1–20 minutes did not differ from comparisons on the AFT, $p = .46$. Group differences were not observed on the COWAT, Stroop, MAT, nor on the RAVLT immediate or delayed ($ps > .05$). Results remained unchanged when additionally controlling for probable non-credible performance (two-test invalidity), or when those who exhibited probable non-credible performance were removed from analyses.

Due to small effect size estimates obtained, the MANCOVA was re-run using a randomly selected subset of the sample, in order to generate more interpretable comparisons. In line with power analyses using G*Power 3.1.9.3, 279 participants were randomly selected for each of the three groups in order in order to detect small size effects, with Cohen's f of 0.14, with a power of 0.80. This MANCOVA was not significant, $F(6, 826) = 1.16$, $p = .33$.

Neuropsychological impairment

Single-test impairment

As described above, the comparison group had fewer men relative to women when compared to the mTBI groups, and so a random sample of women equal in number to men (6233 participants of each sex) were selected to develop impairment rates. Groups remained similar with respect to age and education, $ps > .05$. Rates of impairment on the neuropsychological measures are presented in Table 2. Impairment rates differed across groups on the MAT, χ^2 (2) = 10.71, $p < .01$. Pairwise comparisons indicated that people with LOC 1–20 mins ($p < .01$, OR = 1.55, 95% CI = 1.14–2.12) were more

Table 2. Neuropsychological test and impairment rates across study groups.

	Control (n = 13609)		Mild Traumatic Brain Injury: LOC < 1 min (n = 548)		Mild Traumatic Brain Injury: LOC 1-20 min (n = 441)			
Test	M	SD	M	SD	M	SD	p-value	Effect-size η_p^2
Declarative memory raw scores								
RAVLT immediate	6.09	1.86	6.19	1.88	6.05	1.88	.29	0.000
RAVLT delayed	4.28	2.15	4.41	2.14	4.14	2.11	.14	0.000
Impairment rates								
RAVLT immediate (%)	10.6		10.4		15.2		**.01**	0.001
RAVLT delayed (%)	10.6		10.4		15.2		**.01**	0.001
Executive functioning raw scores								
Stroop interference	2.11	0.73	2.07	0.55	2.13	0.87	.52	0.000
Mental Alternation Test	27.49	8.30	28.06	8.13	27.70	8.41	.69	0.000
COWAT	40.72	12.44	41.44	12.08	40.95	12.51	.42	0.000
Animal Fluency Test	20.25	5.58	21.30	5.61	20.45	5.28	**.01**	0.001
Impairment rates								
Stroop Interference (%)	3.1		2.9		5.0		.07	0.000
Mental Alternation Test (%)	7.7		8.8		11.6		**.01**	0.001
COWAT (%)	8.5		8.6		12.9		**.01**	0.001
Animal Fluency Test (%)	8.2		5.5		7.3		.07	0.000
Two-test impairment								
Declarative memory	10.6		10.4		15.2		**.01**	0.001
Executive functioning	5.5		7.3		8.2		**.04**	0.001
Non-credible RAVLT								
Immediate ≤ 4 (%)	19.2		16.8		19.5		.36	
Delayed ≤ 2 (%)	19.3		17.5		20.9		.40	

LOC = loss of consciousness; RAVLT = Rey Auditory Verbal Learning Test; COWAT = Controlled Oral Word Association Test; neuropsychological raw scores are presented and rates of impairment based upon scoring 1.5 SD below the gender balanced control group (n = 12466) mean and standard deviations (i.e., Z-scores); p-values considered significant ($p < .05$) have been bolded. Effect sizes reflect variance on omnibus level tests – pairwise effect size estimates are presented in the article.

likely than comparison participants to be impaired, but not more likely than those with LOC <1 min (p = .50). Those with LOC <1 min did not differ from comparison participants on the MAT (p = .08). Across the entire sample, any LOC was associated with MAT impairment, (OR = 1.41, 95% CI = 1.14–1.75).

Group differences also emerged on the COWAT, χ^2 (2) = 10.43, p < .01: people with LOC 1–20 min were more likely to be impaired than comparison participants (p < .01, OR = 1.55, 95% CI = 1.20–2.12) and people with LOC <1 min (p = .03, OR = 1.43, 95% CI = 1.02–1.85), while those with LOC <1 min did not differ from comparison participants (p = .97). Any LOC was associated with COWAT impairment across the sample, (OR = 1.28, 95% CI = 1.04–1.59).

Similar results were found for RAVLT immediate and delayed (χ^2 (2) = 9.46, ps <.01): people with LOC 1–20 were more impaired than comparison participants (ps < .01, OR = 1.051, 95% CI = 1.16–1.97) and people with LOC <1 min (ps < .05, OR = 1.54, 95% CI = 1.06–2.25). People with LOC <1 min did not differ from comparison participants on the RAVLT immediate or delayed (ps > .10). Across the sample, LOC was associated with impairment on the RAVLT immediate and delayed (OR = 1.27, 95% CI = 1.03–1.57). Groups did not differ on the Stroop (p = .07) or the AFT (p = .06). Notably, across single impairment analyses results were consistent when gender-balanced impairment analyses were re-run excluding those with probable non-credible performance (RAVLT immediate and delayed invalidity).

Two-test impairment

Rates of impairment on two or more within-domain tests (i.e., two declarative memory tests, or two or more executive function tests) are presented in Table 2. Groups differed on two-test 1.5 SD impairment for both declarative memory, χ^2 (2) = 9.45, p < .01, and executive functioning, χ^2 (2) = 6.23, p = .04. People with LOC of 1–20 mins were more impaired on declarative memory (15.2% vs. 10.6%) than comparison participants (p < .01, OR = 1.51, 95% CI = 1.16–1.97) and people with LOC <1 min (p = .02, OR = 1.54, 95% CI = 1.06–2.25), while comparison participants did not differ from people with LOC <1 min, p = .88. People with LOC 1–20 mins were more impaired than comparisons on ≥2 executive functions (8.2% vs. 5.5%, p = .02, OR = 1.52, 95% CI = 1.06–2.18); people with LOC <1 min did not differ from comparison participants or those with LOC 1–20 mins (ps > .10). Across the sample, LOC was associated with two-test impairment for both declarative memory (OR = 1.21, 95% CI = 1.01–1.48), and executive functioning (OR = 1.31, 95% CI = 1.02–1.67). Significance across two-test impairment analyses did not change when reexamined after two-test invalidity exclusion.

Discussion

Previous research examining long-term cognitive impairment after mTBI has provided mixed evidence, with studies generally finding persistent cognitive deficits among 4% to 10% of individuals (Karr et al., 2014), although it has recently been argued that these figures may be vast underestimates (McInnes et al., 2017). Our understanding of persistent cognitive impairment following mTBI has unfortunately been limited by varied definitions of impairment across studies (Karr et al., 2014; McInnes et al., 2017). From this perspective, adopting guidelines commonly used to identify mild cognitive impairment (Schinka et al., 2010) would provide a consistent definition for identifying impairment, particularly with respect to impairment within any particular cognitive domain.

We present findings from a large nationally representative sample, from which prevalence estimates indicate that 6.77% of participants were found to have experienced a single mTBI with LOC (LOC <1 min = 3.02%, and LOC 1–20 min = 3.75%). The present data suggest that those with greater duration of unconsciousness (i.e., LOC 1–20 minutes) are more likely to be impaired at 1.5 or more standard deviations below the mean of comparison participants on the MAT (11.6% vs. 7.7%) and the COWAT (12.9% vs. 8.5%), which assess mental set-shifting, inhibitory comparison, and verbal initiation. Moreover, people with LOC 1–20 minutes had higher impairment rates than comparison participants on the RAVLT immediate and delayed declarative memory tasks (15.2% vs. 10.6%).

These group impairment rate differences were also found when two-test impairment criteria were used: a larger proportion of people with LOC 1–20 min were impaired on two or more tests of executive functioning (8.2% vs. 5.5%) and on the two tests of declarative memory (15.2% vs. 10.6%) compared to comparison participants. It is also notable that those who reported LOC <1 min were not more likely be impaired than comparisons when using two-test criteria. That is, consistent with findings from recent meta-analyses (Karr et al., 2014; McInnes et al., 2017), these data suggest that a small proportion (8.2% to 15.2%) of people may experience persistent mild executive and declarative memory impairment following a single mTBI with loss of consciousness. Our findings indicate that most people who experience a single mTBI with LOC do not go on to exhibit long-term cognitive impairment, but support the prevailing view that a small minority of individuals

may experience persistent cognitive dysfunction. These deficits were most apparent among those who reported having spent a longer time unconscious.

While the large sample size of CLSA is a significant strength of the present study, several limitations must also be taken into account. Although these data suggest that people who experienced mTBI with LOC of 1–20 minutes are more likely to be cognitively impaired than people who report mTBI with shorter periods of unconsciousness or no head injury comparisons, the data may also support the notion of greater score variability as opposed to greater impairment. Moreover, the CLSA provides only self-report of previous TBIs; thus, under- or over-reporting of mTBI status, as well as length of time spent unconscious, may have occurred. The absence of Glasgow Coma Scale Scores and data regarding post-traumatic amnesia makes it difficult to assess TBI severity. Participants may have perceived questions related to head injury and concussion differently than intended, and thus some people who experienced a head injury with or without LOC within the past year may have gone undetected. Data on the exact date of head injury are not available, and caution is thus warranted when considering the time-scale of executive dysfunction. Moreover, there was a large sample size and gender imbalance, particularly between comparisons and the mTBI groups, which may have influenced reported findings. However, steps were taken to alleviate these biases both in parametric and non-parametric analyses. We also do not report ethnicity or cultural background, which is an important limitation when considering clinical translation of these findings. Finally, information regarding premorbid functioning (e.g., occupational attainment or estimates of intellectual ability) is not available. Differences in premorbid functioning may account in part for the unexpected findings for performance on the AFT.

With respect to the test battery, standalone measures of performance validity were not available to assess non-credible performance, and so embedded RAVLT measures were considered. However, only RAVLT immediate (Trial 1) and the 30 minute delayed trial were available in the dataset, which is a considerable limitation of the present study. For example, recognition indices have been found to more optimally balance sensitivity and specificity in noncredible performance (Boone et al., 2005). Sensitivity in identifying noncredible performance came at a loss to prioritizing specificity in the current investigation. Moreovoer, although failure of three embedded measures of performance validity is suggested to identify non-credible performance (Larabee, 2014; Rickards, Cranston, Touradji, & Bechtold, 2018), our results did not change when we used a more conservative cutoff of two-test invalidity.

A related limitation in the present study has to do with family-wise error within impairment analyses; when uncorrected, proclivity for false-positive errors is increased (see Huizenga, Agelink van Renterem, Grasman, Muslimovic, & Schmand, 2016). Even in the presence of highly correlated tests, family-wise error may be unfavorably elevated. Correlational absolute values between neuropsychological tests in the present study ranged between .11 (RAVLT immediate vs. Stroop) and .68 (RAVLT immediate vs. delayed), with most correlations falling between .20 and .40, suggesting that family-wise error rates were likely elevated. Therefore caution is advised in interpreting the odds ratios attributed to significant impairment analyses, as they may be slightly elevated. However, the testing battery also made use of two tests of declarative memory and four measures of executive functioning, which were examined within a two-test impairment framework as another index of impairment (Schinka et al., 2010), which fits with the understanding that deviation on multiple tests to infer impairment would better satisfy family-wise error rates (Axelrod & Wall, 2007; Huizenga et al., 2016). Moreover, there is an inherent discrepancy in psychometric equivalence for between-domain impairment analyses, notwithstanding that the same verbal information is used for both measures of declarative memory. The two-test impairment analyses should be weighed with this in mind, and considered as a way to characterize within-domain impairment as opposed to elucidating differential impairment.

Moreover, in considering the odds ratios attributed to varying levels of LOC, it should be noted that odds of impairment attributed to any experienced unconsciousness (i.e., agnostic to head injury status) is not discernible. The current data set only included information related to unconsciousness relevant to a head injury, used for the current analyses, and data concerning any other experienced unconsciousness is not reported. Therefore, although comparison participants did not include those who had reported experiencing a concussion or brain injury, it should be noted that the odds ratios provided cannot be considered within the scope of any unconsciousness experienced across the entire sample. With that said, we do report odds ratios attributed to any LOC experienced across the mTBI sample as a point of comparison.

Research has shown lower processing in people with mTBI compared to control participants with no history of head injury (Karr et al., 2014). The current study focused on memory and executive function exclusively; future research should investigate whether processing speed impairments may be implicated in the observed deficits. Similarly, the testing battery relied solely on verbal output, and so we cannot comment on, or extend findings to other cognitive functions such as motor

output, or visual memory. This will limit clinical inferences that can be drawn from these data.

Conclusions

The current study provides evidence that people who self-reported mTBI with LOC more than 12 months ago are more likely to present with executive and declarative memory impairment than people who have not experienced head injury. More time spent unconscious increased the likelihood of impairment, suggesting that length of time spent unconscious may be a relevant factor in considering long-term outcomes in mTBI. Future work will aim to identify specific predictors that may differentiate those who experience ongoing impairment from those who fully recover.

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