Past History of Substance Misuse Impedes Attentional Recovery After Moderate to Severe Traumatic Brain Injury

by

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Abstract

Degree of cognitive recovery from a moderate-severe traumatic brain injury (TBI) will affect the extent of permanent disability sustained; therefore, it is critical to understand which factors may enhance or impede recovery. Since attentional impairments affect 40-60% of moderate-severe TBI patients, and elevated use of psychotropic substances can have lasting effects on attention and attention-related structures, the role of pre-injury substance misuse on attentional recovery was examined. Attentional recovery from 2 to 5 months post-injury in moderate-severe TBI patients was compared in those with versus without self-reported high levels of substance misuse. Those with high substance misuse recovered significantly less on an aggregate score of attention, and on 4 of the 8 individual tests of attention that comprised the aggregate: Trail-Making Test A, Stroop Colour-Word, Stroop Word, and Verbal Fluency Test (Phonemic). This is the first study to demonstrate that pre-injury substance misuse may reduce attentional recovery after moderate-severe TBI.

Abbreviations: TBI = traumatic brain injury; PAI = Personality Assessment Inventory; GCS = Glasgow Coma Scale; PTA = length of post-traumatic amnesia; YOE = years of education; SDMT = Symbol Digit Modalities Test; VF-P = Verbal Fluency Test, Phonemic; HSU = High Substance Use
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Appendix 1: Component tests of the aggregate and their respective weightings
List of Abbreviations

ACC = anterior cingulate cortex
CBD = cannabidiol
CIQ = Community Integration Questionnaire
CT = computed tomography scan
dlPFC = dorsolateral prefrontal cortex
DSM-V = Diagnostic and Statistical Manual of Mental Disorders, Version 5
EEG = electroencephalogram
ERP = event-related potential
FA = fractional anisotropy
FIM = Functional Independence Measure
fMRI = functional magnetic resonance imaging
GCS = Glasgow Coma Scale
HSU = high substance use
LAQ = Lifestyle Activities Questionnaire
LECN = left executive control network
LTA = long-term abstinent
mPFC = medial prefrontal cortex
MRI = magnetic resonance imaging
PAI = Personality Assessment Inventory
   - ALC = Alcohol Problems scale
   - DRG = Drug Problems scale
   - NIM = Negative Impression Management validity index
   - NON = Non-support scale
   - INC = Inconsistency validity index
   - INF = Infrequency validity index
-PIM = Positive Impression Management validity index

-RXR = Resistance to Treatment scale

PTA = length of post-traumatic amnesia

REM = rapid-eye movement

SDMT = Symbol Digit Modalities Test

SES = socioeconomic status

STA = short-term abstinent

TBI = traumatic brain injury

THC = Δ9-tetrahydrocannabinol

TMT = Trail Making Test

VF-P = Verbal Fluency Test, Phonemic

YOE = years of education
Chapter 1

1 General Introduction and Literature Review

1.1 General Introduction

Traumatic brain injury is a ubiquitous injury that can cause devastating consequences, including severe cognitive impairments. After moderate-to-severe TBI, most recovery tends to occur within this first year post-injury, with the most rapid recovery occurring within the first 5 months; however, improvements have been found to continue up to 5 years after in some cases (Christensen et al, 2008; Sigurdardottir et al, 2009). Recovery for different cognitive domains may follow different trajectories, with some (e.g., learning and memory, complex attention, speed of processing) recovering more slowly or to a lesser extent than other domains (Christensen et al, 2008). The extent of recovery plays a critical role in the degree to which a person can return to prior vocational/academic, leisure and social activities. Therefore, there is a large body of research focused on cognitive recovery, and on the factors that can enhance or impede recovery. In the current study, we examine the role of alcohol and substance misuse.

Before proceeding to the methods of the study, I will first provide an overview of the literature regarding substance misuse as it relates to attention and traumatic brain injury commencing in the following section. Following this chapter, Chapter 2 includes the full empirical study of the thesis, concerning the role of substance misuse on recovery of attention after moderate-severe traumatic brain injury. Chapter 3 provides a general discussion of the results of the study, its implications for future research and clinical rehabilitation, and conclusions.

1.2 Traumatic Brain Injury

Traumatic brain injury (TBI) is the leading cause of disability worldwide (Maas, Stocchetti & Bullock, 2008). A traumatic brain injury differs from other brain injuries in that it occurs as a result of a trauma (Centers for Disease Control[CDC], 2015). It is often the result of the head striking or being struck by an object; however, contact with an object is not necessary, as it can occur from rapid acceleration and deceleration forces without a direct blow to the head, as in the case of a belted passenger in a car accident (CDC, 2015; Lezak et al, 2012).
1.2.1 Moderate-Severe TBI

The severity of a TBI is often determined based on the patient’s score on the Glasgow Coma Scale (GCS) or the period of time after their injury during which memory is not continuous, otherwise known as their length of post-traumatic amnesia (PTA) (Lezak et al, 2012). TBIs are usually classified as either mild, moderate or severe, with approximately 25% falling under the latter two classifications (CDC, 2003). Moderate-severe TBIs are often the result of serious vehicular accidents, very bad falls or assault (CDC, 2015). With a moderate-severe TBI, there is often a marked loss or alteration of consciousness at the time of injury, permanent damage to the brain and lasting impairments in cognitive, emotional and motor functioning (Lezak et al, 2012), and there is also growing evidence for longer term declines in the chronic stages of injury (Green et al, 2014). Additionally, there are likely to be changes to the brain that are visible on neuroimaging (Lezak et al, 2012).

1.2.2 Typical Recovery

To be conservative, one might say that most cognitive recovery tends to occur in the first year post-injury, however, the majority of the measurable cognitive improvement actually typically occurs in the first 5-6 months (Christensen et al, 2008). This is also when most patients (in Canada) are receiving inpatient and outpatient rehabilitation. After the first year, improvement may continue, but it may just be the result of the brain developing compensatory mechanisms (Eldreth et al, 2004; Lezak et al, 2012; Nicholls et al, 2015). Such mechanisms result in the appearance of recovery, but may actually be the result of using a less efficient process to achieve unimpaired performance (Eldreth et al, 2004; Nicholls et al, 2015). Indeed, in one study on long-term cognitive changes, it was observed that for two neuropsychological tests, 27% of the participants in the sample actually declined between 1-3 years post-injury (Till et al, 2008).

According to Lezak et al (2012), while rates of improvement vs decline after 1 year post-TBI tend to vary based on the study, the most common finding is simply that cognitive impairments in those with moderate-severe TBI remain largely unchanged. It is also important to note that recovery for different cognitive domains may follow different trajectories, with some (e.g., learning and memory, complex attention, speed of processing) recovering more slowly or to a lesser extent than other domains (Christensen et al, 2008; Jourdan et al, 2013).
1.2.3 Attention Impairments

Lasting impairments in attention affect 40-60% of patients with moderate-severe TBI (Sivan, 2010; Warden et al, 2006). It is one of the most common complaints of symptoms persisting long after the injury occurred (Ponsford, 2014). Research on attention in both healthy and clinical populations has resulted in the development of several theories of attentional function (Corbetta and Shulman, 2002; Duncan and Miller, 2002; Posner and Petersen, 1990; Posner and Petersen, 2012; Stuss, 2006). One major theory posits that there are 3 distinct networks of anatomical areas that carry out different attentional functions (Posner and Petersen, 1990; Posner and Petersen, 2012). The first network is responsible for “Alerting”, which makes use of the norepinephrine arousal system from the brainstem to produce and sustain vigilance using the right hemisphere. The second attentional network is responsible for “Orienting” which relates to the ability to prioritize sensory stimuli. This attentional network is primarily throughout the parietal cortex and determines where to focus attention. Regarding the process of orienting, Corbetta and Shulman (2002) theorized that this can occur in a manner that is either “bottom up” (ventral) or “top-down” dorsal. Ventral processing occurs when attention is biased toward behaviourally relevant stimuli, particularly if they are salient or unexpected. Dorsal processing occurs when attention is directed toward the person’s goals (Corbetta and Shulman, 2002). The final attentional network in Posner and Petersen’s theory is referred to as the “Executive” network. This network makes use of the midline cortex and anterior cingulate cortex. It is also referred to as “focal attention” and plays a role in remaining conscious of the limited capacity of the attentional system. An opposing theory of attentional function was made by Miller and Duncan (2002) who posit that no distinct areas of attention networks exist, instead, structures of the frontal lobes can adapt to any attentional requirement. Furthermore, in a study by Stuss (2006) it was suggested that the question of fractionation of the frontal lobes vs general adaptability might be futile, as neither theory fully encompass human attentional functioning.

There are four aspects of attention that have become the focus in clinical populations due to susceptibility to damage: selective attention, sustained attention, divided attention and alternating attention (Lezak et al, 2012). Selective attention refers to the ability to filter out unnecessary information and inhibit inappropriate responses, and can also be referred to as focal attention (Leclercq, 2002). This aspect encompasses the processing of information and the subsequent reactions and decision making that follow. Sustained attention (also referred to as vigilance)
refers to the ability to focus on a task for a long period of time (Sinclair et al, 2013). Divided attention refers to multitasking or being able to split your attention between two or more stimuli or tasks (Leclercq, 2002). For example, taking notes in class requires both listening to the professor as well as writing down important points. Lastly, alternating attention, which is also referred to ask “task-switching” refers to the ability to move back and forth between tasks without losing one’s train of thought in either task. An example of an everyday activity requiring alternating attention would be cooking. For example, a recipe might require you to periodically stir something while doing something else, and forgetting to return to stirring between tasks could result in ruining the meal. While TBI is associated with general attention problems encompassing several or all of these aspects of attention, selective and divided attention tend to be particularly sensitive to the effects of brain injury (Lezak et al, 2012). Problems with attention can affect every facet of the patient’s life, including their academic, vocational, and social lives (Virk et al, 2015). The ability to pay attention also affects other cognitive functions, such as memory, so it is important to understand why people may be experiencing reduced or delayed recovery of attention after their TBI.

1.3 Predictors of Recovery

1.3.1 Why it’s important

Predictors of both acute and long-term outcome after TBI are of importance because they allow for appropriate goals for rehabilitation as well as implementation of appropriate educational or vocational support (Jourdan et al, 2013). Since more accelerated recovery tends to occur in the first 5-6 months post-TBI, it is important to understand how predictors affect early outcome in case there is a rehabilitation intervention that may be able to change any modifiable predictors or provide more support to those that are predicted to have poorer recovery (Christensen et al, 2008; Jourdan et al, 2013).

1.3.2 Previously established predictors of cognitive recovery

A large body of research has examined demographic and injury-related variables as predictors for cognitive recovery after TBI (Green et al, 2008; Jourdan et al, 2013; Konigs et al, 2012). In a study by Jourdan et al (2013), cognitive function outcomes after TBI were predicted by educational history, with more education predicting better outcomes. In another study, it was
found that length of post-traumatic amnesia (PTA) strongly predicted post-TBI impairment of intelligence, with a longer duration of PTA predicting more impairment in intelligence (Konigs et al, 2012). Recovery of speed of processing was found to be moderated by age as age significantly predicted cognitive outcomes at 2 months and 12 months post-injury for both simple and complex speed of processing (Green et al, 2008). Interestingly, however, they found no effects of age on recovery of memory, executive function, or simple attention, indicating that some predictor variables may only predict recovery of certain cognitive domains.

1.4 Alcohol Misuse

1.4.1 What constitutes “misuse”?

Recent research has posited that alcohol consumption, in moderation, can afford cardiovascular and cerebrovascular benefits (Lezak, 2012). Consuming alcohol in moderation is typically defined as 1-2 drinks per day, whereas heavy or high intake is typically defined as 3-4 per day or more than 8 drinks per week for females or more than 15 drinks per week for males (World Health Organization, 2014). Due to metabolic differences based on genetics and body proportions, as well as the well-documented issue of underreporting in alcoholics, some have argued that using quantity of intake to evaluate the impact of alcohol has limitations (Lezak et al, 2012). One alternative to this approach, as employed by the DSM-V, is the measurement of the health, social and vocational consequences of drinking. This meant that those whose health, interpersonal relationships and/or occupational functioning were disrupted as a consequence of their drinking were considered to have an alcohol problem (American Psychiatric Association, 2013). In Canada, 6.8 percent of the population has an alcohol use disorder, with 4.1 percent reaching the level of alcohol dependence (World Health Organization, 2014). Depending on the circumstance, even temporary effects of alcohol can be dangerous, such as: increased impulsivity, decreased inhibition, increased violence as well as motor problems including balance, coordination and vision (NIH, 2015).

1.4.2 How it relates to TBI (cause and effect)

In a review by Taylor et al (2003), it was found that prevalence of alcohol abuse was much more common in the TBI population than the general population, with up to 79% of the group reporting substance use problems pre-injury. Alcohol use is also a common factor in cause of
brain injury and up to 50% of patients seeking treatment for TBI in the emergency room of hospitals in the United States were found to be under the influence of alcohol in a recent study (Niemeier et al, 2016). Intoxication at time of brain injury is not only common, but it is also associated with more post-traumatic complications such as a greater length of stay in hospital, increased risk of hospital-acquired infections, and slower wound healing (Niemeier et al, 2016). After a TBI, those with pre-morbid substance use issues, including alcohol misuse, are at risk of relapse and those without pre-morbid substance use may be at greater risk of developing substance abuse problems post-TBI (Niemeier et al, 2016). In summary, alcohol misuse has significant associations with cause, complications and consequences of TBI.

1.4.3 Temporary effects

Alcohol has temporary effects on the brain during intoxication that including motor impairments (speech, balance and coordination), behavioural changes (increased aggression and poorer judgment) and cognitive impairments (slower speed of processing, poorer memory and attention) (Stavros et al. 2012). A study by De Sousa Uva et al (2010) measured affective and cognitive functioning in alcoholics on Day 1 of withdrawal up to 2-3 weeks after withdrawal from alcohol and compared these to measurements taken from matched non-alcoholic controls at the same time points. At the first assessment, the alcohol group had significantly higher ratings of negative affect, significantly higher alcohol cravings and significantly impaired cognitive function. By 2-3 weeks later, at the second assessment, alcohol craving and negative affect were reduced in the alcohol group. Conversely, cognitive impairments - specifically components of attention, including selective attention - persisted in the alcohol group, with no significant improvements at the 2-3 week assessment. From this study it appears that cognitive effects may persist past intoxication, into and even beyond withdrawal.

1.4.4 Enduring brain changes

Alcohol has been shown to transiently disrupt cognitive and motor functioning (e.g., attention, memory, balance) (Stavros et al, 2012). Several lines of research have also shown lasting effects of alcohol on neural and cognitive functioning in otherwise healthy adults (Fortier et al, 2014; Kopera et al, 2012; Svanberg & Evans, 2013; Tedstone & Coyle, 2004; Weiland, 2014). In a study by Fortier et al. (2014), magnetic resonance imaging (MRI) identified widespread reductions in white matter volume in abstinent alcoholics. Participants in the Alcohol group had
a mean of 25 years of alcohol abuse and mean lifetime alcohol exposure to 819, 499g of alcohol but were abstinent for at least a month prior to the MRI. The greatest reduction in fractional anisotropy (FA) was found in the frontal and superior tracts. In particular, the inferior frontal gyrus had significant bilateral reduction of FA. An fMRI study done by Weiland (2014) analyzed differences in functional connectivity in 255 participants with alcohol use disorder and 97 controls. The groups were matched based on age and gender. There were significant reductions in functional connectivity in the participants with alcohol use as compared to the controls for four networks: left executive control network (LECN), basal ganglia, sensorimotor network and primary visual network. For the alcohol group, there was a significant negative correlation between scores on measures of severity and problem drinking and functional connectivity. The significantly reduced functional connectivity within the LECN was primarily driven by connections of the dorsolateral prefrontal cortex, middle frontal cortex and temporal regions to the parietal regions.

1.4.5 Enduring cognitive changes

In extreme cases of alcohol abuse, extensive and enduring damage to the brain is observed in the form of alcohol-related brain disorders such as alcoholic dementia, Wernicke’s encephalopathy and Korsakoff’s syndrome (Svanberg & Evans, 2013). These individuals have severe cases of brain damage, often resulting from thiamine deficiencies or metabolic disruptions, both of which can be caused by patterns of prolonged periods of alcohol consumption or cycles of intoxication and withdrawal (Svanberg & Evans, 2013). Even in the absence of an alcohol-related brain disorder, high levels of chronic alcohol consumption can have enduring detrimental effects on cognition.

In a study examining attentional impairments in sober alcoholics, it was found that the effects of chronic alcohol use varied for different aspects of attention (Tedstone & Coyle, 2004). Compared to non-alcoholic controls, the sober controls (who had been abstinent for a median of 28 days) performed significantly worse on tests of selective attention, with the largest effect found on the test of Stroop Colour-Word. Tests of divided attention also revealed that sober alcoholics made significantly more errors and had a significantly worse reaction time, however, the effect size for the differences in divided attention were small. These results indicate that aspects of attention may be differentially sensitive to the effects of chronic alcohol use.
Kopera et al (2012) found significant problems in alternating attention in short-term abstinent alcoholics (STA) as compared to non-alcoholic controls. Those in the STA group had been abstinent from alcohol for a mean of approximately 5 months. They were found to have significantly worse reaction times on a task of attentional set shifting, as well as significantly more errors than controls. Interestingly, another group of abstinent alcoholics, the long-term abstinent (LTA) group differed significantly from the STA group in terms of attentional errors as well. The LTA subjects, who had been abstinent for ≥ 1 year, with a mean abstinence period of almost 3 years, showed significantly fewer errors than the STA group, an encouraging finding suggesting some reversibility of the cognitive effects of alcohol misuse. It should be noted that the cross-sectional design of the study limits the generalizability of the findings.

1.5 Marijuana Misuse

Aside from alcohol and tobacco, cannabis is the most commonly used psychotropic substance (Curran et al, 2016; Hall et al, 2013; Volkow et al, 2016). Cannabis is composed of hundreds of cannabinoids, the two most well-studied are: Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD). THC is considered to be the more psychologically and cognitively detrimental component, whereas CBD has opposing effects that are believed to actually counteract the negative effects that THC has on attention, memory, learning and anxiety (Curran et al, 2016; Volkow et al, 2016). In the last 20 years, however, the THC content in street drugs has increased from 4% to 12%, with CBD levels decreasing to approximately 0.1% (Curran et al, 2016). Pending legalization of marijuana in Canada, it is important to have a better understanding of how marijuana can affect not only an otherwise healthy population, but those populations that may already be affected by disability, such as people with traumatic brain injury.

1.5.1 How it relates to TBI (cause and effect)

In a review by Taylor et al (2003) it was found that while less prevalent than pre-injury alcohol abuse, pre-injury drug use (which was reported as primarily marijuana) was mentioned by up to 37% of participants in TBI studies. In the same review, it was mentioned that brain injury can increase likelihood of a relapse in those with pre-injury substance use problems. As well, some of the studies mentioned in the review found that even those that did not have pre-injury substance misuse were at a greater risk of developing substance use problems post-TBI. Even in already high-risk populations such as young offenders, a study by Williams et al (2010) found a
significant correlation between marijuana use and history of traumatic brain injury. Based on the above findings, it appears that marijuana use is highly associated with TBI – both before and after injury.

1.5.2 Temporary effects

Many studies have documented the acute effects that marijuana has on the brain. These include impairments in behaviour, motor function and cognition (Panlilio et al, 2015). Acute effects of intoxication are considered to last between 2-3 hours after inhalation (Curran et al, 2016; Panlilio et al, 2015), but some researchers argue residual effects exist at 12 hours after use (Harding et al, 2012; Panlilio et al, 2015; Zalesky et al, 2012). With regard to cognition, what is primarily observed are effects on memory, attention and executive function (Conroy et al, 2015; Curran et al, 2016; Hall et al, 2013). Conroy et al (2015) found that participants with heavy, current marijuana use self-reported significantly worse cognition problems including difficulties with problem-solving, reasoning, memory and attention. This study compared those with no use, non-daily use and daily use and for users also collected data on how many minutes were spent using marijuana. Higher marijuana use (more minutes) was significantly associated with more self-reported cognitive problems. These findings were similar for both males and females.

Several studies have found acute differences in brain function in marijuana users as well. Zalesky et al (2012) used diffusion-weighted MRI and connectivity mapping and found microstructural alterations in axonal pathways in cannabis users that had abstained for 12 hours when compared to controls. The same study also found that cannabis users had decreased grey matter in the limbic system and impaired axonal connectivity in the fimbria of the hippocampus and the splenium of the corpus callosum. A study by Harding et al (2012) found increased connectivity between right prefrontal to left occipito-parietal areas in marijuana users with 10 years of use or more. These participants had been abstinent for 12 hours before completing a cognitive control task. The increased functional connectivity between these areas was thought to represent a compensatory mechanism for abnormal attention and visual processing. This theory that marijuana users require more effortful activation to compensate for impairments was based off of two other studies where hyperactivity of the anterior cingulate cortex, insular cortex and lateral prefrontal cortex were observed in marijuana users as they performed attention tasks (O’Leary et al, 2007; Weinstein et al, 2008). These effects have been observed to last beyond
the immediate effects of intoxication. Other studies have examined more enduring brain changes, however.

1.5.3 Enduring brain changes

Chronic cannabis use has been linked to reduced regional cerebral blood flow, which is thought to explain the mechanism by which cannabis users may have a decreased ability to process information (Lundqvist, 2005; Solowij et al, 2007). In the study by Solowij et al (2007), the patterns of activation measured by event-related potentials (ERPs) differed in cannabis users when compared to controls. The P300 wave was smaller at all amplitude sites in the users and the Negative (N200) peak was present in cannabis users but was not present or was minimally present in non-users. This indicated difficulty filtering out unnecessary information.

Reduced activation in the dorsolateral prefrontal cortex (dLPFC) and the anterior cingulate cortex (ACC) were noted in several studies (Eldreth et al, 2004, Kempel et al, 2003; Nicholls et al, 2015). In one study, Eldreth et al. (2004) observed hypoactivity in both the dLPFC and ACC as well as hyperactivity in the hippocampus during a modified Stroop task in marijuana users as compared to controls. The users had been abstinent for 25 days but previously had been heavy users (at least 4 times per week for at least 2 years). This abnormal pattern of activation is thought to support the theory that marijuana users recruit an alternate pathway to compensate for marijuana-related changes in executive functioning. In a study by Nicholls et al (2015), chronic marijuana users that had been abstinent for at least 24 hours also reported an abnormal activation pattern. Despite no significant differences in errors on a Flanker Go/No-go task between the chronic marijuana users and drug naïve controls, marijuana users had significantly longer reaction times and an atypical amplitude pattern of event-related potentials. For example, in a healthy population, N1 amplitudes should increase during incongruent trials of the Flanker Go/No-go task, reflecting the narrowing of the visual field of attention to block out the unnecessary information provided by Flanker stimuli. This was observed in the drug-naïve control group, as expected, but no such increase in amplitude was found in the chronic marijuana users. This altered pattern of activation found in chronic cannabis users is believed to be the result of users engaging in a different, less efficient process to compensate for marijuana-related alterations to the attentional network.
1.5.4 Enduring cognitive changes

Lundqvist (2005) undertook a review on the effects of several classes of drugs on the brain. In this review, he mentioned that the cognitive domains most affected by chronic marijuana use were memory and selective and divided attention. Whether impairments are lasting or reversible remains a question of interest, however. For example, one of the studies (Pope et al, 2001) did not find lasting impairments after 28 days of abstinence, but others (Bolla et al., 2002; Pope et al, 2002; Solowij et al, 2007) found persistent deficits related to dose as well as age of onset of marijuana use, with selective attention being the most noticeable lasting impairment.

In the study by Solowij et al (2007), it was observed that marijuana users were less accurate and made more mistakes than controls in a task where they had to detect a target auditory tone. Users had significantly less positive hits and significantly more false alarms than controls. Users and controls did not, however, differ significantly on reaction time, indicating that they were perhaps processing information equally quickly but less effectively. To summarize, cannabis users had impaired selective attention, as ERPs indicated they paid less attention to target cues and more attention to unnecessary information. Similarly, in a study of adolescent heavy marijuana users, Hanson et al (2010) observed enduring problems with attention accuracy. The study spanned 3 weeks during which the participants were abstinent from marijuana use. Participants were compared to matched controls on measures of cognitive function: verbal learning, verbal working memory, and attention. Initially, all three were impaired in marijuana users compared to controls. After 3 weeks, only attention remained impaired in the marijuana users. Reaction speed on the attention tasks was not significantly different between groups, which - similar to Solowij et al (2007) - suggests that accuracy rather than speed of processing is affected.

1.6 TBI Recovery and Substance Misuse

1.6.1 How substance misuse and TBI are related

While research has shown that demographic and injury variables can affect cognitive recovery after a traumatic brain injury, to date, past history of substance misuse has not been studied extensively, though growing findings on a population without brain injury in the substance abuse literature suggests that it may compromise cognitive functioning. While many studies look at incidences of TBI in the context of substance abuse or else examine incidences of alcohol and
drug misuse in a TBI population, few studies examine how recovery from TBI might be affected by substance misuse (Barnfield et al, 1998; Parry-Jones et al, 2006; Taylor et al, 2003; Williams et al, 2010).

### 1.6.2 Niemeier study

A recent study by Niemeier et al. (2016) revealed that substance abuse was found to predict impairments in executive function post-TBI. This study examined post-TBI functional and neurobehavioural status by using various scales of disability and competency. Both the Disability Rating Scale and Functional Independence Measure (FIM) were used. These measures have reliable findings with regards to brain injury outcome and response to rehabilitation. The Patient Competency Rating Scale, Frontal Systems Behavioural Scale, and Neurobehavioural Rating Scale – Revised were also used. These measures examine the TBI patient’s competence and independence post-TBI and are self-report but are also compared with other raters (such as relatives or a physician) to determine a patient’s self-awareness of their functional status. It was found that executive function – especially self-awareness – was more impaired in patients with TBI that had a history of substance abuse, as the discrepancy between scores given by the patient and other raters was much larger for them. This study did not focus on recovery of attention.

### 1.7 Rationale

#### 1.7.1 Sleep disturbances

Marijuana can affect attention in many ways. One way was demonstrated in studies by Ly and Gehricke (2013) as well as Bolla et al (2008), which was through sleep disturbances. Marijuana can lead to poor sleep quality, which can result in attention problems (Ly and Gehricke, 2013). Although circadian rhythms such as the sleep-wake cycle are primarily driven by biological factors, some can be disrupted by environmental factors. These factors typically involve changes to one’s exposure to sunlight, such as shift work or jetlag, however, recent studies have found that chronic substance abuse can also disrupt the sleep-wake cycle (Bolla et al, 2008; Hasler & Clark, 2013). Studies have demonstrated that chronic marijuana use can change sleep architecture, elongating slow-wave sleep and shortening REM sleep. Additional changes reported included reduced total sleep time and poorer quality of sleep (Bolla et al, 2008; Ly and Gehricke, 2013). A recent review of the literature on alcohol and sleep architecture has provided
important insights into the effects of alcohol on sleep (Chakravorty et al, 2016). Insomnia and sleep disorders are prevalent among those with alcohol use disorders. Both subjective measures of sleep (Insomnia Severity Index) and objective measures (polysomnography) were reviewed. It was found that those with alcohol use disorders had increased sleep onset latency, decreased total sleep time and fragmented sleep (more awakenings) as well as abnormalities in slow wave sleep and REM sleep (Chakravorty et al, 2016). While sleep onset latency was found to resolve after several months of abstinence, total sleep time, sleep fragmentation and slow wave sleep abnormalities took nearly 2 years to fully resolve (Chakravorty et al, 2016). REM sleep abnormalities were inconsistent, with some evidence of reversal early in abstinence but also evidence of REM issues persisting beyond 2 years of abstinence (Chakravorty et al, 2016). These changes to sleep architecture provide a mechanism through which alcohol and marijuana can indirectly affect attention. This is especially important to acknowledge in those with both substance abuse and TBI since sleep is also neuroprotective, and can modulate neuroplasticity (Nakase-Richardson et al, 2013).

1.7.2 Social support

The relationship between substance misuse and social support is bidirectional. Not only are those with substance misuse more likely to be socially isolated, but a lack of social support is often a contributing stressor resulting in substance misuse (Galea et al, 2004; Nobre, 2016). Marijuana users are more likely to have family conflict and poor parental relationships (Galea et al, 2004; Resnick et al, 1997). Alcohol is also often used as an anxiolytic in those with social anxiety, and withdrawal from alcohol can actually result in greater levels of social anxiety than existed before onset of alcoholism (Nobre, 2016). Increased social anxiety following withdrawal from alcohol may result in avoidance of social situations. Additionally, recovering alcoholics often choose to avoid social activities in order to reduce their exposure to alcohol (Galea et al, 2004). Misuse of alcohol and drugs can also lead to relationship problems, family discord and alienation (Galea et al, 2004). Even after abstinence, the damage to these relationships may be difficult to repair. As a result of this bidirectional relationship between a lack of social support and substance misuse, it follows that those with substance misuse problems may lack a supportive network. Since social support is predictor of TBI recovery, those with substance misuse problems and TBI may be at risk for a poorer recovery (Tomberg et al, 2007).
1.7.3 Cognitive stimulation/Environmental Enrichment

Similar to social support, the relationship between cognitive stimulation and substance misuse is also bidirectional. In some circumstances (especially in adolescent onset), substance use is initiated in part because of a lack of non-drug (or alcohol) reinforcement (Bickel et al, 1998). So, in the absence of a cognitively stimulating environment (such as academic or extra-curricular pursuits), one might be more likely to engage in substance use. Elevated use of alcohol and/or drugs is also associated with a reduction in activities unrelated to substances (Galea et al, 2004). This means that those with alcohol and/or marijuana misuse might neglect hobbies, athletics, socialization as well as vocational or academic pursuits (Galea et al, 2004). The decrease in cognitively stimulating activities could be due to increased time spent acquiring and using substances or decreased motivation to engage in them. Since cognitive stimulation (or environmental enrichment) has been found to act as a potential buffer against brain atrophy post-TBI, a deficit in cognitive stimulation could put those with substance misuse problems at risk of poorer recovery (Frasca et al, 2013; Miller et al, 2013).

1.7.4 Motivation

In an experiment with rhesus monkeys, it was found that chronic marijuana use resulted in amotivational behaviour (Lane et al, 2005). Marijuana has been found to produce a similar amotivational state in humans when participants were under acute intoxication (Lane et al, 2005). One study noted that, according to subjective measures such as self-reports, heavy marijuana use may be associated with lower levels of motivation, but objective neuropsychological assessments failed to find significant differences between heavy users and those with minimal use (Kouri et al, 1995). Cross-sectional studies have noted that marijuana use is correlated with lower educational achievement, negative attitudes towards school and early dropout (Brook et al, 1998; Jones et al, 1998; Resnick et al, 1997). Longitudinal studies, however, are confounded by a multitude of socioeconomic and environmental factors which make it difficult to determine causality (Lynsky and Hall, 2000). As of yet there has been no definitive conclusion as to whether or not a lack of motivation persists in humans with chronic marijuana use that have been abstinent for long periods (Kouri et al, 1995; Lynsky and Hall, 2000). Boosman et al (2016) summarized that low motivation is a barrier to good outcomes after brain injury and something that is already often observed in the brain injury population. As such,
it is possible that chronic marijuana users with TBI may be especially lacking in motivation, which may impede their progress in rehabilitation.

1.8 Summary of Literature

Moderate-severe traumatic brain injury can result in lasting impairments in cognition, including attention. The ability to pay attention plays a key role in social, educational and vocational activities. As such, any factors that may be related to a reduced or delayed recovery of attention after TBI are important to understand so that they may become targets for future rehabilitation interventions. The effects of alcohol and marijuana on the brain and cognition have been examined in several studies. It appears that these substances can have effects on the brain and cognition beyond the initial effects of intoxication and the acute periods of abstinence. Although the research to date is inconclusive regarding whether or not extended periods of abstinence may reverse the enduring effects of alcohol and marijuana on attention, there is sufficient evidence to continue to research in this area. Since it is common for those with moderate-severe TBI to have persisting attentional impairments and since alcohol and marijuana appear to have a negative impact on attention in a non-brain-injured population, we chose to explore whether these substances might be associated with a reduced the recovery of attention post-TBI.

1.9 Objectives and Hypotheses

The primary objective of this study was (1) to compare longitudinal recovery of attentional functions from 2 to 5 months post-injury in 2 groups of moderate-severe TBI patients who were case-matched for age, education and injury severity: those with an elevated T-score on the Alcohol Problems and/or Drug Problems scales of the PAI (High Substance Use “HSU” Group, N = 36) versus those scoring within the normal range (“Non-HSU” Group, N = 36). We hypothesized that there would be less recovery of attention in the HSU group compared to the Non-HSU group.

The secondary objectives were to determine how severity and type of substance misuse affected the recovery of attention after a TBI. (2a) To measure the impact of severity, two sub-groups of the high substance use group were created: (i) those with a higher index of self-reported substance misuse, operationalized as PAI scores on the Alcohol and/or Drug clinical scales of T ≥70 (HSU-severity level 2 subgroup) vs. those with a lower index of self-reported substance
misuse, T = 60 to 69 on the same scales (HSU-severity level 1 subgroup). We hypothesized that the HSU-severity level 2 subgroup would have less recovery than the HSU severity level 1 subgroup. (2b) To compare how different types of substance abuse affect recovery of attention post-TBI we divided the HSU group into subgroups: Drug-HSU (n=18), Alcohol-HSU (n=11), and Both-HSU (n=7). Here, we hypothesized that those with elevated scores on both alcohol and drugs (the Both-HSU group) would demonstrate less recovery of attentional function than those that showed misuse on the PAI Drug clinical scale only (Drug-HSU) or the PAI Alcohol clinical scale only (Alcohol-HSU).

The final secondary objective was (2c) to generate hypotheses for future research regarding possible mechanisms for reduced recovery.
Chapter 2 Past History of Substance Misuse Impedes Attentional Recovery After Moderate to Severe Traumatic Brain Injury

2.1 Introduction

2.1.1 Predictors of Cognitive Recovery

Predictors of both acute and long-term outcome after TBI are of importance because they allow for appropriate goals for rehabilitation as well as implementation of appropriate educational or vocational support (Jourdan et al, 2013). Since more accelerated recovery tends to occur in the first 5-6 months post-TBI, it is important to understand how predictors affect early outcome in case there is a rehabilitation intervention that may be able to change any modifiable predictors or provide more support to those that are predicted to have poorer recovery (Christensen et al, 2008; Jourdan et al, 2013).

A large body of research has examined demographic and injury-related variables as predictors for post-TBI cognitive recovery. According to the literature on predictors of cognitive function outcomes after TBI, more education, shorter length of post-traumatic amnesia (PTA), higher socioeconomic status and younger age at time of injury predict better cognitive outcomes (Green et al, 2008; Hoofien et al, 2002; Jourdan et al, 2013; Konigs et al, 2012). Interestingly, however, Green et al (2008) found no effects of age on recovery of memory, executive function, or simple attention, indicating that some predictor variables may only predict recovery of certain cognitive domains.

2.1.2 Alcohol, the brain and cognition

Alcohol is a psychoactive substance that is known to transiently disrupt cognitive and motor functioning (eg. attention, memory, balance). Several lines of research have also shown lasting effects of alcohol on neural and cognitive functioning in otherwise healthy adults (Fortier et al, 2014). Studies employing a variety of methodologies have demonstrated enduring effects on brain structure and function (De Sousa Uva et al, 2010; Fortier et al, 2014; Weiland et al, 2014). In a study by Fortier et al. (2014), magnetic resonance imaging (MRI) identified widespread reductions in white matter volume in abstinent alcoholics. Participants in the Alcohol group had a mean of 25 years of alcohol abuse and mean lifetime alcohol exposure to 819, 499g of alcohol.
but were abstinent for at least a month prior to the MRI. The greatest reduction in fractional anisotropy was found in the frontal and superior tracts. In a study measuring affective and cognitive functioning in alcoholics after a prolonged period of withdrawal, it was found that while negative affect recovered, cognitive impairments - specifically components of attention, including selective attention - persisted, with no significant improvements at the 2-3 week assessment (De Sousa Uva et al, 2010). From this study it appears that cognitive effects may persist past intoxication, into and even beyond withdrawal. Indeed, Kopera et al (2012) found significant problems in alternating attention in alcoholics that had been abstinent for at least 5 months. They were found to have significantly worse reaction times than non-alcoholic controls on a task of attentional set shifting, as well as significantly more errors. In summary, neurotoxic effects of alcoholism on the brain and cognition, including attention, have been found to persist even in those who ceased use. As such, past alcohol use could be an important predictor of recovery of attention after TBI.

2.1.3 Marijuana, the brain and cognition

Cannabis is another widely used psychoactive substance (Nicholls et al, 2015) that is well known to transiently disrupt cognitive function, most noticeably memory and attention (Lundqvist, 2005). Relevant to the current research, there is some recent evidence that cannabis is related to lasting cognitive and neural deficits.

Chronic cannabis use has been linked to reduced regional cerebral blood flow which is thought to explain the mechanism for which cannabis users may have a decreased ability to process information (Lundqvist, 2005; Solowij et al, 2007). In the study by Solowij et al (2007), the patterns of activation measured by event-related potentials (ERPs) differed in cannabis users when compared to controls. The P300 wave was smaller at all amplitude sites in the users and the Negative (N200) peak was present in cannabis users but was not present or was minimally present in non-users. This indicated difficulty filtering out unnecessary information. Reduced activation in the dorsolateral prefrontal cortex (dLPFC) and the anterior cingulate cortex (ACC) were noted in several studies (Eldreth et al, 2004; Kempel et al, 2003; Nicholls et al, 2015). These studies also found that the marijuana users had abnormal patterns of activation in response to cognitive tasks. This abnormal pattern of activation is thought to support the theory the brains of chronic marijuana users have developed alternate, less efficient pathways to compensate for

In a review of the impact of several classes of drugs on the brain and cognition, Lundqvist (2005) found that the cognitive domains most affected by chronic marijuana use were attention (selective and divided) and memory. Whether these impairments are lasting or reversible remains a question of interest, however. For example, an initial study by Pope et al, 2001 did not find lasting impairments after 28 days of abstinence, while a subsequent study by the same group (Pope et al, 2002) along with other studies, (Bolla et al., 2002; Solowij et al, 1995) found persisting deficits related to dose as well as age of onset of marijuana use, with selective attention being the most noticeable lasting impairment.

In the study by Solowij et al (2007), it was observed that marijuana users were less accurate and made more mistakes than controls in a task where they had to detect a target auditory tone. Users had significantly less positive hits and significantly more false alarms than controls. Users and controls did not, however, differ significantly on reaction time, indicating that they were perhaps processing information equally quickly but less effectively. It was concluded that cannabis users had impaired selective attention, as ERPs indicated they paid less attention to target cues and more attention to unnecessary information. Another study (Hanson et al, 2010) had similar findings with regard to persisting impairments in attention without any differences in reaction time. This suggests that accuracy of attention rather than speed of processing is affected (Hanson et al, 2010; Solowij et al, 2007).

To summarize, besides the acute effects of intoxication, psychoactive substances such as alcohol and marijuana can have lasting effects on cognition when used excessively, including increased distractibility, increased inattention and decreased ability to focus on target cues (De Sousa Uva et al, 2010; Hanson et al, 2010; Kovera et al, 2012; Solowij et al., 2007). Despite the growing research on their deleterious effects in otherwise healthy adults, there remains a paucity of research about how these substances affect recovery after a brain injury.

### 2.1.4 Traumatic brain injury and substance misuse

While many studies have examined the incidence of substance misuse in TBI populations (Barnfield et al, 1998; Parry-Jones et al, 2006; Taylor et al, 2003; Williams et al, 2010), few studies have examined how recovery from TBI might be affected by substance misuse. A recent
study by Niemeier et al. (2016), revealed that substance abuse predicts impairment in executive function post-TBI using the Frontal Systems Behavioural Scale (FrSBe), and Neurobehavioural Rating Scale – Revised (NRS-R). These measures compare self-report to the reporting of a surrogate to determine a patient’s self-awareness of their functional status. It was found that executive function – especially self-awareness – was more impaired in patients with TBI that had a history of substance abuse, with the discrepancy between self vs other ratings much larger for this group.

We chose to focus on attention because moderate-severe TBI can result in permanent damage to the brain, with attentional impairments affecting 40-60% of brain injury patients and being one of the most common persisting complaints (Sivan et al., 2010; Warden et al, 2006). Moreover, other cognitive functions (e.g., memory) rely on the ability to pay attention and are affected by lasting impairments in attention (Sinclair et al., 2013). It is therefore important to understand which factors might impede the recovery of attention.

The aim of this study was to better understand the role of abuse of alcohol and other psychotropic drugs on the attentional recovery process and to ascertain how various characteristics of substance abuse can impact attentional outcomes. This was accomplished in a retrospective study in which participants were classified according to their score on Alcohol Problems and/or Drug Problems scales on the Personality Assessment Inventory (Morey, 1991). Recovery in the two groups was then compared on a series of conventional neuropsychological measures of attention from two to five months post-injury.

2.1.5 Objectives and hypotheses

The primary objective of this study was to compare longitudinal recovery of attentional functions from 2 to 5 months post-injury in 2 age-, education- and injury severity-matched groups of moderate-severe TBI patients: those with a high T-score on the Alcohol Problems and/or Drug Problems scales of the PAI (N = 36) versus those scoring within the normal range (N = 36). We hypothesized that there would be less recovery of attention in the HSU compared to the Non-HSU group.
The secondary objectives were to determine how severity and type of substance misuse affected the recovery of attention after a TBI. To measure the impact of the severity, two sub-groups of the high substance use group were created: (i) those with a higher index of self-reported substance misuse, operationalized as PAI scores on the Alcohol and/or Drug clinical scales of T ≥70 vs. those with a lower index of self-reported substance misuse (T = 60 to 69 on the same sub-scales). We hypothesized that the more severe substance misuse group would have less recovery than the less severe substance misuse group. To compare how different types of substance abuse affect recovery of attention post-TBI we divided the HSU group into three sub-groups: (i) those with scores ≥60 on the PAI Drug Problems scale only, (ii) those with scores ≥60 on the PAI Alcohol Problem scale only, and those with scores ≥60 on both scales of Alcohol and Drug Problems on the PAI. Here, we hypothesized that those with elevated scores on both alcohol and drugs would demonstrate less recovery of attentional function than those that showed misuse on the PAI Drug clinical scale only or the PAI Alcohol clinical scale only. Lastly, we compared scores on lifestyle and environment scales as well as levels of activity and hours of rehabilitation between the HSU and Non-HSU groups to generate hypotheses for potential mechanisms by which attention recovery was reduced.

2.2 Methods

2.2.1 Participants

Participant data was taken from a database compiled over the course of 10 years (2004–2014) for the Toronto TBI Recovery Study (Christensen et al., 2008; Green et al., 2008). This was a prospective, longitudinal study, the purpose of which was to create a database with data on injury and demographic variables as well as neuropsychological assessments on TBI patients in order to determine patterns of long-term recovery after TBI. The database is comprised of approximately 200 participants, aged 17-79, with moderate to severe TBI. Participants were recruited from the Toronto Rehab Institute’s inpatient neurorehabilitation program. Assessments were conducted at approximately 2, 5, 12, and 24 months post-injury. There was a high retention rate due to the comprehensive clinical neuropsychological assessment with clinical feedback that was completed at each visit. Inclusion criteria for this study were: (1) an acute care diagnosis of TBI, (2) moderate-severe TBI with one or more of the following: at least 1 hour of post traumatic amnesia (PTA), a score on the GCS of less than 12 or positive CT or MRI findings, (3) 18-80
years old, (4) ability to understand basic commands in English, (5) competency to provide informed consent or availability of a legal decision-maker. Participants were excluded if they had (1) orthopedic injuries affecting both of upper limbs, (2) diseases that primarily affect the central nervous system, (3) current or past diagnosis of psychotic disorder, (4) PTA lasting more than 6 weeks post-TBI, (5) TBI secondary to another type of brain injury (e.g., a fall due to a stroke), or (6) failed test of symptom validity (which would therefore indicate possible malingering).

For the current retrospective study, participants’ data were taken from the database if they had a self-reported history of elevated drug and/or alcohol use. This was operationally defined as a T-score of ≥60 on the Personality Assessment Inventory (PAI) clinical scales of Drug Problems and/or Alcohol Problems. This cut-off score was used because it is one standard deviation above the mean reflecting the conventional clinical criterion of mildly to moderately impaired. This subset of the database was labelled the High Substance Use group (HSU). The participants in the HSU group (n=36) were then matched to control TBI participants (n=36) that were also from the database. These controls had scores on the PAI scales of Drug and Alcohol Problems of ≤59. Participants were excluded if their scores on any of the PAI’s indexes of reliability were flagged for unreliability. The controls were case-matched to the HSU participants based on age, years of education and injury severity (as measured by the Glasgow Coma Scale). However, when Glasgow Coma Scale score was missing for one or both of a matched pair, participants were matched for injury-severity on PTA. Length of post-traumatic amnesia was recorded as a rank: 1=less than 5 minutes, 2= 5-60 minutes, 3=1 hour – 24 hours, 4=1-7 days, 5=1-4 weeks, 6= more than 4 weeks, based on the Lezak approach (Lezak 2012). Where possible, patients were also matched on sex and mechanism of injury (See Table 1).

To verify that participants in the control group did not have a history of high substance use, their clinical interviews were reviewed for self- or surrogate-reported alcohol and/or drug use. Where there was suspicion of elevated drug or alcohol use, the control was replaced. Five controls whose PAI clinical Drug Problems and Alcohol Problems scales were below 60 were replaced on the basis of review of clinical histories. Due to a dearth of well-matched male controls, five of the males in the HSU group were matched to females.
2.2.2 Materials

Substance Use Measure

Personality Assessment Inventory (PAI)

The PAI is a 344-item, self-report measure of adult personality (Morey, 1991). It has been used extensively in various normative and clinical populations, including brain injured persons. Each item is rated on a 4-point scale comprising “False”, “Slightly True”, “Mostly True”, and “Very True”. Scores from 0 to 3 are assigned to each response. Typically F=0, ST=1, MT=2 and VT=3, except in cases where (False) is indicated in brackets after the item. In such cases, the values are assigned in reverse order (i.e., F=3, ST=2, MT=1 and VT=0). Scores are then totaled for each subscale. For this study, the subscales of interest were the Alcohol Problems subscale and the Drug Problems subscale. The Alcohol Problems and Drug Problems subscales have 12 items each. The items focus on problematic consequences of alcohol and drug use as well as features indicative of dependence. Items in the Alcohol Problems subscale include statements such as “Drinking helps me get along in social situations” and “My drinking has caused problems with my work”. Items in the Drug Problems subscale include statements such as “Sometimes I use drugs to feel better” and “I’ve tried just about every type of drug”. The subscale totals are transformed to T-scores based on norms for age, race, gender and clinical population where the mean is a T-score of 50T with a standard deviation of 10T.

Two other subscales of interest were the PAI: Non-support (NON) and Resistance to treatment (RXR). The non-support subscale represents the participant’s feelings of isolation and lack of support. The 8 items that comprise the non-support subscale represent the participant’s perception of both the availability of support and the quality of that support. Some examples of items in this subscale are: “My friends are available if I need them (False)”, “I like being around my family (False)”, “If I’m having problems, I have people I can talk to (False)”. Participants who score 60T or higher are considered to feel isolated and lack support (Morey, 1991). The resistance to treatment subscale indicates how open the participant is to change, how motivated they are to improve and how much responsibility they accept for their problems. There are 8 questions in this subscale. Example questions include: “Many of my problems are my own doing (False)”, “I can solve my problems by myself” and “I’m comfortable with myself the way I am”. Participants that score 62T or higher on this subscale are considered resistant to
treatment, unmotivated to seek help and see little value in therapy according to the PAI manual (Morey, 1991).

The PAI has 4 validity scales: Positive impression management (PIM), Negative impression management (NIM), Inconsistency (INC) and Infrequency (INF). These scales are used to determine if the results are valid or if the participant is either trying to manipulate their answers (PIM, NIM) or are answering in a random or careless manner (INF, INC). In other words, these four scales help the interpreter to determine if the participant’s answers are representative of the participant. Reliability of the PAI has been examined in numerous studies. Median test-retest reliability over 4 weeks was found to be 0.86 (Morey, 1991). Internal consistency was found to be good for scales (Cronbach’s alpha in the 0.80s) and fair for the subscales (Cronbach’s alpha in the 0.70s) (Alterman et al, 1995; Karlin et al, 2005).

*T-scores*

On all of the scales of the PAI, test scores are reported in terms of T-scores. T-scores are a standardized score where 50T is the population mean based on norms for sex and age. Each 10T above or below 50T represents 1 standard deviation. Therefore, if a participant’s raw score is converted to a T-score of 60T, this means they scored 1 standard deviation above the mean.

**Neuropsychological Tests of Attention**

**Trail Making Test**

The Trail Making Test (TMT) A and B is a timed, paper and pencil test originally designed to measure visual attention and task-switching (Reitan, 1958). It was first designed in 1944 by the U.S. army with the purpose of assessing intelligence. It has since proven very effective in the diagnosis of cognitive dysfunction due to brain injury, and has been used primarily for that purpose since being included in the Halstead-Reitan Battery in 1985 (Reitan & Wolfson, 1985). The test requires the participant to connect a set of 25 dots as fast as possible, without making mistakes. In TMT-A, the dots are numbered (1-25) and must be connected in numerical order. For TMT-B, the test consists of both numbers and letters. The participant must alternate between the alphabetized and numbered dots and connect them in an ascending order (i.e., 1-A-2-B-3-C etc.). If an error is made, the test administrator will correct the participant before they
can move on. Thus, the measure is also considered to be sensitive to divided attention as one must scan for the next letter or number in the sequence while remaining aware of where they are currently (Reitan & Wolfson, 1985). The dependent measures used were the T-values for each of Trails A and Trails B.

Test re-test reliability coefficients are moderate (0.65) and practice effects tend to depend on how far apart the testing is spaced, with gains being made when testing was a week to a few weeks apart, but without practice effects when the testing was spaced 3 months apart (Lezak et al, 2012).

**Stroop Colour and Word Test**

The Stroop test was developed after John Ridley Stroop, who first discovered what is known as the “Stroop effect” (Stroop, 1935). This occurs when a colour word – for example “Red” – is written in a different colour – for example blue. The person taking the test then has to inhibit the reflex of saying the colour the word is written in and instead must just read the word. This test measures selective attention, as the person must filter out unnecessary and competing information (the colours of the words) and selectively focus only on reading (Dyer, 1973; Zajano & Gorman, 1986; Jensen & Rohwer, 1966). The full test comprises 3 conditions, each of which requires timed reading or naming from a sheet of paper. For “Colour naming”, a series of x’s are presented in one of the four colours used in the Stroop test and the subject is asked to name the colour. For “Word reading”, words naming colours are written in black and the subject must read the words. The final condition is the Stroop interference (Stroop Colour-Word) condition, or the Stroop effect condition, as described above. The first two conditions are subtracted from the third condition, to produce a Stroop “interference” score. The dependent measures for the study included the T-scores for all three: Stroop Colour, Stroop Word and Stroop Colour-Word tests.

The Stroop tests have satisfactory reliability (Strauss, Sherman & Spreen, 2006) and practice effect results are inconsistent, with some studies showing very minimal effects of practice and others showing substantial gains (Beglinger et al, 2005; McCaffrey, Duff & Weservelt, 2000; Sacks et al, 1991). The Stroop tests are frequently used in the TBI population to assess frontal lobe dysfunction, although damage to non-frontal brain structures can lead to poor scores on this test as well. Even patients perceived to have good subjective recovery were found to perform abnormally slowly at 5 months post-injury (Lezak et al, 2012).
Symbol Digit Modalities Test

The Symbol Digit Modalities Test- Oral (SDMT-O) and the Symbol Digit Modalities Test – Written (SDMT-W) are timed, paper-and-pencil substitution tasks where participants are given 90 seconds and must use a reference key to match symbols with numbers (Smith, 1982). For the written version, for each symbol presented, they must write the number that corresponds to it by looking it up in the key. Since the stimuli comprise exclusively numbers and geometric shapes, it has reliability for in those whose first language is not English (Smith, 1982). SDMT, like other symbol substitution tests, is considered to be a test of complex attention and processing (Smith, 1982; Lezak et al, 2012). Sensitivity has been shown to be strong for detecting cognitive dysfunction as well as response to treatment (Lezak et al, 2012). This test has been used extensively in many clinical populations, including those with head injury, who tend to score an average of approximately 10T lower in oral and 20T lower on written (Ponsford & Kinsella, 1992). Test-retest reliability ranges from 0.74-0.80 (Hinton-Bayre et al, 1997; McCaffrey, Duff & Westervelt, 2000; Smith, 1982; Snow et al, 1988).

Verbal Fluency Test: Phonemic version

Verbal fluency is a timed test of word generation. For Phonemic Fluency, participants are asked to come up with as many words as possible that begin with the letter given to them by the test administrator (Malek-Ahmadi et al, 2012). They are given 1 minute to come up with as many words as possible. This is generally done 3 times, each time with a different letter. The most common version of the task uses the letters F, A and S (Benton, Hamsher & Sivan, 1989). Verbal fluency tests are sensitive to deficits in attention and executive function, including generative ability, working memory and cognitive flexibility. It is considered to be a sensitive measure for identifying brain damage and is often used to assess impairment after brain injury (Crowe, 1992; Lezak, 1995). The phonemic version typically has good test-retest reliability (0.73-0.82) (Harrison et al, 2000).

Lifestyle Measures

Community Integration Questionnaire
The Community Integration Questionnaire was developed by Barry Willer and colleagues for use in a TBI population (Willer et al, 1993; Dijkers, 2000). The questionnaire is a paper-and-pencil, untimed, self-report measure, with participants answering questions about their activities. The scale has 15 items, divided into 3 categories of activities: Home, Social and Productive. Six of the items are scored based on frequency of activities: times per month engaged in the activity ranges on a three-point scale from “5 or more”, “1-4 times” or “never”. Another six items are scored based on a three-point scale of independence of activity (“doing activity alone,” “yourself and someone else” or “someone else”). And the last three are scored based on with whom they are sharing recreational activities (“alone”, “family”, “friends with TBI”, or “friends without TBI”). Total score ranges from 0-29, with higher scores indicating greater community integration. This measure can be completed by patients themselves or their significant others. Test-retest reliability was strong for both patient completion (0.91) and completion by significant other (0.97) (Willer et al, 1993).

**Lifestyle Activities Questionnaire**

The lifestyle activities questionnaire (LAQ) was developed by Salthouse et al. (2002) to provide an index of weekly cognitive stimulation for everyday and leisure activities. There are 22 activities that are measured. Each activity is rated based on how cognitively demanding it is on a scale from 1 (absolutely no cognitive demands) to 5 (high cognitive demands). An individual’s weekly index of cognitive stimulation is generated by multiplying the hours spent per week on that activity by its cognitive demand and creating a sum of these products for all 22 activities.

**Level of Activity**

In order to derive further information on activity level, each patient’s clinical interview responses were clinically classified on a scale from 1 to 3, with a level 3 indicating the highest level of activity. These scores are assigned to participants based on clinicians’ ratings of the participant’s description of “a typical day”, that was provided in the clinical interview. This is a course, descriptive measure of activity and to date, psychometric properties of the outcome have yet to be established. This information is included only for the purpose of generating hypotheses and is not intended as a valid and reliable index of activity. Classifications were made broadly as follows: A “typical” day involving little or no outpatient therapy, no social activities and no vocational or school activity would receive a score of 1. A “typical” day in which a patient
engaged in some activities (e.g., everyday errands and walks, but no social outings, limited therapy and no vocational or school activities) would receive a score of 2. A “typical day” that involved social activities and therapy or school or work would receive a score of 3.

2.2.3 Design and procedures

The study design was a between-subjects, secondary analyses of data from a large, longitudinal database. For the current study, participants’ data were included if patients had a self-reported history of high substance use. This was defined as a T-score of $\geq 60$ on the Personality Assessment Inventory (PAI) scales of Drug Problems (DRG) and/or Alcohol Problems (ALC) (Morey, 1991). The resultant subset of the database was categorized as the High Substance Use Group (HSU). The participants in the HSU group were then matched to control participants. To address the primary objective (comparing recovery of attention in those with self-reported HSU vs the Non-HSU group), scores were obtained from the database on 8 neuropsychological tests of attention described above: TMT A, TMT B, Stroop Colour-Word, Stroop Colour-naming, Stroop Word-naming, Symbol Digit Modalities Test - Oral, Symbol Digit Modalities Test – Written, and Phonemic Verbal Fluency Test. Scores were obtained from each participant at 2 months post-injury and at 5 months post-injury and a percent change calculation was done to determine the percent improvement in scores between assessments.

To address the secondary objectives (determining how pattern of substance use affected recovery of attention), two sets of sub-group analyses were undertaken focusing on participants in the TBI HSU group. Here, the HSU group was divided into subgroups to determine if type or severity of substance misuse had an impact on outcomes.

To test the hypothesis that those with more severe substance misuse problems would experience less recovery, we divided the HSU group into those with scores on the PAI scales of Drug and/or Alcohol Problems of 60-69T, whom we termed HSU-severity level 1 ($n=13$) and those with scores $\geq 70T$, whom we termed HSU-severity level 2 ($n=23$).

To test the hypothesis that combined, elevated use of drugs and alcohol would result in less recovery than elevated use of only one substance or the other, we divided the HSU group into three groups: DRG-HSU ($n=18$; T-scores $\geq 60$ on PAI-DRG only), ALC-HSU ($n=11$, T-scores $\geq 60$ on PAI-ALC only) and Both-HSU ($n=7$, T-scores $\geq 60$ on both PAI-DRG and PAI-ALC).
To address the last of the secondary objectives, we compared scores on lifestyle and environment scales as well as levels of activity and hours of rehabilitation between the HSU and Non-HSU groups to generate hypotheses for potential mechanisms by which attention recovery was reduced.

For this objective, we did not have any hypotheses nor did we have sufficient data to test each lifestyle/environment variable. Instead, we compared these variables on the basis of descriptive statistics in order to generate hypotheses for future research.

**Data Processing**

For each participant, scores on the 8 tests of attention were obtained from their 2 month post-injury and 5 month post-injury assessments. From these two scores for each test, the participant’s “percent improvement” was calculated using the following formula: \((\frac{T_2-T_1}{T_1}) \times 100\), where \(T_1\) indicates a participant’s T-score on the test at 2 months post-injury, and \(T_2\) indicates their score at 5 months post-injury. On some tests, some participants were performing at a level suggesting they were unimpaired by the TBI at \(T_1\) (since TBI affects some but not all cognitive functions). A lack of impairment would preclude an evaluation of the impact of misuse on “recovery”. In order to minimize such cases, for each test we removed cases that obtained a score higher than 50\(T\) (indicating they were within the average range) and did not show improvement (or decline) by greater than 5\(T\)-scores from 2 to 5 months post-injury. Lastly, since we had to convert the z-scores of SDMT Oral and SDMT Written to T-scores before calculating the percent improvement, we removed any outliers that were greater than 3 standard deviations above or below the mean percent improvement for that test (4 cases in total, resulting in removal of 2.77% of the data from SDMT-O and SDMT-W each).

In order to increase analytic stability, an aggregate was formed for each participant at \(T_1\) and \(T_2\) by combining all 8 of the attention tests using weighted means. Here, subtests from the same measure (e.g., TMT-A and B) were weighted proportionately less, that is, as 0.5 on measures with 2 sub-tests (i.e., TMTA and B; SDMT Oral and Written) or 0.33 (for Stroop Colour Naming, Word Reading and Colour-Word). Where all 8 scores were not available for a participant (due to outlier or unimpairment removal, as mentioned above), the means were calculated using the remaining many scores. Note that none of the participants had fewer than 5
of the attention tests contributing to their aggregate attention improvement score, and the majority (53%) had all 8 tests.

**Data Analysis**

In order to confirm that matching was effective, t-tests were undertaken to demonstrate that differences were neither significant nor showed a trend towards significance. Effect size calculations were done to demonstrate that any differences were of small magnitude. For all significance testing, Cohen’s D effect sizes were calculated.

To test hypothesis 1, that those with a history of self-reported substance misuse (HSU group) would have worse attentional recovery than those without (Non-HSU group), a paired t-test was undertaken comparing the aggregate recovery scores. In order to provide a more granular assessment of the impact of substance use on attentional recovery, comparisons were made between the individual tests that comprise the aggregate. Unpaired t-tests were used to compare percent improvement of the HSU group compared to the percent improvement of the Non-HSU group on each of the 6 tests of attention. The other two of the individual tests of attention (Trail Making Test B and SDMT-Written), were compared using the non-parametric equivalent of a t-test, the Mann-Whitney U test, as the distributions were non-normal.

In order to test hypothesis 2a, that those with more severe misuse (HSU-severity level 2 subgroup) would have worse attentional recovery than those with less severe misuse (HSU – severity level 2 subgroup), paired t-tests were undertaken to compare the differences in recovery for each with their respective controls. The Bonferroni correction (Bland and Altman, 1995) was then applied to account for multiple comparisons. Pearson’s correlation coefficient was also used to determine if there was a correlation between severity of misuse (PAI-ALC and/or PAI-DRG score) and improvement in attention (aggregate percent improvement). In doing so, we controlled for age and injury severity (GCS).

In order to test hypothesis 2b, that those with combined alcohol and marijuana misuse (Both-HSU) would have worse attentional recovery than those with marijuana misuse only (DRG-HSU) or alcohol misuse only (ALC-HSU), paired t-tests were undertaken to compare the differences in recovery for each group with their respective controls. The Bonferroni (Bland and Altman, 1995) correction was then applied to account for multiple comparisons.
There was no hypothesis tested for objective 2c. Instead, for each lifestyle and environmental variable, descriptive statistics were calculated and absolute comparisons of the means were made to examine differences between the HSU and Non-HSU group. In cases where there was sufficient data collected, such as PAI-NON (n=36) and PAI-RXR (n=36), paired t-tests were undertaken.

2.3 Results

2.3.1 Group comparisons

Participants in the control group (Non-HSU) were case-matched to participants in the HSU group based on age, \( t(70)=0.75, p = 0.23 \), Cohen’s \( d = 0.06 \), years of education, \( t(70)=0.99, p = 0.16 \), Cohen’s \( d = 0.24 \), and injury severity as per Glasgow Coma Scale, \( t(60) = 0.94, p = 0.23 \), Cohen’s \( d = 0.19 \). None of the above variables that were case-matched were significantly different between the groups or had large effect sizes.

Where possible, they were also matched for sex and mechanism of injury, and another measure of injury severity: length of post-traumatic amnesia. The two groups were very closely matched on all other demographic and injury variables with the exceptions of post traumatic amnesia (PTA) and sex. There were 5 males in the substance abuse group that had to be matched with 5 control females due to a lack of appropriate male controls.

Table 1. *Demographic and injury variables for the HSU and Non-HSU groups.* Values are means and standard deviations. For categorical variables (Sex, Post-injury Substance Use, Insurance Status, Race, Ethnicity and Socioeconomic Status), frequency count is provided with proportions in brackets. Number of participants for which data were available is represented by N values. P-values with significant findings are provided. Effect sizes calculated using Cohen’s d.

<table>
<thead>
<tr>
<th>Variabnel</th>
<th>TBI HSU Group (PAI ≥ 60)</th>
<th>N</th>
<th>TBI Non-HSU Group (PAI &lt;60)</th>
<th>N</th>
<th>p</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Males</td>
<td>30 (83%)</td>
<td>36</td>
<td>25 (69%)</td>
<td>36</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Females</td>
<td>6 (17%)</td>
<td>11 (31%)</td>
<td>36</td>
<td>.23</td>
<td>.06</td>
</tr>
<tr>
<td>Age</td>
<td>37.67 ± 15.80</td>
<td>36</td>
<td>36.72 ± 14.89</td>
<td>36</td>
<td>.23</td>
<td>.06</td>
</tr>
<tr>
<td>Years of Education</td>
<td>14.08 ± 2.41</td>
<td>36</td>
<td>14.64 ± 2.34</td>
<td>36</td>
<td>.16</td>
<td>.24</td>
</tr>
<tr>
<td>Injury Severity (GCS)</td>
<td>5.10 (severe) ± 3.03</td>
<td>29</td>
<td>5.82 (severe) ± 2.97</td>
<td>34</td>
<td>.23</td>
<td>.24</td>
</tr>
</tbody>
</table>
Injury Severity (PTA)  4.79 (severe) ± 1.01  30  5.24 (severe) ± 0.66  30  <0.05*  0.53
Pre-morbid IQ (WTAR)  101.42 ± 16.28  35  107.91 ± 13.08  34  0.13  0.44
Inpatient Cognitive FIM  24.71 ± 3.83  35  24.38 ± 4.79  31  0.38  0.08
Depression (PAI)  56.44 ± 12.63  36  54.17 ± 13.20  36  0.41  0.18
Anxiety (PAI)  51.72 ± 13.67  36  45.22 ± 7.06  36  <0.05*  0.60
Anxiety-related disorders (PAI)  53.58 ± 12.74  36  46.78 ± 9.16  36  <0.05*  0.61
Post-injury Substance Use  Yes: 7 (19%)  No: 39 (81%)  36  Yes: 0  No: 36  36  N/A  N/A
Insurance Status  Yes: 10  No: 13  23  Yes: 14  No: 9  23  N/A  N/A
Race  White: 26  Black/African American: 3  Asian: 7  Other: 0  36  White: 26  Black/African American: 0  Asian: 6  Other: 4  36  N/A  N/A
Ethnicity  European: 27  African/Caribbean: 2  Chinese: 3  South Asian: 3  West Asian: 1  Arab: 0  Other/Mixed: 0  36  European: 26  African/Caribbean: 0  Chinese: 2  South Asian: 4  West Asian: 0  Arab: 1  Other/Mixed: 3  36  N/A  N/A
Socioeconomic Status  1: 3  2: 8  3: 10  4: 8  5: 6  35  1: 3  2: 20  3: 5  4: 3  5: 2  33  N/A  N/A
History of ADHD  Yes: 1  No: 35  36  Yes: 3  No: 32  36  N/A  N/A

N.B. Socioeconomic status measured using Hollingshead: 1 is the highest, Abbreviations: PAI = Personality Assessment Inventory, GCS = Glasgow Coma Scale, PTA = length of post-traumatic amnesia, WTAR = Weschler Test of Adult Reading, FIM = Functional Independence Measure)

Table 2. Lifestyle and environment variables for the HSU and Non-HSU groups. Values are means and standard deviations. For categorical variables (Level of Activity), frequency counts were provided. Number of participants for which data were available is represented by N values. P-values with significant findings are provided. Effect sizes calculated using Cohen’s D.
### N.B.
Outpatient therapy hours are per week, Level of activity: 3 is the highest, CIQ total calculated with Home + Social + Productivity.
Abbreviations: PAI = Personality Assessment Inventory, PAI-NON = PAI Non-support, PAI-RXR = PAI Resistance to Treatment, LAQ = Lifestyle Activities Questionnaire, CIQ = Community Integration Questionnaire

### 2.3.2 Objective 1: Comparing longitudinal recovery of attention outcomes in TBI High Substance Use group vs TBI non-High Substance Use group

Paired t-tests were employed to compare the percent improvement for the aggregates of attention recovery between the TBI HSU Group and the TBI Non-HSU Group. For the aggregate, those with high substance use improved 9.91 percent from 2 to 5 months after their brain injury, whereas the controls improved an average of 21.19 percent from 2 to 5 months after their brain injury. This difference was statistically significant, (t(35) = 3.27, p<0.01, Cohen’s d = 0.82) indicating that high substance use appears to impede overall recovery of attention between 2 and 5 months post-TBI.

Differences in recovery were statistically significant for four of the tests of attention: Trail Making Test A, t(66) = 1.69, p<0.05, Cohen’s d = 0.41; Stroop Colour-Word, t(54) = 2.07, p<0.05, Cohen’s d = 0.56; Stroop Word, t(70) = 1.97, p<0.05, Cohen’s d = 0.46; and Verbal Fluency Phonemic, t(68) = 2.13, p<0.05, Cohen’s d = 0.51. A trend toward significance was found for Stroop Colour, t(68) = 1.49, p = 0.07, Cohen’s d = 0.36. The other 3 tests did not approach significance: Trail Making Test B (p = 0.56, Cohen’s d = 0.23), SDMT Oral (p = 0.17, Cohen’s d = 0.24) and SDMT Written (p = 0.17, Cohen’s d = 0.49) but moderate effect sizes suggest that this may be due to a lack of power.
2.3.3 Objective 2a and 2b: Effect of substance use patterns on recovery of attention

Severity was also tested using paired t-tests to determine if there was a significant difference based on the subgroups: HSU-severity level 1 (n=23) and HSU – severity level 2 (n=13). Both the HSU-severity level 1 subgroup and the HSU-severity level 2 subgroup recovered significantly less than their matched controls on the aggregate for attention. Once Bonferroni correction for multiple comparisons was done, however, only the HSU-severity level 2 group remained significant, $t(24) = 2.98$, $p<0.025$, Cohen’s $d = 1.17$. 

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**Fig 1.** Mean percent improvement on aggregate and individual tests of attention from 2-5 months post-TBI in HSU group (n=36) and Non-HSU group (n=36). (N.B. Significance of $<0.05$ denoted with *, significance of $<0.01$ denoted with **, trend toward significance denoted with (*). Abbreviations: HSU = High Substance Use, TMT-A and -B=Trail Making Tests A and B, Stroop CW=Stroop Colour-Word, Stroop C= Stroop Colour, Stroop W= Stroop Word, Verbal Fluency = Verbal Fluency Test Phonemic, SDMT-O and -W = Symbol Digit Modalities Test Oral and Written)
To take a closer look at severity, we plotted a correlation between score on PAI (either drug or alcohol, whichever was higher) and aggregate percent improvement on recovery. Figure 2 represents the correlation between highest score on PAI (PAI-DRG or PAI-ALC) and aggregate percent improvement on attention. We used participants from both the HSU and Non-HSU groups to calculate the correlation. In the correlation, we controlled for the differences in anxiety and anxiety-related disorder scores between the HSU and Non-HSU groups on the PAI. We found a negative correlation between PAI scores and aggregate improvement in attention, $r(70) = -0.26$, $p<0.05$.

![Figure 2. Correlation between highest score on PAI (PAI-DRG or PAI-ALC) and aggregate percent improvement on attention](image-url)
To test hypothesis 2b, the HSU group was then divided into subgroups: Alcohol-HSU (n=11), Marijuana-HSU (n=18) and Both-HSU (n=7), which were analyzed using paired t-tests to determine if there was a significant difference based on these subgroups. The Alcohol-HSU Group and the Both-HSU Group both recovered significantly less than their matched controls on the aggregate for attention. Once the Bonferroni correction for multiple comparisons was applied, however, the significance did not remain.

2.3.4 Objective 2c: Comparing lifestyle and environmental factors between High Substance Use and Non-High Substance Use groups to generate hypotheses regarding possible mechanisms for reduced recovery

Supportive Environment

To generate a hypothesis that a lack of social support might be a possible mechanism for reduced recovery of attention, we compared the scores of both the HSU and Non-HSU groups on the PAI’s subscale of Non-support. We compared these scores to examine if there was a difference between the HSU group and the Non-HSU group in terms of the social support each group was receiving. The differences we found between the HSU and non-HSU group for level of Non-support were statistically significant: t(35) = 4.10, p < 0.005, Cohen’s d = 0.95. Additionally, descriptive statistics indicated that the HSU group scored an average that fell into the range of being above the norm (M = 53.22, SD=12.40), reflecting that this group may be at risk of greater feelings of lack of support. While the mean did not reach the clinical cut-off that is indicative of concerning levels of non-support (PAI-NON≥60T), there were several (n=8, 22.2%) HSU participants that did reach that level, while only 1 (2.8%) from the Non-HSU group did.

Stimulating Environment

To generate a hypothesis that a lack of cognitive stimulation might be a possible mechanism for reduced recovery of attention, we compared both HSU and Non-HSU groups on a measure of rehabilitation (outpatient hours per week) and lifestyle and activities that might provide cognitive stimulation (LAQ and Level of Activity). Statistical analyses for these variables were limited by the data available as these data were only collected partway through the original prospective
study and are therefore missing for several participants (therapy hours missing n=5, LAQ missing n=13, LoA missing n=7). Data available were reported in Table 2 along with the number of participants for which we had data. Based on descriptive statistics, we noticed several differences between the HSU group and the Non-HSU group across these variables. On average, the HSU group was participating in less hours per week of outpatient rehabilitation than was the non-HSU group (M=4.53, SD=5.17, vs M=7.51, SD= 8.96). They also scored lower on the LAQ (M=61.07, SD=31.17 vs M=6.03, SD=37.77). Lastly, while few from either group had reached a Level 3 on the Level of Activity measure by 5 months post-injury, many more people in the Control group had reached a Level 2 than in the HSU group (n=13, 38.2% vs n=22, 71.0%).

Motivation

To generate a hypothesis that a lack of motivation to participate in rehabilitation might be a possible mechanism for reduced recovery of attention, we compared both HSU and Non-HSU groups on the PAI scale of Resistance to Treatment (PAI-RXR). Due to the finding that neither the HSU group (M = 49.39T, SD= 9.92), nor the Non-HSU group (M=54.67, SD=7.27) met the clinical cut-off (T≥62) and because both fell within 1 SD of the mean, there was no relevant information to be gained by performing a t-test.

2.4 Discussion

The primary objective of this study was to compare longitudinal recovery of attentional functions from 2 to 5 months post-injury in 2 age-, education- and injury severity-matched groups of moderate-severe TBI patients: those with a high T-score on the Alcohol Problems and/or Drug Problems scales of the PAI (N = 36) versus those scoring within the normal range (N = 36). It was hypothesized that there would be less recovery of attention in the HSU group compared to the Non-HSU group, and the results provide support for this hypothesis. High scores on the PAI measures of alcohol and/or drug use are associated with poorer recovery on attention tests between 2 to 5 months post-TBI. The aggregate showed significant differences in recovery of attention between the HSU and non-HSU groups. In order to understand what aspects of attention were affected we also compared the HSU and Non-HSU groups on their attentional recovery on each test individually. There were four tests in particular which had significantly worse percent improvement for the HSU Group: Trail Making Test A, Stroop Colour-Word,
Stroop Word and Verbal Fluency Test Phonemic. A trend towards worse recovery for the HSU Group was also observed on the Stroop Colour Naming sub-test.

In the literature, alcohol has been found to result in enduring deleterious changes to the brain and cognition, including attention, even after extended periods of abstinence (De Sousa Uva et al, 2010; Fortier et al, 2014). Our study does provide support for the suggestion that alcohol has lasting effects on attention, and perhaps more importantly, on neural structures associated with attention, since most (n=31, 86.1%) of our HSU participants denied continued use of alcohol after their injury. These studies looked only at the effect of chronic alcohol use on otherwise healthy controls; however, so it is not possible to make a direct comparison from those studies to our own, which deals with participants with moderate-severe TBI in addition to alcohol misuse.

There is literature suggesting that marijuana has lasting effects on the brain, including brain-structures associated with attentional functioning (Bolla et al., 2002; Hanson et al, 2010; Pope et al, 2002; Solowij et al, 2007), while some studies suggest that the effects of marijuana are fully reversible (Curran et al, 2016; Lundqvist, 2005; Pope et al, 2001). The present results are compatible with the former, providing evidence that previous marijuana use may have had lasting effects that resulted in compromise to attentional recovery after TBI.

A secondary objective was to determine how severity of substance misuse affected the recovery of attention after a TBI. Since the two subgroups differed on various demographic and injury variables and there was insufficient power to directly compare the low and high dose HSU groups controlling for these variables, each group was compared to respective controls. Both groups differed significantly from their respective controls, but the effect size for the HSU-severity level 2 subgroup (Cohen’s d = 1.17) was larger than that of the HSU-severity level 1 subgroup (Cohen’s d = 0.54). We further explored the impact of severity of misuse by examining the correlation between scores on the PAI measures of Alcohol Problems and/or Drug Problems and recovery of attention. While controlling for differences between the groups on Anxiety and Anxiety-Related Disorder scores on the PAI, we found a small, significant negative correlation between PAI Alcohol and/or Drug scores and the aggregate improvement in attention, suggesting an impact of dose on recovery of attention. Future studies should attempt to replicate findings with a greater sample size and a direct comparison of the respective contributions of dose examined within the same statistical model. Prospective studies could also
collect more specific data regarding pattern of misuse, such as frequency and quantity as well as cumulative years of misuse and age of onset. As ours was a retrospective study, we were limited to the variables for which we had already collected data.

The final objective was to characterize the HSU and Non-HSU groups in terms of lifestyle and environmental variables in order to generate hypotheses for future research with regards to the mechanism for reduced attentional recovery. One pre-injury explanation could be that the alcohol and/or marijuana caused damage to the brain that made it susceptible to a greater magnitude of damage when the brain injury occurred. Past research on structural changes to the brain following alcohol and marijuana misuse certainly support this theory (Eldreth et al, 2004; Fortier et al, 2014; Lundqvist, 2005; Nicholls et al, 2015). There has yet to be any longitudinal research using imaging to note whether damage to the brain as a result of the TBI could have been exacerbated by previous damage from substance use and unfortunately we were unable to examine this possible mechanism in our study. The logistics of such a study would be complicated as there would need to be imaging done in high substance users pre-injury and post-injury (and ideally before onset of substance use).

Another possible explanation – and one which could be examined preliminarily - is that of post-injury lifestyle factors. In Table 1 and Table 2, we provided a comparison of the two groups (HSU and non-HSU) for 21 variables. We observed differences between the two groups on 6 variables which could be logically grouped into two broad areas: (i) Stimulating Environment and (ii) Supportive Environment.

(i) **Stimulating Environment**

Under this category we included the following variables: Hours of outpatient rehabilitation (per week), Lifestyle Activities Questionnaire score, and Level of Activity. Preliminary descriptive statistics suggest the absolute differences between the groups were notable. On average, the HSU group was participating in less hours per week of outpatient rehabilitation than was the non-HSU group (4.53 ± 5.17, vs 7.51 ± 8.96). They also scored lower on the LAQ (61.07 ± 31.17 vs 76.03 ± 37.77) indicating that on average, they were participating in fewer stimulating activities in their spare time. Lastly, while few from either group had reached a Level 3 (high level of activity) on the Level of Activity measure by 5 months post-injury, far fewer participants
in the HSU group reached a Level 2 (moderate level of activity) than in the Non-HSU group (n=13, 38.2% vs n=22, 71.0%). In summary, these measures indicate that the HSU group might be experiencing lower levels of stimulation in their everyday lives. Environmental enrichment has been found to be an effective way to improve post-acute functional and cognitive outcomes in TBI patients (Frasca et al, 2013; Miller et al, 2013). This may be especially true for a group that has had substance misuse in the past and may be lacking stimulation in their everyday life.

(ii) Supportive Environment

Under this category, the following variables were included: Degree of Non-support, Insurance and Socioeconomic Status. The differences between the HSU and non-HSU group for level of Non-support were significantly different: t(35) = 4.10, p < 0.05, Cohen’s d = 0.95. According to the PAI’s measure for Non-support, the HSU group scored an average that fell into the range of being above the norm, reflecting that this group may be at risk of greater feelings of lack of support. While the mean did not quite reach the clinical cut-off indicative of a concerning level of non-support (T≥60), there were several (n=8, 22.2%) HSU participants that did reach that level, while only 1 (2.8%) from the non-HSU group did. While the rest of the data we collected on these variables were used to make descriptive statistical comparisons and not used in statistical analyses, we did notice compelling absolute differences between the HSU group and the non-HSU group on these variables. It was observed that fewer of the HSU participants had insurance (n=10, 43.5% vs n=14, 60.9%) and that there were more people in the lower levels of SES (Level 3 or lower) in the HSU group (n=24, 69.6% vs n=10, 30.3%). Taken together, these may indicate a need to focus on providing adequate support for participants with substance misuse, as they may be at risk for lower levels of support when recovering from their brain injury.

2.4.1 Conclusions

High substance use, as measured by the PAI-ALC and PAI-DRG scales, impeded recovery of attention in patients with a moderate-severe traumatic brain injury. Preliminary evidence was also obtained that greater severity of substance misuse was associated with poorer recovery of attention, indicating that more severe alcohol and marijuana problems could have a greater negative impact on recovery of attention after a TBI. Whether the observed negative impact of
substances on attentional recovery post-TBI is a result of pre-injury factors or post-injury factors is worth investigating. Preliminary descriptive statistics on lifestyle and environmental factors suggest individuals with substance misuse may have a lifestyle that is deficient in cognitive stimulation and social support. These findings, if replicated, indicate potential targets for interventions to ameliorate recovery of attention in a population of people with both TBI and substance misuse.
3 Chapter 3 General Discussion

3.1 Summary of Findings

Given the gaps in the literature regarding the role of substance misuse and attentional recovery post-TBI, and the compelling evidence from a non-TBI population that suggests substance misuse may cause lasting attentional impairments, our primary objective was to compare longitudinal recovery of attentional functions from 2 to 5 months post-injury in 2 age-, education- and injury severity-matched groups of moderate-severe TBI participants: in 36 participants with a high T-score on the Alcohol Problems and/or Drug Problems scales of the PAI versus 36 participants scoring within the normal range.

We hypothesized that there would be less recovery of attention in the HSU group compared to the Non-HSU group. Our results supported the hypothesis that high substance use scores on the PAI were associated with poorer recovery on an attention aggregate from 2 to 5 months post-TBI. To provide a more granular analysis of the impact of substance use on attentional functioning we compared differences in attentional recovery on all of the individual tests. We found four tests which showed significantly less percent improvement for the HSU group than the non-HSU group: TMT A, Stroop Colour-Word, Stroop Word, and Phonemic Verbal Fluency. For the other four measures, the absolute differences were in the same direction as predicted, and moderate effect sizes of the differences suggest that there may have been insufficient power to detect a significant difference.

The secondary objectives were to determine how patterns of substance misuse such as severity of substance misuse and type of substance misuse affected the recovery of attention after a TBI.

Regarding the primary outcome measures, both HSU-severity level 1 (T-score on PAI=60-69) and HSU-severity level 2 (T-score on PAI≥70) did have significantly worse aggregate attention improvement than their respective matched controls. After using the Bonferroni correction to adjust for multiple comparisons, however, significance only remained for the HSU – severity level 2 group, which had a very large effect size. This indicated that there could be an effect of severity of misuse on recovery of attention. To further understand this relationship, a Pearson’s correlation was undertaken to measure the correlation between severity of substance misuse and recovery. A significant negative correlation was observed, indicating that higher PAI scores for
Alcohol and/or Drug Problems were correlated with lower percent improvement on the attention aggregate.

When comparing each subgroup to their respective matched controls, the primary outcome (i.e., aggregate score) showed that being a user of alcohol only or of both alcohol and drugs seemed to be more detrimental to recovery of attention than using only drugs. These results, however, did not hold up after using the Bonferroni correction to adjust for multiple comparisons. It is also likely that the sub-group analyses evaluating type of substance misuse were confounded by the inability to control for length of use due to lack of information regarding age of onset as well as the inability to control for the significant differences in age and sex among subgroups.

The last of the secondary objectives was to generate hypotheses regarding the potential mechanism of reduced attentional recovery by examining differences between HSU and Non-HSU group on lifestyle and environmental factors.

We found that the HSU and Non-HSU groups differed on 6 variables, with two groups of variables (1) stimulating environment and (2) supportive environment suggesting two potential mechanisms of reduced recovery.

### 3.2 Comparison to Literature

Alcohol has been found to result in enduring deleterious changes to the brain and cognition, including attention, even after extended periods of abstinence (De Sousa Uva et al, 2010; Fortier et al, 2014; Kopera et al, 2012; Tedstone & Coyle, 2004; Weiland et al, 2014). These studies examined the effects of chronic alcohol use on otherwise healthy controls, and this supports the interpretation that enduring effects of alcohol pre-injury might indeed leave participants with moderate-severe TBI more neurologically vulnerable, with the result shown in our study of poorer attentional recovery. Given that most (n=31, 86.1%) of our HSU participants denied continued use of alcohol after their injury, yet the group still had significantly less recovery of attention compared to the Non-HSU group, it is likely that it is the pre-injury use rather than continued use that gave rise to our findings.

Marijuana has been found to cause impairments in cognition, including attention (Conroy et al, 2015; Nicholls et al, 2015; Solowij et al, 2007). Studies have found lasting changes in brain
structure and physiology, however, lasting cognitive impairments are still debated (Lundqvist, 2005; Zalesky et al, 2012). In past studies of lasting effects of marijuana on the brain in a non-TBI population, the period of abstinence before testing cognition ranged from 12 hours-6 weeks (Bolla et al., 2002; Lundqvist, 2005; Pope et al, 2001; Pope et al, 2002; Solowij et al, 1995; Solowij et al 2007). Since most of the participants in the HSU group denied post-injury use of marijuana (n=32, 88.9%) at both the 2-month and 5-month assessments of attention, most of our participants were abstinent for much longer than those in the other studies, yet we still found their attention to be more impaired than the non-HSU group. While some studies did find lasting impairments in attention, (Conroy et al, 2015; Nicholls et al, 2015; Solowij et al, 2007) some studies found that attentional deficits resolved with continued abstinence (Lundqvist, 2005; Pope et al, 2001). Our study suggests that in a TBI population, attentional impairments do not appear to recover even after prolonged abstinence. Instead they are maintained, and may be a factor impeding recovery of attention after traumatic brain injury.

Among the studies that found lasting changes on the brain and attention in those with substance misuse: most did not further divide their Substance Misuse groups (Eldreth et al, 2002; Hanson et al, 2010; Kopera et al, 2012; Nicholls et al, 2015; Tedstone and Coyle, 2004), three analyzed results by quantity or dose of misuse (Bolla et al, 2002, Fortier et al, 2014; Pope et al, 2002) and only one analyzed results according to severity of substance misuse (Weiland et al, 2014). As such, it is difficult to compare the correlation we found between severity of substance misuse and reduced recovery of attention. Despite this, it is interesting to note that the one study that did analyze by severity (Weiland et al, 2014) found significant associations between measures of severity of alcohol misuse and reduced functional connectivity in the brain in areas of attention (such as the dlPFC).

For our primary objective, we examined recovery of all HSU participants, whether elevations were observed on the Alcohol Problems or Drug Problems scales of the PAI, or both. While we did find that those with high substance use had reduced recovery of attention, this study did not distinguish between use of alcohol, drugs or both. Sub-group analyses by type of substance provided no significant evidence that type of substance had an effect on the reduced recovery of attention. As Lundqvist (2005) described in his review, psychoactive substances act on neurotransmitters that have diffuse patterns of innervations throughout the cerebral cortex. Although he did not directly compare alcohol and marijuana, other studies in which the
substances were studied individually suggested that effects can be diffuse and overlapping for both substances (Conroy et al, 2015; De Sousa Uva et al, 2010; Fortier et al, 2014; Harding et al, 2012; Kopera et al, 2014; Nicholls et al, 2015; Niemeier et al, 2016; Stavros et al, 2012; Zalesky et al, 2012).

3.3 Limitations and Modifications for Future Studies

We chose to use the PAI to characterize the participants into the HSU and Non-HSU groups as opposed to relying on participants’ reports of presence and quantity of substance use in the clinical interviews (though we did use that information to determine if use continued post-TBI and as grounds to replace controls that did not score ≥60 on PAI-ALC or PAI-DRG but still reported problematic patterns of substance use). We chose to use the PAI to establish groups because it was considered to be more reliable than trying to use quantity of self-reported drinks or marijuana to determine if this was considered high use, especially since underreporting of number of drinks and quantity of marijuana are well-documented issues in the literature (Lezak et al, 2012). Additionally, “high use” is hard to determine based on quantity alone as there are a number of factors involving metabolism (such as body proportions, genetics) that would create different thresholds for each individual. By contrast, the PAI measures problematic use of drugs and alcohol, with a focus on how these substances affect social relationships, employment and health, to provide a more overarching definition of high substance use.

We used the PAI as opposed to the criterion that is more typically found in the literature which is based on quantity of substance (amount per week) and duration of abuse (months to years). Quantity-based classifications allow for a more exact determination of dose-response effects. An advantage of the PAI, however, is that it is designed to measure the effects of substance use from a biopsychosocial standpoint, which can allow us to understand the ways in which substance use affects a person’s functioning within their environment. Additionally, self-reports about quantity of drinks or marijuana use have been shown to have poor reliability (Lezak et al, 2012), whereas the PAI has validity indices to help to evaluate the reliability of responding in a given individual (INC and INF). A limitation that remains, however, is that a person must have some degree of self-awareness in order to recognize that their substance use is affecting their relationships, work, and overall health.
A limitation of the current study was the sample size. Because of the smaller sample size, there ended up being a lack of appropriate male controls (several of the males in the control pool reported problematic levels of alcohol and drug use in clinical interviews and had to be removed as controls). As such, some of the males in the HSU group were matched with female controls. Additionally, with a larger sample size, more complex statistical analyses such as hierarchical regression could be undertaken to more precisely determine the relative amounts of outcome variance of factors such as type and level of severity on the attention outcomes, while also controlling for relevant demographic and injury variables. For example, in the current study, it was not possible to determine if combined alcohol and marijuana did make recovery worse than marijuana alone as the relationship was confounded by the effects of other variables of pattern of misuse (e.g., severity, continued use post-injury, age of onset, etc.).

Another limitation was the retrospective design and secondary analysis of the data. A prospective study of recovery would allow researchers to have control over the outcome measures on substance use, such as the pattern of use, quantity, and age of onset. Prospective studies could also collect information on how post-injury relapses might affect recovery, as well as the effect of onset of substance use post-TBI. They could have more ecologically valid measures to determine recovery of attention. For example, future prospective studies could examine whether attention impairments related to poor performance at or delayed return to school or work. Future prospective studies should also ask questions about other aspects of life that may be affected in substance users, such as sleep, nutrition and mental and physical health (besides TBI). If unaccounted for, these may confound results. Since the original prospective study recruited from inpatient neurorehabilitation at Toronto Rehab, the results may lack generalizability to a non-neurorehabilitation population. Future prospective studies should attempt to recruit from trauma centres or emergency departments as well, in order to include a part of the population of people with a history of substance misuse and TBI that did not end up in inpatient neurorehabilitation.

Lastly, future studies should aim to have follow-ups at a later time point, or multiple time points. This would allow researchers to determine if there is reversibility with longer abstinence (an argument that is frequently debated in the marijuana literature). Perhaps the marijuana users simply required more time after their brain injury to recover to the same extent as non-users and might “catch up” later in the recovery trajectory. Thus, it would be of interest to re-examine
patients much later in the recovery period to see whether eventually attention outcomes are comparable between those with and without elevated substance use.

3.4 Mechanisms by which past substance misuse affects attentional recovery

Pre-injury factors are those due to the substance misuse that caused damage before the injury, where such damage continues to exert its effects on attention and recovery once the injury has occurred. Post-injury factors refer to factors that may or may not have been present before the injury (such as a lack of social support or cognitive stimulation) that would create an environment post-injury that may result in reduced recovery of attention.

3.4.1 Pre-injury factors

Physiological Damage to Brain caused by Substance Use

While we had insufficient imaging data to make conclusions about differences in structure and physiology of the brain that might exist between the HSU group and the non-HSU group, it remains an interesting theory for the mechanism of reduced recovery of attention. The literature on alcohol and marijuana misuse describes widespread damage to the brain, including diffuse reductions in white matter volume (Fortier et al, 2014). TBI is also causes widespread disruption to white matter tracts (Kinnunen et al, 2011). As well, two regions of the prefrontal cortex are consistently implicated: the dorsolateral prefrontal cortex (dPFC) and the medial prefrontal cortex (mPFC), especially the anterior cingulate cortex (ACC) (Fortier et al, 2014; Harding et al, 2012; Kempel et al, 2003; Lundqvist et al, 2005; Nicholls, 2015). These areas are heavily involved in attentional processes (Corbetta and Shulman, 2002; Duncan and Miller, 2002; Petersen and Posner, 2012; Shallice et al, 2007). These areas, involved in attentional functioning, are also often compromised in TBI (Hart et al, 2005; Hillary et al, 2015; Lezak et al, 2012). These findings offer the hypothesis that damage to white matter and the dPFC and the ACC of the mPFC from alcohol or marijuana use combined with TBI, causes deleterious synergistic effects. In other words, pre-injury alcohol and marijuana use set up the brain to be disproportionately compromised by damage in these areas after TBI.

Sleep disturbances One way physiological damage to the brain from substance misuse can affect attention is through sleep disturbances. Marijuana can lead to poor sleep quality, which
can result in daytime effects of sleep deprivation, including attention problems (Ly and Gehricke, 2013). Circadian rhythms such as the sleep-wake cycle can be altered by misuse of alcohol and marijuana (Bolla et al, 2008; Hasler & Clark, 2013). Insomnia and other sleep disorders are prevalent among those with alcohol use disorders. While certain aspects of sleep architecture have been found to resolve after several months of abstinence, total sleep time, sleep fragmentation and slow wave sleep abnormalities can take nearly 2 years to fully resolve (Charavorty et al, 2016). These changes to sleep architecture provide a mechanism through which alcohol and marijuana can indirectly affect recovery of attention. This is especially important to acknowledge in those with both substance abuse and TBI since sleep is also neuroprotective, and can modulate neuroplasticity (Nakase-Richardson et al, 2013). Sleep problems are also common among those with TBI.

It is possible that those with sleep issues that were caused by past abuse of substances such as (insomnia, reduced sleep efficiency and frequent awakenings) could be at risk of these issues worsening after their TBI. It is also possible that those with pre-injury substance-related sleep disorders may have a more difficult time progressing in cognitive rehabilitation programs for their TBI because they are too exhausted to be productive, motivated, engaged etc. There are several ways in which disrupted sleep might affect the recovery of attention in people with TBI and substance misuse and, as such, it remains an interesting explanation to test in future research.

### 3.4.2 Post-injury factors.

**Motivation for therapy engagement**

As mentioned previously, motivation and engagement have been found to be a key factor in outcomes post-TBI (Boosman et al, 2016). There is also evidence to support a lack of motivation in those with substance misuse, particularly chronic marijuana users (Brook et al, 1998; Jones et al, 1998; Lane et al, 2005). To explore the theory that those with higher substance use in our group might have lower motivation, we looked at the PAI subscale of Treatment Resistance (PAI-RXR). High T-scores (PAI-RXR $\geq 62$ T) on this measure indicate a resistance to change, lack of self-awareness of any deficits, and skepticism about the efficacy of therapy or rehabilitation (Morey, 1991). Since the mean for the HSU group was well below this cut-off, it suggests that at least in our study, the majority of participants with high substance use do not lack motivation as a group, and are in fact open to change and motivated in their rehabilitation.
Our results are more compatible with a smaller group of studies that suggest there are minimal to no differences in terms of motivation between previous heavy marijuana users that are now abstinent and controls (Kouri et al, 1995; Lynsky and Hall, 2000). Our results are more in line with those, suggesting that motivation for treatment is not impaired in abstinent previous marijuana users. Even after removing those participants in the HSU group that did not report marijuana use, (ie. removing the Alcohol-HSU group) we ended up with a highly similar mean, which differed by only 1 T-score. This suggests that a lack of motivation to engage in rehabilitation or therapy is likely not the best explanation for the reduced recovery we observed in our HSU group.

Social Support

Social support has been found to be an important predictor of TBI recovery (Tomberg et al, 2007), however, there is evidence that substance misusers may lack social support either before onset of substance misuse or as a result of substance misuse (Galea et al, 2004; Nobre, 2016; Resnick et al, 1997). We therefore compared those variables in the database that might shed light on a person’s degree of social support. The variables included were the PAI Non-support (PAI-NON) score, Insurance status, and Socioeconomic Status. These variables describe the supports (or lack of supports) available to the participant as they recover from their brain injury. According to the PAI-NON score, the HSU group scored an average that fell into the range of being above the norm (mean = 53.22T), reflecting that this group may be at risk of greater feelings of lack of support. While the mean did not quite reach the clinical cut-off indicative of a concerning lack of support, (PAI-NON≥60T), there were 8 (22.2%) HSU participants that did reach that level, while only 1 (2.8%) from the non-HSU group did. It was also observed that fewer of the HSU participants had insurance (n=10, 43.5% vs n=14, 60.9%) and that there were more people in the lower levels of SES (Level 3 or lower) in the HSU group (n=24, 69.6% vs n=10, 30.3%). Taken together, these may indicate a need to focus on providing adequate support for participants with substance misuse, as they may be at risk for lower levels of support when recovering from their brain injury. And based on the differences in insurance and SES, they may be lacking financial and vocational support as well. If they lack insurance coverage and financial security, it may also be difficult for them to afford the intensiveness of rehabilitation that is optimal for recovery after TBI, which could put them at risk for lower levels of cognitive stimulation (Frasca et al, 2013).
Cognitive Stimulation/Environmental Enrichment

Since a lack of cognitive stimulation has been found in the literature to play a role in both developing a substance use issue and as a potential consequence of substance misuse, it is important to consider that those with substance misuse may be lacking cognitive stimulation (Bickel et al., 1998; Galea et al., 2004). In order to better understand whether or not a lack of cognitive stimulation in the HSU group was a possible explanation for the reduced recovery of attention we observed in this group, we examined the following variables: Hours of outpatient rehabilitation (per week), Lifestyle Activities Questionnaire score, and Level of Activity. We noticed several differences between the HSU group and the Non-HSU group across these variables. On average, the HSU group was participating in less hours per week of outpatient rehabilitation than was the non-HSU group (M=4.53, SD=5.17 vs M=7.51, SD=8.96). When related back to the literature, the differences between the two groups on rehabilitation hours are concerning. This is because Till et al. (2008) found that fewer therapy hours at 5 months post-injury were significantly associated with degree of cognitive decline between 1-2 years. Keeping in mind that those with moderate-severe TBI may have several impairments that could preclude them from being active, socializing, returning to work and might actually leave them housebound for much of the day, rehabilitation may be their best opportunity for cognitive stimulation (Christensen et al., 2008; Sander et al., 2010). They also scored lower on the LAQ (M=61.07, SD=31.17 vs M=76.03, SD=37.77) indicating that on average, they were participating in fewer stimulating activities in their spare time. Lastly, while few from either group had reached a Level 3 (high level of activity) on the Level of Activity measure by 5 months post-injury, many more people in the Non-HSU group (n=22, 70.97%) had reached a Level 2 (moderate level of activity) than in the HSU group (n=13, 38.24%).

In summary, these findings raise the possibility that the HSU group might be experiencing lower levels of stimulation in their everyday lives. Environmental enrichment has been found to be an effective way to improve rehabilitation outcomes in TBI patients (Frasca et al., 2013; Miller et al., 2013). This may be especially true of a group that has had substance misuse in the past as the results of our study indicate that they may actually have a deficit of stimulation in their everyday life. Therefore TBI rehabilitation professionals should screen for substance use and focus on providing additional environmental enrichment to this population to compensate for those whose post-discharge environment may be devoid of it.
3.5 Conclusion and Rehabilitation Implications

In conclusion, the results of our study indicate that a history of alcohol and/or marijuana use may impede the recovery of attention after a traumatic brain injury. There also appears to be a negative correlation between severity of substance misuse and recovery of attention. Future studies should focus on understanding why attentional recovery may be reduced in this population. Speculation about pre-injury mechanisms include lasting pre-injury damage to the brain from substances or substance-induced pre-injury sleep disturbances. Possible post-injury mechanisms include an environment that is lacking cognitive stimulation and social support or psychological factors such as low motivation. While pre-injury damage to the brain and sleep architecture are not possible to address and motivation problems are not supported by our preliminary data, interventions could target social support and cognitive stimulation. If these explanations are supported by future research, suggestions for rehabilitation include: referring patients to a support group specific to people with TBI and substance misuse and providing more cognitive stimulation in the form of environmental enrichment activities.

Those with a history of substance misuse and TBI may face different problems than members of separate support groups for substance misuse or TBI (such as possibility of relapse after injury). As such, it is important to ensure that their needs are met. The SUBI project (Substance Use and Brain Injury) is an example of a collaboration between relevant organizations that provides support to this population. Based on the research of Corrigan et al (2005), it aims to provide ongoing interdisciplinary management of health issues pertaining to those with a history of substance misuse and brain injury.

From our study, it appears that those with substance misuse may be engaging in less cognitively stimulating activities outside of their rehabilitation. Therefore, it may be necessary to ensure that their environments can provide them adequate cognitive enrichment. This may be done by either providing them with “homework” - some type of therapy activity that can be done from home, outside of therapy hours - or by educating this group on what type of activities they could be doing in their spare time that may improve recovery (ie. light reading, light exercise, social interactions) versus which activities may be less helpful (ie. watching television, playing video games).
References


# Appendix 1: Attentional Improvement Aggregate

<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
<th>Relative Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trail Making Test A</td>
<td>Similar to connect-the-dots, visual attention and task switching</td>
<td>1/2</td>
</tr>
<tr>
<td>Trail Making Test B</td>
<td>Same as above but alternate between numbers and letters, divided attention</td>
<td>1/2</td>
</tr>
<tr>
<td>Stroop Colour Naming</td>
<td>List colours used in sequence of X’s</td>
<td>1/3</td>
</tr>
<tr>
<td>Stroop Word Reading</td>
<td>Read words in the sequence</td>
<td>1/3</td>
</tr>
<tr>
<td>Stroop Colour-Word</td>
<td>Response inhibition, selective attention</td>
<td>1/3</td>
</tr>
<tr>
<td>Symbol Digit Modalities Test Oral</td>
<td>Using reference key, match symbols to numbers</td>
<td>1/2</td>
</tr>
<tr>
<td>Symbol Digit Modalities Test Written</td>
<td>Same as above, but written</td>
<td>1/2</td>
</tr>
<tr>
<td>Verbal Fluency Test Phonemic</td>
<td>List as many words with the given letter (F, A, or S) as the first letter</td>
<td>1</td>
</tr>
</tbody>
</table>
Appendix 2: Power Analysis

We did a post-hoc calculation that determined that in order to have adequate power (1-\(\beta = 0.20\)), we needed a sample size of at least 26 participants per group. Sample size calculation was as follows:

\[
n = \frac{2\sigma^2 (Z_\beta + Z_\alpha)^2}{(\mu_1 - \mu_2)^2}
\]

Where:

\(Z_\alpha = z\)-score for \(\alpha\) of 0.05 = 1.96

\(Z_\beta = z\)-score for \(\beta\) of 0.80 = 0.84

\(\mu_1 - \mu_2 = \) the difference in group means = 11.28

\(\sigma = \) standard deviation = 15.40

Therefore, \(n = 26\) participants required per group. Since we had 36 participants per group, we had a sufficient sample size.