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**ASSESSING THE LONG-TERM SEQUELAE OF MILD TRAUMATIC BRAIN  
INJURY**

A Dissertation Presented

by

JANNA MANTUA

Submitted to the Graduate School of the  
University of Massachusetts Amherst in partial fulfillment  
of the requirements for the degree of

DOCTOR OF PHILOSOPHY

February 2018

Neuroscience & Behavior Program

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## **ABSTRACT**

### **ASSESSING THE LONG-TERM SEQUELAE OF MILD TRAUMATIC BRAIN INJURY**

FEBRUARY 2018

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Directed by: Professor Rebecca Ready

A mild traumatic brain injury (mTBI), also known as a concussion, is defined as an injury that results in an alteration of consciousness or mental status. Previous studies have shown mTBI populations experience a number of chronic (> 1 year) symptoms, such as sleep disturbances (e.g., sleep stage alterations), mood alterations (e.g., depressive symptoms), and cognitive alterations (e.g., poor concentration). The three chapters of this dissertation sought to explore these long-term sequelae and the possible interrelations between them. In the first experiment, sleep-dependent memory consolidation of neutral stimuli was probed in a chronic mTBI sample and a control, uninjured sample. I hypothesized memory consolidation would be reduced in the mTBI sample. However, sleep-dependent consolidation was found to be intact in the mTBI sample, despite differences in sleep architecture between groups. Given that risk for mood disorders is elevated following mTBI, in the second experiment, sleep-dependent memory consolidation of emotional images was assessed in groups that were similar to those assessed in Study 1, with the hypothesis that mTBI participants would have reduced consolidation. The mTBI group had reduced sleep-dependent memory consolidation (i.e., memory consolidation that occurred over a sleep period) but enhanced wake-dependent

consolidation (i.e., memory consolidation that occurred over a wake period) of emotional (but not neutral) images. The mTBI group also unexpectedly exhibited a lack of emotion habituation (i.e., emotion desensitization). The third experiment attempted to replicate the latter (unexpected) finding (i.e., reductions in habituation in the mTBI group) while also probing physiological measures of emotion (e.g., heart rate deceleration), which provide an objective measure of emotion. I theorized that reduced habituation might increase the risk for mood disturbances in this population. I was not able to replicate findings of the second experiment, and, on the contrary, found mTBI participants had enhanced emotion habituation in the three experiments, we failed to find expected cognitive and emotional processing deficits in the mTBI samples. In future work, recruiting alternative subsamples of mTBI individuals (e.g., those with Post-concussive syndrome or those with 3 or more mTBIs) could provide insight into which individuals experience negative outcomes in the chronic stages of mTBI.

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## CHAPTER 1

### GENERAL INTRODUCTION

#### **A. Traumatic Brain Injury**

Traumatic brain injury (TBI) is defined as any change in brain functioning resulting from blunt or penetrating force to the head (Bruns & Hauser, 2003). An alteration in brain functioning may manifest as confusion, loss of consciousness, coma, seizure, or sensory/motor deficit. There are an estimated 1.4-3 million TBIs each year in the United States, and an additional 50,000 deaths resulting from TBI (Rutland-Brown, Langlois, Thomas, & Xi, 2006; Silver, McAllister, & Yudofsky, 2005). However, these approximations may be underestimated because it has been projected that 25% of all individuals with TBI do not seek medical treatment (Silver et al., 2005).

Severity of TBI is gauged via diagnostic interview or examination following injury.

Using the Glasgow Coma Scale, individuals are determined to have a mild (13 or above), moderate (9-12), or severe (8 or below) head injury, based on patient responses to visual, motor, and verbal stimuli (Sande & West, 2010). Severity may also be categorized based on time spent without consciousness, or based on time that the patient experienced retrograde amnesia, although this approach is less common. The majority of TBI cases are mild (80%), while moderate (10%) and severe (10%) injuries are less frequent (Bruns & Hauser, 2003). Mild TBI (mTBI) is defined as acute brain dysfunction resulting from impact or acceleration/deceleration which causes temporary alteration of consciousness, a short period of anterograde amnesia, and/or brief loss of consciousness (Levin & Diaz-

Arrastia, 2015). Given the increasing prevalence of mTBI, it is critical to assess the sequelae that may come as a consequence of these injuries.

### **B. Neurobiology of mTBI**

Although each TBI differs in cause and severity, brain injury can induce two forms of damage (Blennow, Hardy, & Zetterberg, 2012). First, focal cellular/neurochemical damage may occur at the site of injury. These effects, which arise when neuronal membranes are stretched or bent from trauma, induce a chemical cascade that results in excitatory neurotransmitter release, acidosis and edema. Diffuse axonal injury, a second form of damage, occurs when axons are stretched or sheared by brain movement, rotational forces, and acceleration/deceleration. This type of damage can occur with or without an impact, as axons may be stretched or sheared by rotation within the brain (Broglia et al., 2014). Axonal injury results in disrupted axonal transport and/or axonal swelling, which can ultimately lead to degeneration.

There are deep brain regions that may be affected by brain injury even when the impact is on the surface of the skull. Specifically, rotational forces tend to impact the orbitofrontal cortex and regions of temporal lobes (including the hippocampus), because these brain regions are likely to scrape against bony prominences on the base of the skull during rotation (Warriner & Velikonja, 2006). Prefrontal and temporal damage may lead to the disruption of the structurally linked limbic system, which is involved in memory, affective processing, and modulation of emotion.

Neuroimaging studies have identified subtle but potentially meaningful axonal damage years after an mTBI. The most compelling evidence comes from studies utilizing diffusion tensor imaging (DTI). DTI gauges white matter tract integrity by calculating diffusion of water in the brain. The most typical measure of DTI, fractional anisotropy (FA) measures diffusivity of water within a tract, ranging from 0 (i.e., unrestricted, random flow) to 1 (flow occurring in the same direction). In theory, unbroken, strong myelin tracts, which would facilitate a strong connection between cortical areas, will restrict water flow, resulting in a high FA. Consequently, low FA represents “broken” or weak connectivity between cortical areas. White matter (comprising axons) is vulnerable to the shearing forces associated with brain injury (Frost, 2011), and it follows that FA reductions have been identified globally (Lipton et al., 2008), in the corpus callosum (Grossman et al., 2012; Lipton et al., 2008; Lo, Shifteh, Gold, Bello, & Lipton, 2009), surrounding the dorsolateral prefrontal cortex (Lipton et al., 2008), in the internal capsule, (Grossman et al., 2012; Lipton et al., 2009), and in the thalamus (Grossman et al., 2012) following chronic mTBI.

Damage to white matter may, in turn, influence gray matter integrity. A recent study that utilized magnetoencephalography (MEG), which measures electric currents in the brain, found abnormal low-frequency neuronal signals generating from 4-8 cortical (gray matter) regions within each mTBI participant. In the non-injured controls, however, these electric signals were not seen in a single region (Huang et al., 2012). An additional study demonstrated that abnormal cortical signals were generated by regions of cortex tethered to white matter fibers with reduced FA (Huang et al., 2009). Thus, injury-induced

decreases in white matter integrity may underlie cortical abnormalities following brain injury. These findings have recently been corroborated by a second group of researchers who found that abnormal bursts of low frequency activity occur during wake in chronic mTBI participants (4.8 years since mTBI) and also in mice that underwent experimental mTBI (Modarres, Kuzma, Kretzmer, Pack, & Lim, 2016).

### **C. Long-term Dysfunction following mTBI**

The Center for Disease Control and Prevention (CDC) groups the sequelae of mTBI into four clusters: (1) thinking/remembering, (2) physical, (3) mood/emotional, and (4) sleep. The CDC also notes that whereas most of the effects of mTBI occur and dissipate in a short period of time (e.g., a couple of hours to a couple of days), other effects may not become visible until months after injury. Further, these domains have features that potentially overlap or interact.

#### **1. Thinking/Remembering**

Cognitive deficits have been observed chronically after an individual has sustained an mTBI but not consistently and not in all persons. Broadly, mTBI may subtly impact executive functioning, working memory and memory consolidation. For instance, 5 years after injury, information processing (serial addition test) was reduced following chronic mTBI (O’Jile et al., 2006). However, differences between groups did not emerge until the most difficult condition. Furthermore, mTBI participants were found to exhibit memory consolidation (delayed cued recall) deficits roughly 6 years after injury (Konrad et al., 2011). Similarly, 7 years after mild injury, Sterr and colleagues found participants have

difficulty with shifting attention and working memory, yet this was only true for subjects with cognitive complaints (Sterr, Herron, Hayward, & Montaldi, 2006). Other investigations have failed to identify differences between mTBI and non-head injured populations on neuropsychological measures (Belanger & Vanderploeg, 2005). Therefore, long-term cognitive deficits in mTBI may be subtle and hard to detect or may only exist in a minority of head injured individuals (Ruff et al., 1994).

## **2. Physical**

The majority of the physical sequelae of mTBI (e.g., headache, dizziness, vomiting) occur immediately after injury (Centers for Disease Control and Prevention). However, fatigue is a physical symptom that may be chronic. Fatigue is a subjective feeling of lethargy or weakness, an “indescribable” tiredness that is separate from sleepiness (Neu et al., 2010). Fatigue overlaps with the other symptom clusters of mTBI: a recent study investigating the prevalence of fatigue in a community-dwelling sample of TBI participants found fatigue to be associated with elevated levels of depression, anxiety, and cognitive disturbances (Ouellet & Morin, 2006). Therefore, fatigue may either exacerbate other symptoms, or alternatively, cognitive and emotional symptoms may bring about feelings of fatigue.

## **3. Mood/Emotional**

There are well-documented long-term emotional outcomes following mTBI. Depression, specifically, has been identified in some individuals after mTBI, and post-TBI depression tends to last for years after injury (Holsinger et al., 2002). For instance, 7 years after self-

reported mTBI, participants had a significantly higher risk for having depression, even when controlling for pre-morbid psychiatric illness (Vanderploeg, Curtiss, Luis, & Salazar, 2007). Further, a recent meta-analysis, which aggregated findings from nine studies, found post-TBI anxiety, namely Acute Distress Disorder, to be a robust occurrence (Scholten et al., 2016), albeit not as robust as depression. Finally, perhaps as a consequence of increased depression and anxiety, suicide rates are higher 6 years after a single mTBI than in controls. This is true even when controlling for pre-injury psychiatric issues (Fralick, Thiruchelvam, Tien, & Redelmeier, 2016).

There are also subtle differences in emotional functioning between mTBI participants and controls. For instance, when comparing mTBI participants to another injured population (i.e., a group with bodily injury), chronic mTBI participants had decreased reaction time to threatening (negative) stimuli (i.e., faster attention allocation) during a go/no-go task (Mäki-Marttunen et al., 2015). In parallel, Event Related Potential (ERP) measures showed faster attention allocation to threatening stimuli. In other words, mTBI participants were more vigilant to the emotional stimuli. The authors of this study suggested the relationship between bottom-up (i.e., emotion enhancing) and top-down (i.e., emotion dampening) processes may be diminished in this population. However, there is some evidence to suggest that emotional processing deficits occur in only a subgroup of mTBI participants, rather than in all mTBI participants. For instance, individuals with ongoing mTBI-related complaints had more difficulty recognizing fearful faces than mTBI participants without complaints or uninjured controls, suggesting



only those with ongoing mTBI-related symptoms may have poorer emotional processing (Drapeau, Gosselin, Peretz, & McKerral, 2017).

#### **4. Sleep**

Sleep disturbances are one of the most prevalent complaints following mTBI (Haboubi, Long, Koshy, & Ward, 2001), with some estimates as high as 80% of individuals having sleep issues after mTBI (Parcell, Ponsford, Rajaratnam, & Redman, 2006). Chronically injured individuals report poorer sleep quality (Parcell, Ponsford, Redman, & Rajaratnam, 2008) and daytime sleepiness (Kaiser et al., 2010) relative to healthy controls. Objective recordings of sleep (via polysomnography [PSG]) have validated these sleep complaints. For instance, individuals with a history of chronic mTBI had decreased sleep efficiency (time asleep/time in bed; Shekleton et al., 2010) and an increased number of awakenings relative to uninjured controls (Parcell et al., 2008). Furthermore, veterans with a history of combat-related mTBI (average 6 years after injury) had significantly more sleep complaints than veterans without mTBI (Martindale et al., 2017), and the association between mTBI and sleep was independent of posttraumatic stress disorder (PTSD) status, mood disturbances, combat exposure, and drug use. Lastly, sleep stage proportion alterations (e.g, alterations in the time spent in each sleep stage per night) also occur chronically following mTBI (see meta-analysis: Grima, Ponsford, Rajaratnam, Mansfield, & Pase, 2016).

Additionally, in a recent study, it was found that individuals with a chronic history of mTBI (average 4.9 years from mTBI) have altered bursting of EEG waveforms during

sleep (Modarres et al., 2016). When transitioning from wake to sleep (and transitioning from lighter stages of sleep to deeper stages of sleep), slow wave bursts typically increase over time. However, in mTBI participants, the increase in slow waves over time was significantly smaller than uninjured controls. Importantly, within the same study, these findings were replicated in mice who had undergone fluid percussion injury, suggesting altered sleep EEG may be a biomarker of mTBI. Importantly, sleep disturbances following mTBI are predictive of a longer recovery time, and therefore, sleep disruptions or EEG alterations may be causal in exacerbating symptoms (Bramley et al., 2016).

## **5. The Current Work**

The overarching aim of this line of work was to examine the sequelae of mTBI to identify potential targets for interventions to mitigate the long-term consequences of mTBI. Two mechanisms in particular were examined as contributing to additional problems in mTBI: (1) sleep difficulties, and (2) emotion habituation difficulties. Recently, a national working group, which consists of brain injury experts from 20 research centers, released a statement outlining the need for investigations focusing on sleep after mTBI (Wickwire et al., 2016). Within this outline, the authors state that mTBI-related sleep problems may exacerbate mTBI-related sequelae. Identifying a link between poor sleep and poor outcomes following mTBI would be critical. In theory, if poor sleep exacerbates outcomes that would otherwise be minimal or non-existent, sleep could be a target for improvement following mTBI. Therefore, the first two studies focus on whether poor sleep after mTBI is associated with cognition and emotional processing in this population.

The third project, which is based on results of **Study 2**, attempted to probe an equally critical gap in the knowledge. Specifically, the third project aimed to characterize emotional functioning following mTBI and determine whether impaired processing of emotion stimuli is predictive of poor mood outcomes (e.g., depressive and anxiety symptomology). To our knowledge, emotion reactivity and habituation, two components of normative emotional responding, have not been directly measured in a chronic mTBI population. However, incidental findings from **Study 2** provide preliminary evidence that these two components may be disrupted after mTBI in a pattern similar to individuals with depressive symptoms. Therefore, this work sought to provide a link between mTBI and depression. Furthermore, findings from these studies were expected to inform clinicians of special considerations that must be taken when treating an individual with a history of mTBI.

### **6. Sleep and Cognition (Study 1: Spencer Lab)**

Memory consolidation is the process by which memory traces (i.e., engrams) are solidified in long-term memory storage. Memory consolidation occurs preferentially over a period of sleep. Sleep-dependent memory consolidation can be observed by comparing memory retention after a period of sleep relative to an equivalent period of time spent awake. For example, memory for information learned in the evening and recalled 12 hours later is often superior to memory for information learned in the morning and recalled 12 hours later. Importantly, sleep-dependent memory consolidation is not due to sleep per se, but rather due to the characteristics (e.g., staging) of the sleep bout.

Slow wave sleep (SWS), the deepest stage of sleep, is particularly beneficial to memory consolidation of declarative information (i.e., things you can speak about). During SWS, information moves from the hippocampus to the neocortex, the site of long-term storage, via the perforant pathway (Hyman, Van Hoesen, Kromer, & Damasio, 1986).

Concurrently, neurons that were activated in the hippocampus during encoding are reactivated during subsequent SWS (Wilson & McNaughton, 1994), and this reactivation facilitates the transfer of information from the hippocampus to long-term storage.

Typically, when more time is spent in SWS, declarative memory consolidation is superior (Gais & Born, 2004; Rasch, Büchel, Gais, & Born, 2007; Cairney, Durrant, Hulleman, & Lewis, 2014; Mander et al., 2015; Baran, Mantua, & Spencer, 2016).

As previously mentioned, the temporal lobes (hippocampus) and the prefrontal cortex are often the site of damage following mTBI. Damage to one or both of these structures could hinder communication or information transfer between these regions. Therefore, it was unknown whether hippocampal or cortical damage would prevent efficient sleep-dependent memory consolidation (and encoding) from occurring after mTBI. If damage were present, we could expect consolidation to be reduced. **Study 1** aimed to probe whether basic declarative sleep-dependent memory consolidation was intact following chronic mTBI.

Hypotheses:

- Sleep-dependent declarative memory consolidation would be disrupted in a

population with chronic mTBI

### **7. Sleep and Emotion (Study 2: Spencer Lab)**

Sleep and emotion are tightly linked. In fact, every major psychiatric disorder is associated with sleep disturbances (Benca, Obermeyer, Thisted, & Gillin, 1992). Poor sleep and sleep deprivation/restriction worsen emotional health symptomology. For instance, researchers found sleep deprivation increases symptoms of psychopathology, such as anxiety, depression, and paranoia (Kahn-Greene, Killgore, Kamimori, Balkin, & Killgore, 2007). Furthermore, improving sleep quality minimizes existing poor emotional outcomes, as sleep improvement therapy (e.g., sleep apnea treatment, insomnia treatment) lowers depressive symptomology in depressed individuals (Manber et al., 2008).

Several facets of emotion, such as emotion reactivity (i.e., one's initial emotional arousal [ranging from bored to excited] to stimuli) have been linked with sleep. For instance, sleep restriction causally impacts emotion arousal both in a naturalistic setting and an experimental setting. In a sample of medical residents, sleep deprived individuals had increased emotion reactivity to negative stimuli and decreased reactivity to positive stimuli (Zohar, Tzischinsky, Epstein, R., & Lavie, 2005). Laboratory studies have demonstrated the REM sleep stage, in particular, influences and modulates arousal. Following REM deprivation, adaptation to stress was decreased (relative to a normal night of sleep; (Greenberg, Pillard, & Pearlman, 1972), indicating a lack of REM sleep prevents proper arousal modulation (i.e., reduction) when faced with an emotional

stimulus. However, this effect is not specific to sleep deprivation. Other work has demonstrated that after a full night of sleep (relative to a day spent awake) amygdala activation was decreased in response to previously seen emotional stimuli. The decrease in emotional activation over sleep was correlated with REM sleep EEG waveforms (van der Helm et al., 2011), suggesting REM sleep plays an active role in diminishing emotional arousal.

Interestingly, although sleep tends to aid the proper modulation (i.e., reduction) of arousal, it alternatively preserves emotional valence (i.e., ratings of emotion ranging from positive to negative). This was demonstrated in the Spencer lab in a prominent investigation. A sample of young adults was shown the same set of emotional stimuli twice, each 12 hours apart. Half of the participants had a period of sleep between these two viewing sessions, whereas the other half had a normal waking day between sessions. Although a period of wake led to habituation (i.e., participants rated images as less negative during the second viewing session), a period of sleep preserved the negativity between both sessions. In this study, greater REM sleep during the third quarter of the night (which is often REM-rich) predicted valence preservation. Therefore, REM may be causal in preserving emotionality between sessions. A recent meta-analysis, which aggregated findings from nine separate studies on sleep and TBI, found REM sleep is reduced following a mild-severe TBI relative to uninjured individuals (Grima et al., 2016). An expanded meta-analysis (comprising 15 studies) that I have conducted corroborates these findings (Mantua et al., [Under Review]). Given this, we hypothesized mTBI-induced REM alterations would impact sleep-dependent ratings of valence

following chronic mTBI with the rationale that a disruption in sleep-dependent emotional processing could lead to poor waking emotional outcomes. **Study 2** aimed to test these hypotheses.

Hypotheses:

- Sleep-dependent emotional memory consolidation would be reduced in a population with chronic mTBI
- Sleep-dependent valence preservation would be reduced in a population with chronic mTBI

### **8. Emotion Reactivity and Habituation (Study 3: Ready Lab)**

In **Study 2**, an incidental finding occurred in the “wake” group. We found that although the non-TBI group rated emotional stimuli as less emotional during a second viewing session (i.e., emotion habituation occurred), the mTBI group did not. That is, the mTBI group rated images as equally negative during a second viewing session. However, because habituation was not a primary focus in **Study 2**, there are limitations that prevent us from drawing strong conclusions. Therefore, **Study 3** aimed to directly probe and characterize emotion habituation in a chronic mTBI population. This study was novel and had the potential to be highly informative, as it sought to identify factors linking depression and mTBI.

Additionally, in **Study 2**, we found near-significant differences in reactivity (ratings of the images during the first viewing session) between mTBI and non-TBI groups in the

morning (Cohen's  $d = .65$ ). The mTBI group rated the images as less negative than the non-TBI group. However, no clear differences between groups were present in the evening. Given this, we may have detected circadian rhythmicity differences between injury groups. Previous work has found individuals tend to rate negative stimuli as more negative when they are in a circadian trough ("off-peak"; (Tucker, Feuerstein, Mende-Siedlecki, Ochsner, & Stern, 2012). We aimed to test this hypothesis in an exploratory manner in Study 3 by testing emotion reactivity at each hour to determine whether circadian fluctuations in emotional responses would differ between the mTBI and non-TBI group.

Hypotheses:

- Emotion habituation would be reduced in a chronic mTBI population
- Emotion reactivity would be blunted in a population with chronic mTBI (after controlling for circadian or time-of-day effects)
- Alterations in habituation and reactivity would predict depressive and anxiety symptomology

#### **D. Summary**

The three projects in this dissertation collection were used to explore the long-term sequelae of mTBI. The first two projects (**Study 1** and **Study 2**) were novel because they were the first investigations to probe sleep-dependent processes following TBI. In aggregation, these studies found sleep-dependent memory consolidation of emotional stimuli is uniquely disrupted in this population. **Study 2** also found peculiar wake-



dependent effects that suggest individuals with chronic mTBI have emotion blunting and also deficiencies in emotion habituation. **Study 3** aimed to replicate and expand the findings of **Study 2**. We predicted physiological and self-reported differences in habituation and emotion reactivity (after controlling for circadian effects in reactivity) would be present in this population. These data had the potential to provide insight into the connection between mTBI and depressive symptoms. Overall, findings from this work will guide future research and will inform clinicians who may be providing treatment to individuals with a chronic history of mTBI.

## CHAPTER 2

# ALTERED SLEEP COMPOSITION AFTER TRAUMATIC BRAIN INJURY DOES NOT AFFECT DECLARATIVE SLEEP-DEPENDENT MEMORY CONSOLIDATION

### A. Introduction

Over 1.7 million incidences of traumatic brain injury (TBI), ranging from mild concussions to severe head trauma, are recorded each year through emergency department visits, hospitalizations, and deaths (Cornado et al., 2011). Notably, even a single, mild TBI may have long-term psychological and physiological consequences (AFHSC, 2013; Bhalerao et al., 2013), as TBI encompasses both a primary mechanical insult and also a prolonged secondary injury. Secondary injury may be sustained through lactic acid accumulation from local glycolysis, edema, breakdown of the blood brain barrier, excessive neurotransmitter release, lipase activity, protease activity, and apoptosis (Werner et al., 2007). This assortment of physiological and chemical abnormalities may create adverse, long-lasting symptoms, including short-term memory deficits (Dean & Sterr, 2013) and an increase in subjectively disturbed sleep (AFHSC et al., 2013; Bhalerao et al., 2013; Orff et al., 2009; Pillar et al., 2003; Verma et al., 2007).

Subjective sleep complaints are likely rooted in physiological changes in sleep. Objective measures of sleep reveal decreased sleep efficiency (time asleep / time in bed) and increased wake after sleep onset time (WASO) following TBI (Kaufman et al., 2001; Parcell et al., 2008; Shekleton et al., 2010). An increased need for sleep, evidenced by self-reported and objectively measured hypersomnia (Baumann et al., 2007; Kempf et al., 2010; Sommerauer et al., 2013; Imbach et al., 2015) has also been found in post-TBI

individuals. Additionally, overnight sleep recordings after chronic TBI show alterations in sleep architecture. Reports of sleep architecture vary, however, suggesting either lower percentage of sleep in non-rapid eye movement stage 2 (NREM2) and REM (Parcell et al., 2008; Schreiber et al., 2008) or a higher percentage of Slow Wave Sleep (SWS; Parcell et al., Shekleton et al., 2010; Sommerauer et al., 2013) when compared to those without a history of TBI. Finally, alterations in spectral power, a measure of synaptic strength and synchronization, have also been found following injury (Khoury et al., 2013).

Atypical sleep architecture may exacerbate long-term cognitive deficits caused by injury, as sleep is beneficial for the formation of new memories. Specifically, sleep rich in NREM2 and SWS facilitates declarative memory consolidation, which is the stabilization and transfer of memory traces from short-term to long-term memory (Diekelman & Born, 2010; Plihal & Born, 1997; Stickgold, 2005; Wilson et al., 2012). For instance, it has been suggested that, during NREM2, declarative memory traces are reactivated and redistributed from the hippocampus to neocortex (Kempf et al., 2010), and this transfer is enhanced through increased cortical synchronization that occurs during SWS (Sirota et al., 2002; Takashima et al., 2006). Moreover, specific traits of NREM2 (e.g., sleep spindles or sigma power [Genzel et al., 2009; Ruch et al., 2012; Clemens et al., 2005; Holz et al., 2012]) and SWS (e.g., %SWS and delta power [Holz et al., 2012]) have been linked with declarative memory performance following a sleep bout (Marshall et al., 2006), particularly early in the night (Plihal et al., 1997; Genzel et al., 2009). Combined NREM measures (e.g., spindle density across both stages and total %NREM; Plihal et al.,

1997; Clemens et al., 2005; Holz et al., 2012) have also been linked with overnight consolidation. The latter studies align with recent notions that sleep stages may act sequentially or in concordance to have beneficial declarative memory consolidation effects (Ruch et al., 2012; Clemens et al., 2005; Göder et al., 2007; Ficca et al., 2000; Mazzoni et al., 1999).

Despite well-established sleep deficits following brain injury, to our knowledge, sleep-dependent memory consolidation has never been examined in individuals with a history of TBI. Given that both NREM2 and SWS stages have reportedly been affected by TBI, we sought to examine whether these changes in sleep impair sleep-dependent consolidation. To this end, we utilized a word-pair learning task and investigated memory following intervals containing overnight sleep or spent fully awake. We used polysomnography, a system that objectively quantifies sleep quality and architecture, to examine sleep physiology in those with a history of mild TBI (i.e., having suffered from a concussion) compared to controls without a history of TBI. We hypothesized that TBI subjects would have impaired sleep, in measures of sleep stage duration and fragmentation (i.e., lower sleep efficiency and greater WASO) compared to those without a history of TBI. Moreover, we posited that poorer sleep quality would hinder sleep-dependent memory consolidation when compared to those without a history of TBI.

## **B. Methods**

### **1. Participants**

Participants were 58 healthy young adult participants (18-22 yrs). Subjects were recruited through an online recruitment system (SONA) or by word-of-mouth and were compensated with extra credit for a Psychology course or monetary payment. To be eligible, participants were required to habitually sleep more than 6 hrs per night and have less than 3 naps per week. Participants were excluded if they typically consumed more than 14 cups of coffee or alcohol per week, had a neurological disorder (other than a history of TBI in the TBI group), were taking anti-psychotic or anti-seizure medications, or were taking sleep-affecting medications. Importantly, to specifically examine the chronic effects of TBI (as opposed to transient, acute effects), participants in the TBI group had a history of TBI with injury at least one year prior to participation in the study.

Participants were assigned to one of four groups: TBI Wake, TBI Sleep, non-TBI Wake, or non-TBI Sleep. Participants were first assigned to a group based on TBI history and then semi-randomly assigned to a Sleep or Wake group, with careful balance of numbers of TBI incidents and severity of TBIs across the TBI Sleep and TBI Wake groups.

### **2. Word-pair learning task**

The word-pair task has been utilized to examine declarative memory consolidation in previous studies in our lab (Wilson et al., 2012). Stimuli were 40 semantically-unrelated word pairs consisting of single-syllable nouns. The task had three phases: Encoding, Immediate Recall, and Delayed Recall. During encoding, word pairs appeared on a

computer monitor for 5s with a 100ms inter-stimuli interval. Participants passively viewed the pairs and were instructed to use a mnemonic strategy to help remember the pairs. Specifically, participants were told to think of associations between the pairs and to picture this association in their mind (e.g., if “aunt-zoo” was presented, they could imagine their aunt on display at a zoo). This instruction was designed to facilitate hippocampal-dependent contextual learning (Toki et al., 2014). Subsequently, participants practiced recalling the pairs with feedback. The first word from each pair was presented individually in a random order. The first and last two pairs of the encoded list were removed to eliminate primacy and recency effects (leaving a total of 36 pairs). If the participant’s response was incorrect, the correct response was displayed on the computer monitor for 750ms. If the response was correct, the next stimuli appeared on the screen. Recall practice continued until participants reached 65% proficiency or the full list of words had appeared 5 times.

The Immediate Recall phase began following the Encoding phase. Participants were presented with one word from the encoded pairs and were instructed to recall the corresponding word in the pair. There was no feedback for correct or incorrect responses. In Session 2, which occurred after a 12-hr break, participants completed the Delayed Recall phase, which was identical to the Immediate Recall phase.

### **3. Procedure**

Procedures were approved by the Institutional Review Board at the University of Massachusetts, Amherst. Before the study commenced, each participant provided written

informed consent. Participants then underwent one of two in-lab sessions. For those in the Wake group, session 1 took place in the morning and session 2 took place in the evening, following 12 hrs awake. For the Sleep group, session 1 took place in the evening and session 2 took place the next morning, following 12 hrs containing an overnight sleep interval.

In the first session, after completing the consent process and the Stanford Sleepiness Scale, Morningness-Eveningness Questionnaire, Epworth Sleepiness Scale, Pittsburgh Sleep Quality Index, forward digit span test, and TBI questionnaire (all described below), participants performed the Encoding and Immediate Recall phases. Participants returned 12hrs later to complete the Delayed Recall phase. Subsequently, participants in the Wake group were instructed not to nap. Participants in the Sleep group were equipped with polysomnography electrodes in their home, 1 hr prior to their typical bedtime. Twelve hrs after session 1, session 2 took place in the lab. Subjects completed the Stanford Sleepiness Scale followed by the Delayed Recall phase of the word-pair task.

#### **4. Questionnaires**

During Session 1, participants completed an in-house questionnaire that recorded self-reported number of TBIs, cause of TBI(s), presence of post-concussive syndrome, and symptoms present after the injury. To assess the participant's sleepiness level, or tendency to fall asleep during certain everyday activities, the Epworth Sleepiness Scale (ESS) was completed (Johns et al., 1994). The Pittsburgh Sleep Quality Index (PSQI) was administered to assess the participant's habitual sleep quality and sleep disturbances

during the past month of sleep (Buysse et al., 1989). The Morningness-Eveningness Questionnaire (MEQ) was used to determine the participant's chronotype, or preference for performing tasks and activities during the morning hours or evening hours (Horne & Ostberg, 1976). The Stanford Sleepiness Scale (SSS) was used to determine the participant's level of sleepiness at the time of the session (Hoddes et al., 1973). Lastly, the participants in the Sleep group were given a sleep survey to gather subjective information about the participant's sleep during the night prior.

We used the Forward Digit Span task (FDS) from the Wechsler Adult Intelligence Scale IV to assess possible working memory deficits in the TBI group (Dean & Sterr, 2013). The FDS requires a series of digits to be read to the subject, who is then asked to verbally repeat the digits in the same order. This task begins with a series of 2 digits and increases in length by a single digit per trial up to a series of 10 digits (Wechsler, 2008). Due to late adoption of this measure, the FDS was performed by 18 participants in the TBI group and 24 in the non-TBI group.

## **5. Polysomnography**

Polysomnography was recorded with the Aura PSG ambulatory system (Grass Technologies). An electrode montage was applied in the participants' home approximately 1 hr before their typical bedtime. The montage included 2 EOG leads (right and left ocular canthus), two chin EMG leads, and six cortical EEG leads (F3, F4, C3, C4, O1, O2) with each electrode referenced to Cz. Data analysis was conducted according to the revised AASM manual (Silber et al., 2007).



## 6. Data Analysis

Word pair data were individually reviewed for total number of correct word pair responses, allowing for misspelling. Recall accuracy was measured as percentage of the total number of word pairs (of 36 possible). The change in performance between Immediate and Delayed Recall was assessed using an Intersession Change score. Intersession Change in recall was calculated by subtracting the Immediate Recall accuracy from the Delayed Recall accuracy and normalizing to baseline accuracy.

Intersession Change was compared across groups using t-tests to determine whether there was a difference between Sleep and Wake group performance. T-tests were also used to compare sleep staging and spectral power between TBI Sleep and non-TBI Sleep groups. Circadian effects at time of encoding were tested using a 2x2 ANOVA, with between-subject variables condition (Sleep v. Wake) and group (TBI v. non-TBI). Similarly, ANOVA tests were used to compare subjective sleep scores (SSS, ESS, PSQI, MEQ), cognitive performance on the FDS, and Intersession Change. Finally, Pearson's correlations were performed to investigate relationships between sleep factors (e.g., WASO and %SWS) with Intersession Change to determine whether specific qualities of sleep are related to memory performance. Given the large number of statistical analyses, alpha was set to .01.

EEG, EMG, and EOG data were scored using the American Academy of Sleep Medicine (AASM) Manual for the Scoring of Sleep and Associated Events (Silber et al., 2007),

identifying periods of wake and sleep stages NREM1, NREM2, SWS, and REM. Two trained sleep researchers scored all polysomnograms. Total sleep across the night and percent in each sleep stage was calculated and compared across TBI and non-TBI groups. A combined %NREM2 and %SWS composite (%NREM) was created to address sleep stage interaction effects (Clemens et al., 2005; Göder et al., 2007). Pearson's R coefficients were used to assess correlations between percent total sleep time spent in each sleep stage and intersession change in recall.

The spectral power density ( $\mu\text{V}^2/\text{Hz}$ ) in the sigma (12-15Hz) and delta (0.5-4Hz) range was quantified using BrainAnalyzer 2.0 Software (BrainVision, Berlin, Germany). Delta was examined during SWS, and sigma was examined in both NREM2 and over a combined NREM2 and SWS measure (Clemens et al., 2005; Holz et al., 2012). EEG data was first segmented into stages and filtered to 0.3-25Hz. Raw data inspection was performed to eliminate artifacts, and data were again segmented into 4 s sections. Semi-automatic artifact rejection was performed on individual channels. Fast-Fourier transformation was performed with a Hanning window with 10% overlap. Analyses with delta and sigma utilize relative power (Khoury et al., 2013) in which power in the given spectrum was divided by time in the sleep stage measured (i.e., delta power divided by minutes in SWS; sigma power divided by minutes in NREM2 and NREM2/SWS combined).

## **C. Results**

### **1. Group descriptions**

One TBI Sleep participant, 1 TBI Wake participant, and 1 non-TBI Wake participant were excluded for falling above or below 3 standard deviations of the mean in terms of Intersession Change in recall. The final sample included 56 participants across the four groups. We confirmed all Wake participants slept >5 hrs the night before the experiment and all Sleep participants slept >5 hrs the night of the experiment. No Wake participants reported napping during the 12-hour interval between session 1 and 2. No participants reported using alcohol or sleep medications during the study. There were no significant differences in age, gender ratio, or years of education between groups.

There were no significant differences between TBI Sleep and Wake groups for TBI history or symptoms. Among the 26 TBI participants, there were 34 diagnosed concussions (19 in the Sleep group and 15 in the Wake group; 6 participants had more than 1 diagnosed TBI), 11 of which were accompanied by post-concussive syndrome. The average time since most recent concussion was  $4.35 \pm 3.14$  yrs. The most common symptoms in both groups were dizziness, headache, decreased ability to concentrate, and fatigue. Interestingly, only 2 TBI Wake participants and no TBI Sleep participants reported (TBI questionnaire) having sleep disturbances since the time of TBI.

Groups also did not differ in terms of habitual sleep or sleepiness or chronotype. There were no significant differences observed in PSQI, SSS at Immediate Recall, SSS at

Delayed Recall, ESS, or MEQ scores. Importantly, no significant differences were found for FDS scores, indicating that TBI condition did not affect short-term memory and attention.

## **2. Word pair learning task**

There were no significant differences in baseline performance across all groups as measured by Immediate Recall accuracy,  $F(3,52)=.655;p=.58$ , or by number of rounds to reach criteria,  $F(3,52)=1.51;p=.22$ , indicating circadian effects and time-of-day did not affect performance. Moreover, there was no significant difference in Immediate Recall for TBI and non-TBI groups,  $t(52)=-1.38;p=.187$ , or for the number of rounds to reach criteria,  $t(52)=.345;p=.63$ , suggesting that the history of TBI did not impair word-pair learning.

We examined whether performance improvements were greater following sleep compared to wake, as predicted by our previous work (Wilson et al., 2012). There was a significant main effect of condition (Sleep v. Wake) with greater reduction in recall in the Wake groups,  $F(1,51)=9.30;p=.004$  (Figure 1). The main effect of group (TBI v. non-TBI) was not significant,  $F(2,51)=.421;p=.658$ , and there was no interaction between the Sleep/Wake condition and TBI/non-TBI status,  $F(1,51)=.006;p=.939$ . These results indicate both Sleep groups significantly outperformed the Wake groups, and there were no differences in sleep-dependent consolidation between the TBI and non-TBI groups.

## **3. Sleep assessments**

Due to equipment malfunction and operation errors, 5 sleep reports were unusable. The following results are based on polysomnography recorded in 11 participants in the TBI Sleep and 13 participants in the non-TBI Sleep group.

Contrary to our predictions there were no differences in sleep efficiency or WASO between the TBI and non-TBI Sleep groups. However, a two-tailed t-test showed a significant difference in %SWS between groups, where the TBI Sleep group had greater %SWS than the non-TBI Sleep group,  $t(22)=4.675$ ,  $p<.001$ . This excess of SWS was at the expense of %NREM1, as an additional t-test revealed TBI participants had near-significantly less %NREM1 compared to non-TBI Sleep participants,  $t(22)=-2.502$ ,  $p=.02$  (Figure 2). There were no differences between groups in total sleep time, sleep latency, %NREM2 or %REM. The TBI Sleep group spent more time, albeit not significantly more, in %NREM than did the non-TBI Sleep group,  $t(22)=1.96$ ,  $p=.062$ , likely as a result of increased %SWS.

Spectral power in the relative sigma (12-15Hz) and relative delta (0.5-4Hz) bands was compared between TBI and non-TBI Sleep groups using two-tailed t-tests. No differences were found in sigma power, or a combined NREM2/SWS sigma measure at any frontal or central locations. However, the central delta band differed near-significantly between the groups,  $t(22)=-1.78$ ,  $p=.08$ , such that that TBI group had lower relative delta power, as has been previously found (Khoury et al., 2013).

#### **4. Sleep and memory performance**

We used correlations to assess the relationship between sleep parameters and Intersession Change, a measure of memory consolidation. Given that there were no differences in the Intersession Change between the TBI and non-TBI groups, we initially considered these groups combined, and then analyzed the both the non-TBI and TBI groups separately. Counter to previous work (Holz et al., 2012), there was no significant correlation between Intersession Change and %SWS, %NREM2, delta power, sigma power in NREM2 or sigma power combined over NREM2 and SWS in any of the groups. There was, however, a significant positive correlation between total %NREM and Intersession Change in the combined group (see Figure 3,  $r=.52$ ;  $p=.01$ ) and a near-significant positive correlation with Intersession Change ( $r=.56$ ;  $p=.05$ ) in the non-TBI group.

Given that NREM during the first half of the night is particularly beneficial for memory consolidation (Plihal et al., 1997) we performed a post-hoc correlation between %NREM and Intersession Change in each half of the night, including all participants (values not reported). Consistent with prior reports, %NREM in the first half of the night was nearly positively correlated with Intersession Change ( $r=.437$ ;  $p=.04$ ) but this relationship was not present for %NREM2 ( $r=.228$ ;  $p=.19$ ).

#### **D. Discussion**

This study investigated whether young adults with a history of TBI have decreased sleep quality and architecture and whether this affects sleep-dependent declarative memory consolidation. Contrary to our predictions, TBI subjects did not have increased WASO or

decreased sleep efficiency. However, we report an increase in %SWS sleep, at the expense of %NREM1 sleep, in individuals who have experienced a TBI. This study is also the first to show preserved declarative sleep-dependent memory consolidation in those with a history of TBI. Interestingly, sleep-dependent memory consolidation was exhibited despite atypical sleep architecture.

As has been previously reported, after performing a declarative word-pair learning task, those who slept had a significantly greater Intersession Change than those who remained awake for an equivalent period of time, a hallmark of sleep-dependent memory consolidation. We do not believe this difference in recall is due to circadian effects, as there were no differences between learning at Immediate Recall for those who learned in the morning (Wake groups) and those who learned in the evening (Sleep groups).

Moreover, a significant correlation between %NREM and Intersession Change support an active role of sleep in memory consolidation (Wilson et al., 2012; Holz et al., 2012). We did not find a correlation between %SWS, %NREM2, or spindles and Intersession Change as reported in previous studies (Genzel et al., 2009; Ruch et al., 2012; Clemens et al., 2005; Holz et al., 2012). However, the association between Intersession Change and %NREM is consistent with hypotheses that sleep stages may interact or act sequentially (Ruch et al., 2012; Clemens et al., 2005; Göder et al., 2007; Ficca et al., 2000; Mazzoni et al., 1999). For example, recent studies using experimental sleep stage manipulations have found enhancing both NREM2 and SWS boost declarative sleep-dependent consolidation (Mednick et al., 2013), whereas enhancing only SWS did not (Feld et al., 2013). It has

therefore been suggested that the shared components of NREM2 and SWS (e.g., sleep spindles, slow oscillations) underlie consolidation in concert (Ackermann & Rasch, 2014). Thus, it may be that both NREM2 and SWS are important for declarative sleep-dependent memory consolidation.

Despite prior studies showing that short-term memory is affected in those who have suffered from a TBI (Dean & Sterr, 2013), we did not see deficits in sleep-dependent memory consolidation for those with and without a history of TBI. It has been posited that SWS facilitates restoration following brain injury (Sommerauer et al., 2013; Gao et al., 2010), and it may be that the normal-to-increased amount of SWS, which is a stage that is beneficial for cortical communication and plasticity, conserved both short-term memory and sleep-dependent consolidation in this sample.

Previous studies found decreased sleep efficiency and increased WASO in those with TBI (Kaufman et al., 2001; Parcell et al., 2008; Shekleton et al., 2010), yet we did not find a difference in these measures between groups in the present study. Differing sample demographics may account for these discrepancies in findings. Kaufman et al. (2001) studied younger individuals (10-16.5yrs), who have considerably different sleep characteristics and needs than our young adult sample. Participants in the young adult age range are often sleep deprived and may therefore have a higher homeostatic sleep drive than younger adults (Herschner et al., 2014). An increased homeostatic drive may minimize awakenings, which ultimately increases sleep efficiency. Additionally, Parcell et al. (2008) investigated individuals with a history of moderate to severe brain injury, whereas our sample had only mild TBI. It may be that poorer sleep quality accompanies



more severe brain injury, and that sleep efficiency remains intact following a mild brain injury in young adults. Finally, because none of the TBI Sleep individuals reported sleep issues following injury, it may be that, by chance, our sample did not include subjects with poor sleep quality.

An increased %SWS was previously found in those with a history of TBI (Parcell et al., 2008; Shekleton et al., 2010; Sommerauer et al., 2013). Consistent with these findings, our non-TBI sample had %SWS in the normal range (~20%), and the TBI group had an unusually high %SWS compared to previous reports (Ohayon et al., 2004), with some exceeding 30%. Additionally, the TBI group had notably lower normalized delta power during SWS. There are multiple hypotheses that attempt to explain increased SWS post-TBI. First, following a series of investigations that found increased sleep need after both acute and chronic TBI, it was posited that SWS and its neuroplastic processes (e.g., axonal sprouting, synaptic remodeling) act as a recovery mechanism that may aid in healing (Sommerauer et al., 2013). This hypothesis is supported by investigations in which SWS accelerates healing following a stroke (Gao et al., 2010). Paralleling this hypothesis, Parcell and colleagues (2008) suggested TBI may trigger a compensatory mechanism that occurs in response to brain injury, and this mechanism may increase %SWS and delta power. This hypothesis is supported by the increased neuronal reorganization, synaptic potentiation and neural proliferation seen following brain injury (Nudo et al., 2011; Kernie et al., 2011). Strengthening of neurons in response to injury may contribute to the synchronicity required for initiation and maintenance of %SWS. Finally, it has been suggested that the trauma itself increases SWS, as most brain injuries

having a widespread affect on multiple brain circuits (Sommerauer et al., 2013). Given the current results, we posit that increased %NREM may be necessary to compensate for marginally lower delta power in the central sites.

At the expense of increased %SWS, the TBI individuals had decreased %NREM1. Of note, %NREM1 found in the current sample is higher than that reported previously in young adults (15-20% vs. 2-5%: Ohayon et al., 2004). However, a closer examination of previous work shows that whereas %NREM1 is low when nocturnal sleep follows an adaptation night (Martin et al., 1997; Fischer et al., 2002), nights without an adaptation period often have NREM1 in a range of 14-23% (Crowley et al., 2002; Baran et al., 2012).

It is important to address the potential limitations of this study. Our sample included subjects who suffered from a concussion at least 1 year prior to enrollment, as we sought to include only those with long-term consequences of TBI. However, we did not require neurological records to verify TBI presence and severity. It is therefore possible that the TBI group included participants who did not suffer from a concussion as reported.

Likewise, the non-TBI group may have included individuals who have indeed suffered from a concussion. However, given that we provided equal compensation for participants in both groups, it is doubtful that participants would deliberately falsely report their TBI history.

This sample lacked sleep efficiency and WASO deficits, as have been shown previously. They also lacked cognitive impairment, indicated by Digit Span scores and also unimpaired Immediate Recall performance. It may be, then, that our sample included an atypical population that is not representative of others with acute TBI. The heterogeneity of our sample (e.g., time since TBI, site of injury, etc.) may account for a lack of overlap with previous reports. However, given that differences observed in %SWS and relative delta power are consistent with prior work (Parcell et al., 2008; Shekleton et al., 2010; Khoury et al., 2013), it is unlikely that our sample was dissimilar from others. These results, in fact, highlight the severity of mild TBI, as our heterogeneous group in the chronic TBI stage exhibits characteristics that have been found in more homogenous groups with acute injury. Nonetheless, future work would benefit from neurological exams characterizing the TBI and identifying a more uniform group.

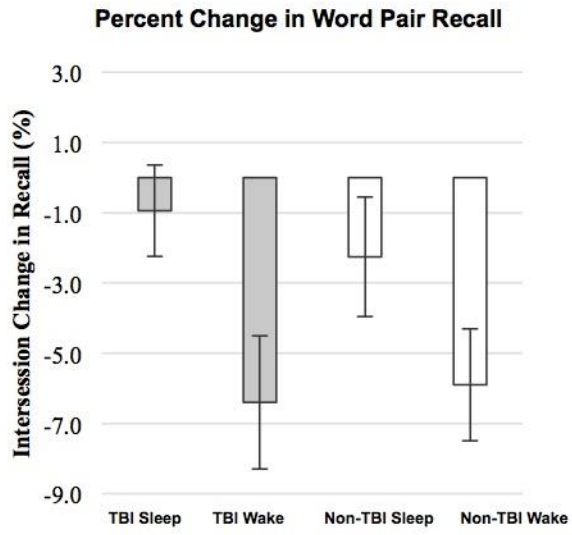


Figure 2.1: Differences in Inter-session Change between Sleep and Wake groups. Error bars represent standard error of the mean.

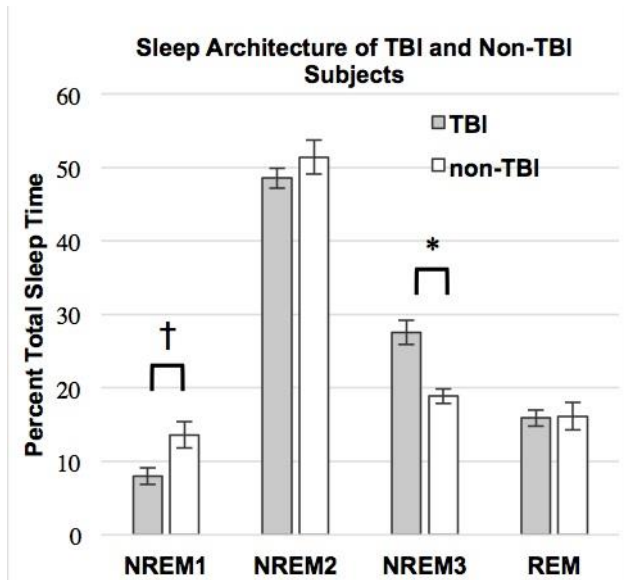


Figure 2.2: Percent total sleep time spent in each stage of sleep. Error bars represent standard error of the mean.

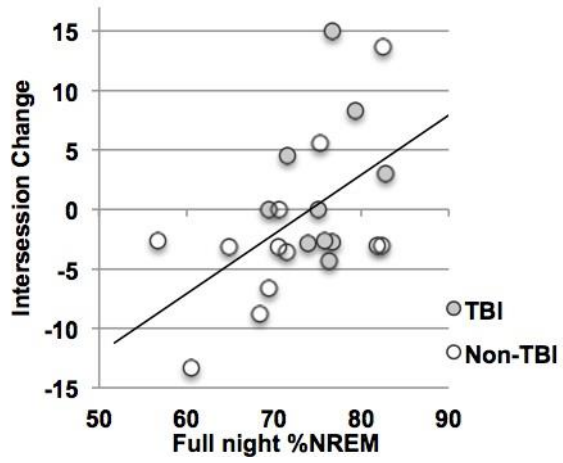


Figure 2.3: Intersession Change and percent of the night in NREM (%NREM2 + %SWS).

Line represents line of best fit for combined groups.

## CHAPTER 3

### MILD TRAUMATIC BRAIN INJURY CHRONICALLY IMPAIRS SLEEP- AND WAKE-DEPENDENT EMOTIONAL PROCESSING

#### A. Introduction

Mild traumatic brain injuries (TBIs), or concussions, occur pervasively. It is estimated that 1.4-3 million people suffer from a TBI each year in the United States, with 70-80% of these injuries being classified as mild (Glasgow Coma Score  $\geq$  13; Rutland-Brown et al., 2006; Silver et al., 2005). Importantly, TBIs classified as mild are not necessarily benign: in 2003, the US Centers for Disease Control and Prevention released a report stating that mild TBI is a “silent epidemic,” the prevalence and severity of which are highly underestimated (Gerberding, 2003). Moreover, recent evidence from empirical studies suggests just a single, mild TBI can cause lasting, unfavorable consequences. Therefore, the need for exploration of this topic is both critical and broadly impactful.

#### **1. Emotional disturbances following mild TBI**

Mild TBI patients exhibit a wide range of physical, cognitive, and emotional complaints chronically (>1 yr since injury). One of the most well-documented, long-term impacts of mild TBI is an increased risk for mood disturbances. Specifically, new-onset depression is common following mild TBI (Chi et al., 2016; Rao et al., 2010), and elevated depression rates have been detected as long as 6 years after injury (Konrad et al., 2011). A recent meta-analysis also identified an increased prevalence of anxiety symptoms following TBI, relative to a non-injured, control population (Scholten et al., 2016). Additionally, perhaps as a consequence of post-TBI depression and anxiety, risk for

suicide is elevated ~10 years after an individual sustains a concussion, even if mood disorders were not present pre-injury (Fralick et al., 2016). Yet despite clear evidence linking head injury and emotional disturbances, the link between these two factors remains largely unexplored and poorly understood.

## **2. Sleep disturbances following mild TBI**

Sleep alterations are similarly common after TBI, both immediately (Haboubi et al., 2001; Ponsford, Parcell, Sinclair, Roper, & Rajaratnam, 2013) and many years post-injury (Mantua, Mahan, Henry, & Spencer, 2015). Specifically, chronically injured individuals report poorer sleep quality (Parcell et al., 2008) and daytime sleepiness (Kaiser et al., 2010) relative to healthy controls. Objective recordings of sleep (via polysomnography [PSG]) demonstrate decreased sleep efficiency (time asleep/time in bed; Shekleton et al., 2010), increased awakenings (Parcell et al., 2008), hypersomnia (Imbach et al., 2016), and sleep stage proportion changes several years post-TBI. Recently, a large meta-analysis, which comprised 9 studies, found individuals with a history of TBI tend to have less REM than uninjured individuals (Grima et al., 2016). However, at present, it remains unclear whether TBI-induced sleep alterations have chronic, deleterious effects on health after brain injury.

## **3. Sleep and emotional processing**

Sleep is a pillar of mental health: every major psychiatric disorder is associated with a high prevalence of sleep disturbances (Benca et al., 1992). Interestingly, it has been proposed that these sleep disturbances causally impact mood (Mellman, Bustamante,



Fins, Pigeon, & Nolan, 2002; Walker & van der Helm, 2009). That is, sleep alterations are not merely a side effect of the disorder but actively contribute to and maintain dysfunction. Accumulating evidence from the last decade supports this hypothesis.

Sleep, relative to wake, uniquely impacts cognition and emotion. For instance, we and others have shown that sleep, relative to a period spent awake, strengthens emotional memories through a process called sleep-dependent memory consolidation (Baran, Pace-Schott, Ericson, & Spencer, 2012; Jones, Schultz, Adams, Baran, & Spencer, 2016; Payne, Stickgold, Swanberg, & Kensinger, 2008). In a separate study, we found sleep-dependent memory consolidation may causally impact subsequent (i.e., next-day) mood. Specifically, we found sleep staging predicts post-sleep affect/mood but only when sleep-dependent emotional memory consolidation occurred (Jones et al., 2016). These findings indicate emotional memory consolidation plays a critical role in the relationship between sleep and emotional state. Therefore, a disruption in this underlying mechanism (sleep-dependent memory consolidation), potentially due to sleep stage or sleep quality alterations, can have consequences for emotional well-being.

Further, we (Baran et al., 2012; Jones et al., 2016) and others (Lara-Carrasco, Nielsen, Solomonova, Levrier, & Popova, 2009; Wagner, Fischer, & Born, 2002) demonstrated sleep and wake differentially impact emotion generation (e.g., subjective valence ratings). Specifically, when individuals are shown the same set of negative stimuli twice (with a period of sleep between viewing sessions), emotionality to negative stimuli is preserved. However, individuals who remain awake between the two sessions (during a normal

waking day) habituate to negative stimuli, rating them as more neutral during the second presentation. Similar to memory, sleep-dependent preservation of emotion has been linked to sleep physiology, such that more REM leads to greater emotion preservation over a sleep period (Baran et al., 2012). Therefore, a disruption of sleep staging, and particularly REM, could disrupt this process.

#### **4. The current study**

One aim of the current study is to assess whether sleep-dependent memory consolidation is altered in individuals with a chronic, mild TBI with the rationale that disrupted sleep-dependent processes could be a mechanism causing or maintaining mood disturbances in this population. To test this hypothesis, we utilized an emotional memory paradigm (Baran et al., 2012; Jones et al., 2016; Pace-Schott et al., 2011). We predicted emotional sleep-dependent memory consolidation would be reduced in a chronic, mild TBI population. Additionally, given the reduction in REM sleep following a mild TBI (Grima et al., 2016), the second study aim was to assess whether sleep-dependent emotion generation is intact in a mild TBI population. We hypothesized that sleep's preservation of emotionality might be disrupted in individuals with chronic TBI as well.

### **B. Methods**

#### **1. Participants**

Eighty-one individuals (59 female, 22 male) between 18 and 30 years ( $20.01 \pm 1.34$ ) participated in the experiment. Participants had normal or corrected-to-normal vision and no history of neurological disease, sleep disorders, psychological disorders, or use of medications known to affect sleep or cognitive functioning (this information was self-reported). All participants were compensated with payment or course credit.

Experimental procedures were approved by the University of Massachusetts, Amherst Institutional Review Board, and written informed consent was obtained. Procedures are in accordance with the Declaration of Helsinki.

Participants were assigned to a TBI or non-TBI group. Inclusion criteria for the TBI group included a history of a concussion  $>1$  yr prior to testing. Time since injury ranged from 1-10 years, with 64.1% of the sample having had a concussion within 1-3 years. Sixty-six percent of the participants had 1 concussion, 19.3% had a history of 2 concussions, 5.3% had 3 concussions, and 10.4% had 4 concussions. Concussion and symptom diagnosis were self-reported, as in our previous work (Mantua et al., 2015). In the past, self-reported mild TBI has been linked with cognitive, neuropsychological, and physical impairments (Baker & Good, 2014; Bernstein, 2002; Kerr, Marshall, Harding, & Guskiewicz, 2012; van Noordt & Good, 2011; Vanderploeg et al., 2007). Therefore, we feel participants' self-reports are a valid measure of having had a concussion. Participants in the non-TBI group were required to have never had a concussion. Individuals unsure of their concussion status were not eligible. The criteria of mild TBI states that (at the very least) an "alternation in brain functioning" (e.g., confusion, disorientation, loss of concentration) must occur following head injury (Menon, Schwab, Wright, & Maas,

2010). Given this, we only included participants with at least 1 symptom of altered brain functioning. We did not count the presence of a headache as altered brain functioning, as a headache can also come from external pain (e.g., superficial injury). Given that participants were not aware of the hypotheses of the study, the sample comprised individuals with a range of symptoms following mild TBI (i.e., the sample was not only comprised of individuals with cognitive or sleep complaints). However, the aim of this study was to investigate individuals with chronic, mild TBI, who are often “high functioning” (i.e., those who may have little to no ongoing consequences of TBI), and, consequently, our sample comprises individuals on the very mild end of the TBI spectrum.

Participants in each group were further divided into either the Sleep or Wake condition. These conditions differed only in the timing of the performed behavioral tasks (described below).

## **2. Materials**

Ninety emotionally negative and 90 emotionally neutral pictures were used. The majority of stimuli were obtained from the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 1997) The rest were from an in-house set, chosen to match the IAPS pictures in content and emotionality (Jones et al., 2016; Wilson, Baran, Pace-Schott, Ivry, & Spencer, 2012). Normative data from our lab found negative pictures were moderate to high in arousal, and neutral pictures were low in arousal.

### 3. Procedure

This experiment had a between-subjects design with two conditions. Each condition consisted of two sessions. Participants in the “Sleep condition” had Session 1 (Encoding) in the evening (between 20:00 and 22:00) and Session 2 (Recognition) 12-hr later (in the morning). On the other hand, participants in the “Wake condition” had Session 1 in the morning (between 8:00 and 10:00) and Session 2 12-hr later (in the evening). Individuals in the Wake condition were asked not to nap or consume excessive amounts of caffeine between sessions. All participants were asked not to consume alcoholic beverages.

In the first session, participants provided written informed consent and completed a set of questionnaires including: (1) the Pittsburg Sleep Quality Index (PSQI; Buysse, Reynolds, Monk, Berman, & Kupfer, 1989)), a well-validated measure of subjective sleep quality during the month prior, (2) the Morningness-Eveningness Questionnaire (MEQ; Horne & Ostberg, 1976)), an assessment of chronotype, (3) the Epworth Sleepiness Scale (ESS; Johns, 1992)), which gauges habitual sleepiness, and (4) the Stanford Sleepiness Scale (SSS; Broughton & Dinges, 1989)), which assesses the participant’s subjective sleepiness at that given moment. Participants completed the SSS at both Session 1 (SSS1) and Session 2 (SSS2). Additionally, all participants performed a working memory task, the Digit Span Forward (Wechsler, 2008), at Session 1 to confirm similar encoding ability between TBI and non-TBI groups.

A questionnaire regarding TBI characteristics was administered to the TBI group. This questionnaire probed time since TBI, number of TBIs, and which symptoms they

experienced immediately after the most recent concussion occurred.

During Encoding, participants viewed 30 negative and 30 neutral target stimuli in pseudorandom order (Figure 4). Each picture appeared on the computer screen for 1000 ms followed by a 1000 ms inter-stimulus interval. After each picture, participants were prompted to rate the valence of the image on a nine-item self-assessment manikin (SAM) valence scale (1=negative, 5=neutral, 9=positive). Immediately after, participants were prompted to rate the arousability of the image on a nine-item SAM arousal scale (1=no arousal, 9=highly arousing). Ratings were entered using numbers on a keyboard without any time limit. Importantly, participants were not informed that memory for the pictures would be subsequently tested. For this reason, each participant could only participate in one condition so that the unanticipated memory test could be preserved.

During Recognition, which occurred 12 hours later, participants were shown 180 pictures: the 60 images from Encoding (targets) intermixed with 120 novel pictures (foils; 60 neutral and 60 negative). Pictures were displayed for 1000 ms, and participants again rated each for valence and arousal and indicated whether they had seen each picture during Session 1 by pressing “Y” for yes and “N” for no.

#### **4. Polysomnography**

Polysomnography was recorded in the Sleep condition participants (20 TBI, 20 non-TBI) in participants’ homes using the Aura PSG ambulatory system (Grass Technologies). Electrodes were applied after completion of the Encoding phase. The electrode montage

included two EOG (electrooculogram; right and left ocular canthi), two chin EMG, and six cortical EEG leads (O1, O2, C3, C4, F3, F4), with all channels referenced to the contralateral mastoid. Recordings were obtained and scored according to the specifications provided by the American Academy of Sleep Medicine (Silber, Ancoli-Israel, & Bonnet, 2007). Due to equipment failure and failure of participants to initiate PSG devices prior to sleep, sleep physiology results are based on 14 participants in the non-TBI group and 16 in the TBI group.

## **5. Data analysis**

Statistical analyses were performed on SPSS 22 Software (IBM, Armonk, NY).

Participants' individual valence ratings of the pictures were used to categorize each stimulus for analyses (Baran et al., 2012; Jones et al., 2016; St. Jacques, Dolcos, & Cabeza, 2009). Targets were categorized based on ratings during the Encoding phase and foils were categorized based on ratings during the Recognition phase. Negative and neutral pictures were defined as those rated 1-3 and 4-6, respectively. Therefore, the number of items in each emotion category (negative, neutral) varied across participants. Participants were excluded from analyses if they had fewer than 10 negative or neutral targets ( $n=3$ ; 2 non-TBI and 1 TBI). On average, participants rated  $29.5 \pm 8.5$  images as neutral and  $21.2 \pm 4.9$  as negative. These numbers did not differ between groups or conditions ( $p$ -values  $> .29$ ).

Hit Rate (HR) was defined as the percentage of target pictures correctly identified as previously seen. False Alarms (FA) were defined as the percentage of foils that

participants indicated as having been seen before. Finally,  $d'$  (recognition memory discriminability) was calculated from these measures (reported in supplemental material). Corrected recognition (CR; HR-FA) was used as the main outcome measure, and  $d'$  was used as a supplementary outcome measure.

Changes in valence ( $\Delta$ Valence) and arousal ( $\Delta$ Arousal) ratings were calculated separately for negative and neutral target pictures. Specifically:  $\Delta$ Valence = Session 2 mean valence rating – Session 1 mean valence rating;  $\Delta$ Arousal = Session 2 mean arousal rating – Session 1 mean arousal rating. Thus, a positive  $\Delta$ Valence score for a negative picture indicates a decrease of the initial negative reaction (toward neutrality). A positive  $\Delta$ Arousal score indicates an increase in arousal from the first to the second session. All arousal data is reported in the attached supplemental material.

Comparisons of means were conducted using two-way Analyses of Covariance (ANCOVAs). Group (TBI vs. non-TBI) and Condition (Sleep vs. Wake) were entered as predictor variables. The outcome variables were those calculated for memory, arousal, and valence (described above). Analyses were performed for neutral and negative emotions separately, resulting in 6 total ANCOVA tests. PSQI scores and gender were entered as covariates (Baran et al., 2012). Post-hoc comparisons were conducted using planned comparisons when significant interactions between groups were present.

Where behavioral differences were found between groups, we used a linear regression to identify whether head injury factors, sleep characteristics, or both predicted behavioral



outcomes in the TBI population. In the first step of the model, we entered head injury factors: number of TBIs, time since most recent TBI (yrs), and number of symptoms post-TBI. In the second step, we entered sleep factors: total sleep time, percent of the night in non-REM sleep stage 2 (N2), percent of the night in slow wave sleep (SWS), and percent of the night in rapid eye movement (REM) sleep. These three sleep stages were included given that N2 and, more so, SWS have been implicated in sleep-dependent declarative memory consolidation (Baran et al., 2016; Gais & Born, 2004; Mantua et al., 2015; Schabus et al., 2004) and, more recently, emotional memory consolidation (Benedict, Scheller, Rose-John, Born, & Marshall, 2009; Cairney, Durrant, Hulleman, & Lewis, 2014; Groch et al., 2011; Payne et al., 2015). REM has also been implicated in sleep-dependent emotional processing (Bengi Baran et al., 2012; Vandekerckhove & Cluydts, 2010; Walker & van der Helm, 2009). For the ANOVA analyses, the whole sample, excluding outliers, was included. However, for the follow-up regressions, only participants with PSG were used.

When calculating descriptive statistics, a chi-square test was used to compare categorical variables (e.g., gender) between groups, and independent-sample t-tests were used to compare continuous variables. Multivariate outliers were identified and removed using Cook's Distance with a cutoff of  $4/n$  ( $n=2$ ). Univariate outliers were identified and removed using the Median Absolute Deviation (MAD) method with a moderate cutoff criterion (median  $\pm 2.5 \times$  MAD). In the case of univariate outliers, individuals who were an outlier in one domain (e.g., memory) were not removed entirely but were removed only from that specific analysis. Therefore, when including multivariate outliers

and those removed for having fewer than 10 negative or neutral targets (discussed above), there were 6 participants without memory data, 5 participants without valence data, and 7 participants without arousal data.

## **C. Results**

### **1. Demographic information**

Demographic information is listed in Table 1. TBI and non-TBI groups did not differ in age, years of education, or gender. Similarly, participants assigned to Sleep and Wake conditions did not differ in age, years of education, or gender. Notably, there was a large proportion of female participants in this sample, representative of a typical psychology undergraduate program from which the sample was drawn.

TBI and non-TBI participants did not differ in terms of MEQ, ESS, SSS1 or SSS2 scores. However, consistent with previous work (Gosselin et al., 2009; Grima et al., 2016; Shekleton et al., 2010), the TBI group had marginally higher PSQI scores, which was driven by a significant difference in the sleep latency component of the scale (time to fall asleep; non-TBI = 1.42, TBI = 2.1;  $t(78) = 2.57, p=.01$ ). The Sleep and Wake conditions did not differ based on MEQ, SSS2, or ESS scores. However, the Wake conditions had higher SSS1 scores, indicating the Wake participants were sleepier during Session 1 (which was a morning session) than the Sleep participants (for whom Session 1 was an evening session). These results are consistent with work showing high sleepiness in young adults in the morning due to a circadian phase delay (Millman, 2005). For this

reason, SSSI scores were included as a covariate in all analyses. Finally, participants in the non-TBI and TBI groups did not differ in Digit Span performance, indicating no difference in working memory abilities.

Given that PSG data of several individuals were not available in the analyses (as previously discussed), we conducted an additional set of analyses without such participants. Demographic results were unchanged.

## **2. Head injury characteristics**

The average time since the most recent concussion in the TBI group was  $3.7 \pm 2.9$  yrs. Concussions were sustained from a sports-related injury (68%), fall (17%), car accident (8%), or by other means (6%). No concussions were sustained in a combat-related situation. Participants had an average of  $4.5 \pm 1.2$  symptoms following concussion. As indicated in Table 2, the prevalence of loss of consciousness and post-traumatic amnesia were fairly low, indicating this sample was on the “minor” end of the mTBI spectrum. Sleep and Wake TBI groups did not differ on number of TBIs, time since TBI, and number of symptoms experienced after TBI.

## **3. Sleep architecture**

Sleep characteristics are listed in Table 3. There were no differences between the TBI and non-TBI Sleep groups for total sleep time, sleep efficiency, or time spent awake after sleep onset. There was a marginal difference for sleep latency, such that the TBI group

had longer sleep latency than did the non-TBI group ( $t(19.3)=1.85$ ,  $p=.08$  when adjusting for homogeneity of variance). The TBI group also had significantly longer REM latency ( $t(28)=2.37$ ,  $p=.02$ ). There were no significant differences between the percent of the night groups spent in N1, N2, or SWS. However, the TBI group had significantly less REM than the non-TBI group ( $t(28)=-2.7$ ,  $p=.01$ ).

#### **4. Baseline ratings of stimuli**

An ANCOVA test was used to probe whether there were differences in baseline ratings of valence between groups and conditions. For valence of neutral images, there was no main effect of Injury Group ( $F(1,67)=.78$ ;  $p=.38$ ), no main effect of Condition ( $F(1,67)=1.67$ ;  $p=.20$ ), and no interaction between factors ( $F(1,67)=.72$ ;  $p=.40$ ). Similarly, for negative valence, there was no main effect of Injury Group ( $F(1,67)=2.34$ ;  $p=.13$ ), no main effect of Condition ( $F(1,67)=.27$ ;  $p=.60$ ), and no interaction between factors ( $F(1,67)=2.4$ ;  $p=.12$ ).

#### **5. Memory accuracy**

Memory was assessed following an interval including sleep or wake. ANCOVA analyses were used to separately gauge memory performance (CR) for negative and neutral stimuli. For neutral stimuli, we identified a main effect of Condition ( $F(1,66)=6.64$ ;  $p=.03$ ), such that the Sleep condition had significantly higher CR than the Wake condition. There was no main effect of Injury Group ( $F(1,66)=1.63$ ;  $p=.20$ ) and no interaction between these two factors ( $F(1,66)=.05$ ,  $p=.83$ ), indicating that the TBI group did not have a detectable deficit in sleep-dependent memory consolidation of neutral

stimuli.

For negative stimuli, there was no main effect of Condition ( $F(1,66)=.90$ ;  $p=.32$ ) and no main effect of Injury Group ( $F(1,66)=.009$ ;  $p=.92$ ) for CR. However, there was a significant interaction between these factors ( $F(1,66)=9.04$ ,  $p<.01$ ). As shown in Figure 5, the non-TBI Sleep condition performed significantly better than the non-TBI Wake condition ( $F(1,66)=4.30$ ;  $p=.04$ ), but the TBI Sleep and Wake conditions did not differ ( $F(1,66)=.46$ ;  $p=.49$ ).

The TBI Sleep group had significantly reduced CR for negative stimuli relative to the non-TBI Sleep group ( $F(1,66)=4.27$ ;  $p=.04$ ). We therefore examined whether differences in FA or HR accounted for this difference. We found the TBI Sleep group had notably (but non-significantly) higher FA than the non-TBI Sleep group ( $F(1,66)=2.5$ ,  $p=.11$ ). There was also a marginally significant reduction in HR in the TBI Sleep group relative to the non-TBI Sleep group ( $F(1,66)=2.85$ ;  $p=.09$ ).

Interestingly, the lack of differentiation in CR between the TBI Sleep and TBI Wake groups also was influenced by alterations in memory processing in the TBI Wake group relative to the non-TBI Wake group. The TBI Wake group had strikingly lower FA than the non-TBI Wake group ( $F(1,66)=10.87$ ;  $p<.01$ ; Figure 5). A reduction in FA in this group rendered CR scores higher, thus limiting differentiation from the TBI Sleep group for that measure. On the other hand, there was no difference in HR between the non-TBI and TBI Wake groups ( $F(1,66)=.05$ ;  $p=.82$ ). Taking these findings with those above, both

the TBI Sleep and TBI Wake groups had irregularities in FA such that the TBI Wake group performed better than the control group and the TBI Sleep group performed worse than the control group.

## 6. Valence

We next used an ANCOVA to examine whether there were differences between groups or conditions for  $\Delta$ Valence (Table 4). When examining the neutral images, we found no main effect of Injury Group ( $F(1,67)=.519$ ;  $p=.47$ ), no main effect of Condition ( $F(1,67)=.13$ ;  $p=.71$ ) and no interaction between factors ( $F(1,67)=.10$ ;  $p=.75$ ).

However, when examining  $\Delta$ Valence for negative images, we found a main effect of injury group ( $F(1,66)=7.89$ ;  $p<.01$ ) such that the non-TBI group had an overall higher change in the positive direction (toward neutrality). There was no main effect of Condition ( $F(1,66)=1.37$ ;  $p=.25$ ), but there was a significant interaction between factors ( $F(1,66)=4.84$ ;  $p=.03$ ). As shown in Figure 6, consistent with our previous results (Bengi Baran et al., 2012), post-hoc simple effect analyses showed the non-TBI Wake group had a significantly higher  $\Delta$ Valence (became more neutral;  $F(1,66)=6.82$ ;  $p=.01$ ), yet negative valence was relatively preserved for the non-TBI Sleep group. On the other hand, there was no significant difference between TBI Sleep and Wake conditions for change in valence ( $F(1,66)=.40$ ;  $p=.53$ ). As shown in Figure 6, this similarity is present because there is no habituation (i.e., movement in the neutral direction) in the TBI Wake condition.

## 7. Assessing factors predicting emotional processing deficits

Where behavioral differences between Injury Groups and Conditions were detected, we conducted linear regressions to identify which factors predicted behavioral abnormalities in the TBI group. It is notable that the following regressions had relatively low achieved power (ranging from .12 to .40) due to small sample size and a high number of predictors. Therefore, rejecting predictors based on these analyses is preliminary.

We first probed whether clinical measures or sleep characteristics predicted reduced sleep-dependent memory consolidation. We used regressions to predict two measures: CR and FA. For CR, in the first step of the model, number of TBIs significantly predicted sleep-dependent emotional memory consolidation, such that more concussions predicted poorer memory consolidation ( $B = -.14$ ,  $p = .02$ ). Time since most recent TBI and number of symptoms did not predict consolidation ( $p > .3$ ).  $R^2$  was low (.34) and the model was not significant ( $F(3,17) = 2.37$ ,  $p = .11$ ). Sleep characteristics were then added to the model. None of the sleep characteristics significantly predicted memory consolidation ( $p > .27$ ). Although the  $R^2$  value increased (.55), the model remained not significant ( $F(7,17) = 1.39$ ,  $p = .31$ ). Number of TBIs was no longer a significant predictor of memory consolidation, nor were the other clinical measures ( $p > .32$ ).

Notably, as mentioned above, there was an unexpected reduction in FA in the TBI Wake group for both negative and neutral stimuli. Therefore, head injury factors were used to examine potential changes in the Wake group (sleep characteristics were not available in this group). Given the similarity in pattern between FA for negative and neutral stimuli,

these measures were combined (FA negative + FA neutral). None of the aforementioned head injury factors predicted this combined FA score ( $p_s > .30$ ;  $R^2 = .09$ ).

For FA in the TBI Sleep Group, in the first step of the model, we found number of TBIs was a significant predictor of FA, such that more TBIs predicted a higher rate of FA ( $B=.05$ ,  $p=.03$ ). The other clinical predictors were not significant ( $p$ -values  $> .7$ ). The overall model had a low  $R^2$  (.32) and was not significant ( $F(3,17)=2.3$ ,  $p=.12$ ). When the sleep characteristics were added to the model, number of TBIs remained significant ( $B=.06$ ,  $p=.02$ ) while the other head injury factors did not. Additionally, FA was predicted by the percent of the night in N2 ( $B=-.03$ ,  $p=.02$ , change in  $R^2 = .02$ ), SWS ( $B=-.04$ ,  $p=.02$ , change in  $R^2 = .14$ ), and marginally so by REM ( $B=-.02$ ,  $p=.07$ , change in  $R^2 = .13$ ), such that less time in each sleep stage predicted a higher number of FA. Neither total sleep time ( $p=.55$ ) nor REM latency ( $p=.98$ ) predicted FA.  $R^2$  was improved by the addition of the sleep characteristics (.64), and the model neared significance ( $F(7,17)=2.6$ ,  $p=.08$ , change in  $R^2 = .32$ ).

When examining valence, we performed a similar linear regression to identify factors predicting the wake-dependent differences identified above. We tested whether clinical injury outcomes predicted  $\Delta$ Valence in the TBI Wake group. Similar to what was found for memory accuracy, number of TBIs significantly predicted  $\Delta$ Valence, such that individuals with a higher number of TBIs had a lower (more negative)  $\Delta$ Valence ( $B=-.2$ ,  $p=.04$ ). Time since most recent TBI and number of symptoms did not predict  $\Delta$ Valence ( $p_s > .17$ ).  $R^2$  was low (.27) and the model was not significant overall ( $F(3,19)=2.04$ ,



p=.14).

## **8. The influence of multiple TBIs**

Notably, as our results show, the link between the number of TBIs an individual has sustained and their emotional processing is robust. Given this, we re-performed the initial ANCOVA tests using only individuals who had sustained 1 concussion to ensure that individuals with multiple concussions were not driving these results. For memory measures (HR, FA, CR,  $d'$ ), results were nearly identical (HR interaction:  $p<.01$ ; FA main effect of condition:  $p=.04$ ; FA interaction:  $p<.01$ ; CR main effect of condition:  $p<.01$ ; CR interaction:  $p<.01$ ;  $d'$  main effect of condition  $p<.01$ ;  $d'$  interaction:  $p<.01$ ). The  $\Delta$ Valence results were also maintained (main effect of group:  $p=.04$ ; interaction:  $p<.01$ ). Overall, these results indicate that a single concussion produces the emotional deficits discussed above, yet multiple concussions worsen emotional outcome.

## **D. Discussion**

### **1. Sleep quality and architecture in chronic TBI**

Individuals with a history of TBI had marginally higher PSQI scores (i.e., poorer sleep quality) than control participants, in line with several other investigations (Gosselin et al., 2009; Grima et al., 2016; Shekleton et al., 2010). In the current sample, the difference in PSQI scores was mainly driven by the sleep latency component of the scale, which queries how long it takes the individual to fall asleep. Participants with a history of TBI reported significantly longer sleep latency. The TBI group also had marginally longer

objectively measured sleep latency (PSG). Our results support and add to others' findings that subjective sleep quality is poorer several years after a concussion has occurred.

In the current sample, individuals with a history of TBI spent a significantly lower proportion of the night in REM than the non-TBI group. This finding is consistent with a recent meta-analysis that aggregated 9 studies to compare sleep architecture between participants with a history of TBI and healthy controls (Grima et al., 2016). The meta-analysis found no differences between groups for time spent in SWS, N1 and N2, yet the TBI individuals had marginally less REM sleep than healthy controls. Reduced REM, in chronic TBI may be the result of a reduction in melatonin production. (Shekleton et al., 2010) As such, reduced REM seems to be a prominent following chronic, mild TBI.

The TBI group also had significantly longer REM latency than the non-TBI group, similar to what others have reported (Arbour et al., 2015). Interestingly, longer REM latency has been identified in individuals with PTSD (Cowdin, Kobayashi, & Mellman, 2014), and REM latency alterations are a well-established biomarker of major depressive disorder (Giles, Biggs, Rush, & Roffwarg, 1988). It is possible that longer REM latency is a marker of having had a concussion. However, the meta-analysis described above does not support this hypothesis, as no differences in REM latency were found between aggregated TBI and non-TBI groups in that investigation (Grima et al., 2016).

Alternatively, the TBI individuals could be experiencing a TBI-induced circadian rhythm delay (Ayalon, Borodkin, Dishon, Kanety, & Dagan, 2007), which could delay REM onset.

## **2. Emotional memory consolidation in chronic TBI**

We found a specific deficit in the consolidation of negative emotional stimuli in individuals with a history of TBI. It is possible that hippocampal injury that occurs during TBI (Lowenstein, Thomas, Smith, & McIntosh, 1992; Warriner & Velikonja, 2006) is the primary cause of reduced consolidation, but this seems unlikely given that consolidation of neutral stimuli is preserved in the TBI population. Alternatively, hippocampal damage may lead to the disruption of the structurally linked limbic system, which modulates emotional processing (LeDoux, 1993). It is also possible that prolonged frontal lobe damage disrupts downstream emotional processing via disrupted communication with and inhibition of the amygdala. Further work to probe these hypotheses using functional imaging is warranted.

In the TBI group, memory consolidation was affected by lower FA in the TBI Wake group and higher FA in the TBI Sleep group. We probed whether clinical injury factors and sleep characteristics predicted FA rate. For the TBI Wake group, we did not identify any factors predicting FA. However, in the TBI Sleep group, we found individuals with a history of more TBIs had a higher rate of FA. We also found the percent of the night in N2 and SWS significantly predicted FA, such that more time in these stages predicted lower rates of FA. REM marginally predicted FA in the same manner. Importantly, total sleep time did not predict FA, suggesting an active contribution of each sleep stage rather than a passive effect of sleep (i.e., a lack of interference caused by less wake time). We propose the dearth of REM in this population contributed to reduced memory consolidation (discussed further below).

In our sample, the TBI Wake group unexpectedly had low FA rates but normal HR rates relative to non-TBI Wake participants. Interestingly, these data are consistent with work demonstrating patients with moderate to severe head injury respond with fewer errors during a reaction time task (Battistone, Woltz, & Clark, 2008) and during a memory recognition task (Brooks, 1974, 1975). The author of these studies suggested that reduced errors may have resulted from either a general increase in hesitancy or a failure to encode. Although assessing the former hypothesis is beyond the scope of this study, we do not feel the latter hypothesis to be true. Specifically, if TBI-related encoding deficits were the sole mechanism underlying reductions in FA, we would expect the TBI Sleep group to also have low FA. However, the TBI Sleep group had marginally higher FA than the non-TBI Sleep group. This leads us to believe either (1) encoding deficits are not responsible for lower FA in the TBI Wake group, or (2) poor encoding indeed affected FA in all TBI subjects, but the TBI Sleep group experienced additional, unrelated interference, which led to an increase in FA. We believe the latter to be the case.

We propose that inefficient or incomplete reorganization of memory during sleep may have resulted in higher FA in the TBI Sleep group. According to the synaptic homeostasis hypothesis, global downscaling of synapses during sleep (namely SWS) eliminates weak synaptic connections while strengthening stronger connections (Tononi & Cirelli, 2003). An incomplete downscaling could leave weaker connections in place, increasing interference and decreasing the signal-to-noise ratio. TBI induces deficiencies in synaptic function and plasticity (via oxidative stress; Ansari, Roberts, & Scheff, 2008), and it is possible that lingering synaptic damage hinders the downscaling process. Yet it

must be stressed that neutral sleep-dependent consolidation is intact in the TBI population, and consolidation deficits must therefore be emotion dependent. Given this, our results cannot be fully explained by this hypothesis.

Separately, it has been proposed that efficient sleep-dependent memory processing depends on both REM and non-REM episodes (Grosmark, Mizuseki, Pastalkova, Diba, & Buzsáki, 2012). That is, sleep-dependent consolidation is optimized when both non-REM and REM are present and also sequential (Diekelmann & Born, 2010; Ficca, Lombardo, Rossi, & Salzarulo, 2000; Sonni & Spencer, 2015). The delay in REM onset and general reduction in REM in this sample may have hindered consolidation by reducing such REM/non-REM interactions. Relatedly, it has long been proposed that amygdala activation during REM is critical for sleep-dependent emotional processing (McGaugh, 2004). Recent evidence suggests activation of the amygdala occurs predominantly after rapid eye movement bursts during REM sleep (Corsi-Cabrera et al., 2016). Thus, a reduction in REM should limit amygdala activation, reducing the sleep-dependent ‘boost’ for emotional stimuli.

An interesting alternative hypothesis regarding low FA in the TBI Wake group comes from emerging work suggesting brain injury causes sleep and wake to become less dissociated. Specifically, a recent study found more “microsleep” bouts (i.e., spontaneous slow waves) occur during wake following mild TBI than controls (in both mice and humans, with humans being ~5 years post-injury; Modarres, Kuzma, Kretzmer, Pack, & Lim, 2016). The authors suggested that sleep-wake states are blurred following TBI, even

years after injury. Given the unexpected decrease in FA observed in the TBI Wake group, it is possible that spontaneous slow wave activity during the day facilitated consolidation, which manifested as lower FA.

### **3. Emotional valence changes in chronic TBI**

The TBI and non-TBI groups did not exhibit differences in baseline valence ratings of either emotional or non-emotional stimuli. This is counter to what we would expect, as an increased risk for mood disturbances could alter initial ratings of stimuli. Nevertheless, groups differed in terms of  $\Delta$ Valence. In the control group, we replicated our previous results (Baran et al., 2012; Jones et al., 2016) that showed sleep significantly preserves valence ratings (i.e., maintains negativity) relative to a period spent awake. That is to say, the Wake group experiences desensitization or habituation to negative images, but the Sleep group does not. In comparison, we unexpectedly found that although the TBI Sleep group preserved negativity, the TBI Wake group did as well. Therefore, both the TBI Sleep and the TBI Wake groups found the negative images to be almost as negative at the second presentation.

These results are compatible with current theories of depression development and maintenance. Depressive thoughts arise and are perpetuated when an individual is unable to use proper emotional regulation strategies (e.g., suppression, reappraisal) to habituate when emotional experiences occur (Teasdale, 1988). In the current sample, a failure to habituate to negative stimuli during a waking period might suggest a prolongation of negative information processing, which could ultimately maintain negative thoughts and

facilitate depression. Clinical populations that have experienced trauma, such as individuals with Borderline Personality Disorder and Post Traumatic Stress Disorder, show a similar lack of habituation over a waking period (Hazlett et al., 2012; Hendler, Rotshtein, & Hadar, 2001). Therefore, a lack of habituation may either be a ‘marker’ of brain circuitry decrements or simply a reflection of poor mental health. Future work should investigate the effectiveness of emotional regulation strategies in a TBI population relative to uninjured controls.

#### **4. The role of multiple TBIs**

We found number of TBIs to be a significant predictor of memory and  $\Delta$ Valence such that more TBIs predicted (1) poorer sleep-dependent memory consolidation (FA) and (2) a greater preservation of valence. Importantly, we did not find any correlations between  $\Delta$ Valence and memory consolidation, suggesting number of TBIs was separately predictive of emotional deficits for valence and memory. These findings indicate individuals who have sustained multiple concussions have poorer emotional processing during sleep, during a waking period, and overall.

These data are consistent with a broad range of literature showing individuals with multiple concussions have poorer recovery outcomes than individuals with no concussions or one concussion. For instance, active duty military members with multiple concussions were found to have greater ongoing emotional distress (e.g., PTSD, depression, anger symptoms) than military members with no concussions or one concussion (Spira, Lathan, Bleiberg, & Tsao, 2014). Athletes with a history of 2 or more

concussions demonstrated significant cognition and sleep changes relative to individuals with no concussions or one concussion (Schatz, Moser, Covassin, & Karpf, 2011), and in a similar population, number of concussions predicted the incidence for depression (Guskiewicz et al., 2007). Our findings add to this growing body of literature by demonstrating one concussion, relative to none, worsens emotional functioning, but more concussions produce more severe emotional dysfunction.

### **5. Strengths and limitations**

There are several limitations to the current study that must be addressed. First, there are no clinical outcome measures (e.g., depression and anxiety symptomology questionnaires) available. We are therefore limited in drawing conclusions about how the sleep- and wake-dependent alterations exhibited in this population contribute to negative mental health outcomes or whether sleep- and wake-dependent alterations mediate the relationship between TBI and poor emotional outcomes. Furthermore, this study did not include physiological measurements of arousal (e.g., skin conductance). However, we feel that our measures of self-rated arousal are accurate and valid, as our participant ratings of arousal are similar to those found with this same stimuli set (Baran et al., 2012; Jones et al., 2016). Nevertheless, future work could include physiological measurements in order to draw more complex conclusions about which mechanisms are disrupted in this population.

Previous work has demonstrated medications may impact both emotional functioning and sleep staging. For instance, anti-depressants impact valence perception (Rizvi et al.,



2013). In the current study, we screened against individuals with an active psychiatric disorder (self-reportedly). Given this, we did not include individuals taking anti-depressants. Additionally, over-the-counter antihistamines have been shown to impact the percentage of REM sleep. According to the PSQI, two participants in the TBI Sleep group and three participants in the non-TBI sleep group reported using over-the-counter sleep aids within the last month. However, we are unaware whether participants used over-the-counter antihistamines, which increase REM latency and reduce REM (Boyle, Eriksson, Stanley, Fujita, & Kumagi, 2006), during the day of testing. If a greater proportion of TBI individuals were on antihistamine medication during the day of testing, sleep architecture could have been impacted.

Finally, the use of a retrospective study design with self-reported TBI comes with limitations. If participants incorrectly recalled details (e.g., regarding post-concussive symptoms), error variance may have been added to the sample, thereby creating null effects when they are not present. Furthermore, without a formal TBI diagnosis, we are limited in our ability to draw conclusions about injury location or whether participants had complicated mTBI, which is usually identified with MRI. Ideally, future work could utilize longitudinal data following specific populations (e.g., student athletes) before and after brain injury.

Despite these limitations, this investigation also has substantial strengths. This study included a large clinical sample with a range of TBI characteristics (e.g., time since TBI, symptoms following TBI). Moreover, the TBI population in this sample was recruited

within a university setting, and participants were not aware of the hypotheses of the study before participating. That is, this sample was not comprised of individuals with sleep or emotional complaints, but rather it contained community-dwelling, high-functioning individuals. Given this, we can conclude that our study detected sleep- and wake-dependent emotional deficits in a “high functioning” mild TBI population who have seemingly recovered normally. Finally, we included individuals who have suffered from multiple concussions, allowing us to observe how repeated brain injuries affect sleep- and wake-dependent emotional processing.

## **6. Conclusions**

Mild TBI is a major public health issue for a wide range of individuals – from the football field to the battlefield. Individuals who have sustained a concussion are often plagued with both emotional issues and sleep problems. Importantly, healthy sleep-dependent emotional processing is posited to contribute to emotional health. We therefore aimed to test whether chronic sleep issues in a TBI population had an effect on sleep-dependent emotional processing. This study is the first to detect specific sleep-dependent emotional deficits (e.g., reductions in memory consolidation) in a TBI population. Given the purported role of emotional memory consolidation in emotional health, this study provides a viable link between poor sleep and mental health in individuals with a history of chronic, mild TBI.

Table 3.1: Participant demographics.

	Non-TBI (n = 41)	TBI (n = 40)	p- value	Sleep (n = 41)	Wake (n = 40)	p- value
Age (yrs)	20.15±1.18	19.87±1.5	.37	19.82±1.04	20.2±1.6	.22
Education (yrs)	14.85±1.25	14.53±1.28	.27	14.6±1.2	14.77±1.34	.56
Gender (%F)	70.0	75.6	.37	68.3	77.5	.24
MEQ	44.82±8.11	44.91±9.3	.96	46.07±8.85	43.6±8.41	.20
ESS	8.35±3.56	8±3.72	.66	8.06±3.6	8.29±3.69	.75
SSS1	2.8±1.38	3.17±1.08	.18	2.68±1.03	3.3±1.37	<b>.02</b>
SSS2	2.65±1.57	2.42±1.37	.49	2.68±1.33	2.38±1.61	.36
PSQI	4.97±2.52	5.87±1.97	.08	5.56±2.33	5.28±2.28	.59
Digit Span	9.4±2.2	10.3±2.6	.11	10.0±2.1	9.7±2.7	.64
Time since TBI (yr)	---	---		4.32±2.97	3.19±2.77	.21
Concussions (#)	---	---		1.55±1.05	1.73±1.33	.62

MEQ = Morningness-Eveningness Questionnaire; ESS = Epworth Sleepiness Scale;

SSS1 and SSS2 = Stanford Sleepiness Scale at Sessions 1 and 2; PSQI = Pittsburgh Sleep

Quality Index; bold indicates p-value < .05.

Table 3.2: Concussion parameters.

Symptom	Sleep (n = 20)	Wake (n = 20)	p-value
LOC (%)	30.0	38.1	.74
PTA (%)	10.0	4.7	.60
Nausea (%)	50.0	52.4	--
Vomiting (%)	25.0	14.2	.45
Dizziness (%)	80.0	85.7	.69
Headache (%)	100	100	--
Fatigue (%)	95.0	85.7	.60
Concentration (%)	80.0	66.6	.48
Sleep Issues (%)	10.0	28.5	.23
Total symptoms (#)	4.7±1.4	4.4±1.0	.56

LOC = loss of consciousness; PTA = post-traumatic amnesia

Table 3.3: Sleep characteristics.

Sleep Parameter	Non-TBI (n = 14)	TBI (n = 16)	p- value
TST (min)	339.8±61.5	365.8±51.2	.21
Sleep Efficiency (%)	90.2±2.2	88.2±6.2	.25
WASO (min)	26.9±13.1	27.7±15.2	.87
Sleep Latency (min)	10.4±6.2	18.9±17.0	.08
REM Latency (min)	107.6±33.8	141.6±43.2	.02*
N1 (%)	2.4±1.7	2.3±1.9	.89
N2 (%)	54.2±6.9	56.8±7.6	.33
SWS (%)	28.1±7.4	30.1±6.2	.43
REM (%)	15.4±3.7	10.8±5.03	.01*

TST = total sleep time; WASO = wake after sleep onset; N1 = non-REM stage 1; N2 = non-REM stage 2; SWS = slow wave sleep; REM = rapid eye movement sleep; \* = p-value < .05.

Table 3.4: Valence Ratings.

	Non-TBI		TBI	
	Wake	Sleep	Wake	Sleep
Valence (neg)	1.69±0.43	1.94±0.49	1.94±0.46	1.82±0.39
Valence (neu)	4.96±0.15	4.94±0.09	4.97±0.16	5.0±0.13

Neg = negative; neu = neutral

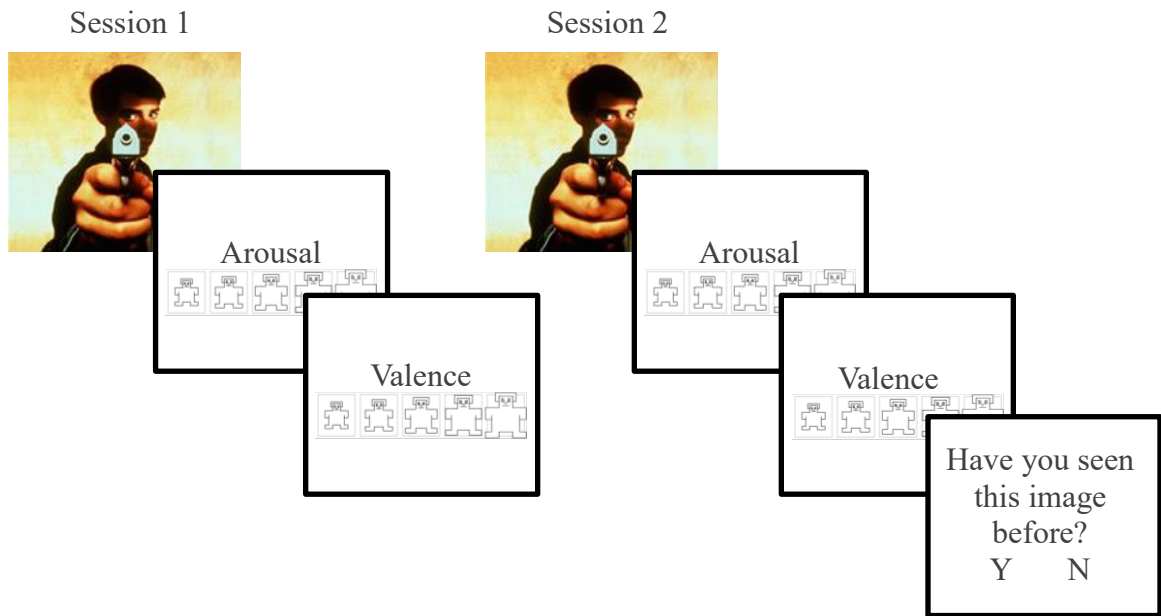


Figure 3.1: Emotional memory consolidation and memory processing task.

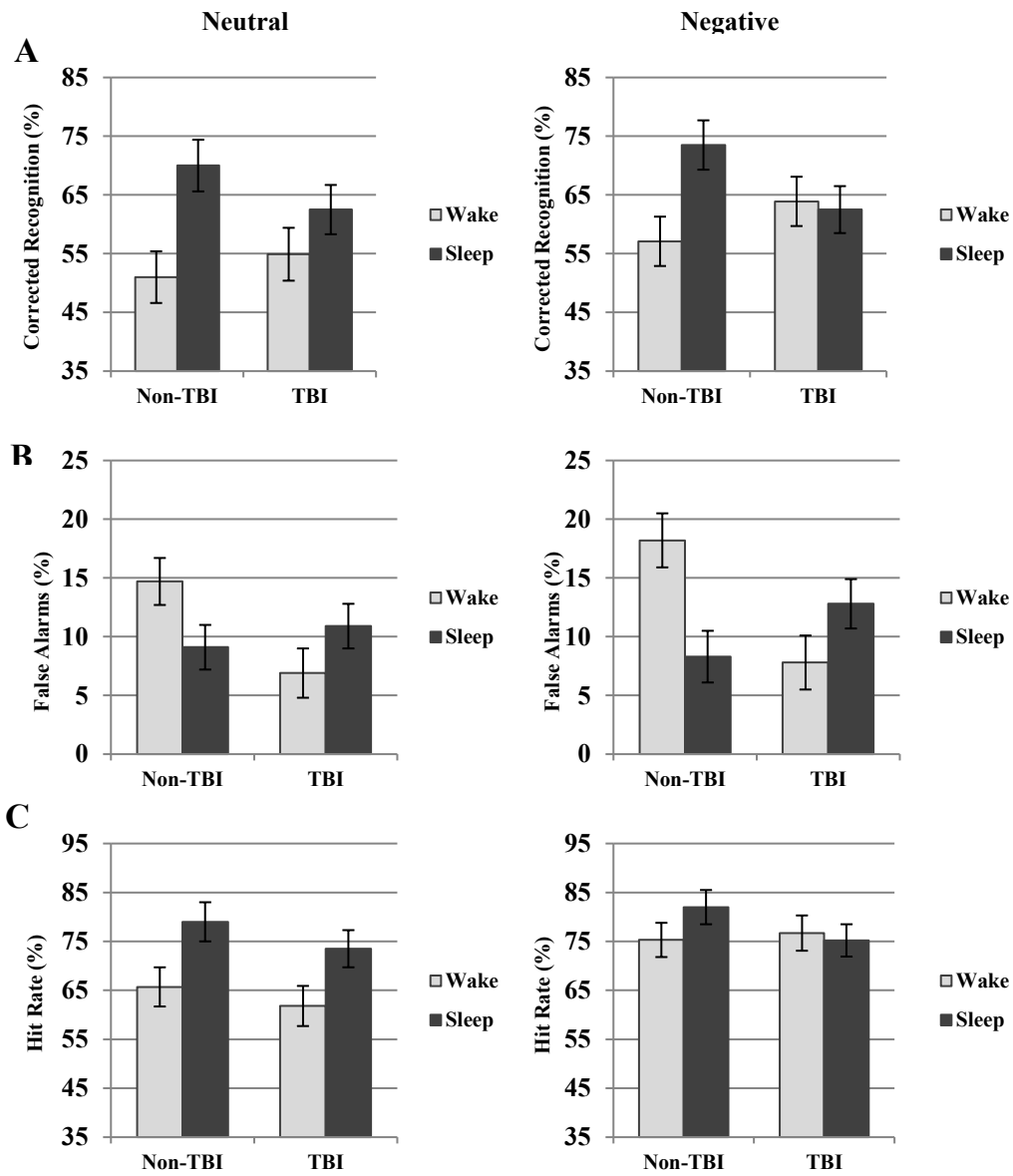


Figure 3.2: Emotional memory consolidation (Panel A: Corrected Recognition; Panel B: False Alarms; Panel C: Hit Rate) for neutral and negative stimuli. Marginal means (not raw values) are plotted.



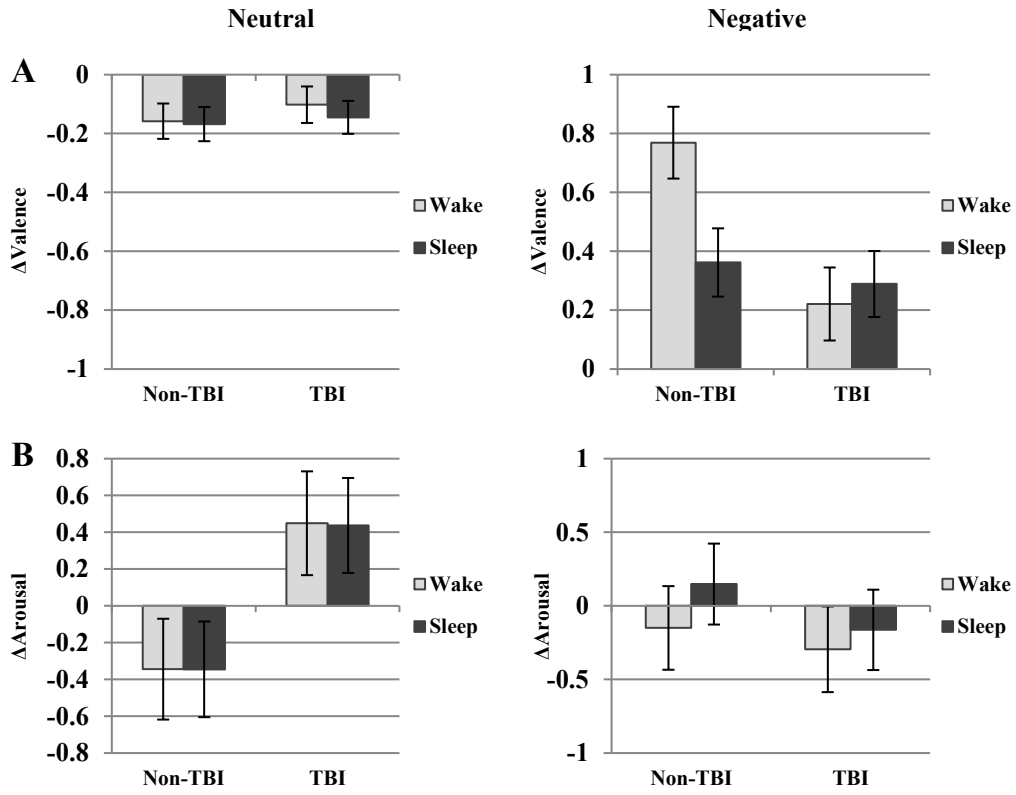


Figure 3.3: Change in valence and arousal for neutral and negative stimuli (Panel A:  $\Delta$ Valence; Panel B:  $\Delta$ Arousal). Marginal means (not raw values) are plotted.

## CHAPTER 4

### EMOTION HABITUATION IN CHRONIC MILD TRAUMATIC BRAIN INJURY

#### A. Introduction

A traumatic brain injury (TBI) is any change in mental status due to a blunt or penetrating force (Silver et al., 2005). In 2003, the Centers for Disease Control and Prevention (CDC) presented a report to the US Congress stating that mTBI is a “silent epidemic,” the prevalence and severity of which are underestimated (Gerberding, 2003). The report calls for an increase in research to identify and evaluate the long-lasting sequelae of mTBI, which hinder quality of life and well-being (Vanderploeg et al., 2007).

#### **1. Mood Disturbances and mTBI**

One of the prominent long-term effects of mTBI is an increased risk for mood disturbances. Depressive symptoms are increased following an mTBI, even in the chronic stages (>1 year since injury). For instance, a recent investigation found 30% of a chronic mTBI sample endorsed clinically relevant depressive symptoms (i.e., Center for Epidemiologic Studies Depression [CESD] Scale scores  $\geq 16$ ) 3-5 years after head injury (Dikmen, Bombardier, MacHamer, Fann, & Temkin, 2004). Comparatively, about 17% of the general population has CESD scores in that range (Comstock & Helsing, 1976). Similarly, six years after injury, subjects with no detectable brain damage had increased depressive symptoms (according to the Beck Depression Inventory) and an increased occurrence of depressive episodes (via the Structured Clinical Interview for the DSM) relative to controls (Konrad et al., 2011). These individuals also had elevated levels of

anxiety, which is highly co-morbid with depression. Finally, a recent large cohort study (>68,000 individuals) found risk for major depression incidence is increased by 1.4 times 6 years after brain injury (Chi et al., 2016).

Despite evidence linking mTBI with mood disturbances, an investigation of emotional processes that are disrupted following mTBI – and might be associated with the increased risk for depression – has not been conducted. There are many known alterations in emotion functioning associated with depression, and, incidentally, we detected one of these alterations in a chronic mTBI population. Specifically, we found emotion habituation might be disrupted following mTBI. The current study will further probe this process through the use of self-reported and physiological measures and will expand the original results by probing (1) emotion reactivity, (2) both negative and positive affect in an mTBI population, and (3) potential circadian influences on emotion ratings.

## **2. Habituation to Emotion in mTBI and Depression**

Emotion habituation, also known as emotion desensitization, plays a critical role in adaptive emotional functioning. According to the original definition outlined by Thomson and Spencer (1966), habituation is a non-associative form of learning that occurs when a neural or behavioral response weakens when the same stimulus is repeatedly presented. Habituation is strongest when the repeated stimuli are themselves not overlapping (i.e., dissimilar in content), and when the presentations of stimuli are close temporally (i.e., presented rapidly). Habituation, which is considered to be the “simplest form of learning,” is adaptive because neural resources need not be wasted on a

stimulus deemed familiar or non-threatening (Wedig, Rauch, Albert, & Wright, 2005). It is hypothesized that habituation occurs because a lack of negative feedback is associated with previous stimulus exposure (Zald, 2003). A disruption to this process, often manifesting as a prolongation of arousal to familiar stimuli, is maladaptive, because it is an inflexible response, and emotion malleability/flexibility is regarded as important for proper emotional functioning (Kuppens, Allen, & Sheeber, 2010). Consequently, clinical treatments that utilize and promote habituation (e.g., exposure therapy; Arntz, Tiesema, & Kindt, 2007) are effective in minimizing psychiatric symptoms.

Neural models implicate both the prefrontal cortex and the amygdala as playing a role in emotion habituation (Wright et al., 2001). The amygdala is highly active in response to an emotional stressor (LeDoux, 1993). On the other hand, the prefrontal cortex provides top-down modulation of amygdalar activity, such that the prefrontal cortex “dampens” amygdala activation in order to lessen perceived emotionality. Given these findings, it has been proposed that dysfunction in the prefrontal cortex may prevent adaptive emotion habituation (Silbersweig et al., 2007). Additionally, a lack of prefrontal cortical efficiency could prevent proper emotion regulation strategies (e.g., reappraisal) from occurring with each subsequent exposure (Schiller & Delgado, 2010). It is possible, then, that populations with improper prefrontal cortex functioning have disrupted emotion habituation.

Indeed, habituation deficiencies have been identified in several clinical populations, all of which exhibit hypo-activity in the prefrontal cortex (Gilboa et al., 2004; Pascual-Leone,

Rubio, Pallardó, & Catalá, 1996; Silbersweig et al., 2007). For instance, patients with Borderline Personality Disorder (BPD) exhibited a prolonged return to baseline amygdalar reactivity (via fMRI) relative to controls after repeatedly viewing negative images (Hazlett et al., 2012), thus demonstrating impaired habituation. Similarly, veterans with post-traumatic stress disorder (PTSD) exhibited less habituation in the visual cortex (Hendler et al., 2001) and in the amygdala (Shin et al., 2005) to negative images relative to a control group matched for combat experience. Finally, individuals with a history of depression showed deficits in self-reported emotion habituation to repeated negative images relative to a never-depressed control group (Neumeister, Henry, Herscovitch, Charney, & Drevets, 2006; Schaefer, Putnam, Benca, & Davidson, 2006).

Emotion habituation may also be disrupted in individuals with a chronic history of mTBI, who are characterized by prefrontal cortex hypo-activation (van der Horn, Liemburg, Aleman, Spikman, & van der Naalt, 2016). In our previous work (**Study 2**), we identified irregularities in emotion measures that may be suggestive of dysfunction in emotion habituation in chronic mTBI (Mantua, Henry, Garskovas, & Spencer, 2017). Participants with and without a history of chronic mTBI were shown 30 highly arousing negative images (from the IAPS picture set, e.g., a bloody human limb) on two occasions, once in the morning and once again in the evening (12 hr later). The control (uninjured) participants rated negative images as less negative (more neutral) during the second viewing session (i.e., demonstrating normative habituation), while those with a chronic history of mTBI in the sleep group rated negative stimuli as equally negative during the second viewing session (Figure 7). Therefore, normative habituation to the negative

stimuli was not observed in the mTBI group. Given that this finding was incidental and participants were not monitored between image exposure sessions (i.e., participants experienced a normal 12 hour waking day between sessions), a more controlled investigation of this phenomenon is warranted in a chronic mTBI population.

### **3. Reactivity to Emotion Stimuli in Depression and mTBI**

Patients with depressive symptoms also have abnormalities in physiological reactivity to emotional stimuli. Physiological reactivity is the instinctive activation of the autonomic nervous system (which is triggered by the amygdala) in an emotionally laden situation (Levenson, 2003). Physiological responses can be gauged using a number of measures, including heart rate deceleration, skin conductance, and facial muscle tone. A meta-analysis, which aggregated findings from eight studies (and included nearly 500 participants) found a robust decrease in physiological reactivity to a range of both positive and negative stimuli (e.g., IAPS pictures, videos) in individuals with major depression (Bylsma, Morris, & Rottenberg, 2008). Interestingly, greater (i.e., normal) physiological reactivity to emotional stimuli predicts a reduction in subsequent depression symptoms (Canli et al., 2005; Rottenberg, Kasch, Gross, & Gotlib, 2002), suggesting blunted emotion reactivity may contribute to depression maintenance.

Similarly, in two recent studies by Good and colleagues (van Noordt & Good, 2011; Baker & Good, 2014), individuals with a chronic history of mTBI had blunted reactivity (via skin conductance measures but not self-reported arousal measures) during the Trier Stress Test (in which individuals must deliver an unrehearsed speech to peers) and during

a challenging cognitive task. Although the control (non-TBI) groups had an increase in skin conductance when stressed, the mTBI groups did not. It has been suggested TBI-induced damage to the prefrontal cortex (i.e., an emotion modulating region) alters emotion reactivity (de Sousa et al., 2010, 2011; van der Horn et al., 2016). As previously mentioned, blunted physiological reactivity may contribute to maintaining depression, and thus it is possible that TBI-induced arousal blunting may contribute to initiating or maintaining depression.

In unpublished analyses from our previous work (**Study 2**), we did not find significant differences in reactivity to emotional stimuli. Specifically, we did not detect differences in valence or arousal ratings to negative or neutral IAPS images between non-TBI and mTBI groups. However, reactivity measures were acquired both in the morning and in the evening. Interestingly, we found near-significant differences in reactivity between mTBI and non-TBI groups in the morning (mTBI mean =  $1.95 \pm .47$ , non-TBI mean =  $1.70 \pm .43$ ;  $F(1,31) = 2.82$ ,  $p = .08$ ), yet no clear differences between groups in the evening (mTBI mean =  $1.82 \pm .39$ ; non-TBI mean =  $1.94 \pm .49$ ;  $F(1,34) = .50$ ,  $p = .48$ ; Figure 7. Although it is difficult to draw conclusions about why these data differ depending on the time-of-day, it is possible that we detected circadian rhythmicity differences between injury groups. The circadian rhythm, which cycles in a predictable manner throughout the night and day, can impact ratings of emotional stimuli: individuals who are “off-peak” tend to rate stimuli as more negative than individuals who are not off-peak (Tucker et al., 2012). Differences in emotion ratings between two groups at the same time might reflect differences in circadian rhythmicity. In other words, although the

non-TBI group was off-peak, the mTBI group may not have been. In effect, emotion ratings differed between groups in the morning. Given that circadian effects on emotion could have implications for treatment of mood disturbances (e.g., for correct temporal placement of a therapy session), identifying whether reactivity differs as a function of time-of-day (and between controls and those with mTBI) is of interest.

#### **4. Positive Emotions**

Individuals with depression have blunted reactivity to both negative and positive emotional stimuli (Bylsma et al., 2008). In addition, many treatments for depression (e.g., behavioral activation therapies) focus on increasing positive affect (Cuijpers, Van Straten, & Warmerdam, 2007). Given this, a study of emotional functioning would be incomplete without the incorporation of a paradigm investigating reactivity and habituation to both negative and positive stimuli following mTBI.

Contemporary models of depression indicate that individuals with more depressive symptoms have lower positive affect than healthy controls (Clark & Watson, 1991; den Hollander-Gijsman, de Beurs, van der Wee, van Rood, & Zitman, 2010). Given this, alterations in habituation and reactivity in response to positive stimuli may be more predictive of depressive symptoms than responses to negative affect. Therefore, the inclusion of a positive condition will be exploratory yet informative. Positive and negative stimuli were separated into two conditions in order to minimize spillover effects. Given that the included physiological measures take, at most, roughly 10 seconds to recover after an emotional image (Dawson, Schell, & Courtney, 2011), we do not feel



that the presentation of the negative images impacted responses to positive imagery, and vice versa.

## **5. The Current Project**

Measuring habituation and reactivity to emotional stimuli provides a dynamic view of emotional processes that might be disrupted in mTBI and may be associated with increased risk for depressive symptoms. In the current study, we will assess emotion reactivity and habituation in individuals with and without a history of chronic mTBI. We will do so by presenting a series of negative and positive highly arousing images. We will gauge initial reactivity to the stimuli, and, by presenting the same images multiple times, we will assess whether reactivity to the stimuli during subsequent presentations is reduced (indicating normative habituation) or whether there is minimal change (indicating habituation dysfunction). We will track both physiological and self-reported measures of emotion. Overall, we aim to (1) assess habituation to repeated emotional stimuli in mTBI relative to controls, (2) determine differences in reactivity to emotional stimuli in mTBI relative to controls and whether reactivity is linked to circadian rhythmicity, and (3) assess whether reactivity and habituation characteristics predict mood symptomatology (e.g., depressive symptoms, anxiety symptoms).

## **6. Significance**

This study will be the first to study two facets of emotional functioning in mTBI – reactivity and habituation – and will include self-reported and physiological measures of emotion for both negative and positive stimuli. These data will provide insight into which

emotional mechanisms are disrupted in this population and will have implications for further research and treatment. For instance, a finding of blunted negative emotion reactivity in mTBI would reaffirm previous findings (Baker & Good, 2014; van Noordt & Good, 2011) and indicate whether reactivity reductions are a biomarker in chronic mTBI. On the other hand, clinically, an indication of poor habituation to negative stimuli would prompt therapy providers to consider mTBI as a factor when a patient is undergoing certain treatments (e.g., exposure therapy) that require systematic and repeated emotion habituation sessions. Reactivity and habituation to positive stimuli have not been studied in this population, and thus our findings will be both novel and informative. For example, preservation of reactivity to positive stimuli might prove useful in psychotherapies that rely on behavioral activation techniques.

## 7. Predictions<sup>1</sup>

Aim 1: Assess habituation to repeated emotional stimuli in mTBI relative to controls  
For behavioral data, as in **Study 2**, we predict there will be no significant differences in arousal ratings of emotional stimuli between the mTBI and non-TBI group. However, we predict the mTBI group will exhibit reductions (i.e., a flattened trajectory) in valence habituation relative to the non-TBI group.

EMG tone often corresponds with valence ratings (Lang, Bradley, & Cuthbert, 1998).

Therefore, we predict EMG to exhibit habituation to emotion to a greater extent in the

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<sup>1</sup> Predictions for positive and negative conditions are assumed to go in the same direction unless otherwise specified (Wright et al., 2001).

non-TBI group relative to the TBI group. We predict the Corrugator muscle will exhibit increased tone to negative stimuli in all participants (Manber, Allen, Burton, & Kaszniak, 2000), yet a flattened habituation slope to repeated negative stimuli in the mTBI group. We predict the Zygomaticus muscle, on the other hand, will exhibit increased tone to positive stimuli in all participants (Manber et al., 2000), yet a flattened habituation slope to repeated positive stimuli in the mTBI group.

Skin conductance often corresponds with self-reported ratings of arousal. Although we do not predict habituation to occur in self-reported measures of arousal, skin conductance is more sensitive to subtle changes in emotion than self-reported measures. We predict skin conductance to exhibit habituation to emotion to a greater extent in the non-TBI group.

Similar to skin conductance, heart rate often corresponds with ratings of arousal, yet this measure is more sensitive to subtle changes in emotion than self-reported measures of emotion. We predict heart rate will decelerate in response to both negative and positive images (Critchley et al., 2005; Hamann, Ely, Hoffman, & Kilts, 2002; Pollatos, Herbert, Matthias, & Schandry, 2007) but deceleration will be less pronounced with each subsequent image exposure (thereby demonstrating habituation).

Aim 2: Determine differences in reactivity to emotion stimuli in mTBI relative to controls and whether reactivity is linked to circadian rhythmicity<sup>2</sup>

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<sup>2</sup> Predictions for reactivity assume a cubic circadian effect in reactivity was detected and used as a control variable.

For reactivity, we predict the Corrugator muscle will exhibit increased tone to negative stimuli (Manber et al., 2000), yet the mTBI group will exhibit less of an increase than the non-TBI group. We predict the Zygomaticus muscle will exhibit increased tone to positive stimuli (Manber et al., 2000), yet the mTBI group will exhibit less of an increase than the non-TBI group. For skin conductance, as in previous work (Baker & Good, 2014; van Noordt & Good, 2011), we predict the mTBI group to have blunted reactivity to emotional stimuli relative to the non-TBI group. Similar to skin conductance, we predict heart rate to exhibit blunted reactivity to emotional stimuli in the mTBI group as compared to the non-TBI group. We predict heart rate will decelerate in response to both negative and positive images (Lang et al., 1998), yet the mTBI group will exhibit less of a decrease than the non-TBI group. Lastly, we believe there will be a rhythmic pattern (with 3 roots/crosses in the horizontal axis) in emotion ratings (negative/positive arousal and valence).

Aim 3: Assess whether reactivity and habituation characteristics predict mood symptomology

We predict reduced habituation (i.e., a shallower slope between the first viewed image and the last viewed image) will predict increased **depressive** symptoms (Bylsma et al., 2008) and reduced reactivity (i.e., more neutral image ratings and physiology during the first image presentation) will predict increased **depressive** symptoms (Bylsma et al., 2008). We also predict reduced habituation will predict increased **anxiety** symptoms (Bradley, Mogg, Falla, & Hamilton, 1998; Hare et al., 2008) and that increased reactivity

will predict increased **anxiety** symptoms (Shah, Klumpp, Angstadt, Nathan, & Phan, 2009).

## **B. Methods**

### **1. Participants**

Ninety young adults (18-30 years) from UMass, Amherst and surrounding communities were recruited for this study using the SONA system or with flyers. Participants were compensated in experimental credit or with monetary payment. Three participants in each group received monetary compensation. Experimental procedures were approved by the University of Massachusetts Amherst Institutional Review Board, and written informed consent was obtained. Procedures were in accordance with the Declaration of Helsinki.

Participants were either in the mTBI (n = 45) or non-TBI group (n = 45). Participants in the mTBI group had a concussion >1 year prior to testing. On the other hand, participants in the non-TBI group never had a concussion. Participants completed a questionnaire with several concussion options: (1) I have definitely had a concussion. It was diagnosed by a physician; (2) I have had a concussion but it was not diagnosed by a physician; (3) I do not know if I have had a concussion; and (4) I have definitely not had a concussion. Individuals endorsing option 2 or 3 were not be invited to participate. We recruited an equal number of males and females in each group because there are known differences in processing of emotion stimuli between genders (Fischer, Rodriguez Mosquera, van Vianen, & Manstead, 2004).

## 2. Procedure

There may be time-of-day effects on reactivity. To test this notion, we sampled participants across the day (9AM-9PM), with roughly 8 participants (~4 non-TBI, ~4 mTBI) sampled each hour (Table 5).

Participants first completed the consent form, questionnaires, and neuropsychological tests (discussed below). Immediately after, participants were equipped with physiology-measuring equipment (also discussed below). Participants then began the behavioral task.

Each participant completed two experimental conditions. One condition comprised negative and neutral images, and the other condition comprised positive and neutral images. Negative and positive conditions were randomly counterbalanced across participants.

Participants viewed 5 blocks of 22 images (15 negative or 15 positive, 7 neutral in each block) from the International Affective Picture System (IAPS), which have been normed for valence (positive – negative) and arousal (calm – exciting/activating; (Lang et al., 1997). The negative images had an average valence of 2.6 and an average arousal of 5.9 (image numbers: 1090, 3530, 6213, 6560, 6830, 8480, 9040, 9102, 9140, 9250, 9403, 9520, 9584, 9911, 9921). The positive images had an average valence of 7.3 and an average arousal of 6.2 (image numbers: 1722, 4659, 4687, 5621, 5629, 8090, 8161, 8185, 8190, 8300, 8370, 8400, 8420, 8501, 8531). The set of neutral images paired with negative images had an average valence of 5.1 and arousal of 2.7 (image numbers: 2190,

5390, 5520, 7090, 7150, 7175, 7550), and the neutral images paired with positive images had an average valence of 5.0 and arousal of 2.9 (image numbers: 7100, 7205, 7211, 7224, 7235, 7705, 7950). Negative and positive images were matched for arousal based on normative data (Lang, Bradley, & Cuthbert, 1997). We chose negative images that were slightly more neutral than those included in **Study 2** so that positive and negative images could be matched for valence (i.e., equidistant from neutral) given that few positive images have a strongly positive valence.

Image timing was based on physiological response time. Each image appeared for 4 seconds, and participants were instructed to not look away from the screen while the image was displayed. After each image is shown, participants rated the image for valence and arousal on a 1-9 Self-Assessment Manikin (SAM) rating scale (Bradley & Lang, 1994). There were 3 seconds between each image (Pace-Schott et al., 2011) before the next image appeared. When each rating was complete, the next block began. Importantly, the same images were used in each block but images were randomly ordered between blocks to minimize order effects. Between blocks, participants reported their mood using an on-screen rating scale (described below); participants also rated their mood before the first exposure and after each subsequent exposure (i.e., set of images).

After a 5-minute break, participants repeated this paradigm viewing 5 blocks of 22 images (15 positive or 15 negative, 7 neutral in each block).

During the entire duration of the experiment (with the exception of questionnaire administration and neuropsychological testing), participants were monitored by a video camera. Participants were asked to not look away from the screen when the stimuli were being presented. A researcher, who was always in the room, confirmed this to be the case, and this was further verified (and facial EMG recordings were confirmed by reviewing the video recordings with a webcam and ADOBE software). If participants failed to keep their eyes on the screen during stimulus presentation, those trials (or participants) would be removed. Each video was reviewed by a research assistant to ensure participants did not look away from the screen prior to making their ratings. Notably, no participants were removed for this reason.

### **3. Questionnaires**

Prior to completing the experiment, participants were asked to fill out the following questionnaires/forms: (1) Pittsburgh Sleep Quality Index (PSQI) to assess and control for differences in habitual sleep patterns (sensitivity of 90% and specificity of 87% in differentiating good from poor sleepers (Buysse et al., 1989); (2) the Beck Depression Inventory-II (BDI-II) to assess depressive symptoms (internal consistency of .9; reliability alpha of .93; (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961; Wang & Gorenstein, 2013); (3) State Trait Anxiety Inventory (STAI) to assess anxiety symptoms (internal consistency of between .86 and .95; (Spielberger, 1987); (4) Rivermead Post Concussion Symptoms Questionnaire items to assess which post-concussive symptoms (e.g., dizziness, headaches) in the last 24 hours (if any; Potter, Leigh, Wade, & Fleminger, 2006), (5) Behavior Rating Inventory of Executive Function (BRIEF) to



assess self-report about executive functioning behaviors (internal consistency alpha of .96 and clinical scales alpha between .72 and .96; (Gioia, Isquith, Guy, & Kenworthy, 2000), (6) Morning/eveningness Questionnaire (MEQ), which can accurately discriminate circadian chronotypes (e.g., morning, intermediate, evening; Horne & Ostberg, 1976), and (7) PTSD Check List (Civilian Version) to assess the presence of PTSD symptoms (Blanchard, Jones-Alexander, Buckley, & Forneris, 1996). After the completion of the behavioral task, participants completed the Dissociative Experiences Scale, which gauges dissociation (reliability alpha of .93; Van IJzendoorn & Schuengel, 1996).

#### **4. Executive Function Tasks**

Participants completed the following neuropsychological tests: (1) The Stroop test to assess response inhibition/reaction time (Stroop, 1935); (2) Delis–Kaplan Executive Function System (D-KEFS) Verbal Fluency to assess letter fluency, category fluency, and category switching (Delis, Kaplan, & Kramer, 2001); and (3) Digit Span Backward to assess working memory ability (Holdnack, Zhou, Larrabee, Millis, & Salthouse, 2011).

#### **5. Physiological Recordings and Data Reduction**

Four physiological signals were recorded throughout the duration of the experiment (with the exception of questionnaire administration and neuropsychological testing): one channel for electrocardiogram (heart rate [HR]), two channels for facial electromyography (EMG, that measure tension in the muscles that control facial expression of emotion), and one channel for skin conductance (SC).

Heart Rate was recorded using ECG100C, ECG Electrocardiogram Amplifier to which is connected a LEAD110S-R and a LEAD110S-W (Red and White Clip 1M TP Shielded Leads) each connected to an EL503 disposable electrodes. One such electrode is attached to the torso over the first intercostal space, and the other is attached below the lowest rib. As in previous work (Cunningham et al., 2014), HR was analyzed in 1-second bins. The 1-second bin prior to stimulus onset was used as a baseline HR. The minimum beats per minute (BPM) from the 4 1-second bins after stimulus onset were subtracted from the baseline BPM, such that deceleration is the maximum deceleration (maximum autonomic response) following stimulus onset (Abercrombie, Chambers, Greischar, & Monticelli, 2008). Therefore, a positive number represents deceleration.

Facial EMG was recorded using the EMG100C Electromyogram Amplifier. Two MEC110C cables with BIOPAC EL254S Ag-AgCl 4-mm TP shielded recording electrodes were attached to the amplifier. Electrodes were filled with CG04 Saline Base Signa Gel, and electrodes were placed on the Corrugator and Zygomaticus muscles (Fridlund & Cacioppo, 1986). EMG tone was calculated based on methods established in previous work (Pace-Schott et al., 2011). EMG muscle tone was integrated over a 250 ms time constant. EMG response to each stimulus was calculated by subtracting the mean signal amplitude in the 4 seconds following stimulus presentation from the 1 second preceding stimulus presentation.

Skin conductance was measured with two disposable BIOPAC EL507 adhesive sensors on the hypothenar surface of the non-dominant hand (10mm apart). ACQ, built-in

BIOPAC software, will be used for SC analyses. As in previous work (Cunningham et al., 2014), tonic SC was filtered through a 0.05 Hz high pass filter to create phasic waveforms. ACQ algorithms detected a change in electrical conductance (P0.02 microSiemens; (Dawson, Schell, & Filion, 2000) within 4s of stimulus presentation. The maximal SC after stimulus presentation will be used for analysis. Skin conductance maximum from the 4 seconds after stimulus onset was subtracted from tonic skin conductance prior to stimulus onset to determine how the stimulus affected autonomic arousal (Cunningham et al., 2014).

Physiological measures were recorded using the MP150 BIOPAC data acquisition unit (BIOPAC Systems, Inc., Goleta, CA) and its AcqKnowledge analysis software with data acquisition performed on a Macintosh. SuperLab 4-triggered square pulse outputs coincided with each stimulus presentation and were transmitted directly to the MP150 using a BIOPAC STP100 optical interface. Square pulse signals acquired synchronously with ongoing recording allowed precise alignment of each stimulus onset with physiological data. Sampling rate was 2000 Hz.

## **6. Subjective Measures of Mood**

Participants rated their mood on 2 scales (positive mood and negative mood) before exposure to the first set of images and after each subsequent exposure set, resulting in 6 total ratings for each emotion stimulus set. Participants rated their current negative and positive mood on a 1-9 scale (1= low; 9 = high).

## 7. Statistical Analyses

Analyses were performed on SPSS 23 software (Armonk, NY). Results are reported as significant if  $p < .01$ . Effect sizes for statistically significant ANCOVA tests are reported as partial-eta squared ( $\eta$ ). Effect sizes for regression tests ( $B$ ) are reported in each respective regression table. When comparing subsamples, rather than reporting  $p$ -values, Cohen's  $d$  effect sizes are reported.

## 8. Preliminary Analyses

Demographic and descriptive differences between the mTBI and non-TBI groups were assessed using independent-sample  $t$ -tests (for continuous variables) and chi-squared tests (for categorical variables). The presence of order effects was examined by comparing reactivity values and habituation slopes using independent-sample  $t$ -tests. If differences in sleep quality, circadian chronotype, executive functioning, or trauma symptoms (i.e., PTSD and dissociation) were detected, those variables were used as covariates. Gender was also used as a covariate in each analysis (Fischer et al., 2004). We planned to use time-of-day as a covariate if circadian differences were found between groups.

The relationship between self-reported reactivity and circadian rhythmicity was tested. Circadian curvature was sought using a cubic regression, which is achieved by cubing the independent variable and conducting a linear regression (Daan & Beersma, 2002; Loudon, Ihara, & Menaker, 1998; Perry, Kirwan, Jessop, & Hunt, 2008). A significant cubic curve in reactivity signifies circadian variation. Although seeking between-subject circadian rhythmicity, relative to a within-person analysis, is not ideal due to increased

error variance, there have been numerous investigations (using a lesser or equal sample size than in the current study) that have detected a cubic curve using this type of analysis (Michielse et al., 2010; Miller et al., 2012; Mulder, Shek, & Dietz, 2012; Ramirez et al., 2014; Terribilli et al., 2011). These studies come from varying fields, suggesting a cubic regression is a widely utilized test of non-linear distributions. One study of similar design to the current work comprised 89 participants (Terribilli et al., 2011). In this previous study, the researchers initially conducted a cubic regression using the whole sample. They then split the sample in half (into males and females) and repeated the analyses to search for differing trajectories between genders. The analyses in the current study were more conservative. Specifically, we conducted a cubic regression with the whole sample with an interaction term for “Injury Group” (mTBI vs. non-TBI). There was no clear circadian rhythmicity - that is, no clear differences based on time-of-day - in reactivity, and therefore, the sample was not split by group and re-analyzed.

Aim 1 Analyses: Determine habituation to repeated emotional stimuli in mTBI relative to controls. Both physiological and behavioral habituation were gauged using mixed-model ANOVA tests with a between-subject factor of Group (mTBI vs. non-TBI), and a within-subject factor of Exposure (image exposures 1-5). A significant main effect of Group signified an overall difference in habituation between head injury groups. A significant main effect of Exposure signified all participants had reactivity reductions (or increases) over time. A significant interaction between these factors indicated mTBI and non-TBI groups differed in the pattern of Exposures over time. If an interaction occurred, post-hoc

t-tests were conducted to clarify differences in slopes between the mTBI and non-TBI groups. Negative and positive images were combined into one analysis.

**Aim 2 Analyses:** Determine differences in reactivity to emotional stimuli in mTBI relative to controls and whether reactivity is linked to circadian rhythmicity. Analyses for reactivity (i.e., physiological and self-rated reactivity to negative and positive images, sampled during the first exposure) occurred in two phases. First, as described earlier, we sought a cubic curve in valence reactivity using a cubic regression. Circadian effects were not found, so time of testing was not used as a control variable in the subsequent analyses. We then compared reactivity between groups using an ANCOVA with mTBI vs. non-TBI as the between-subject factor.

**Aim 3 Analyses:** Assess whether reactivity and habituation characteristics predict mood symptomology. A “habituation slope” of self-reported and physiological measures was created [as in (Leventhal, Martin, Seals, Tapia, & Rehm, 2007)] for each individual. Both initial reactivity scores (i.e., results from the first exposure) and habituation slopes were separately regressed on BDI-II and STAI scores to determine whether responses to emotional stimuli predict depressive and anxiety symptoms. Although we did not expect group differences in these regressions (i.e., we expected reactivity and habituation to predict symptoms similarly in both groups), we conducted exploratory analyses to examine whether group differences were present. Therefore, interaction terms were created by multiplying each factor by Injury Group. All three terms were included in the model (e.g., EMG tone; Injury Group; EMG tone \* Injury Group), along with gender.

Twenty separate models were conducted, as we have 20 predictors (positive valence, negative valence, positive arousal, negative arousal, skin conductance to positive images, skin conductance to negative images, Corrugator EMG tone, Zygomaticus EMG tone, HR to positive images, heart rate to negative images for both habituation and reactivity). In each model, we were able to determine whether there was an overall effect of one factor (e.g., habituation of arousal ratings) on mood symptomology, and also whether there was an interaction between that factor and head injury status. Given the number of analyses conducted in Aim 3, results should be considered exploratory.

Additionally, given the number of analyses conducted, to increase statistical stringency, we considered two approaches: (1) utilizing one-tailed statistical testing with an alpha of .05 and (2) retaining two-tailed testing while reducing alpha to .01. Both of these methods have strengths and limitations. Using one-tailed statistical testing would allow us to test for statistical significance in an expected direction. This method minimizes the detection of random effects that might occur in the unexpected direction. However, using this approach, meaningful results that occur in the unexpected direction could be missed (i.e., Type II error may occur). This statistical approach is often used when there is strong support for a hypothesis in previous work for results going in one direction. Two-tailed statistical testing on the other hand, is used in more exploratory situations. In our case, given that this work is novel, yet there is previous data on which to base our hypotheses, we chose to use two-tailed testing and to use an alpha of .01. This approach also has strengths and limitations. Using an alpha of .01 (rather than .05) reduces the chances of Type I statistical error. However, it also increases the risk of Type II statistical error

(false negatives). Nevertheless, despite this limitation, we chose to utilize this approach to increase statistical conservativeness of the analyses by reducing Type I error.

We conducted power analyses based effect sizes from **Study 2**. For Aim 1 (habituation), the necessary sample size was calculated using the effect size of habituation (i.e., change of valence ratings between both rating sessions) in the non-TBI group in **Study 2** (partial eta-squared = .18). With power of .80 (with 2 groups; 4 as the F-statement numerator to include co-variates for gender and cognition), 60 participants would be needed to detect this effect. With 2 more covariates (time-of-testing, order of testing), 69 participants would be needed to detect the effect. For Aim 2 (reactivity), partial eta-square of morning group difference (i.e., the mTBI and non-TBI groups had differing valence ratings in the morning) in **Study 2** was .087. Using a t-test, to detect this effect with 80% power, 85 participants would be needed. Adding covariates did not change the needed sample size. For Aim 3, we did not have pilot data available for an exemplar of effect size. However, to detect a medium effect for  $R^2$  tests (.15), at 80% power with 1 predictor, 55 participants would be needed. For analyses including Injury Group as a moderator, 3 predictors are needed (the independent variable, the moderator, the interaction term). In order to detect a medium effect size with this type of analysis, 77 participants would be needed. When including gender as a covariate (i.e., when including 4 predictors), 85 participants would be needed. Therefore, for the current analyses, we had sufficient power to detect effects in this sample. However, for the circadian analyses, which focused on highly variable data, we may not have had sufficient power.



## **C. Results**

### **1. Preliminary Analyses**

As shown in Table 6, there were no significant differences between mTBI and non-TBI groups for age, years of education, ethnicity, or gender. There were no differences in sleep quality (via the PSQI), or morningness-eveningness preference (via the MEQ). Finally, there were no group differences in executive functioning (via the BRIEF), PTSD symptoms, or dissociation symptoms. Therefore, none of these factors were used as covariates in subsequent analyses. Gender, however, was used as a covariate.

Unexpectedly, the mTBI group performed significantly better on one of the cognitive tests (Verbal Fluency Word Pair Condition; Table 6). Given this, we included this variable as a covariate for behavioral analyses. Although this cognitive difference emerged, cognitive measures were not correlated with emotion measures (Table 7). Therefore, we do not believe cognition influenced emotion, or vice versa.

The mTBI group had significantly higher anxiety scores on the STAI (Table 6). However, there were no differences between groups for depressive symptoms. STAI scores were not used as a covariate because they were used as an outcome measure in **Aim 3**. However, notably, the inclusion of STAI scores as a covariate did not change behavioral results for Aims 1 and 2.

### **2. mTBI Characteristics**

The mTBI group had their most recent mTBI  $3.27 \pm 1.52$  years prior to participation in the study. On average, participants had  $2.22 \pm 1.61$  mTBIs. Forty two percent suffered from 1 mTBI, 31% suffered from 2 mTBIs, and 27% had 3 or more mTBIs.

Participants were asked how many physical symptoms (items taken from the Rivermead Concussion Questionnaire) they had suffered over the past two weeks, without probing them about whether the physical symptoms were related to head injury. mTBI subjects reported significantly more dizziness (Table 8).

Of the mTBI sample, 71.1% suffered from sports-related mTBIs, 15.6% received the mTBI from a fall, 8.9% received the mTBI from a car accident, and 4.4% received the mTBI from another type of incident. When comparing those who suffered from a sports-related incident to those who received an mTBI from another source, there were no differences in reactivity ratings or habituation rates.

To determine whether mTBI factors (e.g., time since mTBI, number of mTBIs) were related to reactivity or habituation, we conducted correlations between these factors. There were no correlations between mTBI factors and behavioral/physiological factors (Tables 9 and 10, respectively). Therefore, no mTBI factors were used as covariates in subsequent analyses.

### **3. Order Effects**

Participants completed the negative and positive conditions in a counter-balanced order. There were no differences in valence ratings of positive stimuli ( $t(88) = -1.56, p = .12$ ) or negative stimuli ( $t(88) = .32, p = .75$ ) between individuals who completed the positive condition first and those who completed the negative condition first. There were also no differences between groups in positive ( $t(88) = .14, p = .89$ ) or negative arousal ratings ( $t(88) = -.26, p = .80$ ). Similarly, for habituation, there were no order effects for positive valence ( $t(88) = -.15, p = .88$ ), negative valence ( $t(88) = -1.40, p = .16$ ), positive arousal ( $t(88) = -.70, p = .49$ ), or negative arousal ( $t(88) = .70, p = .48$ ).

#### **4. Neutral Images**

Neutral images were included to prevent a response bias (i.e., a habit or pattern of rating) from occurring. Nevertheless, it is necessary to determine whether or not individuals with a history of mTBI perceive neutral images differently than the non-TBI group prior to interpreting results for negative and positive images. There were no differences between groups for valence ratings of neutral images during the positive ( $t(88) = 1.33, p = .19$ ) or negative condition ( $t(88) = -.68, p = .50$ ). There were also no differences between groups for arousal ratings of neutral images during the positive ( $t(88) = -.07, p = .94$ ) or negative condition ( $t(88) = -.73, p = .47$ ).

#### **5. Main Analyses**

##### **a. Aim 1: Valence**

Negative and positive images were combined in one model for analyses. There was no main effect of Injury Group ( $F(1,87) = 1.14, p = .29$ ). As expected, there was a main effect of Emotion ( $F(1,87) = 276.48, p < .001, \eta = .76$ ), indicating differences in valence ratings between the negative and positive stimuli. There was a main effect of Exposure ( $F(4,348) = 289.552, p < .001, \eta = .77$ ) such that valence decreased toward neutrality with subsequent exposures (i.e., habituation occurred; Figure 8). There was also an Emotion by Exposure interaction ( $F(4,348) = 269.89, p < .001, \eta = .76$ ). Follow-up analyses showed a main effect of Exposure for positive images ( $F(4,348) = 7.75, p = .001, \eta = .12$ ); they were rated more neutral over time, but no main effect of Exposure for negative images ( $F(4,348) = .84, p = .50$ ). Finally, there was no interaction between Exposure and Injury Group ( $F(4,348) = 2.60, p = .04$ ), no Emotion by Injury Group interaction ( $F(1,87) = 1.02, p = .32$ ), and no three-way interaction between these factors ( $F(4,348) = 3.18, p = .014$ ).

### **b. Aim 1: Arousal**

Arousal ratings for negative and positive images were included in one model. There was no main effect of Injury Group ( $F(1,87) = .12, p = .73$ ). There was a main effect of Emotion ( $F(1,87) = 13.23, p < .001, \eta = .13$ ), such that negative images were rated as more arousing than positive images, and there was a main effect of Exposure ( $F(4,348) = 23.48, p < .001, \eta = .21$ ), such that arousal ratings decreased over time (Figure 9). There was no Emotion by Exposure interaction ( $F(4,348) = .15, p = .96$ ). However, there was an Exposure by Injury Group interaction ( $F(4,348) = 3.38, p = .01, \eta = .04$ ). Therefore, we

compared habituation slopes between groups. Habituation was significantly greater for the mTBI group than for the non-TBI group ( $t(87) = 7.87, p = .006, \eta = .08$ ). Lastly, there was no Emotion by Injury Group interaction ( $F(1,87) = 2.86, p = .10$ ), and there was no Emotion by Exposure by Injury Group interaction ( $F(4,348) = 2.28, p = .06$ ).

### **c. Aim 1: Skin Conductance**

There were no statistical outliers for skin conductance. There was no main effect of Injury Group ( $F(1,83) = .003, p = .96$ ), no main effect of Emotion ( $F(1,83) = .11, p = .96$ ), no main effect of Exposure ( $F(4,332) = .27, p = .89$ ), and no interaction between Emotion and Exposure ( $F(4,332) = .21, p = .93$ ). There was no Emotion by Injury Group interaction ( $F(1,83) = .17, p = .68$ ) and no Exposure by Injury Group interaction ( $F(4,332) = .88, p = .47$ ). There was no three-way interaction between Emotion by Injury Group by Exposure ( $F(4,332) = 1.14, p = .34$ ). In sum, contrary to predictions, we did not detect any main effect or group differences for rate of habituation in skin conductance.

Given that skin conductance typically mirrors arousal ratings, and giving the significant arousal rating habituation effects described above, several post-hoc analyses were conducted for skin conductance. We conducted a median split and divided participants into “low” habituators and “high” habituators for skin conductance response to both positive and negative stimuli. There was no difference in the proportion of mTBI participants in each of the subgroups (47.6% of habituators and 50% of non-habituators were from mTBI group), and there were no differences in mTBI characteristics between groups.

In another set of post-hoc analyses, we assessed whether number of skin conductance responses (rather than a continuous value of skin conductance) habituated over time. First, a tonic skin conductance tone was calculated using ACQ Algorithms. Next, skin conductance responses were identified as changes in skin conductance  $> .05$  microSiemens above the tonic level (Williams et al., 2001). The number of responses in the 4 seconds after stimulus presentation was counted. There was no main effect of Emotion ( $F(1,87) = 1.60, p = .21$ ), no main effect of Injury Group ( $F(1,87) = .23, p = .63$ ), and no main effect of Exposure ( $F(4,348) = 1.45, p = .22$ ). There was no Emotion by Injury Group interaction ( $F(1,87) = 1.56, p = .22$ ), no Emotion by Exposure interaction ( $F(4,348) = .49, p = .74$ ), and no three-way interaction ( $F(4,348) = .56, p = .69$ ).

#### **d. Aim 1: EMG**

There was one mTBI individual and seven non-TBI individuals who were considered statistical outliers for Corrugator results. There was one mTBI and eight non-TBI individuals who were considered statistical outliers for Zygomaticus results. Given that outlying measures seemed to be electrode-specific (and not person-specific), removing participants from one set of measurements did not necessarily exclude them from the second set. Note that Corrugator and Zygomaticus analyses were for only negative and positive image sets, respectively, as we did not have *a priori* hypotheses for Corrugator response to positive images or Zygomaticus response to negative images.

For the Corrugator muscle, there was no main effect of Exposure ( $F(4,316) = .18, p = .14$ ), no Exposure by Injury Group interaction ( $F(4,316) = .81, p = .52$ ), and no main effect of Injury Group ( $F(1,79) = .85, p = .36$ ). For the Zygomaticus muscle, there was no main effect of Injury Group ( $F(1,78) = 3.36, p = .07$ ). There was no main effect of Exposure ( $F(4,312) = 1.67, p = .16$ ) and no significant Exposure by Injury Group interaction ( $F(4,312) = 4.98, p = .03, \eta = .04$ ).

#### **e. Aim 1: Heart Rate Deceleration**

There were five mTBI and four non-TBI statistical outliers for HR. There was no main effect of Emotion ( $F(1,78) = .02, p = .88$ ). There was no main effect of Exposure ( $F(4,312) = 2.71, p = .10$ ). There was no Emotion by Exposure interaction ( $F(4,312) = .10, p = .98$ ), no Emotion by Injury Group interaction ( $F(1,78) = 2.16, p = .15$ ), and no Exposure by Injury Group interaction ( $F(4,312) = 1.34, p = .25$ ). There was no significant a three-way interaction between Emotion, Exposure, and Injury Group ( $F(4,312) = 2.81, p = .03, \eta = .04$ ).

#### **f. Aim 2: Circadian Analyses**

As mentioned, a cubic analysis was performed to assess whether a circadian variation was present in the reactivity data for negative and valence (Figure 10). Gender was included as a covariate. There was no cubic curve while either controlling for MEQ scores ( $B < .001, p = .37$ ) or without controlling for these scores ( $B < .001, p = .37$ ). We conducted an exploratory analysis to determine whether a quadratic curve might be present in the data (meaning there is one curve in the data, whereas a cubic curve has two

curves in the data). This test did also not reach significance ( $B = -.001$ ,  $p = .53$ ). Lastly, although we did not have *a priori* hypotheses for positive valence (as no positive valence pilot data were available in **Study 2**), we conducted an additional exploratory analysis assessing whether circadian curvature might be present for positive valence reactivity. This test also did not reach significance ( $B = .001$ ,  $p = .79$ ).

We conducted similar tests for arousal ratings (Figure 11). For negative arousal reactivity, there was no cubic curve while either controlling for MEQ scores ( $B < .001$ ,  $p = .62$ ) or without controlling for MEQ scores ( $B < .001$ ,  $p = .96$ ). Similarly, for positive arousal, there was no cubic curve while either controlling for MEQ scores ( $B < .001$ ,  $p = .95$ ) or without controlling for MEQ scores ( $B < .001$ ,  $p = .98$ ).

A set of post-hoc analyses was conducted that explored whether we could replicate the group differences seen in the morning in **Study 2**. We tested differences between the mTBI and non-TBI groups for participants who completed the task in the morning (9-11AM) and in the evening (5-8PM). We compared negative valence ratings between the mTBI and non-TBI groups within each time slot. Because reducing the sample into time slots reduced statistical power, no significant differences between groups were expected. We therefore focused on effect sizes. For morning participants (mTBI  $n = 12$ , non-TBI  $n = 13$ ), similar to what was seen in **Study 2**, the mTBI group exhibited blunted valence ratings relative to the non-TBI group, but the effect size was small (mTBI mean =  $2.93 \pm .75$ ; non-TBI mean =  $2.67 \pm .82$ ; Cohen's  $d = .32$ ). In **Study 2**, the effect size was moderate (i.e.,  $.65$ ). Therefore, although we were able to replicate the pattern of findings



from **Study 2**, the effect size is smaller in the current work. For the 6-8PM time slot (mTBI n = 10, non-TBI n = 11), the mTBI group had slightly less emotional valence ratings, with a very small effect size (mTBI mean =  $2.68 \pm .75$ ; non-TBI mean =  $2.61 \pm .47$ ; Cohen's  $d = .11$ ). These results are also similar to those seen in **Study 2**; we see a smaller difference between groups during the evening time point than the morning time point.

Circadian rhythmicity of habituation also was explored for arousal and valence. We did not have *a priori* hypotheses for these analyses, because our pilot data did not suggest circadian differences in habituation. Yet given that habituation and reactivity might be associated, we conducted these analyses in an exploratory manner. For negative valence habituation, there was no cubic curve while either controlling for MEQ scores ( $B < .001$ ,  $p = .61$ ) or without controlling for MEQ scores ( $B < .001$ ,  $p = .62$ ). For positive valence habituation, there was no cubic curve while either controlling for MEQ scores ( $B < .001$ ,  $p = .80$ ) or without controlling for MEQ scores ( $B < .001$ ,  $p = .80$ ).

For negative arousal habituation, there was no cubic curve while either controlling for MEQ scores ( $B < .001$ ,  $p = .98$ ) or without controlling for MEQ scores ( $B < .001$ ,  $p = .97$ ). Lastly, for positive arousal habituation, there was no cubic curve while either controlling for MEQ scores ( $B < .001$ ,  $p = .81$ ) or without controlling for MEQ scores ( $B < .001$ ,  $p = .84$ ). Therefore, time-of-testing was not used as a covariate in subsequent analyses.

### **g. Aim 2: Behavioral results**

There were no differences in valence reactivity (i.e., valence ratings at Exposure 1) for negative images ( $t(86) = .89, p = .35$ ). There was no difference between groups for positive valence ( $t(86) = 3.19, p = .08$ ). There were no differences in arousal reactivity (i.e., arousal ratings at Exposure 1) for negative ( $t(86) = 1.13, p = .29$ ) or positive stimuli ( $t(86) = .04, p = .84$ ).

### **h. Aim 2: Physiological Results**

For skin conductance, there were no group differences in reactivity (i.e., the first phasic response) to positive stimuli ( $t(83) = .02, p = .87$ ) or negative stimuli ( $t(83) = .47, p = .49$ ). For Corrugator EMG tone, there were no differences for EMG Corrugator change in response to the first negative image set ( $t(79) = 1.64, p = .20$ ). For Zygomaticus EMG tone, there were no differences in EMG between groups in response to the first positive set ( $t(78) = 1.12, p = .29$ ). For heart rate deceleration there were no differences in reactivity to positive images ( $t(1,78) = 2.04, p = .16$ ) or negative images ( $t(78) = .16, p = .69$ ). In sum, for reactivity (i.e., during the first image exposure), no group differences were detected either behaviorally or physiologically.

### **i. Aim 3: Overview**

We next conducted analyses to probe whether reactivity and habituation were predictive of mood outcomes. Given the high correlation between BDI-II and STAI scores ( $r = .63$ ), we approached these analyses in two ways. First, we conducted analyses separately for BDI-II and STAI scores. Second, these measures were combined (the average of z-scores

for both measures) and used as a single outcome variable. All factors (e.g., arousal ratings of positive images, Zygomaticus EMG tone, etc.) were entered into models separately. Collinearity was high between positive and negative stimuli (e.g., between skin conductance response to positive images and to negative images; variance Inflation Factor > 5 for all physiological and behavioral measures). Therefore, positive and negative analyses were conducted separately. For all analyses conducted below, gender was a significant predictor of symptomology, such that females had higher symptomology throughout.

**j. Aim 3: Main Effects Predicting Depressive Symptomatology**

For reactivity, lower arousal ratings for positive images was predictive of higher depressive symptomatology (Table 11). No other behavioral or physiological predictors were significant for reactivity.

**k. Aim 3: Main Effects Predicting Anxiety Symptomatology**

For reactivity, there were no significant behavioral or physiological predictors of anxiety symptomatology (Table 12). Similarly, for habituation, there were no significant predictors.

**l. Aim 3: Main Effects Predicting Combined Symptomatology**

For reactivity, negative and positive valence ratings did not predict symptomatology (Table 13). Arousal ratings for negative stimuli did not predict symptoms, but lower

arousal ratings for positive stimuli predicted higher mood symptomatology. For physiological measures, there were no significant predictors of symptomatology.

Habituation of valence ratings and arousal ratings did not predict combined symptomatology (Table 13). Habituation of skin conductance and heart rate did not predict symptomatology. However, habituation of Zygomaticus muscle tone was a significant predictor, such that greater habituation (i.e., losing tone more quickly in response to positive images) predicted higher symptomatology.

#### **m. Aim 3: Interactions to Predict Depressive Symptoms**

In an additional set of analyses, interaction terms were created by multiplying Injury Group by each predictor variable and entering all variables into the model (e.g., a full model: Injury Group; EMG Reactivity; Injury Group \* EMG Reactivity; gender). Given that Injury Group was dummy coded (0 = non-TBI, 1 = mTBI), when an interaction was present, results were interpreted at each level of Injury Group (i.e., with and without mTBI) for clarity. In each model, gender was a significant predictor of mood symptomatology, such that females had higher symptomatology. In the first model, there were no significant interactions that predicted depressive symptomatology for reactivity or habituation (Table 14).

#### **n. Aim 3: Interactions to Predict Anxiety Symptoms**

Similar to the tests conducted above, we tested whether Injury Group and the included factors interacted to predict anxiety symptomatology. There were no significant interactions to predict anxiety symptoms for reactivity or habituation (Table 15).

**o. Aim 3: Interactions to Predict Combined Symptomatology**

As shown in Table 16, there were no significant interactions that predicted combined symptomatology for reactivity or habituation.

**6. Examining the “Miserable Minority”**

Given the lack of expected differences between the mTBI group and the non-TBI group, we tested whether the most “severe” mTBI subgroup may differ from the non-TBI group. Previous work has shown that roughly 15-20% of participants (the “miserable minority”) have ongoing complaints (i.e., suffer from post-concussive syndrome) years after injury (Ruff, 2005). The diagnostic criteria for post-concussive syndrome require a person with a history of mTBI exhibits at least 3 of the following 8 symptoms after brain injury: headache, dizziness, fatigue, irritability, sleep problems, concentration problems, memory problems, or problems tolerating stress/alcohol/emotions (World Health Organization, 1992). All of these items (with the exception of the last item) were included in the Rivermead Questionnaire. Therefore, we categorized participants based on whether they reported experiencing at least three of the first seven items. Eleven of the 45 mTBI participants (24.4%) met the adjusted criteria for post-concussive syndrome.

First, we sought to explore whether the post-concussive syndrome group differed from others in the mTBI group. The post-concussive syndrome group had significantly higher levels of depression ( $t(43) = -2.84, p = .007$ ), anxiety ( $t(43) = -3.21, p = .002$ ), and PTSD symptoms ( $t(43) = -3.22, p = .002$ ) than the higher functioning mTBI group. The groups did not differ in terms of self-reported executive functioning, dissociation symptoms or mTBI characteristics (e.g., time since mTBI).

We next sought to explore whether the post-concussive syndrome group differed from the non-TBI group for the measures of habituation and reactivity. When comparing the post-concussive syndrome group with the full non-TBI group, there were no significant group differences (Table 17). These results suggest that even the most “severe” mTBI participants is relatively normative.

#### **D. Discussion**

Risk for developing mood disturbances is elevated for some persons following mTBI. Accordingly, in this sample, we found elevated anxiety symptoms in the mTBI sample relative to controls. However, beyond surveying this population for depressive and anxiety symptoms, little has been done to examine or pinpoint specific emotional irregularities that may lead to or exacerbate mood disturbances. In our previous work (**Study 2**), we identified what seemed to be a lack of emotion habituation to negative stimuli in chronic mTBI participants relative to a control, uninjured population. We aimed to replicate those findings in a larger sample while also probing

psychophysiological measures of emotion, which provide a deeper understanding of cortical and somatic mechanisms, and also probing psychological outcomes (e.g., depressive and anxiety symptoms). In addition to habituation, we assessed reactivity, or the initial emotional/psychophysiological response to the emotional images, in both groups. We hypothesized that poor (slow) habituation and blunted reactivity would be predictive of mood disturbances. We included both positive and negative stimuli in this study to gain a broader understanding of emotional functioning in this population.

First, hypotheses of reduced habituation in the mTBI group were not supported. Contrary to expectations, the mTBI group had enhanced (or faster) habituation with respect to arousal ratings to the presented images. Patterns of habituation did not differ between the mTBI group and the non-TBI group in any psychophysiological measures. Behavioral and psychophysiological reactivity did not differ between groups.

Nevertheless, we found some measures of reactivity and habituation predicted mood symptomology. Specifically, lower arousal ratings for positive images predicted higher depressive (and combined) symptomatology, and faster habituation of Zygomaticus tone predicted combined symptomatology as well.

### **1. Habituation Differs Between Groups, Predicts Symptomatology**

We predicted, based on **Study 2**, that valence ratings for both negative and positive images would move toward neutrality over time. We also predicted that the mTBI group would have a flattened trajectory of habituation for valence, relative to the non-TBI

group. These hypotheses were not supported. We found habituation for positive valence ratings in the full sample, but no habituation occurred for negative valence ratings. We predicted that no participants would exhibit habituation in arousal ratings for positive or negative stimuli. We saw, however, a main effect habituation for arousal ratings in the full sample and this effect was significantly stronger in the mTBI group. Lastly, we tested whether valence and arousal habituation were predictive of mood outcomes. Previous work has shown individuals with depressive symptomatology have lower habituation ratings (Neumeister et al., 2006), and therefore, we predicted lower habituation would be predictive of higher mood symptoms. However, this hypothesis was not supported because we did not find behavioral habituation was predictive of symptomatology in this sample.

We hypothesized that we would detect habituation of physiological measures, but none of these hypotheses were supported. We did not see habituation of any physiological measurements, and we did not see group differences in physiological measures. However, we found higher habituation of Zygomaticus tone in response to positive stimuli was related to higher combined mood symptomatology in the whole sample.

There is a broad literature on how preserving or savoring positive experiences can benefit wellbeing. According to Fredrickson's "Broaden and Build" theory, savoring positive emotionality can enhance life satisfaction, increase the likelihood of experiencing subsequent positive emotionality, and increase resiliency to negative emotionality (Fredrickson & Branigan, 2005; Tugade & Fredrickson, 2004). There are several



savoring strategies that are utilized to enhance positive emotionality. For instance, individuals can use Behavioral Display (e.g., smiling), Being Present (focusing attention on the positive experience), Capitalizing (communicating and celebrating experience with others), and Positive Mental Time Travel (anticipating or thinking back on positive experience; Quoidbach, Berry, Hansenne, & Mikolajczak, 2010). In our study, we found that individuals who exhibit low habituation of Zygomaticus muscle tone (when viewing positive images) have better mood outcomes. Thus, these individuals might utilize strategies for savoring positive experiences. To our knowledge, no studies have been conducted to link habituation to the savoring of positive experiences, and this could be a new interesting future direction to explore.

As mentioned, there was no relationship between other physiological measures and mood outcomes. We are not aware of any studies that have tracked EMG tone habituation in an mTBI population. However, there are two previous studies in which skin conductance was tracked over time after the introduction of a stress-inducing paradigm (van Noordt & Good, 2011; Baker & Good, 2014). Skin conductance was lower in the mTBI group initially, and habituation seemed to happen more rapidly. However, because of baseline differences, conclusions about habituation could not be made (and the authors did not analyze it specifically). In our sample, there were no baseline differences in reactivity of skin conductance, making our mTBI and non-TBI groups more comparable.

Nevertheless, despite comparability, there were no detected differences in habituation between groups. Lastly, to our knowledge, no studies have been performed that examine habituation of heart rate deceleration following mTBI.

## **2. Reactivity does not Differ Between Groups but Predicts Mood Symptomology**

Based on pilot data from **Study 2**, we predicted that group differences in negative valence ratings may be a function of time-of-day. We therefore collected data throughout the day (with several participants in each group tested at each hour) to determine whether circadian rhythmicity may influence behavioral ratings. These hypotheses were not supported using our planned analyses.

There was no circadian curvature seen for valence or arousal reactivity ratings of positive or negative images. There was also no curvature for valence or arousal habituation of positive or negative images. Post-hoc analyses were performed to assess whether group differences in negative valence ratings (as seen in **Study 2**) were present in individuals who completed the experiment in the morning and in the evening. In these subsets of participants, results of **Study 3** paralleled those of **Study 2**, albeit with a smaller effect size. These results indicate that individuals with a history of mTBI may have blunted emotional ratings in the morning.

The implications of these findings are not yet clear. To explore this phenomenon further, a follow-up experiment could be conducted exclusively in the morning to assess whether morning group differences play a role in how receptive participants are to clinical treatment (e.g., behavioral activation techniques, which require increasing positive affect). Such an experiment could yield important information for clinicians treating individuals with chronic mTBI.

It is important to note that there are limitations in the way that the circadian analyses were conducted. First, a within-subject circadian analysis is more optimal than a between-subject analysis because a within-subject analysis minimizes variance in emotion ratings. However, as has been demonstrated with the habituation results, ratings of images change with repeated exposure, and thus we were not able to show participants the same images across the day without avoiding habituation effects. Next, another limitation is that our analyses (cubic regressions) were set up to detect a circadian curve in the data. However, in theory, the mTBI group may not have the same curvature in their circadian rhythm that the non-TBI group does. Thus, this type of analysis may not have been useful for detecting differences in rhythmicity between groups.

In future studies, a more optimal study design would be to test all participants in two groups, rather than in many groups. In previous work, participants were grouped into a morning group or afternoon group (between-subject design, 20 participants in each group; Tucker et al., 2012). Participants rated images as more negative when they were in their circadian off-peak (at 2PM) relative to what the authors considered to be on-peak (10AM). Unfortunately, with the current study design, although we sampled across the day, we are unable to assess participants in “blocks,” because we only have 4 participants in each group tested at each hour. Therefore, we are limited in our attempts to detect on- and off-peak circadian differences. Future work could probe all mTBI and non-TBI subjects at 8AM and 2PM (or all in a morning group, as mentioned above) in an attempt to elucidate the effect of circadian rhythmicity on emotion reactivity following mTBI.

We found no reactivity differences between groups for valence or arousal ratings. These results are particularly interesting when examining them in conjunction with the habituation results (**Aim 1**). As discussed, we found habituation differences between groups for arousal ratings (regardless of valence). Given that groups did not differ in reactivity, we can conclude that the habituation differences were not a function of baseline differences. Rather, habituation differences occurred despite no significant differences in initial image ratings.

We are not aware of any experiments in which chronic mTBI participants were asked to rate IAPS images. In one experiment in which participants were subjected to a stressor, mTBI participants rated their arousal state as lower during baseline (prior to the stressor initiation) and lower after a stressor was introduced (Baker & Good, 2014). However, ratings of emotional stimuli from our study are not necessarily comparable to ratings of one's arousal state, and therefore, our results are distinct and indicate there may not be differences in IAPS ratings between individuals with a chronic history of mTBI and controls.

Lastly, we found that reduced arousal ratings to positive stimuli were predictive of higher mood symptomology in both groups combined. This is consistent with literature showing that blunted emotional reactivity to emotional stimuli (both negative and positive) is predictive of higher depressive symptoms (Bylsma et al., 2008). We did not find a significant interaction between Injury Group and reactivity, suggesting that the

relationship between reactivity and mood symptomatology does not differ based on mTBI status.

Similar to what was seen for the behavioral measures, there were no group differences in physiological reactivity to emotion stimuli for EMG, skin conductance, or heart rate. In previous studies examining skin conductance in mTBI participants (van Noordt & Good, 2011; Baker & Good, 2014), those with mTBI had a blunted skin conductance response to a stressful cognitive task relative to uninjured controls. To our knowledge, our study was the first to test skin conductance in response to emotional stimuli in an mTBI population. It is possible that responses to emotional stimuli are preserved in this population, just as reactivity of arousal ratings also are similar between groups.

In retrospect, our study design was not adequately constructed to detect skin conductance responses or fluctuations. We presented each stimulus for 4 seconds, with a 3 second gap between each presentation. According to previous work, a skin conductance response takes 1-3 seconds to initiate, and it may take another 1-3 seconds before skin conductance reaches its peak response (Dawson, Schell, & Courtney, 2011). Because each stimulus was only presented for 4 seconds, we were likely not able to detect skin conductance peaks during stimulus presentation. Furthermore, given that we used the 1 second bin prior to each stimulus presentation as our baseline level (to which skin conductance responses were compared), it is possible that participants were not reaching their skin conductance peak until the baseline bin of the subsequent stimulus. Therefore, it is

possible that both the baseline skin conductance measure and the skin conductance response were invalid.

It is also notable that the two studies on mTBI and skin conductance discussed above found the largest group differences when participants were in the anticipatory stage of the experiment (i.e., while waiting for the experiment to begin), rather than in response to the stimuli itself. Unfortunately, the current study did not test skin conductance responses during the anticipatory period of stimuli presentation. Based on previous work, it seems an anticipatory response is adequately gauged using a 10-60 second inter-stimulus interval (Crone, Somsen, Beek, & Van Der Molen, 2004; Spottiswoode & May, 2003), and thus, our inter-stimulus interval may have been too short.

### **3. Neural Underpinnings of mTBI**

Neuroimaging studies have demonstrated alterations in prefrontal cortex functioning in chronic mTBI. In one study, which gauged cerebral blood flow via SPECT imaging, chronic mTBI participants showed hypo-perfusion of blood flow in several frontal regions (Bonne et al., 2003). Hypo-perfusion was predictive of higher executive functioning deficits. In a study using DTI, in the mTBI group, white matter reductions were present in several regions, including the superior longitudinal fasciculus, which connects the frontal lobe with each other brain lobe (Kraus et al., 2007). In the latter study, unfortunately, correlations between white matter integrity and behavior were not conducted. Lastly, in a recent meta-analysis of neuroimaging studies of chronic mTBI, it was found that mTBI-related brain damage is more commonly found in anterior regions

than posterior regions (Eierud et al., 2014). Furthermore, brain alterations (specifically in DTI measures) tended to be related to deficits in neurocognitive functioning.

Given that neurocognitive differences between chronic mTBI participants and controls are small (if they exist; (Belanger, Curtiss, Demery, Lebowitz, & Vanderploeg, 2005), we did not expect to find cognitive differences between experimental groups. However, we included neuropsychological tests in order to control for cognitive differences between groups if they were present. In this study, we unexpectedly found a cognitive enhancement in the mTBI group, indicating that this group likely does not have frontal cortex damage (at least that is detectable by these cognitive tests). Ideally, neuroimaging could be utilized to seek differences in functional or structural brain integrity following chronic mTBI, and these brain alterations could be linked with changes in emotional functioning (e.g., higher anxiety symptoms).

It has also been proposed that mTBI-induced frontal damage leads to downstream emotional alterations (Baker & Good, 2014; van Noordt & Good, 2011). Specifically, it has been hypothesized that mTBI-induced damage in the prefrontal cortex hinders communication between the frontal lobe and the amygdala. The amygdala activates in response to emotional stimuli, and the prefrontal cortex dampens that emotional response when appropriate (LeDoux, 1993). Therefore, it has been hypothesized that miscommunication between these regions can lead to emotional abnormalities. We hypothesized that this miscommunication might lead to altered habituation. Although we found the mTBI group had enhanced habituation, we did not find evidence for prefrontal

cortex abnormality or abnormal communication between the prefrontal cortex and the amygdala. On the contrary, prefrontal cortex functioning may be enhanced in the mTBI population, given their higher rate of habituation and superior cognitive functioning.

In recent years, techniques have been developed to non-invasively stimulate or dampen discrete brain region activity. For instance, repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) can both stimulate and hinder brain functioning in specific cortical areas. By changing brain activity, researchers can better understand how regional activation relates to behavior. The prefrontal cortex is a common target for non-invasive brain stimulation. For instance, stimulating the dorsolateral prefrontal cortex has been effective in enhancing cognitive functions (e.g., working memory, reaction time) that depend on this brain region (see meta-analysis: (Brunoni & Vanderhasselt, 2014).

Likewise, stimulating the prefrontal cortex has been shown to alter emotional processing. For instance, in healthy controls, emotion identification of facial stimuli was improved by tDCS stimulation of the left dorsolateral prefrontal cortex (Nitsche et al., 2012). In another study, tDCS stimulation of the left dorsolateral prefrontal cortex caused participants to rate negative stimuli as less emotional (Peña-Gómez, Vidal-Piñero, Clemente, Pascual-Leone, & Bartrés-Faz, 2011). Lastly, in a study in which participants were asked to actively down- or up-regulate emotional reactivity while viewing negative images, right dorsolateral tDCS stimulation during down-regulation resulted in lower arousal ratings (Feesser, Prehn, Kazzner, Mungee, & Bajbouj, 2014). On the other hand,



when participants were asked to up-regulate emotion reactivity, brain stimulation resulted in higher arousal ratings. The authors of this study suggested higher cortical excitability in the prefrontal cortex may act as a “gain” to maximize emotional down- or up-regulation.

Although no studies, to our knowledge, have probed prefrontal cortical stimulation and emotion habituation, the latter study suggests that activating or dampening prefrontal activity during a habituation task might alter habituation (especially when individuals are instructed to habituate). An interesting future direction might be to utilize tDCS on individuals with a chronic history of mTBI in an attempt to reduce arousal habituation ratings by either stimulating or hindering prefrontal cortex activity. Such an experiment could elucidate the role of the prefrontal cortex in habituation, and it could also provide information relevant to potential functional alterations (either enhanced or diminished) in the prefrontal cortex that occurs as a result of mTBI.

#### **4. Inconsistencies Between Studies 2 and 3**

Based on data from **Study 2**, we predicted individuals with a chronic history of mTBI would have blunted habituation. However, habituation results in Study 3 do not support this hypothesis, and, interestingly, go in the opposite direction as predicted. The experimental design in the current study and that in the previous study differ substantially. In **Study 2**, non-TBI and mTBI participants viewed negative and neutral images at two time points, each 12 hours apart. During the 12 intervening hours, participants were not monitored and were simply told to go about their day normally

(while avoiding napping and avoiding alcohol). In the current work, we designed a study that specifically aimed to probe habituation. By presenting the same set of images five times, with only a several second break between image set presentations, we were able to directly probe changes in ratings over time while also excluding extraneous factors (e.g., potential external stressor differences). However, as mentioned, this study design was likely not optimal for gauging physiological habituation.

## **5. Positive Emotions**

Psychopathology is thought to be predicted by three factors: positive affect, negative affect, and arousal (Clark & Watson, 1991). In this study, we included positive stimuli in addition to negative stimuli. We found arousal habituation for positive stimuli was enhanced relative to habituation for negative stimuli. Specifically, we found habituation was present for positive valence ratings but not negative valence ratings. According to Thomson and Spencer's (1996) definition of habituation, individuals habituate more quickly to less emotional stimuli (Natelson et al., 1988; Wright et al., 2001). Although the positive and negative stimuli were matched for valence and arousal based on IAPS normative data, the participants rated positive images as less arousing. Therefore, it may not be surprising that habituation is greater for positive stimuli than for negative stimuli.

We found habituation of Zygomaticus tone to positive stimuli predicted mood symptomology. No such associations were detected for habituation to negative stimuli. As mentioned, habituation to positive images was enhanced relative to habituation to negative images. It is possible that we were able to detect an association between positive

habituation and mood symptomology because greater variability was present in the positive habituation data, allowing for stronger correlations.

Alternatively, as mentioned, there is evidence showing that individuals who savor positive experiences have better emotional well-being. Therefore, although we initially hypothesized that high habituation to both positive and negative images would be an adaptive trait, perhaps high habituation to positive stimuli is not adaptive. Rather, low habituation to positive stimuli might be linked with fewer mood symptoms. These findings provide motivation for future studies on positive habituation, especially when examining the relationship between habituation and psychopathology.

## **6. Clinical Significance**

We hypothesized that individuals with a history of mTBI would have reduced habituation. Given that certain clinical treatments (e.g., exposure therapy) require systematic and repeated emotion habituation sessions, it is important to determine whether habituation deficits might be present in certain populations. We did not find a reduction in habituation, and therefore, history of chronic mTBI may not need to be considered prior to performing these treatments. Our findings also suggest that a high rate of positive habituation is linked with higher symptoms of psychopathology. Exposure therapy treatments could therefore aim to reduce positive habituation (i.e., by training participants how to use a savoring technique) while also enhancing negative habituation.

Additionally, the mTBI group did not exhibit blunted emotionality to negative or positive stimuli. Therefore, clinical treatments that require behavioral activation could still be useful in this population. Lastly, we had hypothesized that circadian fluctuations in emotionality ratings might be present. If circadian differences in emotional processing are present, time-of-day could be considered when administering clinical treatment. However, the current work shows no such fluctuation of emotionality ratings throughout the day, and therefore, these data do not suggest time-of-day should be considered by clinicians. However, given that emotion ratings differed between mTBI and non-TBI groups in the morning, future work should examine whether clinical treatments are more or less effective in mTBI patients when administered during the morning hours.

## **7. Statistical Power Considerations**

As mentioned in the Methods section, we had sufficient statistical power to detect effects for each aim, with the exception of the circadian analyses (and the issue of multiple comparisons for the regression analyses). However, there are factors that may have impacted power in our study. For instance, our sample contained a very small age range. Had we included a sample with a wider age range, we may have had more variability in cognitive outcomes and mood symptomatology (Salthouse, 2004; Kunzmann & Grühn, 2005). More variability in these measures may have increased the likelihood of detecting a relationship between these outcomes and our predictors.

A large number of analyses were performed in this experiment. It follows that the risk for Type I statistical error is high. In an attempt to minimize this risk, we set alpha to .01.

Nevertheless, the significant findings detected in the latter part of the experiment (i.e., the regression analyses) should be considered exploratory. Although we found a significant reactivity predictor and a significant habituation predictor of mood symptomatology, it is possible that those findings were spurious. Future work should aim to replicate these results with a more targeted statistical approach (i.e., a smaller planned set of analyses).

## **8. Future Directions**

We detected several (seemingly benign) emotion alterations in a chronic mTBI population relative to an uninjured control group. The most compelling result is behavioral ratings of stimuli, specifically the steeper slope of habituation in arousal ratings regardless of valence. This difference in habituation, however, was not predictive of mood symptomatology.

Several investigations on the cognitive effects of mTBI demonstrate that, in standard conditions, cognitive functioning is normal following chronic mTBI. However, when dual-task paradigms are utilized, cognitive impairments emerge (Bernstein, 2002b; Dean & Sterr, 2013; Howell, Osternig, Van Donkelaar, Mayr, & Chou, 2013). Authors of these studies speculate that compensatory activity keeps cognition intact until the cognitive load is high enough that the brain no longer has the capacity to compensate. We posit that the same may be true for emotional functioning. If emotional load were to be increased (e.g., if a mood induction were performed prior to this task), for instance, we may see differing patterns of behavior or physiology.

Another avenue for future work would be to focus on other mTBI populations, such as military veterans who have sustained an mTBI. Military populations, which typically come from a lower socioeconomic status than a college student sample (Valentine, Harada, Washington, & Damron-Rodriguez, 2002), such as the sample utilized here, are already at a higher risk for mood disturbances prior to head injury. With added emotional vulnerabilities, veteran populations might show differing patterns of emotional functioning. Furthermore, mTBI populations with PTSD might exhibit different patterns of results. Lastly, blast mTBIs, a form of brain injury with distinct pathology and symptomology than blunt force or rotational injury (Cernak et al., 2011; Blennow et al., 2012), should be examined. Studies on blast injuries, which typically impact separate brain regions than blunt force/rotational mTBI, could contrast the current work, elucidating which brain regions might be impacting emotional functioning.

### **9. The “Miserable Minority”**

It has been suggested that there is a subgroup (15-20%) of mTBI participants (the “Miserable Minority”) who never fully recover from an mTBI (Ruff, 2005). We isolated this subset – a group with at least 3 post-concussive complaints – and compared this group with (1) an opposing mTBI subgroup with low complaints, and (2) the non-TBI group. Our results showed mTBI individuals with post-concussive complaints were more depressed, more anxious, and had more PTSD symptoms than the mTBI group with few complaints. Therefore, the mTBI group could be divided in a meaningful manner based on complaints. These results support previous studies that show there may be two distinct

mTBI populations: a small subset of participants that continues to have mTBI-related complaints, and other mTBI participants who recover quickly after mTBI.

However, when comparing this subgroup with the full non-TBI sample, there were no clear group differences in emotion habituation or emotion reactivity. That is to say, even the most “severe” mTBI subjects (i.e., those with post-concussive complaints) did not show a clear differentiation from the uninjured group (i.e., the effect size for differences were either small or medium). The lack of differences from the control group underscores that our mTBI sample was generally functioning well; additionally, we were not powered for this analysis.

Although it is unknown why some individuals recover from mTBI while others do not, it has been suggested that brain damage, specifically in white matter tracts, may lead to long-term difficulties in this subset of patients (Niogi et al., 2008). It has also been suggested that pre-morbid vulnerabilities (e.g., existing depression) increase the risk of long-term symptoms after mTBI (reviewed in Ruff, 2011). Unfortunately, with data from the current study, we cannot draw conclusions about brain damage or about pre-morbid factors.

The current study design did not allow for a robust comparison of the post-concussive syndrome group with a broader mTBI group (or with the non-TBI group). Ideally, we would have a larger sample to allow for a larger post-concussive syndrome subset. Future studies could aim to recruit participants with post-concussive syndrome and compare

these participants with both mTBI subjects with full recovery and also control subjects. This study design would increase statistical power to detect differences between groups. It would also allow us to examine whether there are differences between the affected and non-affected mTBI subjects (e.g., in gender, number of TBIs, etc.).

## **10. Study Limitations**

There were several limitations to this study. We included a sample of college-attending young adults who had suffered from an mTBI at least 1 year prior. In doing so, we included a sample with a small age range. Because of this, our results may not be generalizable to older age ranges, and especially not older adults, who have characteristic changes in emotion reactivity (Kunzmann & Grühn, 2005). Nevertheless, this work is an important starting point that will inform future work on differing populations (e.g., military veterans with mTBI).

Next, we included participants who self-reported mTBI status. A confirmed concussion diagnosis would enhance these data and physician's records of symptomology after mTBI would be highly informative. Furthermore, restricting the mTBI sample to include individuals with a single concussion (and potentially within a smaller range of time-since-mTBI) would provide more insight about the recovery process following mTBI. There are also several studies demonstrating individuals who have sustained 3 or more mTBIs have poorer emotional functioning (Henry & de Beaumont, 2011; Spira, Lathan, Bleiberg, & Tsao, 2014b). The current work included mostly individuals who only had a single concussion, yet recruiting a larger sample with 3 or more concussions could



provide insight into the effects of repeated concussion, especially given that these individuals are at a higher risk for developing Chronic Traumatic Encephalopathy (Henry & de Beaumont, 2011).

We are also limited in our ability to assess emotional functioning after mTBI relative to pre-mTBI. Certain individuals (e.g., student athletes) are more likely to sustain an mTBI than the general young adult population (Gessel, Fields, Collins, Dick, & Comstock, 2007). They may also have different emotional functioning than non-student athletes (e.g., they may have higher levels of sensation-seeking tendencies or extraversion). Therefore, whether the results seen here are due to an mTBI or due to pre-morbid differences in emotional functioning is unknown. Future work could ideally utilize a longitudinal study design to track emotional functioning before and after brain injury. This would allow researchers and clinicians to assess whether pre-morbid mood disturbances moderate or mediate post-injury habituation and reactivity.

There are also limitations associated with university samples. There is increased risk for mental illness in young adulthood, relative to later adulthood: the stressors and relative instability of college can induce mental illness for the first time or exacerbate existing illnesses. In a large study surveying mental health issues in college students, 18.2% of the population had a diagnosis of depression, 10.1% had anxiety, and 7.8% reported suicide ideation (Ketchen Lipson, Gaddis, Heinze, Beck, & Eisenberg, 2015). In our sample, participants in both the mTBI group and the non-TBI group had relatively high levels of

depressive symptoms, indicating that our non-TBI sample may not have been an ideal control sample.

## **11. Conclusions**

Previous studies have found risk for mood disturbances, namely depression (and anxiety, to a lesser extent), is increased following an mTBI, even in the chronic stages of injury. The current study investigated whether emotion habituation, both behaviorally and psychophysiological, is altered in a chronic mTBI population and whether differences in emotion habituation predict mood disturbances. This study also investigated whether emotion reactivity (i.e., the initial emotional reaction to a stimulus) differs between these groups and whether these differences predict mood disturbances. Results indicate that individuals with a history of mTBI habituate more quickly to emotional images behaviorally, but do not exhibit differential psychophysiological habituation. Interestingly, in the full sample, enhanced habituation of Zygomaticus tone to positive images is predictive of poorer mood outcomes, suggesting enhanced habituation may only be normative in response to negative, but not positive, stimuli. We also found the mTBI participants do not exhibit differences from controls in emotional reactivity (either behaviorally or psychophysiological). However, blunted reactivity (arousal ratings of positive images) was predictive of higher depressive symptoms, consistent with previous work. In conclusion, although there are subtle differences in emotion responses in chronic mTBI participants, these differences do not seem to be associated with mood disturbances.

<b>Hour</b>	<b>9</b>	<b>10</b>	<b>11</b>	<b>12</b>	<b>13</b>	<b>14</b>	<b>15</b>	<b>16</b>	<b>17</b>	<b>18</b>	<b>19</b>	<b>20</b>
<b>non-TBI</b>	4	4	4	4	3	4	3	4	4	4	3	4
<b>mTBI</b>	4	4	4	4	4	3	4	4	4	4	3	3

Table 4.1: Circadian testing distribution. Roughly 4 participants in each group were tested at each hour.

	Non-TBI	mTBI	t-value	p-value
Age	19.89±1.34	20.02±1.57	-0.43	0.67
Years of Education	14.33±1.07	14.33±0.95	0.00	1.00
Gender (% male)	57.8	57.8	0.00	1.00
MEQ	44.02±8.85	47.69±9.35	-1.91	0.06
PSQI	7.00±3.30	6.36±2.79	0.99	.32
BDI-II	9.22±10.38	11.31±10.63	-0.94	0.35
<b>STAI</b>	<b>75.71±17.52</b>	<b>85.33±18.03</b>	<b>-2.56</b>	<b>0.01</b>
BRIEF	123.00±21.66	121.71±23.60	0.27	0.79
PTSD	29.76±9.71	33.22±13.47	-1.40	0.17
Physical Symptoms	4.71±3.36	6.00±3.15	-1.88	0.06
Stroop Black & White	45.87±6.79	43.47±5.98	1.78	0.08
Stroop Color	64.93±10.62	60.51±9.42	2.09	0.04
Stroop Interference	105.31±20.69	99.11±17.99	1.52	0.13
Stroop Int. Minus Color	40.38±15.30	38.60±12.92	0.60	0.55
Digit Span Backwards	8.23±2.63	8.82±2.28	-1.14	0.26
Verbal fluency: Letters	13.54±3.77	14.94±3.27	-1.87	0.07
Verbal fluency: Categories	20.37±3.71	22.16±3.72	-2.28	0.03
<b>Verbal fluency: Pairs</b>	<b>13.57±2.93</b>	<b>16.20±2.66</b>	<b>-4.44</b>	<b>0.001</b>
Dissociative Experiences Scale	7.27±6.66	6.84±7.40	.285	0.77

Table 4.2: Demographic table. Bold indicates significance differences between groups.

For gender, a X-value, rather than a t-value, is presented.

	BDI-II	STAI	BRIEF	PTSD	Stroop	Dig. Span
BDI-II	1					
STAI	.667*	1				
BRIEF	.681*	.564*	1			
PTSD	.813*	.669*	.513*	1		
Stroop	-0.005	-0.065	-0.05	0.048	1	
Dig. Span	0.03	-0.1	0.062	0.141	-0.239	1
Ver. Fluency	0.109	-0.147	0.291	0.045	-0.134	.313

Table 4.3: Correlations between psychological and cognitive tests. Numbers represent r-values. \* indicates  $p < .01$ .

Symptom	Non-TBI (%)	mTBI (%)	X-value	P-value
Headaches	64.4	77.8	1.95	.16
<b>Dizziness</b>	<b>17.8</b>	<b>42.2</b>	<b>6.40</b>	<b>.01</b>
Nausea/vomiting	24.4	24.4	0.00	.99
Noise sensitivity	15.6	28.9	2.31	.13
Sleep issues	31.1	51.1	3.72	.054
Fatigue	68.9	68.9	0.00	.99
Irritability	37.8	44.4	0.41	.52
Depression/tearfulness	35.6	46.7	1.15	.28
Frustration/impatience	42.2	55.6	1.60	.21
Forgetfulness/poor memory	26.7	31.1	0.22	.64
Taking longer to think	40.0	51.1	1.12	.29
Blurred vision	6.7	6.7	0.00	.99
Light sensitivity	8.9	26.7	3.55	.06
Double vision	0.0	6.7	3.10	.08
Restlessness	48.9	37.7	1.13	.29

Table 4.4: Physical complaints of mTBI participants reported on the Rivermead scale (statistical analyses via chi-squared). Bold indicates statistical significance.

	Number of mTBI	Time since mTBI
Number of mTBI	1	
Time since mTBI	-0.24	1
Neg. valence (reac)	0.08	-0.05
Pos. valence (reac)	-0.11	0.20
Neg. arousal (reac)	0.08	-0.09
Pos. arousal (reac)	-0.04	-0.05
Neg. valence (hab)	0.01	0.14
Pos. valence (hab)	0.11	-0.02
Neg. arousal (hab)	-0.11	-0.19
Pos. arousal (hab)	-0.12	-0.08

Table 4.5: Correlations between mTBI characteristics and behavioral ratings. Statistics represent r-values. Reac = reactivity; hab = habituation.

	Number of mTBI	Time since mTBI
Number of mTBI	1	
Time since mTBI	-0.246	1
Pos. skin conductance (reac)	-0.025	0.201
Neg. skin conductance (reac)	-0.072	-0.120
Corrugator tone (reac)	-0.005	0.100
Zygomaticus tone (reac)	-0.181	0.053
Neg. heart rate (reac)	0.077	0.043
Pos heart rate (reac)	-0.108	-0.019
Pos. skin conductance (hab)	0.103	-0.161
Neg. skin conductance (hab)	0.077	0.036
Corrugator tone (hab)	-0.071	0.117
Zygomaticus tone (hab)	0.272	-0.004
Neg. heart rate (hab)	0.159	-0.087
Pos. heart rate (hab)	-0.041	-0.025

Table 4.6: Correlations between mTBI characteristics and physiological measures.

Statistics represent r-values. Reac = reactivity; hab = habituation.



	B	Std. Error	Beta	T	Sig.
Negative Reactivity					
Valence	0.103	0.155	0.071	0.666	0.507
Arousal	-0.091	0.087	-0.111	-1.049	0.297
Skin conductance	0.045	0.093	0.056	0.482	0.631
Corrugator tone	0.025	0.12	0.025	0.213	0.832
Heart rate	0.012	0.014	0.096	0.804	0.424
Positive Reactivity					
Valence	-0.217	0.16	-0.143	-1.355	0.179
<b>Arousal</b>	<b>-0.229</b>	<b>0.068</b>	<b>-0.335</b>	<b>-3.339</b>	<b>0.001</b>
Skin conductance	0.372	0.494	0.087	0.752	0.454
Zygomaticus tone	-0.028	0.106	-0.031	-0.266	0.791
Heart rate	-0.008	0.013	-0.075	-0.633	0.529
Negative Habituation					
Valence	-0.116	0.179	-0.069	-0.651	0.517
Arousal	0.07	0.083	0.09	0.847	0.399
Skin conductance	-0.035	0.095	-0.043	-0.371	0.712
Corrugator tone	-0.006	0.205	-0.003	-0.029	0.977
Heart rate	-0.002	0.013	-0.019	-0.163	0.871
Positive Habituation					
Valence	0.02	0.167	0.013	0.118	0.906
Arousal	0.074	0.086	0.092	0.863	0.39
Skin conductance	-0.336	0.445	-0.087	-0.754	0.453
Zygomaticus tone	0.109	0.084	0.148	1.296	0.199
Heart rate	0.008	0.012	0.08	0.671	0.504

Table 4.7: Regression results for main effects predicting depressive symptoms. Bold indicates statistical significance.

	B	Std. Error	Beta	T	Sig.
Negative Reactivity					
Valence	4.791	2.524	0.198	1.898	0.061
Arousal	-1.54	1.432	-0.114	-1.075	0.285
Skin conductance	-2.281	1.502	-0.173	-1.519	0.133
Corrugator tone	4.646	1.886	0.274	2.463	0.016
Heart rate	0.137	0.235	0.07	0.585	0.56
Positive Reactivity					
Valence	-5.484	2.607	-0.219	-2.103	0.038
Arousal	-2.165	1.179	-0.192	-1.836	0.07
Skin conductance	1.936	8.135	0.027	0.238	0.812
Zygomaticus tone	-0.785	1.742	-0.052	-0.451	0.653
Heart rate	-0.102	0.211	-0.058	-0.485	0.629
Negative Habituation					
Valence	-0.178	2.961	-0.006	-0.06	0.952
Arousal	1.087	1.367	0.084	0.795	0.429
Skin conductance	2.329	1.54	0.172	1.513	0.135
Corrugator tone	2.507	3.343	0.086	0.75	0.456
Heart rate	-0.031	0.207	-0.018	-0.148	0.882
Positive Habituation					
Valence	-1.569	2.762	-0.06	-0.568	0.571
Arousal	-1.982	1.415	-0.148	-1.401	0.165
Skin conductance	10.225	7.235	0.161	1.413	0.162
Zygomaticus tone	2.71	1.354	0.225	2.002	0.049
Heart rate	0.128	0.198	0.077	0.645	0.521

Table 4.8: Regression results for main effects predicting anxiety symptoms.

	B	Std. Error	Beta	t	Sig.
Negative Reactivity					
Valence	0.208	0.119	0.174	1.75	0.084
Arousal	-0.115	0.066	-0.172	-1.729	0.087
Skin conductance	-0.039	0.072	-0.055	-0.536	0.594
Corrugator tone	0.001	0.001	0.032	0.306	0.76
Heart rate	0.001	0.011	0.005	0.048	0.962
Positive Reactivity					
Valence	-0.278	0.121	-0.225	-2.305	0.024
<b>Arousal</b>	<b>-0.163</b>	<b>0.053</b>	<b>-0.292</b>	<b>-3.067</b>	<b>0.003</b>
Skin conductance	0.148	0.315	0.048	0.471	0.639
Zygomaticus tone	-0.032	0.079	-0.044	-0.41	0.683
Heart rate	-0.001	0.01	-0.009	-0.085	0.933
Negative Habituation					
Valence	0.01	0.138	0.007	0.072	0.943
Arousal	0.015	0.065	0.023	0.224	0.823
Skin conductance	0.042	0.074	0.058	0.566	0.573
Corrugator tone	-0.059	0.163	-0.039	-0.36	0.72
Heart rate	0.006	0.01	0.062	0.576	0.566
Positive Habituation					
Valence	0.067	0.129	0.052	0.521	0.604
Arousal	-0.027	0.066	-0.04	-0.401	0.689
Skin conductance	-0.142	0.337	-0.044	-0.422	0.674
<b>Zygomaticus tone</b>	<b>0.156</b>	<b>0.058</b>	<b>0.273</b>	<b>2.672</b>	<b>0.009</b>
Heart rate	0.001	0.009	-0.004	-0.034	0.973

Table 4.9: Regression results for main effects predicting the combined outcome measure.

Bold indicates statistical significance.

	B	Std. Error	Beta	t	Sig.
Negative Reactivity					
Valence	-0.127	0.308	-0.175	-0.411	0.682
Arousal	0.386	0.168	1.011	2.301	0.024
Skin conductance	-0.362	0.51	-0.085	-0.709	0.48
Corrugator tone	0.558	0.272	0.768	2.05	0.044
Heart rate	0.017	0.029	0.087	0.567	0.572
Positive Reactivity					
Valence	0.153	0.334	0.434	0.459	0.647
Arousal	0.081	0.137	0.189	0.594	0.554
Skin conductance	-0.848	0.847	-0.156	-1.002	0.319
Zygomaticus tone	0.096	0.219	0.166	0.441	0.661
Heart rate	0.003	0.046	0.015	0.075	0.94
Negative Habituation					
Valence	0.662	0.348	0.287	1.904	0.06
Arousal	0.08	0.131	0.103	0.608	0.545
Skin conductance	0.461	0.423	0.121	1.089	0.279
Corrugator tone	-0.35	0.447	-0.161	-0.784	0.436
Heart rate	-0.021	0.024	-0.114	-0.857	0.394
Positive Habituation					
Valence	0.156	0.341	0.063	0.458	0.648
Arousal	0.043	0.111	0.053	0.388	0.699
Skin conductance	1.923	0.94	0.387	2.045	0.044
Zygomaticus tone	-0.06	0.163	-0.064	-0.368	0.714
Heart rate	0.054	0.03	0.223	1.797	0.076

Table 4.10: Regression results for interactions predicting depressive symptoms.

	B	Std. Error	Beta	T	Sig.
Negative Reactivity					
Valence	3.408	4.453	0.285	0.765	0.446
Arousal	3.589	2.519	0.569	1.425	0.158
Skin conductance	-0.531	7.579	-0.007	-0.07	0.944
Corrugator tone	-0.393	4.105	-0.033	-0.096	0.924
Heart rate	0.158	0.68	0.042	0.232	0.817
Positive Reactivity					
Valence	-0.688	4.892	-0.118	-0.141	0.888
Arousal	0.495	2.138	0.07	0.232	0.817
Skin conductance	-10.169	12.699	-0.112	-0.801	0.426
Zygomaticus tone	1.149	3.282	0.121	0.35	0.727
Heart rate	0.066	0.44	0.021	0.15	0.881
Negative Habituation					
Valence	7.409	3.314	0.619	2.236	0.028
Arousal	-0.775	1.901	-0.123	-0.408	0.685
Skin conductance	-1.258	6.314	-0.02	-0.199	0.843
Corrugator tone	-0.153	3.743	-0.004	-0.041	0.967
Heart rate	0.013	0.209	0.007	0.06	0.952
Positive Habituation					
Valence	-6.355	3.996	-1.088	-1.59	0.115
Arousal	-1.987	1.668	-0.279	-1.191	0.237
Skin conductance	24.03	14.17	0.291	1.696	0.094
Zygomaticus tone	-2.231	2.396	-0.145	-0.931	0.355
Heart rate	-0.015	0.199	-0.01	-0.078	0.938

Table 4.11: Regression results for interactions predicting anxiety symptoms.

	B	Std. Error	Beta	T	Sig.
Negative Reactivity					
Valence	0.16	0.23	0.27	0.68	0.49
Arousal	0.25	0.13	0.81	1.94	0.05
Skin conductance	-0.15	0.39	-0.04	-0.40	0.68
Corrugator tone	0.15	0.22	0.26	0.70	0.48
Heart rate	0.02	0.03	0.11	0.57	0.56
Positive Reactivity					
Valence	-0.11	0.25	-0.39	-0.44	0.65
Arousal	0.02	0.10	0.05	0.18	0.85
Skin conductance	-0.71	0.64	-0.16	-1.10	0.27
Zygomaticus tone	-0.11	0.13	-0.22	-0.80	0.42
Heart rate	0.006	0.02	0.03	0.25	0.80
Negative Habituation					
Valence	0.40	0.27	0.21	1.46	0.14
Arousal	0.22	0.13	0.30	1.71	0.08
Skin conductance	0.10	0.32	0.03	0.31	0.75
Corrugator tone	-0.17	0.35	-0.09	-0.48	0.63
Heart rate	0.02	0.024	0.10	0.82	0.41
Positive Habituation					
Valence	0.25	0.26	0.12	0.94	0.34
Arousal	0.30	0.13	0.35	2.20	0.03
Skin conductance	1.38	0.72	0.35	1.92	0.05
Zygomaticus tone	-0.01	0.12	-0.01	-0.11	0.91
Heart rate	-0.01	0.01	-0.08	-0.66	0.51

Table 4.12: Regression results for interactions predicting the combined outcome measure.

	MM	non-TBI	T	Sig.
Reactivity				
Negative valence	3.108±0.977	2.694±0.840	0.71	.48
Positive valence	6.016±0.547	6.481±0.848	-1.93	.06
Negative arousal	5.85±1.753	5.011±1.398	1.84	.07
Positive arousal	4.55±1.487	4.531±1.775	0.30	.76
Negative skin conductance	0.261±0.304	0.485±1.911	-0.86	.40
Positive skin conductance	0.065±0.08	0.184±0.242	0.06	.95
Corrugator tone	2.575±1.326	2.696±0.921	-0.93	.36
Zygomaticus tone	3.694±1.61	3.677±1.408	0.26	.80
Negative heart rate	7.579±2.987	9.088±12.408	-0.10	.92
Positive heart rate	5.452±1.955	10.085±12.903	-0.80	.42
Habituation				
Negative valence	0.066±0.580	0.033±0.623	0.26	.78
Positive valence	-0.200±0.336	-0.32±0.644	0.44	.66
Negative arousal	-0.316±0.879	-0.713±1.294	-1.42	.16
Positive arousal	-0.816±1.214	-0.575±1.462	-1.85	.07
Negative skin conductance	-0.07±0.392	-0.309±1.838	1.23	.22
Positive skin conductance	0.132±0.249	-0.024±0.211	1.79	.08
Corrugator tone	0.156±0.672	0.044±0.474	-0.23	.82
Zygomaticus tone	0.422±1.793	-0.303±1.432	-0.71	.48
Negative heart rate	1.096±6.294	-2.489±13.458	0.80	.43
Positive heart rate	0.477±3.446	-3.482±13.404	1.10	.27

Table 4.13: Comparing individuals meeting the adjusted post-concussive syndrome criteria with the non-TBI group.

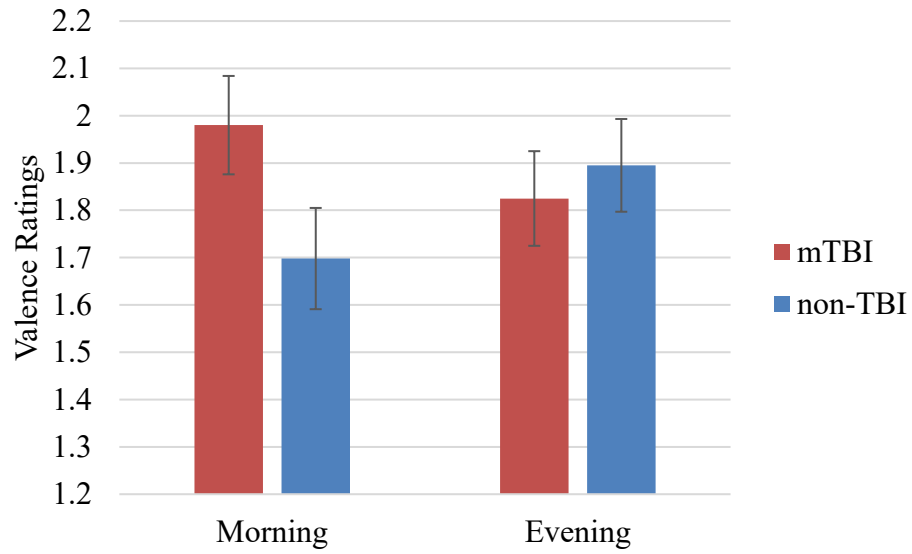


Figure 4.1. Negative valence ratings in Study 2. There were near-significant differences between reactivity ratings in the morning, such that the non-TBI group considered negative images as more emotional.



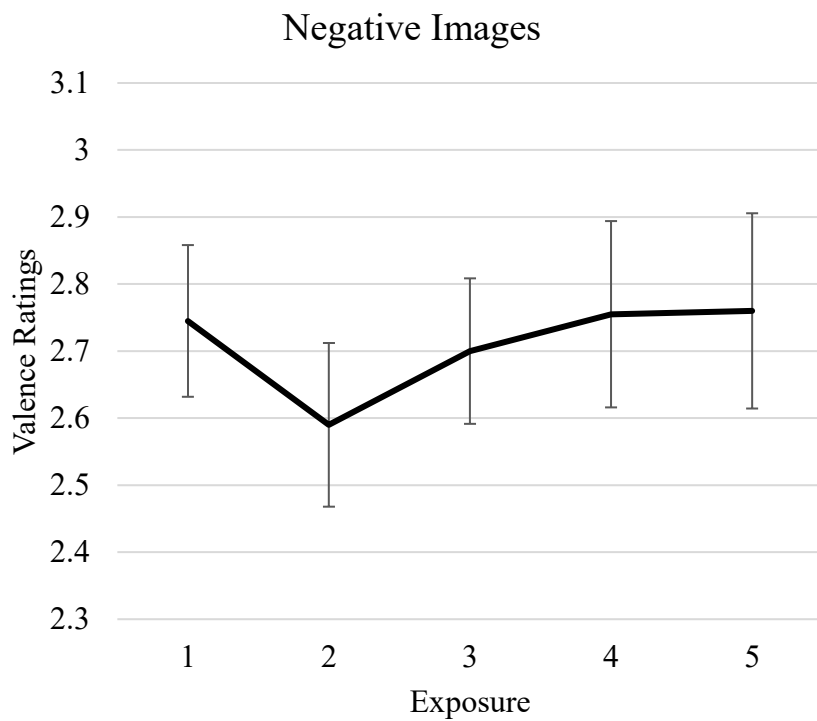
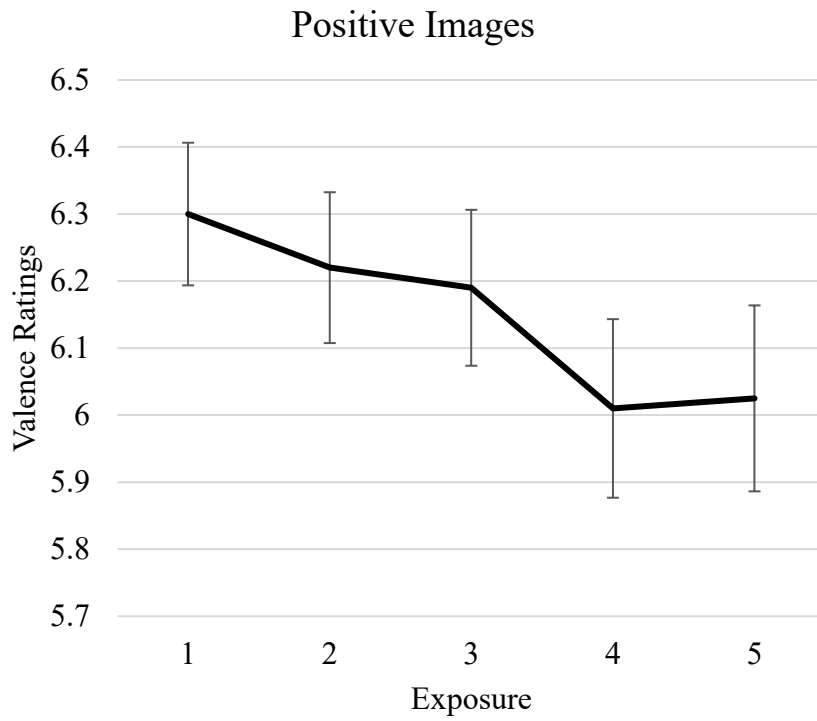


Figure 4.2: Habituation of valence ratings.

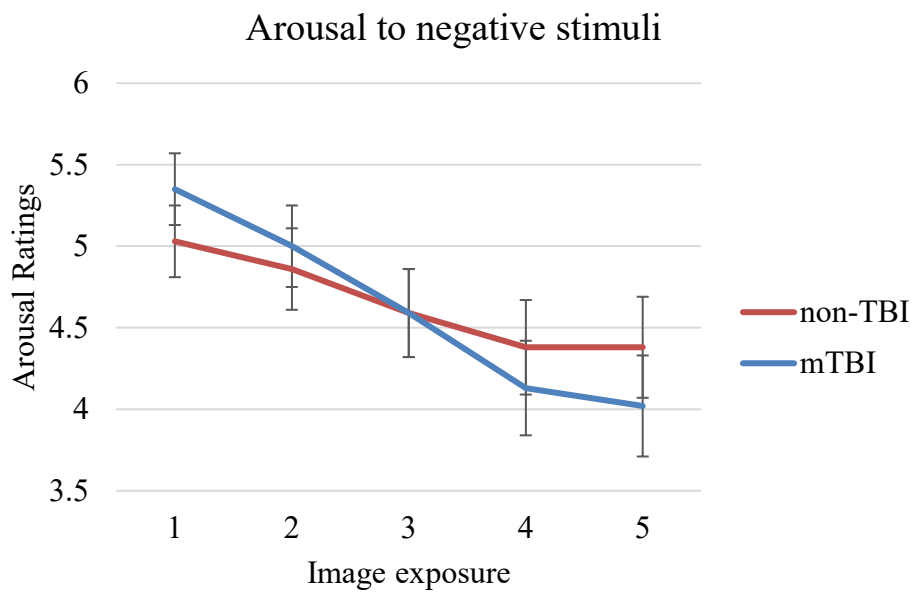
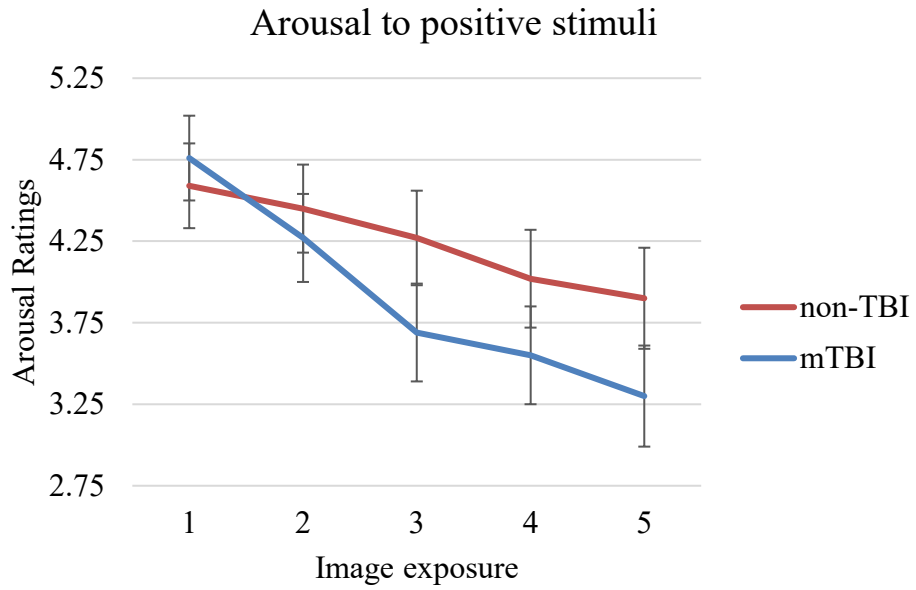


Figure 4.3: Habituation of arousal ratings.

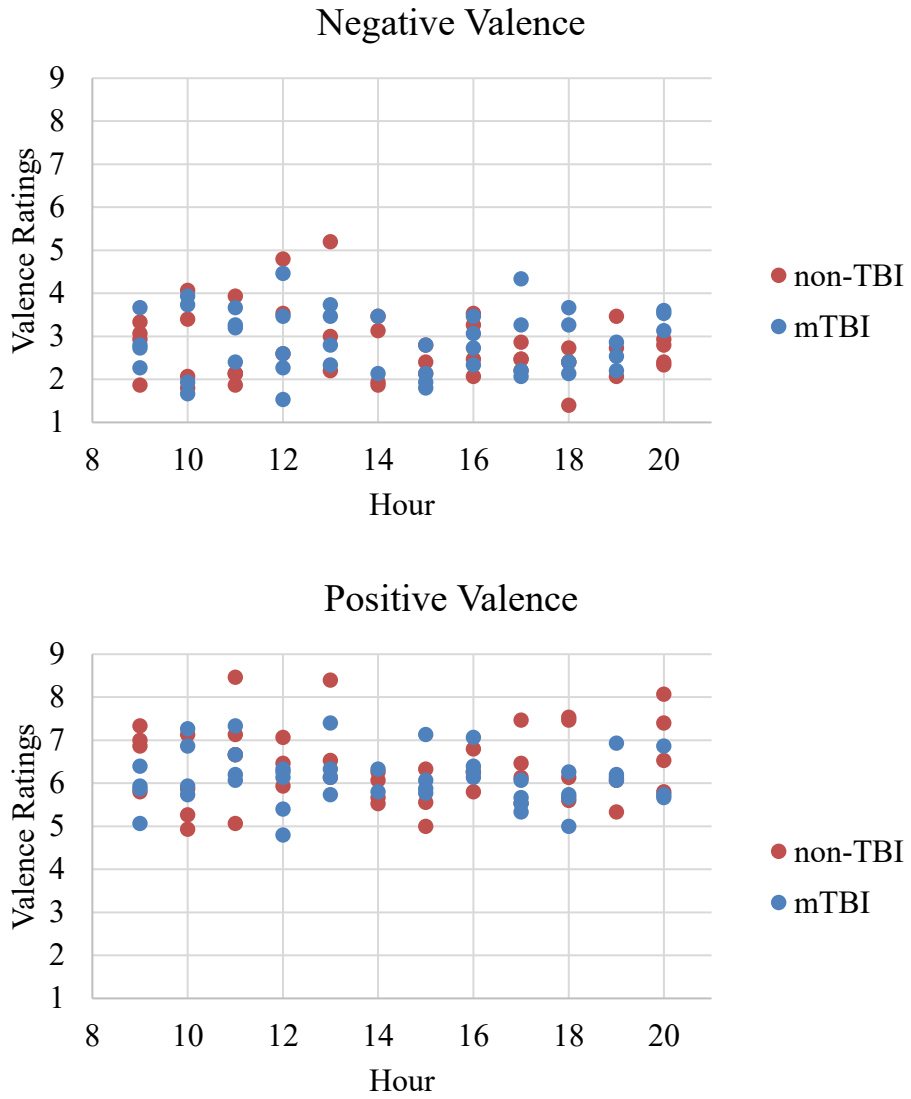


Figure 4.4: Valence ratings by hour of testing.

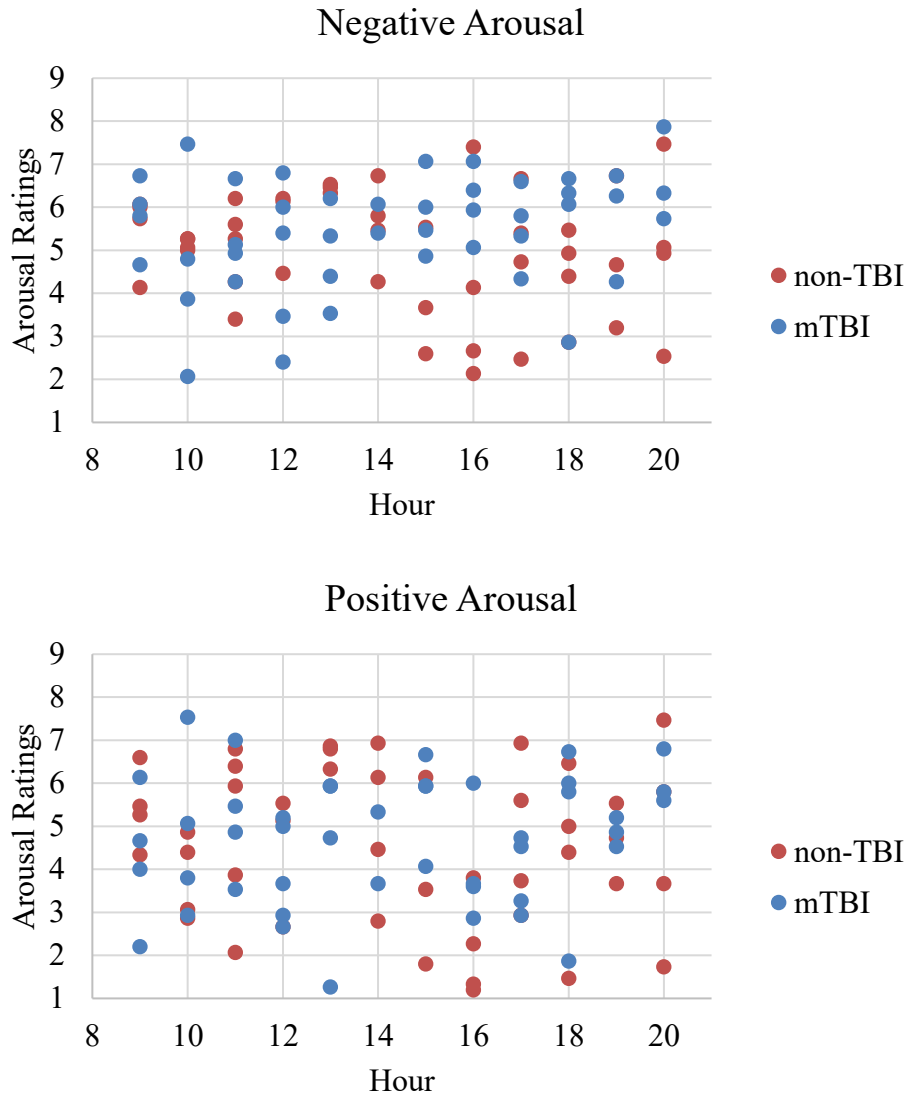


Figure 4.5: Arousal ratings by hour of testing.

## CHAPTER 5

### GENERAL DISCUSSION

#### A. Chronic mTBI

mTBIs are pervasive: no age group, socioeconomic class, or gender is immune to suffering from an mTBI. In adolescents and young adults, sports-related concussions are common. With increasing participation in high school and collegiate sports, mTBI diagnoses in sports are estimated to increase by 15.5% annually (Lincoln et al., 2011). In active duty soldiers, mTBIs are even more prevalent. It is estimated that up to 40% of all active duty soldiers from Operation Enduring Freedom/Operation Iraqi Freedom have or will sustain at least one mTBI while on active duty (Hoge et al., 2008; Terrio et al., 2009). With the increase in sports participation, and with continued deployment of US soldiers, there is a large cohort of young adults who are at a high risk of sustaining an mTBI. Although the immediate, transient effects of mTBI (e.g., dizziness, headache) are well-established, less is known about the chronic, permanent effects of mTBI.

Yet work on chronic mTBI is critical. When mTBI sufferers resume normal activities (e.g., re-immerses in college classes, return to work, resume life following combat), symptoms that were thought to have resolved – and that may impact quality of life and functionality – may re-emerge for a minority of persons. Identifying emotional sequelae of mTBI, and identifying who continues to have post-concussive symptoms, can provide insight into the long-term effects that these individuals may have in the chronic stages of mTBI. Importantly, there are no clear injury characteristics (e.g., length of loss of

consciousness, severity of post-traumatic amnesia) that predict who will recover normally and who will have prolonged recovery. By characterizing long-term mTBI-induced behavioral differences (and their potential mental health consequences), we can retroactively assess whether any of these injury characteristics predict the outcome.

Characterizing the outcomes of chronic mTBI may also clarify the effects of comorbidities. For instance, it can be difficult to distinguish the effects of mTBI from PTSD, because both injuries share common symptoms (e.g., depression/anxiety, irritability, fatigue; Stein & McAllister, 2009). Furthermore, it is difficult to determine the appropriate treatment course given that these disorders have similar presentations (Vasterling, Verfaellie, & Sullivan, 2009). In a pilot study of Cognitive Processing Therapy (a common treatment for individuals with PTSD), treatment completion rate was lower in individuals with PTSD and chronic mTBI than those with only PTSD (Davis, Walter, Chard, Parkinson, & Houston, 2013), suggesting certain features of chronic mTBI may be incompatible with specific clinical treatments. Given this, identifying the emotional sequelae associated with chronic mTBI (in isolation) lays the groundwork for future studies in which mTBI and other diagnoses overlap.

### **B. The Current Work**

Given the points outlined above, I focused my dissertation on a chronic mTBI population. These chapters focus on three distinct categories of sequelae associated with mTBI: sleep, cognition, and emotion. Specifically, in the three chapters in this dissertation, we have explored both sleep- and wake-dependent processes in chronic mTBI. In the first

project (**Study 1**), we did not detect abnormalities in sleep-dependent memory consolidation of stimuli with neutral emotional valence in a chronic mTBI sample relative to controls. Interestingly, consolidation was preserved in this population, even though sleep architecture was altered. In the second project (**Study 2**), we detected irregularities in sleep-dependent memory consolidation in the mTBI sample. These irregularities were only present for consolidation of emotional stimuli, not neutral stimuli. Additionally, wake-dependent consolidation in the mTBI group was unexpectedly superior relative to controls, suggesting the mTBI group had both shortcomings and enhancements relative to uninjured controls. We also found differences in wake-dependent emotion habituation, such that the mTBI group seemed to habituate to emotional stimuli less than controls. However, in **Study 3**, when attempting to replicate the habituation results with a more targeted experimental paradigm, we found opposing findings.

Importantly, we have not yet identified specific mechanisms that increase the risk for mood disturbances. In **Study 2**, although sleep- and wake-dependent irregularities were identified, we did not probe mood symptomology, so we are not aware of whether the identified irregularities are maladaptive or benign. Furthermore, in **Study 3**, although we identified behavioral habituation differences between groups, group differences were not predictive of mood symptomatology (although, in the combined sample, arousal reactivity and Zygomaticus habituation were predictive of symptomatology). In future work, we aim to continue probing the relationship between the alterations in sleep- and wake-dependent processing and how these may impact mood disturbances in chronic

mTBI populations. However, in order to gain more clarity about individuals who have ongoing effects of mTBI, participants with mTBI-related complaints will be specifically recruited in addition to participants who have no ongoing mTBI-related complaints.

### **C. Miserable Minority**

In the mTBI field, it is still debated whether mTBI causes long-term deficits (Ruff, 2011). A meta-analysis found that although there are cognitive difficulties that occur immediately after mTBI, there is little effect on cognition 7 days after injury (Belanger & Vanderploeg, 2005). However, others argue that these meta-analyses hide the subset of individuals who still suffer as a result of mTBI (Rohling, Larrabee, & Millis, 2012). Anecdotally, it is clear that a subset of mTBI suffers *believe* they have long-term deficits as a result of their injury, leading researchers to attempt to identify and quantify these deficits. The work presented in this dissertation aimed to identify these factors as well.

In Study 3, we found that when mTBI participants are divided by ongoing post-concussive complaints, the subset with the most complaints had significantly higher levels of depression, anxiety, and PTSD symptomatology. However, although this mTBI subgroup, by definition, reported more symptoms than the low-complaining mTBI subgroup, we were not able to detect clear behavioral or emotional differences between the mTBI subgroup and the non-TBI group with our measures. A lack of differences between groups suggests that although the MM group continues to have ongoing complaints, they do not show behavioral differences from a general population.



Therefore, based on these data and neurocognitive data discussed above, we conclude that this mTBI group is relatively unimpaired overall.

#### **D. Similarities and Differences Between Studies**

There are a number of similarities between the three conducted studies (Table 18). Specifically, in all studies, study participants (in either the mTBI or non-TBI groups) did not differ in age, years of education, or gender proportion. When comparing mTBI participants between studies, samples did not differ significantly in number of mTBIs sustained or time since mTBI. However, valence ratings for negative images were more neutral in **Study 3** than in **Study 2** for the non-TBI group ( $t(83) = 6.59, p < .001$ ) and the mTBI group ( $t(83) = 7.30, p < .001$ ). As mentioned in **Chapter 4**, we intended to include more neutral negative images in **Study 3** so that negative and positive images could be matched for valence. Therefore, these group differences were expected. Emotion ratings for negative arousal, neutral valence, and neutral arousal did not differ between studies.

The studies differed considerably in their hypotheses, measures, and findings (Table 19). Importantly, although there is some evidence of deficits in the chronic mTBI population (e.g., sleep-dependent memory consolidation of emotional stimuli in **Study 2**), there also is evidence that mTBI performed better than controls on some measures (e.g., wake-dependent emotional memory consolidation in **Study 2**, cognitive performance in **Study 3**). In general, there is no distinctive pattern between studies. For instance, we did not see cognitive deficits in every study, and we did not see emotional deficits in every study.

This pattern of results may be due to the inclusion of a diverse mTBI sample. Future studies should focus on mTBI subgroups (e.g., those with ongoing post-concussive symptoms, those with a certain number of mTBIs) rather than comparing a general mTBI population with a control group.

### **E. Pluses and Minuses**

There are a number of limitations across **Studies 1-3**. First, each study used self-reported mTBI. Self-reported mTBI presents a number of drawbacks: individuals may possibly mis-identify (or mis-remember) the details of a head injury and no objective assessment of mTBI severity was available (e.g., via the Vestibular/Ocular Motor Screening). The inclusion of self-reported mTBI participants likely adds error variance to the sample, making it difficult to statistically detect effects. To remedy this issue, my future projects will be conducted in a facility where participants have confirmed doctor-diagnosed mTBIs.

These studies would have also been improved if they contained pre-injury/pre-morbid data. Specifically, pre-morbid tests of cognitive or emotional functioning would allow us to assess change over time, rather than focus on cross-sectional group differences.

Although we could have used self-reported pre-morbid data, these data are unfortunately not reliable. Several researchers have documented the “good old days” bias in mTBI (Lange, Iverson, & Rose, 2010; Lange et al., 2010). The good old days bias causes participants to underestimate cognitive or mental health problems they had before injury, making them think that symptoms have increased as a result of the injury, although they

might not have changed. The authors of these studies demonstrate that participants often recall having no symptoms (e.g., never experiencing fatigue or lack of focus) in their time prior to concussion, which is unlikely. To alleviate this issue, according to those authors, a clinical interview should be used in conjunction with questionnaires, so that participants can be “reminded” of pre-morbid symptoms. Although the current studies did not probe pre-morbid symptomatology, if I conduct a study gauging pre-morbid symptoms in the future, I will incorporate both a questionnaire and a structured interview to gather a more complete picture of pre-morbid functioning.

Studies 1-3 are limited by the inclusion of a young adult age range. Young adults are not representative of the general mTBI population because mTBIs are sustained across the lifespan. The impact of mTBI on the brain differs based on age at the time of injury. Specifically, in childhood, during which the brain is undergoing several “critical periods” of development, an mTBI can be especially damaging (Choe, Babikian, DiFiori, Hovda, & Giza, 2012). Similarly, on the other end of the age spectrum, older adults take longer to recover from mTBI than young adults with similar injury severity (Mosenthal et al., 2004). Given the complicating effects of young and old age on mTBI recovery, young adults were utilized to minimize extraneous variables, even though, as mentioned, a college-attending population tends to have higher-than-average mental health issues. Nevertheless, this work in young adults is an important starting point that will guide future work in other populations.

As has been noted several times, **Studies 1 and 2** are limited because they did not include mood outcome variables, such as depressive or anxiety symptomology. They also did not include neuropsychological testing, with the exception of the Digit Span Forward test. Although the Digit Span Forward test was included as a measure of working memory, it was later determined that there are more sensitive tests (e.g., the Digit Span Backward) that could have been utilized. In **Studies 1 and 2**, therefore, we are limited in our ability to draw conclusions about cognitive or emotional differences between groups. This limitation is especially regrettable in **Study 2** because we detected differences in emotion memory between groups (both enhancements and reductions), but we are unable to determine whether these emotional differences are predictive of mood outcomes or whether these differences are benign. To address these weaknesses, we included neuropsychological measures in **Study 3**.

These three studies also had strengths. For instance, all studies had adequate statistical power to detect the effects of interest (with the exception of exploratory regressions in **Studies 2 and 3**). The studies included both behavioral data and physiological data. For instance, in **Studies 1 and 2**, polysomnography was recorded to assess whether experimental groups differed in sleep architecture or characteristics. The inclusion of sleep data allowed us to determine whether sleep-dependent differences between groups were related to sleep architecture differences, thus linking neural brain correlates with behavior. In **Study 3**, physiological measures of emotion (e.g., heart rate, skin conductance, EMG tone) were included to supplement behavioral ratings of emotional

images. These measures allowed us to assess whether autonomic differences between groups mirrored those seen in behavioral ratings and also allowed us to assess whether there were autonomic abnormalities in the mTBI group relative to controls. Therefore, these data provided the opportunity for a broad and dynamic view of emotion following mTBI, and, to our knowledge, these are a few of the only extant studies to have probed both behavior and physiology following chronic mTBI.

### **F. Contributions/Importance of This Work**

The three studies conducted here make a substantial contribution to the mTBI literature.

**Study 1** was the first experiment to attempt to link two existing ideas from the mTBI literature: (1) sleep is altered following chronic mTBI, and (2) cognition is potentially altered following mTBI (although our data, in retrospect, do not support this notion).

Although researchers in the field surmised that mTBI-induced sleep alterations may lead to negative cognitive consequences, this idea had never been tested. Even though we did not detect differences in neutral sleep-dependent memory consolidation, the novelty of this study was outlined in a commentary written about **Study 1** (Durrant, 2015):

“...until now there has been almost no investigation of the role of sleep disturbance in memory deficit where the sleep disturbance occurs as a result of another condition...

As such, the new study from Mantua et al. (2015) is especially welcome and will hopefully herald a new era of investigation into the contribution of co-morbid sleep disturbances to memory deficits not only in mTBI, but a wide variety of other

conditions where disturbed sleep and reduced memory are present (such as Alzheimer's Disease and Parkinson's Disease, to give two obvious examples).”

This work led to the development of **Study 2**, which focused on emotional alterations that may occur as mTBI-induced sleep alterations. Although it had been hypothesized that sleep alterations following mTBI might contribute to disrupted emotional processing (e.g., sleep-dependent memory consolidation of emotional stimuli), this idea had not been tested. We demonstrated that both sleep- and wake-dependent memory differences occur in individuals with a chronic history of mTBI. Altered sleep architecture (i.e., less REM sleep) statistically predicted sleep-dependent memory alterations. This work suggests that, indeed, sleep changes following mTBI may disrupt sleep-dependent emotional processing and presents a potential mechanism linking poor sleep with mood disturbances in this population. Interestingly, however, although sleep-dependent consolidation is reduced in an mTBI population, wake-dependent consolidation was enhanced, suggesting some cognitive abilities are superior in this population. Further work could test if sleep- and wake- alterations could contribute to downstream emotional disruptions during subsequent wake.

In **Study 2**, there were incidental findings that suggested the chronic mTBI population has blunted habituation. Given this, **Study 3** sought to replicate and expand these findings. There is a large gap in the mTBI literature: although it was established that some persons with a history of chronic mTBI are at increased risk for mood disturbances in the 1980s, little (or no) work has been done to pinpoint which specific emotional

components are altered in this population. We surmised that a lack of habituation may be a contributing factor to mood disturbances in this population. We found mTBI subjects had enhanced (rather than blunted) habituation, yet group differences in habituation did not predict group differences in mood symptomatology. Although there have been many studies that have detected mental health alterations in this population, to our knowledge, this is the first study to examine factors that contribute to depressive and anxiety symptoms in this population. Therefore, we feel this study contributes conceptually to the field of mTBI.

These studies also provide experimental contributions to the field. To our knowledge, this is the first experiment to test for positive habituation using images (rather than facial expressions (Wright et al., 2001). It is also the first study to attempt to link habituation of positive or negative images (and physiological habituation) with anxiety symptomatology (one other study has linked depression with habituation Neumeister et al., 2006).

Additionally, **Study 2** was the first study to characterize ratings of negative IAPS images in chronic mTBI, and **Study 3** was the first to characterize ratings of positive IAPS images. Therefore, our results can be used as groundwork for future experiments that aim to probe emotional functioning following mTBI.

	Study 1		Study 2		Study 3	
	Non-TBI	mTBI	Non-TBI	mTBI	Non-TBI	mTBI
<b>Demographics</b>						
Sample size	26	30	41	40	45	45
Age	19.6 ± 1.3	20.3 ± 1.5	20.2 ± 19.9	19.9 ± 1.5	19.9 ± 1.3	20.0 ± 1.6
Gender (%F)	70	58.6	70	75.6	42.2	42.2
Years of Ed.	14.3 ± 1.2	15.0 ± 1.3	14.9 ± 1.3	14.6 ± 1.3	14.3 ± 1.0	14.3 ± 0.9
<b>TBI Characteristics</b>						
Num. of mTBI		1.69 ± 1.1		1.65 ± 1.2		2.2 ± 1.6
Years since mTBI		4.35 ± 3.14		3.7 ± 2.9		3.3 ± 1.5
<b>Emotional Stimuli</b>						
Negative Valence			<b>1.8 ± 0.5</b>	<b>1.9 ± 0.4</b>	<b>2.7 ± 0.8</b>	<b>2.9 ± 0.7</b>
Negative Arousal			5.12 ± 2.2	5.62 ± 1.6	1.9 ± 1.1	5.47 ± 1.3
Neutral Valence			4.9 ± .12	4.9 ± .14	5.1 ± .80	5.1 ± 0.5
Neutral Arousal			2.4 ± 1.2	2.3 ± 1.2	1.9 ± 1.1	1.9 ± 1.0

Table 5.1: Quantitative comparison of Studies 1-3. Bold indicates statistical significance between studies.



	<b>Study 1</b>	<b>Study 2</b>	<b>Study 3</b>
Hypotheses	Sleep-dependent memory consolidation of neutral stimuli will be reduced in a chronic mTBI sample	Sleep-dependent memory consolidation of emotional stimuli will be reduced in a chronic mTBI sample	(1) Emotion habituation will be reduced in a chronic mTBI sample (2) Reactivity will be blunted in a chronic mTBI sample, circadian rhythmicity will play a role (3) Habituation and reactivity will predict mood disturbances
Findings	Sleep-dependent memory consolidation was exhibited in both mTBI and non-TBI groups equivalently	(1) mTBI participants had poorer sleep-dependent memory consolidation [lower memory discrimination hit rate] (2) mTBI participants had greater wake-dependent memory consolidation [lower false positives]	(1) mTBI participants habituated arousal ratings more quickly (2) No group differences for reactivity (3) Reduced arousal ratings for positive images predicts higher depressive symptoms; higher habituation of Zygomaticus tone predicts higher combined symptomatology
Hypotheses supported?	No	Partially	No
Cognitive tests	No group differences in Digit Span Forward Test	No group differences in Digit Span Forward Test	mTBI outperformed non-TBI in Verbal Fluency Word Pair condition, no group differences for Verbal Fluency Set Switching, Digit Span Backwards, or Stroop
Mood symptoms	Tests not administered	Tests not administered	mTBI group had higher anxiety symptomatology than non-TBI group
Evidence of impairment in mTBI sample	None	Yes, for sleep-dependent memory consolidation [memory discrimination hit rate]	Yes, for mood disturbances [anxiety symptomatology]
Evidence of enhancement	None	Yes, for wake-dependent memory	Yes, for Verbal Fluency [Word Pair condition]

in mTBI sample		consolidation [false positives]	
Equivocal/ambiguous group differences	None	Yes, group differences in valence habituation.	Yes, group differences in arousal habituation

Table 5.2: Qualitative comparison of Studies 1-3.

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