Photosensitivity and Pain in Traumatic Brain Injury

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Abbreviations

ACC – anterior cingulate cortex
AMPA - α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AMY - amygdala
ANOVA - analysis of variance
ANCOVA - analysis of covariance
AUC - area under the curve
aTBI – asymptomatic traumatic brain injury
BAT-L - Boston Assessment of Traumatic Brain Injury-Lifetime
BMI - body mass index
CPM - conditioned pain modulation
CPWL - chronic pain without limitations
CRPS - complex regional pain syndrome
CTE - chronic traumatic encephalopathy
DNIC - diffuse noxious inhibitory control
DoD – Department of Defense
DSM-5 - Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
EEG - electroencephalography
EKG – electrocardiogram
EMR - Electronic Medical Record
EMG - electromyography
EOG – electrooculography
fMRI – functional magnetic resonance imaging
FOSQ-10 - Functional Outcomes of Sleep Questionnaire-10
FIQR – Fibromyalgia Impact Questionnaire Revised
HICP – high impact chronic pain
HPA - hypothalamic-pituitary-adrenal axis
HTEC - Head Trauma Event Characteristics interview
ipRGC - intrinsically photosensitive retinal ganglion cells
ISI - Insomnia Severity Index
INS - insula
LOC - loss of conscious
MBM - Michigan Body Map
MRI - magnetic resonance imaging
NREM - non-rapid eye movement
NSI – Neurobehavioral Symptom Inventory
OEF/OIF - operation enduring freedom/operation Iraqi freedom
OHSU – Oregon Health & Science University
OPN - olivary pretectal nucleus
OSU TBI-ID - Ohio State University Traumatic Brain Injury Identification Method
OSA - obstructive sleep apnea
PAG - periaqueductal gray
PAP - positive airway pressure
PB - parabrachial nucleus
PCL-5 - post-traumatic stress disorder checklist for DSM-5
PHQ-9 - Patient Health Questionnaire 9

PCS - post-concussive syndrome
PROMIS - patient-reported outcomes measurement information system
PSG - polysomnography
PTA - post-traumatic amnesia
PTSD - post-traumatic stress disorder
REM - rapid eye movement
RVM – rrostral ventromedial medulla
ROC- Receiver Operator Curves
RPQ - Rivermead Post Concussive Questionnaire
SCN - suprachiasmatic nucleus
SIQR – Symptom Impact Questionnaire Revised
SWD – sleep wake disturbances
sTBI – symptomatic traumatic brain injury
TBI – traumatic brain injury
mTBI – mild traumatic brain Injury
mPFC - medial prefrontal cortex
TST - total sleep time
VPT - visual photosensitivity thresholds
VAPORHCS - Veteran Affairs Portland Health Care System
WASO - wake after sleep onset
WHODAS - World Health Organization Disability Assessment Schedule

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Abstract

Humans' ability to navigate through the world relies on our set of senses, yet they are often unreliable and constantly betray us. There are numerous examples of how the human mind is vulnerable to hallucinations of sight and sound, but our sense of touch and pain can also deceive us.

Through central mechanisms of pain modulation, our perception of touch is easily manipulated by circuitry in the central nervous system. This is often adaptive, as it dulls our pain in dire situations of stress and survival. But other times, it turns maladaptive and works against us. This is the radical issue for those who suffer from chronic pain, when neurons turn against their host causing them to feel pain that shouldn't be.

This type of pain is not due to tissue damage or peripheral pain sensors, but is instead caused by hyper-responsive neurons located in the central nervous system. Roughly 50 million Americans suffer from chronic pain, but particularly vulnerable are those sustaining a traumatic brain injury (TBI), a medical condition caused by a severe blow to the head disrupting normal brain function. There are a range of acute symptoms following such an injury, but there is also an unlucky subset of individuals who go on to suffer from chronic symptoms, which can linger for months of years. Poor sleep, mood disorders, and physical disabilities have all been reported, but perhaps the most common is chronic pain.

We know little on why some TBIs quickly resolve, while others do not. One hint could be a common symptom shared among various chronic pain disorders and TBI: photosensitivity. Patients suffering from chronic pain syndromes often have increased sensitivity to light, as do TBI subjects. Recent research has demonstrated that nociceptive neurons in the brainstem can be activated by light, suggesting extreme photosensitivity and chronic pain are both symptoms of a dysfunctional central pain circuit. If true, photosensitivity thresholds could be used as markers of

chronic pain due to altered central pain processing. This could be used not only in subjects with TBI, but other populations susceptible to centralized chronic pain, for example, individuals with Post Traumatic Stress Disorder (PTSD).

To examine this, I first determined if differences in chronic symptoms following a TBI, including chronic pain, were related to differing TBI evaluation methods. We found that the three most common TBI screening methods (clinical interview, medical chart review, and self-report) resulted in significantly different TBI rates. Subjects who received a positive diagnosis across all methods, were also the ones that exhibited chronic TBI symptoms several years after injury.

I next analyzed photosensitivity thresholds using an Ocular Photosensitivity Analyzer (OPA) in subjects with and without TBI. TBI subjects had significantly lower thresholds than control subjects, but this effect was driven mostly by TBI subjects reporting chronic post-concussive symptoms. Photosensitivity was also strongly correlated with chronic pain scores in both TBI and control subjects.

Lastly, I examined the effect of comorbid TBI+PTSD on sleep quality, chronic pain, and photosensitivity levels. Both PTSD and sleep disturbances are strongly linked to chronic pain, and we found that subjects with comorbid TBI+PTSD reported extremely high levels of pain and sensory sensitivity, suggesting that PTSD could exacerbate these TBI symptoms, and that poor sleep quality was strongly correlated with pain levels.

Chapter 1: Introduction

For the past three years I have been researching the long-term effects of traumatic brain injuries (TBI). These injuries are defined as any brain pathology or disruption in brain function as a result from an external force (Wortzel & Arciniegas, 2014). TBIs are extremely common, with the Centers for Disease Control approximating that 2.5 million people in the United States sustain one each year (Center for Disease Control and Prevention, 2016).

I met hundreds of these individuals through my research, each exposing me to their own unique life experience post-injury. Some described the injury as an almost non-event, an inconsequential blip in an otherwise healthy life — small concussion during a football game, or some minor whiplash from a car accident. Just a few minutes, sometimes hours, where they experienced some negligible headaches or disorientation. They briefly described their quick recovery as those trivial symptoms soon vanished and their lives went back to normal.

But there was another side to these injuries: many patients suffered an array of severe symptoms that lasted months, sometimes years. There was no way to link these symptoms directly to the initial brain injury, but there was a clear pattern in the data: those with a history of TBI, even mild ones, were at risk of developing an array of chronic symptoms later in life. For example, one subject, a United States Air Force Veteran, described a relatively minor accident he had during a parachuting training exercise, a standard jump he had already practiced dozens of times. It had started off smoothly enough, but during this jump he misjudged his landing and ending up twisting his ankle. He tried rolling onto his shoulder to brace for his fall, but ended up slamming the right side of his head directly onto the landing field. He immediately lost consciousness, and when he came to, a fellow Airman was standing over him exclaiming that he had been “out cold” for about the last 30 seconds. Afterwards, he described feeling disoriented,

confused, and slightly nauseated, all common acute symptoms of TBI (American Psychiatric Association, 2013a). He received no medical treatment from the on-site physician despite being quickly diagnosed with a mild concussion. After an hour or two, his symptoms eventually passed, but the subject described how he continued to have issues sleeping, problems concentrating, and severe headaches in the weeks that followed. This again is unsurprising, as poor sleep (Barshikar & Bell, 2017; Parcell, Ponsford, Rajaratnam, & Redman, 2006; J. L. Ponsford, Parcell, Sinclair, Roper, & Rajaratnam, 2013), cognitive impairment (Bleiberg et al., 2004; Karr, Areshenkoff, & Garcia-Barrera, 2014; Landre, Poppe, Davis, Schmaus, & Hobbs, 2006), and headaches (D'Onofrio et al., 2014; Riechers II, Walker, & Ruff, 2015) are all common symptoms that can linger for weeks after a TBI. However, at the time of testing, over 10 years after his parachuting accident, the subject continued to endorse severe insomnia, mild depression, cognitive issues, and widespread pain including chronic headaches.

Of course this is just an anecdote, and even in this individual's story there was no apparent direct connection between the initial brain injury and the array of symptoms he suffered from afterward. In fact, there is a large body of evidence that symptoms from mild TBI (mTBI), which make up over 75% of all TBIs, generally resolve within a few days or weeks after the initial injury (Control & Prevention, 2003; Henry, Elbin, Collins, Marchetti, & Kontos, 2016; Kamins et al., 2017; McCrory et al., 2013). Consistent with this idea, early research on TBI patients showed only limited and transient behavioral changes, and most researchers did not consider that any long-term symptoms could persist in these individuals (Karr et al., 2014; McCrea et al., 2003). However, more recent studies have begun focusing on a subset of TBI subjects which experience persistent TBI symptomology lasting several years or even longer. My research has focused on these long-term consequences of TBI.

Post-Concussion Syndrome and Chronic TBI

The term post-concussion syndrome (PCS) has been used by both the DSM-IV and the ICD-11 to describe individuals who report TBI symptoms for at least 3 months following the initial insult, a substantially longer recovery time than average (American Psychiatric Association, 2013). However, the term PCS has been controversial since its conception, with differing opinions on its diagnostic criteria and etiology. The field still lacks a universal definition of which symptoms should qualify as post-concussive, and there is great debate among researchers whether PCS is actually a biological effect of TBI, or rather a psychosocial response to the stress of the injury (Mayer, Quinn, & Master, 2017). This dispute led to changes in the updated DSM-5, which no longer includes this diagnosis and instead recommends clinicians to diagnose patients with persistent psychological symptoms as "major or mild neurocognitive disorder due to traumatic brain injury" (American Psychiatric Association, 2013). This reframing illustrates the difficulty of studying such a population, since neither researchers nor clinicians have agreed on an empirical definition for the disorder. As a consequence, estimates of the prevalence of long-term symptoms have a wide, almost uninterpretable range between 5% - 79% of individuals that have sustained a TBI (Bazarian et al., 1999; Iverson, 2005; Rimel, Giordani, Barth, Boll, & Jane, 1981; Rutherford, 1989).

One thing that is agreed on is that a subset of individuals who experience a TBI will go on to have long-term effects and multifaceted sequelae following the injury. These often include sleep disturbances (Mantua, Henry, Garskovas, & Spencer, 2017; Sandsmark, Elliott, & Lim, 2017), emotional disorders (Jorge, Robinson, Starkstein, & Arndt, 1993; J. Ponsford, Draper, & Schönberger, 2008), poor cognition (Rabinowitz & Levin, 2014), and perhaps most common, chronic pain (Beetar, Guilmette, & Sparadeo, 1996; Faux & Sheedy, 2008; Lahz & Bryant, 1996;

Ofek & Defrin, 2007; Seal et al., 2017). I will refer to this constellation of symptoms in these individuals as “chronic TBI”.

Unfortunately, there is as yet no reliable method to predict who is at risk for chronic TBI. Many individuals who sustain a mTBI will go on to suffer from chronic TBI, while some individuals sustaining a severe TBI will fully recover. One possibility in differences in these chronic post-concussive symptoms could be how the original TBI was diagnosed, which I will further examine in Chapter 2.

Chronic Pain and TBI

Arguably the most prevalent symptom in those with chronic TBI is unexplained chronic pain, with one meta-analysis showing that more than half of individuals with a TBI go on to experience some sort of long-lasting pain disorder (Nampiaparampil, 2008). Chronic headaches are the most common pain complaint in this population, but many patients report widespread pain in multiple body regions including lower back, shoulder, and neck (Nampiaparampil, 2008). Some are also diagnosed with complex regional pain syndrome (CRPS), which can include a wide range of painful somatic sensations in different body areas (Gellman et al., 1992). Regardless of where the pain is manifest, those with chronic TBI are more likely to go on to experience some form of chronic pain later in life.

Chronic pain is often debilitating and affects millions of Americans, with and without TBI (Dahlhamer et al., 2018). The annual cost of chronic pain, due to medical expenses and lost income, exceeds several hundreds of billions of dollars, potentially a greater financial loss than any other individual disease or disorder (Gaskin & Richard, 2012). But money is far from the greatest impact of chronic pain. It can cause severe physical impairment and restriction in daily living activities including cleaning, dressing, exercising, working, and maintaining social

relationships, ultimately leading to an immense reduction in quality of life (Breivik, Collett, Ventafridda, Cohen, & Gallacher, 2006; O'Brien & Breivik, 2012; Reid et al., 2011). The National Pain Strategy recently introduced the term *high-impact chronic pain* (HICP) to capture this manifestation of chronic pain combined with functional disability (Dahlhamer et al., 2018; Pitcher, Von Korff, Bushnell, & Porter, 2019). This term provides an interesting distinction between patients who suffer from persistent pain but otherwise have little disability, and those who experience comorbidities and substantial disability. The multidimensional symptomology of HICP and chronic TBI mirror one another in several ways. Both have high levels of disability are associated with numerous comorbidities, and both are smaller, more severely affected, subsets of a larger clinical population. This suggests that chronic TBI subjects that are experiencing persistent pain and multiple comorbidities should be classified under the HICP umbrella. But several questions remain, including what comorbidities or psychophysiological profiles are associated with HICP.

Central Sensitization

Even though chronic pain has been studied as far back as ancient Egypt and Greece (El Ansary, Steigerwald, & Esser, 2003; Mavrogenis, Saranteas, Markatos, Kotsiou, & Tesseromatis, 2019), much of its etiology remains poorly understood. What we do know is that chronic pain, defined as persisting at least three months beyond normal healing, often does not involve any ongoing tissue damage and may not be directly tied to the activation of sensory neurons in the peripheral nervous system (Merskey, 1986). Instead, it is more likely due to a heightened, or "sensitized", state in pain-processing circuits located in the spinal cord and brain (Woolf, 2011). This "central sensitization" causes normally painful stimuli to be perceived as more intense, and

innocuous stimuli to be perceived as painful. This increased sensitivity is referred to as "hyperalgesia."

Early rodent work from the 1980's demonstrated that sensory transmission neurons in the central nervous system exhibited lowered thresholds and increased excitability after they are repeatedly activated (Cook, Woolf, & Wall, 1986; Woolf, 1983). One mechanism for this phenomenon is long-term potentiation, where repeated activation of central pain circuits results in an upregulation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor channels at the synapse and increased protein synthesis and neurotransmitter release at the presynaptic membrane (Sandkühler, 2007). This work also demonstrated that input from peripheral non-nociceptor primary sensory fibers could amplify neural responses in pain-encoding nociceptive fibers, indicating the role of the central nervous system to induce hyperalgesia (Woolf, 2011).

More recent work has looked at the contribution of descending *pain-modulating* systems to induce chronic changes on pain perception. Several regions of the midbrain and brainstem, including the periaqueductal gray (PAG), rostral ventromedial medulla (RVM), and parabrachial nucleus (PB), can amplify or suppress the pain response (Chen & Heinricher, 2019a; Roeder et al., 2016). For example, a subset of neurons located in the RVM known as "ON-cells" and "OFF cells," send descending projections from the brainstem to the dorsal horn of the spinal cord, where they synapse with sensory afferent terminals, and directly modulate their activity (Fields, Malick, & Burstein, 1995; Zhang et al., 2015). Work from the Heinricher lab has demonstrated that these neurons can become sensitized in models of chronic pain (Chen & Heinricher, 2019a; Cleary & Heinricher, 2013), contributing to hyperalgesia and that they can be recruited by higher structures, such as the amygdala (AMY), anterior cingulate (ACC), insula (INS), and hypothalamus, particularly in the context of stress (Chen & Heinricher, 2019a, 2019b; Martenson,

Cetas, & Heinricher, 2009; McGaraughty & Heinricher, 2002). This fits in nicely with other work demonstrating "top-down' mechanisms of central sensitization, including studies on diffuse noxious inhibitory control (DNIC), where dorsal horn responses to a noxious stimulus are inhibited by a second, spatially distant, noxious stimulus. This DNIC response is often attenuated or even eliminated in animal models of chronic pain (Le Bars, Dickenson, & Besson, 1979). This evidence for brain mechanisms of chronic pain emphasizes the critical role of central processing in converting somatic stimuli to the sensory experience that we refer to as "pain."

Central sensitization has been difficult to study directly in humans, due to the invasive nature of studying such a phenomenon. However, behavioral and function magnetic resonance imaging (fMRI) evidence support its contribution to clinical pain states. Similar to the DNIC phenomenon observed in rodents, humans exhibit conditioned pain modulation (CPM) where a noxious input applied to one area of the body can reduce the perception of pain at another distal body area. This has been demonstrated using a variety of stimuli including thermal, mechanical, and cold-pressor pain (Nir & Yarnitsky, 2015). Functional imaging studies have shown that chronic pain patients exhibit differences in brain activation and functional connectivity that relates to increased central sensitization. For example, Pujol and colleagues found that patients with fibromyalgia, a prototypical chronic pain condition that is characterized by widespread musculoskeletal pain, had increased activation in the anterior cingulate cortex (ACC) while receiving pressure stimulation (Pujol et al., 2009). Considering that the ACC is one of the upstream cortical brain regions in the descending pain circuit, this would suggest increased sensitization compared to healthy controls. Functional connectivity studies also show evidence of disrupted pain circuitry in this population, including greater connectivity between pain-related brain regions such as the medial prefrontal cortex, insular cortex, and thalamus (Cagnie et al., 2014; Cifre et al., 2012; Hashmi et al., 2013; Napadow et al., 2010).

These well-documented changes in central processing and descending pain modulation are likely mechanisms of the HICP experienced by many chronic TBI patients because their pain is often widespread and unassociated with the initial injury site. Clinically, it is important to identify which patients are suffering from pain due to central sensitization, and which ones are suffering peripheral damage, because they are fundamentally different from one another and require distinct approaches to treatment (Woolf, 2011). For example, opioids, though frequently prescribed, are generally ineffective for pain due to central sensitization, and can lead to substance abuse disorder (Edlund et al., 2010; Volkow & McLellan, 2016). Moreover, opioids can even *increase* pain in these individuals through a phenomenon of opioid-induced hyperalgesia (Wanigasekera, Lee, Rogers, Hu, & Tracey, 2011).

Identifying chronic pain patients with central etiology would provide valuable information to deliver precision medicine and prescribe appropriate therapeutic options. A quantitative biomarker for central sensitization could help improve diagnosis and treatment in individuals with chronic TBI and HICP. This has been a major goal in my dissertation research, which ultimately led me to the phenomenon of multi-sensory sensitivity.

Multisensory Sensitivity in Chronic Pain and TBI

Humans are constantly bombarded by a variety of sensory stimuli. Although we are not aware of most of these stimuli, they are all unconsciously processed by our brains. Noises, smells, and lights surround us, but our brains attend only to the most salient stimuli, while ignoring irrelevant stimuli. Yet individuals with chronic pain disorders exhibit an increased sensitivity to different mild stimuli across multiple modalities, not just pain. They also show less tolerance for more intense stimuli compared to healthy controls.

Fibromyalgia patients exhibit increased sensitivity to both auditory and olfactory stimuli in this chronic pain population (Geisser, Glass, et al., 2008; Wilbarger & Cook, 2011), which mirrors their increased sensitivity to somatic stimuli. Individuals with chronic migraines also report non-somatic sensitivities such as hyperacusis and intolerance to strong fragrances (Schwedt, 2013; Sjöstrand et al., 2010; Whiting, Marmura, Hegarty, & Keith, 2015). Indeed, recent studies found that sufferers from some pain disorders exhibit multisensory hypersensitivity (Suhnan, Finch, & Drummond, 2017; Wang et al., 2020). But the most common form of non-somatic sensory sensitivity reported in the literature that is associated with chronic pain, seems to be one towards light, or *photosensitivity*.

Patients with fibromyalgia report photosensitivity and recent research has quantified this hypersensitivity to visual stimuli (Harte et al., 2016; Martenson et al., 2016; Watson, Buchwald, Goldberg, Noonan, & Ellenbogen, 2009). Similarly, photosensitivity is extremely common among migraineurs and is a common trigger of migraine headache (Katz & Digre, 2016; Noseda & Burstein, 2011; Noseda et al., 2010). There is also fMRI evidence that bright light can cause increased activation in the insular cortex, a major hub for processing emotional pain, in chronic pain patients compared to controls (Harte et al., 2016).

Interestingly, photosensitivity is one of the defining symptoms of a TBI and is often used by clinicians when making a diagnosis (American Psychiatric Association, 2013). The approximate prevalence of photosensitivity in mTBI patients is 50%, which is substantially higher than the 10% prevalence in healthy controls (Capó-Aponte et al., 2017; Truong, Ciuffreda, Han, & Suchoff, 2014). The incidence is even higher in mTBI patients with chronic post-concussive headaches, again revealing a relationship between pain and light sensitivity (Katz & Digre, 2016; Katz, Cohen, & Alexander, 2015). Although there has never been a study that directly analyzed these two symptoms together, these studies provide foundational evidence that

photosensitivity thresholds could be a marker for central sensitization. Taken together, these studies strongly suggest that photosensitivity thresholds are a marker for central sensitization. The two phenomena have not, to date, been examined in the same investigation. Furthermore, how photosensitivity relates to other TBI symptoms, and whether it is exacerbated in individuals with multiple comorbidities, has not yet been examined.

Neural Mechanisms of Photosensitivity and Pain

Despite this connection between chronic pain and light sensitivity, there are only a handful of studies that have directly studied the neurobiology of this relationship. What we do know is that this form of photosensitivity does not rely on the image-forming visual system. In fact, multiple case studies on blinded patients have reported severe photosensitivity, despite not being able to consciously see visual stimuli (Amini, Digre, & Couldwell, 2006; Loh, Weis, van Velthoven, Reiff, & Rössler, 2015). These case reports suggest that the non-image forming irradiance detection system is the more likely source of photosensitivity. This system is independent of visual perception and does not project to the visual cortex. Instead, this circuit relies on melanopsin expressing cells in the retina to help regulate our circadian rhythms and the pupillary light reflex.

There are some animal studies that also point to the irradiance detection system as contributing to photosensitivity in chronic pain. For example, mutant rd1 knockout, which lack any image-forming vision due to lack of input from retinal cones but maintain non-image forming irradiance detection from retinal rods, exhibited photo-aversion (Thompson et al., 2010). They were also significantly less active when exposed to bright light compared to both wild type mice and Rpe65-/- mice, which are a mutant mice strain which maintains their non-image forming visual system but lack image-forming vision. Indeed, this irradiance detection pathway is

indirectly connected to the pain-modulating circuitry described earlier as demonstrated in a recent paper from the Heinricher lab (Martenson et al., 2016). This study confirmed that the nociceptive ON-cells in the RVM can be activated by a light stimulus, while OFF-cells are simultaneously inhibited by it (**Figure 1.1)**. This connection can be eliminated by blocking the olivary pretectal nucleus, a brain region known for its role in irradiance detection. Altered processing in irradiance detection pathways could also contribute to recurrent sleep disturbances common in chronic TBI (Castriotta & Lai, 2001; Orff, Ayalon, & Drummond, 2009; Ouellet, Beaulieu-Bonneau, & Morin, 2015; J. L. Ponsford et al., 2013).

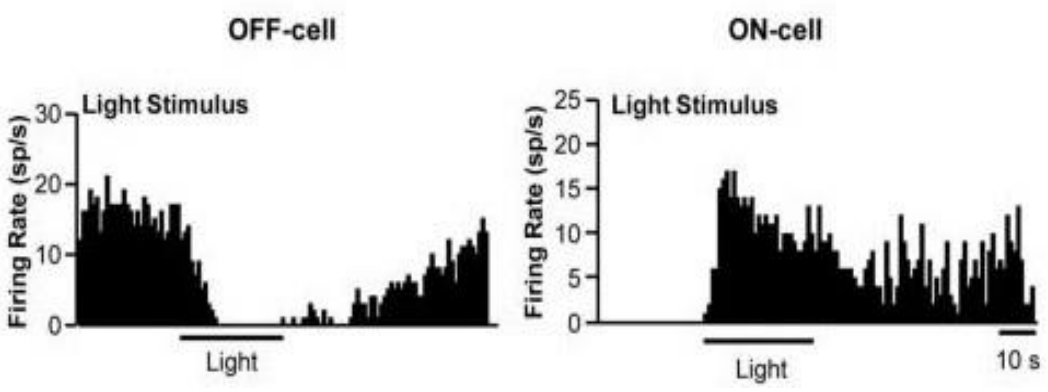

Figure 1.1. Firing rates of OFF-cells and ON-cells during light stimulus
(adapted from Martenson et al., 2016). Anti-nociceptive OFF-cells and pro-nociceptive ON-cells located in the RVM were recorded in anesthetized rats. A 30 second, 1,800 lux light stimulus significantly inhibited OFF-cells and increased ON-cell firing rates.

Relationship between Sleep and Pain

TBI has long been associated with an array of sleep disorders, which can be one of the more disabling symptoms following injury. Studies have found TBI patients are at greater risk for insomnia, hypersomnia, and sleep apnea (Castriotta & Lai, 2001; Orff et al., 2009; Ouellet et al., 2015; J. L. Ponsford et al., 2013), not only during the acute post-TBI phase, but also several years following the initial injury (Balba et al., 2018; Kempf, Werth, Kaiser, Bassetti, & Baumann,

2010; Theadom et al., 2015). There are several theories linking sleep problems with TBI, including changes in melatonin (Shekleton et al., 2010) and hypocretin production (Baumann et al., 2005; Baumann et al., 2009), disruptions to circadian rhythms (Ayalon, Borodkin, Dishon, Kanety, & Dagan, 2007; Boone et al., 2012), and increased prevalence of mood disorders (Jorge et al., 1993).

The fact that TBI can cause sleep issues is important to consider since chronic pain and sleep disturbances are also intricately linked to one another. Although the exact relationship between these disorders remains unresolved, researchers agree that a bidirectional relationship exists between the two. Some studies have shown how poor sleep can intensify pain in patients, while others demonstrate how pain can interfere with sleep. For example, the subjective quality of sleep reported in multiple pain populations has been found to be a predictor for pain intensity the next day (Raymond, Nielsen, Lavigne, Manzini, & Choinière, 2001; Stone, Broderick, Porter, & Kaell, 1997). Conversely, pain intensity ratings in fibromyalgia patients have been used to accurately predict their quality of sleep the following night, likely due to their increased attention towards the pain (Affleck, Urrows, Tennen, Higgins, & Abeles, 1996). Although previous studies have found an association between TBI and chronic pain, or TBI and chronic sleep disorders, there has been little research examining the relationship among all three.

Photosensitivity in Chronic TBI

Taken together, the lines of evidence reviewed above suggest that light could be an important moderator of pain and functional symptoms in individuals who have experienced a TBI, and that photosensitivity could serve as a marker for central sensitization in these individuals. The goal of my project was to analyze the relationship between photosensitivity and chronic pain in individuals with chronic TBI.

As a first step, I considered the multiple, and vastly different, TBI diagnostic tools commonly used by researchers. Different rates of long-term TBI symptomology, including chronic pain, could in part be influenced or explained by the variety of diagnostic methods.

I also adopted more rigorous psychophysical sensory testing to better understand the relationship between pain and photosensitivity in these. Previous studies have relied on subjective measures of photosensitivity, using relatively coarse Likert scales to rank participants' symptoms. To my knowledge, none have attempted to use controlled photic stimuli to accurately quantify photosensitivity levels, nor have pressure pain thresholds been determined in this population. Lastly, the relationship between photosensitivity and the so-called "polytrauma clinical triad," of TBI, chronic pain, and PTSD (Pugh et al., 2014), has yet to be adequately analyzed.

Dissertation aims

Given this background, I attempted to address the following questions in this dissertation: 1) determine how different TBI evaluation methods, obtained simultaneously in the same individuals at high risk for TBI, differed in terms prevalence and severity of chronic TBI symptoms; 2) quantitatively assess photosensitivity thresholds and pressure pain thresholds in subjects with and without TBI using an standardized ocular photosensitivity analyzer and pressure algometry; 3) evaluate the relationship between TBI incidence, chronic pain complaints, and photosensitivity thresholds; and 4) examine whether subjects with a history of comorbid TBI+PTSD exhibit a higher prevalence of photosensitivity and chronic pain complaints compared to subjects with neither or a single disorder.

Chapter 2: Increased chronic post-concussive symptom severity in US Veterans based on different TBI evaluative methods.

[This chapter has been reformatted for inclusion for this dissertation from: **Balba, N.M,** Elliott, J.E, Callahan, M.L., McBride, A.A, Mist, S.D., Butler, M.P., Heinricher, M.M., Lim, M.M. *In-preparation*]

Abstract

Traumatic brain injury (TBI) is an inherently heterogenous injury with multiple modes of evaluation. The purpose of this study was to examine intra-individual variability in TBI determination using three established screening methods and evaluate potential differences in TBI-related symptomology depending on the mode of evaluation. Veterans were recruited from the VA Portland Health Care System (*n*=200) and were evaluated for TBI in three ways: 1) self-report, 2) electronic medical record review, and 3) a structured TBI interview. Participants also completed a battery of validated questionnaires assessing injury symptom severity, current and chronic pain, sleep, and quality of life. Of the total sample, *n*=43 subjects were negative for a history of TBI using all three modes of evaluation. The remaining *n*=157 subjects were grouped according to whether they were positive for TBI based on any one (n=53 composed of n=50 from HTEC and n=3 from EMR), any two, or all three evaluative methods (n=59). Veterans who received a positive TBI diagnosis using all three methods scored significantly higher on surveys measuring TBI symptoms, chronic pain, sleep disturbances, and quality of life compared to Veterans receiving a single type of TBI diagnosis. We found wide discrepancies between the three evaluation methods, which resulted in differences in post-concussive and TBI related symptoms depending on the method used. Subjects who had congruent positive diagnoses across

all three screening tools reported the highest rates of post-concussive symptoms and chronic TBI sequelae.

Introduction

Each year, more than 2.5 million people in the United States sustain a traumatic brain injury (TBI), which is often defined as any type of "structural injury and/or physiological disruption of brain function as a result of an external force" (Faul, Xu, Wald, & Coronado, 2010; O'Neil et al., 2013). However, the incidence of TBI in the US military is considerably higher, with more than 360,000 cases since 2000, and an estimated prevalence of 20% of all active duty members (Department of Defense, 2018). The high prevalence of TBI in Veterans is partly due to the increased risk of suffering a brain injury during military deployment (Regasa, Agimi, & Stout, 2019), but is also due to increased rates following deployment (Brundage, Taubman, Hunt, & Clark, 2015). This ultimately means that US Veterans are a particular vulnerable population marked by poor recovery rates and long-term symptoms.

Several classification schemes exist but in general, injuries range from mild, moderate, to severe. Mild TBI (mTBI) comprises the majority of injuries (>75% in both civilian and Veteran populations), which range from the seemingly innocuous experience of "seeing stars" to any injury with <30 minutes of loss of consciousness (LOC) and <24 hours of post-traumatic amnesia (PTA). Not surprisingly, compared to moderate and severe TBI that have more profound clinical scenarios, mTBI often go undiagnosed or untreated, especially in the military (Tanielian et al., 2008). Consequently, incidents of mTBI are often poorly documented, either in the form of patient's memory or their medical record.

Although most TBI patients are asymptomatic within weeks or a few months following the injury (Cantu, 1998; McCrea et al., 2003; Merrett & McDonald, 1977), several studies have

demonstrated chronic symptoms and long-lasting sequelae. These include an increased incidence of chronic pain (Balba et al., 2018; Beetar et al., 1996; Faux & Sheedy, 2008; Seal et al., 2017), sleep disruptions (Balba et al., 2018; Beetar et al., 1996), sensory sensitivity (Callahan et al., 2016; Dikmen, Machamer, Fann, & Temkin, 2010; J. E. Elliott et al., 2018; Goodrich, Flyg, Kirby, Chang, & Martinsen, 2013), and long-term disabilities (Thurman, Alverson, Dunn, Guerrero, & Sniezek, 1999; Zaloshnja, Miller, Langlois, & Selassie, 2008). A subset of these studies have shown that some symptoms can even last several decades after the initial injury (Balba et al., 2018; J. E. Elliott et al., 2018; R. M. Ruff, Camenzuli, & Mueller, 1996), which could be classified as post-concussive syndrome (PCS).

It remains unknown why some patients with TBI will experience persistent post-concussive sequela and why in others these symptoms spontaneously resolve. This is true in terms of the specific underlying mechanism(s), but also in terms of the variability that exists within the literature. Some in the field believe that chronic post-concussive symptoms are likely due to neurogenic factors related to the initial injury (Iverson, 2005; Ommaya & Gennarelli, 1974), while others have are argued they are due to psychogenic disorders (Alexander, 1995; Ll Wood, 2004). A mix of both altered organic processes and subsequent psychosocial issues (N. S. King, 1996, 2003) also has some support.

A fundamental issue surrounding this question is the considerable variability in terms of how studies define whether patients have a positive or negative history of TBI. This is generally done in one of three ways; 1) based on subject's ability to self-report a history of TBI, 2) based on whether or not a history of TBI is documented within a subject's medical record, and 3) based on a structured clinical interview designed to assist with memory recall. The method used is often study design dependent. For example, retrospective studies using large open-access databases generally rely on self-report questionnaires, while smaller clinical studies are more likely to use

medical record review or a clinical interview. However, it is unclear that each method would lead to consistent rates of diagnoses, as well as whether the long term impact an injury reported by each method would differ.

Each method has a certain degree of inherent limitations. Self-report depends on an individual's understanding of what a TBI is, including being aware of the breadth of diagnostic criteria. These limitations also exist within medical record documentation rates, which are often incomprehensive and may not reflect the entirety of the subject's health history (Hersh et al., 2013), or are inaccurate and may reflect provider bias in coding problem list items. Structured clinical interviews performed by trained providers mitigate most of these issues and are therefore considered the gold standard for the TBI screening. However, the field currently lacks consensus as to the best interview protocol; and different interviews may result in different diagnostic rates (Donnelly et al., 2011). They are also limited by patient's subjective recollection of the injury, and are time-consuming and labor-intensive. Indeed, variance between evaluative methods likely contributes to inconsistencies in the reporting of rates and symptomatology of TBI, especially those in the chronic, out-of-hospital phase of recovery.

Accordingly, the purpose of this study was to determine how different evaluation methods of TBI obtained simultaneously in the same individuals, a large cohort of Veterans at high risk for TBI, differed in the severity of chronic TBI-related symptoms. We hypothesized the rate of TBI diagnosis would differ across the three most common methods of evaluation (i.e., self-report, retrospective medical record review, and following a structured clinical interview). Additionally, given the complementary nature of these three methods, we also hypothesized that subjects would demonstrate a step-wise increase in chronic TBI-related symptom severity corresponding to whether one, two, or all three methods of evaluation resulted in a positive TBI diagnosis.

Methods

The VA Portland Healthcare System (VAPORHCS) institutional review board approved this study (IRB #3988) and all subjects provided verbal and written informed consent prior to participation. Veterans were recruited, between June 2018 and February 2020, using flyers posted throughout the VAPORHCS as well as by clinician referral from the VAPORHCS Sleep Disorders Clinic. “Veterans with eye diseases (e.g. glaucoma, macular degeneration, etc.) or taking eye medications for eye health were excluded, because photosensitivity was a separate outcome measure (see Chapter 3). A total of n=200 subjects were enrolled in the study and included in subsequent analyses.

TBI Evaluation

Head Trauma Event Characteristics (HTEC) interview. All subjects were screened for a history of TBI using a modified version of the Head Trauma Event Characteristics (HTEC) interview (Management of Concussion/mTBI Working Group, 2009). The HTEC is the recommended mTBI screening interview by the Department of Defense and the Department of Veteran Affairs, and is comparable to other TBI semi-structured clinical interviews such as the Boston Assessment of Traumatic Brain Injury-Lifetime (BAT-L) (Fortier et al., 2014) and the Ohio State University Traumatic Brain Injury Identification Method (OSU TBI-ID) (Corrigan & Bogner, 2007). Research assistants received training from the study neuropsychologist in diagnostic interviewing and TBI evaluation using the HTEC. Formal training included role plays and live observation, as well as review of interview reports. HTEC interviews were conducted in-person or over the phone by the research assistants and information recorded into standardized fields (see details below). Subsequently, the study neuropsychologist reviewed and made a

diagnosis of no, mild, moderate, or severe TBI as defined by DoD criteria (Management of Concussion/mTBI Working Group, 2009). In the HTEC protocol, all participants were asked about their TBI and head injury history including: a description of injuries that resulted in confusion, feeling dazed/stunned, or "seeing stars"; whether they experienced a direct or indirect blow to the head; evidence of intracranial injury or skull fracture; location of impact; total time of loss of consciousness; and total time of memory loss.

Self-Report. Prior to completing the HTEC interview, subjects completed a series of written self-report questions, one of which read, “Have you ever had a concussion or traumatic brain injury (TBI)?” Subjects then checked a box indicating a binary "yes" or "no" to this question.

Electronic Medical Record (EMR) Review: Study personnel examined each subject’s Electronic Medical Records (EMR) for chart documentation of TBI history. Study personnel used the same 10 search terms when analyzing each subject’s EMR: “TBI,” “head injury,” “head trauma,” “brain trauma,” “concussion,” “concussive,” “amnesia,” “loss of consciousness,” and “blast.” The results of these searches were recorded in one of three ways. First, subjects with at least one note in their EMR which described a positive diagnosis of TBI were labeled as having “positive” documentation of TBI. Second, subjects with at least one note referencing a screening for TBI, but where the results of all documented screens were negative, were labeled as having “negative” documentation of TBI. Third, subjects with no mention of any screening or documentation of TBI whatsoever were labeled as having “absent” documentation of TBI. Subjects with only negative or absent documentation of TBI were considered to have a negative diagnosis. Subjects with any positive documentation of TBI were considered to have a positive diagnosis.

Subjects received a diagnosis based on each of the 3 evaluation methods, and were then further categorized into 4 groups: Negative for a history of TBI across all three evaluative methods (No TBI); positive for TBI across any one evaluative method (TBI-1dx; i.e., only self-report, only EMR, or only HTEC); positive for TBI across any two evaluative methods (TBI-2dx; i.e., self-report + EMR, self-report + HTEC, or EMR + HTEC); positive for TBI across all three evaluative methods (TBI-3dx; i.e., self-report + EMR + HTEC).

Medical & Military History

General medical and relevant military/service history was obtained via self-report questionnaires as part of the battery of validated questionnaires administered (see below). Medical history collected pertained to subject's history of cancer, cardiovascular health, autonomic management, pain syndromes, trauma history, cognitive complaints, as well as current medication usage for sleep, pain, or depression. Service history collected pertained to subject's duration of service, exposure to combat, degree of service connection, branch of service, and total number of deployments.

Additional specific information pertaining to subject's history of TBI was collected using both self-report metrics, as well as through the HTEC. However, TBI specific metrics presented are based on HTEC-derived data, which, as will be described, includes 153 out of 157 subjects with a positive diagnosis of TBI. This includes data relevant to TBI recency, subject's average age at the time of injury, the approximate number of sustained injuries, the type of injury, injury location, and estimates for LOC and PTA.

Self-Report Instruments

TBI Symptom Severity. The Neurobehavioral Symptom Inventory (NSI) was used as a measure of severity of chronic TBI symptom severity. The NSI is a 22-item questionnaire (each a 5-point Likert scale: 0="none", 1="mild", 2="moderate", 3="severe", 4="very severe") covering the past 2-weeks. Total scores range from 0-88, higher scores indicating greater symptom severity (Cicerone & Kalmar, 1995).

Chronic Pain Complaints. The Symptom Impact Questionnaire-Revised (SIQR) is a 21-item) addressing the intensity of widespread pain and its impact on activities of daily living and independent functioning. Each item is ranked on an 11-point Likert scale; 0 = no impact, to 10=high impact. The SIQR is broken down into three separate domains: Function (9-items; total score of 90/3 = 30), Overall Impact (2-items; total score of 20), and Symptoms (10-items; total score of 100/2 = 50). Thus, total scores range from 0-100, with higher scores indicating greater symptom severity (Friend & Bennett, 2011).

Functioning and Disability. The World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0) is a 12-item measure assessing activity limitations and disability severity. Each question assesses difficulty in performing a certain task using a 5-point Likert scale: 0 = "None", 1 = "Mild", 2 = "Moderate", 3 = "Severe", 4 = "Extreme or cannot do". This survey assesses several functional domains, based on the conceptual framework for the International Classification of Functioning, Disability, and Health, including: 1) Understanding and communication; 2) Self-care; 3) Mobility; 4) Interpersonal relationships; 5) Work and household roles (life activities); and 6) Community and civic roles (participation). This measure produces a raw/simple score ranging from 0-48, with higher scores indicating greater disability.

Sleep Quality. The Insomnia Severity Index (ISI) is a 7-item measure assessing insomnia severity and sleep quality, including difficulty initiating, staying asleep, and the effect of poor sleep on quality of life. Individual items are 5-point Likert scales: 0 = "None", 1 = "Mild", 2 = "Moderate", 3 = "Severe", 4 = "Very severe". Total scores are calculated by summing all responses, resulting in a total score ranging from 0-28, with higher scores indicating poor sleep quality (Bastien, Vallières, & Morin, 2001).

Statistical Analyses

Statistical analyses were performed using GraphPad Prism version 8.4.3 or R version 3.3.6 (R Development Core Team, 2016). Statistical significance was defined *a priori* based on an alpha of <0.05 unless otherwise noted in post-hoc comparisons. Numerical data was assessed via unpaired Student's t-test or one-way analysis of variance (ANOVA) with Tukey's honestly significant difference post-hoc analysis. Categorical data was assessed using a Chi-Square test with Bonferroni post-hoc analysis.

When analyzing differences between self-report measures based on the three TBI evaluation methods (HTEC, EMR, Self-Report), we first compared scores between subjects who screened negative and those who screened positive based on each evaluation type using an unpaired t-test, and calculated the Cohen's *d* effect size for each method. To examine whether there were differences between TBI-positive subjects across evaluation methods (HTEC-positive vs EMR-positive vs self-report-positive), which included partially overlapping data (any subject positive for TBI across two or more evaluative methods were categorized in multiple groups), we estimated the 95% confidence intervals (CI) of the Cohen's *d* effect size for each method using a 10,000 permutation bootstrapping technique via the open-source software R package Bootes and tested for differences in effect sizes between groups (Kirby & Gerlanc, 2013). If the evaluation

method's Cohen's *d* was out of the range of another method's Cohen's *d* CI, this indicated their effect sizes were significantly different from one another (p <0.05). We took a similar approach when comparing differences between the TBI-1dx, TBI-2dx, TBI-3dx groups, which again included partially overlapping. Cohen's *d* effect sizes and their bootstrapped 95% CIs were calculated for each TBI group against the No-TBI group.

Lastly, receiver operator characteristics (ROC) curves were constructed using logistic regression models by plotting sensitivity against (1-specificity), and for each ROC curve, the area under the curve (AUC) was calculated as a measure of accuracy. Logistic regression models were based on the formula:

$$Y\,(\textit{TBI diagnosis}) = \beta_0 + \beta_1\,(\textit{NSI}) + \beta_2\,(\textit{WHODAS}) + \beta_3\,(\textit{SIQR}) + \beta_4\,(\textit{ISI})$$

The CI and comparisons between AUCs were calculated using a 10,000 permutation bootstrapping technique (Robin et al., 2011).

Results

TBI Evaluation & Diagnostic Groups

The analytic sample was predominantly male (82%), middle aged (mean age of 54.9 with a standard deviation of 14.5 years), white (79.5%), with some degree of college education (87.0%), and a recent history of exercising <90 minutes/week (68.5%). None of these general demographic parameters differed based on TBI status (**Table 2.1**).

Of the *n*=200 Veterans included in this data set, *n*=157 (78.5%) were determined to have had a history of TBI based on any one evaluative method (i.e., self-report, EMR, or HTEC). Within these *n* = 157 TBI positive subjects, self-report, EMR, and HTEC separately diagnosed a history of TBI in *n* = 86, *n* = 81, and *n* = 153 subjects, respectively (**Figure 2.1**). Accordingly, there was considerable overlap in terms of subjects who reported a history of TBI using more

than one evaluative method (n = 104; ~66%). There were 53 TBI-1dx subjects, 45 TBI-2dx subjects, and 59 TBI-3dx subjects (i.e., subjects determined to be TBI positive based on any one evaluative method, any combination of two evaluative methods, or all three evaluative methods).

Table 2.1. *Demographic information across all subjects and TBI diagnostic groups*.

	Whole group n=200	**No TBI** n=43 (21%)	**TBI-1dx** n=53 (26%)	**TBI-2dx** n=45 (22%)	**TBI-3dx** n=59 (29%)
Gender					
Male, n	164 (82.0%)	35 (81.4%)	43 (81.1%)	39 (86.7%)	47 (79.7%)
Female, n	35 (16.5%)	8 (18.6%)	10 (18.9%)	6 (13.3%)	11 (18.6%)
Non-binary, n	1 (0.05%)	0	0	0	1 (1.7%)
Age, years	54.9 ± 14.5	57.7 ± 17.8	55.3 ± 13.1	55.2 ± 12.5	52.4 ± 13.7
Race					
American Indian/Alaska Native	6 (3.0%)	1 (2.3%)	2 (3.8%)	1 (2.2%)	2 (3.4%)
Asian	5 (2.5%)	1 (2.3%)	2 (3.8%)	0	2 (3.4%)
Black or African American	9 (4.5%)	0	3 (5.7%)	3 (6.7%)	3 (5.1%)
White	159 (79.5%)	36 (83.7%)	39 (73.6%)	37 (82.2%)	47 (79.7%)
Mixed	16 (8.0%)	4 (9.3%)	5 (9.4%)	3 (6.7%)	4 (6.8%)
Other/Not Reported	5 (2.5%)	1 (2.3%)	2 (3.7%)	1 (2.2%)	1 (1.7%)
Education, ≥ some college	174 (87.0%)	36 (83.7%)	46 (86.8%)	41 (91.1%)	51 (86.4%)
Exercise, ≥ 90 minutes/week	63 (31.5%)	9 (20.1%)	19 (35.8%)	16 (35.5%)	19 (32.2%)
TBI Diagnostic Groups					
TBI-1dx					
Self-Report, n	0	-	0	-	-
EMR, n	3 (1.5%)	-	3 (5.7%)	-	-
HTEC, n	50 (25.0%)	-	50 (94.3%)	-	-
TBI-2dx					
Self-Report + EMR, n	1 (0.5%)	-	-	1 (2.2%)	-
Self-Report + HTEC, n	26 (13.0%)	-	-	26 (57.8%)	-
EMR + HTEC, n	18 (9.0%)	-	-	18 (40.0%)	-
TBI-3dx					
Self-Report + EMR + HTEC, n	59 (29.5%)	-	-	-	59 (100%)

Data are presented as n (% total) or mean ± standard deviation. TBI, traumatic brain injury; TBI-1dx, TBI-2dx, and TBI-3dx, subjects receiving 1, 2, or 3 positive diagnosis using the 3 diagnostic tools, respectively; HTEC, head trauma events checklist; EMR, electronic medical record. Continuous variables were analyzed via one-way ANOVA with Tukey Honestly Significant post-hoc comparison, and categorical variables were analyzed via Chi-square with Bonferroni post-hoc comparison. * = p <0.05 versus No TBI, † = p <0.05 versus TBI-1dx, ‡ = p <0.05 versus TBI-2dx.

The TBI-1dx group was almost entirely composed of HTEC diagnoses (94.3%), without any subjects only endorsing self-report, and the TBI-2dx group was split relatively evenly between self-report+EMR (57.8%), and EMR+HTEC (40.0%). A chi square test of independence

was used to assess whether the proportion of positive TBI diagnosis was different based on the type TBI evaluation method, and the results were found to be significant ($\chi^2 = 47.41$, $p < 0.001$). Post hoc comparisons revealed that the proportion of subjects with positive diagnoses of TBI were significantly higher when using HTEC compared to self-report ($\chi^2 = 35.63$, $p < 0.001$), and EMR ($\chi^2 = 35.91$, $p < 0.001$). These results reveal the major discrepancies among the 3 most common methods to diagnosis TBI.

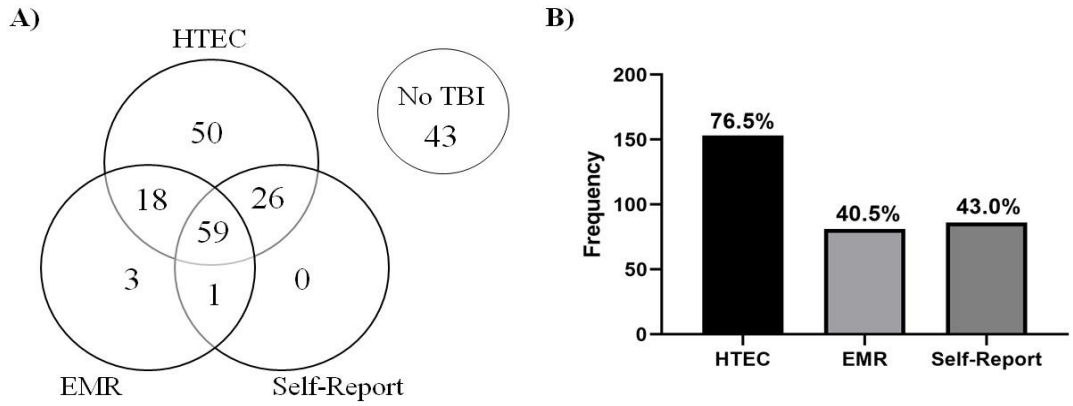

Figure 2.1. Differing TBI rates between TBI evaluation methods
A) Venn diagram depicting the overlap between subjects who screen positive for at least one TBI across our three evaluation methods. In total, only 51% of subjects had congruent diagnoses across evaluations. **B)** The HTEC had a significantly higher prevalence rate for TBI compared to self-report ($p < 0.001$) and EMR methods ($p < 0.001$).

TBI Characteristics

Considering the majority of TBI+ subjects endorsed a history of TBI using the HTEC (n=153/157), these data were used to describe subjects' TBI-related characteristics (**Table 2.2**). There are several components to the HTEC interview, and these data herein reflect subjects' most

severe prior injury (with the exception of subject's approximation of the total number of head injuries incurred).

Table 2.2 *TBI characteristics across all subjects and TBI diagnostic groups.*

	Whole group *n* =153	TBI-1dx *n* =50 (33%)	TBI-2dx *n* =44 (29%)	TBI-3dx *n* =59 (38%)
Severity				
Mild	121 (79.1%)	46 (92%)	36 (81.8%)	39 (66.1%)†
Moderate	23 (15.0%)	3 (6.0%)	8 (18.2%)	12 (20.3%)†
Severe	9 (5.9%)	1 (2%)	0	8 (13.6%)
Recency				
<1 year	4 (2.6%)	1 (2.0%)	2 (4.5%)	2 (3.4%)
1-5 years	19 (12.4%)	4 (8.0%)	3 (6.8%)	9 (15.2%)
6-10 years	9 (5.9%)	1 (2.0)	3 (6.8%)	5 (8.5%)
11-30 years	51 (32.7%)	19 (38.0%)	14 (31.8%)	18 (30.5%)
>30 years	70 (45.7%)	25 (50.0%)	22 (50.0%)	23 (40.0%)
Average, years	27.8 ± 17.9	31.8 ± 17.4	27.7 ± 16.3	24.4 ± 19.0
Age of injury, years	26.1 ± 15.8	23.2 ± 15.1	26.9 ± 16.1	28.0 ± 16.0
Number of Injuries				
1	28 (18.3%)	15 (30.0%)	9 (20.4%)	4 (6.8%)†
2-4	61 (39.9%)	18 (36.0%)	18 (40.9%)	25 (42.4%)
5-10	42 (27.4%)	11 (22.0%)	12 (27.3%)	19 (32.2%)
11-25	13 (8.5%)	5 (10.0%)	3 (6.8%)	5 (8.5%)
>25	7 (4.6%)	1 (2.0%)	2 (4.5%)	4 (6.8%)
Maximum	160	26	46	160
Average, number	7.1 ± 14.8	5.1 ± 6.3	5.9 ± 8.3	9.7 ± 21.9
Type				
MVC	30 (19.6%)	10 (20.0%)	6 (13.6%)	14 (23.7%)
Sports	25 (16.3%)	13 (26.0%)	8 (18.2%)	4 (6.8%)†
Pedestrian-MVC	10 (6.5%)	3 (6.0%)	1 (2.3%)	6 (10.2%)
Blast	9 (5.9%)	2 (4.0%)	2 (4.6%)	5 (8.5%)
Fall	34 (22.2%)	7 (14.0%)	14 (31.8%)	13 (22.0%)
Assault	23 (15.0%)	5 (10.0%)	8 (18.2%)	10 (16.9%)
Other	22 (14.4%)	10 (20.0%)	5 (11.4%)	7 (11.9%)
Loss of Consciousness				
None	69 (45.0%)	30 (60.0%)	23 (52.3%)	16 (27.1%)†‡
<1 minute	17 (11.1%	6 (12.0%)	4 (9.1%)	7 (11.9%)
1-30 minutes	41 (26.8%)	11 (22.0%)	11 (25.0%)	19 (32.2%)
30 min - 24 hours	18 (11.8%)	2 (4.0%)	6 (13.6%)	10 (16.9%)
24 hours - 7 days	6 (3.9%)	1 (2.0%)	0	5 (8.5%)
>7 days	2 (1.3%)	0	0	2 (3.3%)
Post-traumatic Amnesia				
None	131 (85.6%)	45 (90.0%)	37 (84.0%)	49 (83.0%)
Less than 1 minute	1 (0.6%)	1 (2.0%)	0	0
1-30 minutes	8 (5.2%)	3 (6.0%)	2 (4.6%)	3 (5.1%)
30 min - 24 hours	7 (4.6%)	1 (2.0%)	2 (4.6%)	4 (6.8%)
24 hours - 7 days	5 (3.3%)	0	3 (6.8%)	2 (3.3%)
>7 days	1 (0.6%)	0	0	1 (1.7%)

Data are derived from the HTEC (Head Trauma Events Characteristics) interview and are presented as *n* (% total) or mean ± standard deviation. TBI, traumatic brain injury; MVC, motor vehicle collision. This includes *n* =153/157 total subjects with HTEC-derived data and excludes *n* =4/157 who screened negative for TBI on the HTEC. Continuous variables were analyzed via one-way ANOVA with Tukey Honestly Significant post-hoc comparison, and categorical variables were analyzed via Chi-square with Bonferroni post-hoc comparison. † = p <0.05 vs TBI-1dx, ‡ = p <0.05 vs TBI-2dx.

A TBI diagnosis with injury severity was evaluated by a licensed neuropsychologist based on a combination of the length of altered consciousness, total loss of consciousness, and post-traumatic amnesia. Mild, moderate, and severe TBI was diagnosed in n = 121, n = 23, and n = 9 subjects, respectively. The TBI-1dx group was almost exclusively composed of mild injuries (92%), while the relative proportions of the TBI-2dx and TBI-3dx group shifted toward an increase in severity. Mild injuries composed ~82% and ~66% of subjects in the TBI-2dx and TBI-3dx group, respectively. Accordingly, the extent of loss of consciousness and post-traumatic amnesia reported also followed a similar trend of longer durations in the TBI-2dx and TBI-3dx groups. On average, subjects reported this injury to have occurred ~20 years ago (i.e., at an average of ~30 years of age). No differences in injury recency were found across TBI groups. With respect to type of injury, there were no notable differences across groups other than fewer sports related injuries in the TBI-3dx group. There were also no notable differences found in terms of the reported location of injury, with the majority of subjects (~50% of each group) reporting a frontal or occipital lobe injury. Finally, in a similar manner as other characteristics, an increased relative proportion of subjects in the TBI-2dx and TBI-3dx reported a greater number of prior head injuries. For example, 30% of TBI-1dx group reported only one prior TBI, whereas this percentage decreased to ~20% in the TBI-2dx group and to ~7% in the TBI-3dx group.

TBI-related Symptomology

TBI-related symptomology was assessed through a battery of self-reported questionnaires targeting TBI symptom severity, chronic pain complaints, functioning and disability, and sleep quality. We first analyzed differences between subjects screening positive or negative based on each TBI evaluation (**Figure 2.2**).

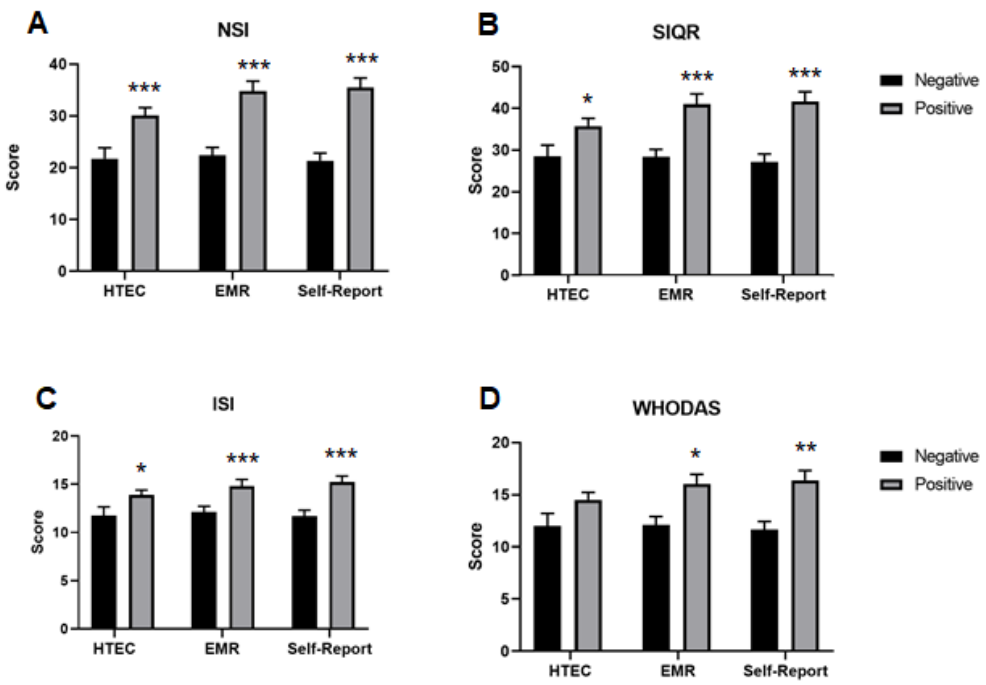

Figure 2.2. Symptom severity based on TBI evaluation method
TBI positive subjects scored higher on the NSI **(A),** SIQR **(B),** and ISI **(C)** compared to subjects who screened negative using the same evaluation method. Subjects who screened positive using self-report or EMR also had higher WHODAS scores than subjects who screened negative, but that was not true using the HTEC **(D).** We found no differences in effect sizes between methods across the four surveys. * $p < 0.05$ vs Negative, ** $p < 0.01$ vs Negative, *** $p < 0.001$ vs Negative.

Subjects who screened positive for TBI based on the HTEC, had significantly higher NSI (d = 0.485, 95% CI = [0.182 - 0.788]; p <0.0001), SIQR (d = 0.631, 95% CI = [0.332 - 0.930]; p = 0.028), and ISI (d = 0.345, 95% CI = [0.035 - 0.654]; p = 0.032) scores compared to subjects who screened negative on the HTEC. There was no significant difference in WHODAS scores (d = 0.242, 95% CI = [-0.128 - 0.610]; p = 0.274). In regards to subjects with a positive diagnosis based on EMR, with higher scores in NSI (d = 0.754, 95% CI = [0.444 - 1.063]; p = 0.002), SIQR (d = 0.608, 95% CI = [0.316 - 0.608]; p < 0.001), and ISI (d = 0.291, 95% CI = [-0.028 - 0.610];

p <0.001), and WHODAS measures (d = 0.448, 95% CI = [-0.156 - 0.739]; p = 0.062) compared to EMR negative subjects. A similar story emerged in regards to subjects with a positive diagnosis based on self-report, with higher NSI (d = 0.8655, 95% CI = [0.531 – 1.198]; p < 0.001), SIQR (d = 0.722, 95% CI = [0.407 - 1.038]; p < 0.001), ISI (d = 0.557, 95% CI = [0.271 - 0.843]; p <0.001) , and WHODAS scores (d = 0.557, 95% CI = [0.271 - 0.843]; p = 0.002) compared to self-report negative subjects. We found no differences in terms of effect size between the 3 different evaluations methods.

Next we examined whether congruent positive TBI diagnoses predicted symptomology by analyzing differences in self-report measures based on the number of positive diagnoses across the three types of TBI evaluation methods (No-TBI, TBI-1dx, TBI-2dx, TBI-3dx; **Figure 2.3**). We found no differences between the No-TBI and TBI-1dx groups on NSI (d = 0.361, 95% CI = [-0.089 - 0.811]; p = 0.16), SIQR (d = 0.109, 95% CI = [-0.284 - 0.501]; p = 0.384), ISI (d = 0.276, 95% CI = [-0.149 - 0.701]; p = 0.276), or WHODAS scores (d = 0.196, 95% CI = [-0.228 - 0.620]; p = 0.197). The TBI-2dx had significantly higher scores than the No-TBI group on the NSI (d = 0.738, 95% CI = [0.312 – 1.163.]; p <0.001), SIQR (d = 0.611, 95% CI = [0.150 - 1.702]; p = 0.008), and WHODAS (d = 0.545, 95% CI = [0.098 - 0.992]; p = 0.004), but not on the ISI (d = 0.329, 95% CI = [-0.113 - 0.771]; p = 0.085). Lastly, we found that the TBI-3dx group scored significantly higher than the No-TBI group on all self-report measures (p <0.001), but also had a significantly greater effect size compared to the TBI-1dx group in terms of diagnosis and NSI (d = 0.738, 95% CI = [0.312 – 1.163.]; p <0.001), and SIQR scores (d = 0.738, 95% CI = [0.312 – 1.163.]; p <0.001). We did not find any differences in effect sizes between the TBI-1dx and TBI-2dx groups, or between TBI-2dx groups and TBI-3dx groups.

ROC Analyses

A ROC curve analysis was used to quantify the predictive value of NSI, WHODAS, SIQR, and ISI scores in logistic regression model predicting TBI diagnosis. First we looked at 3 different models predicting a positive diagnosis using either the HTEC, self-report, or EMR

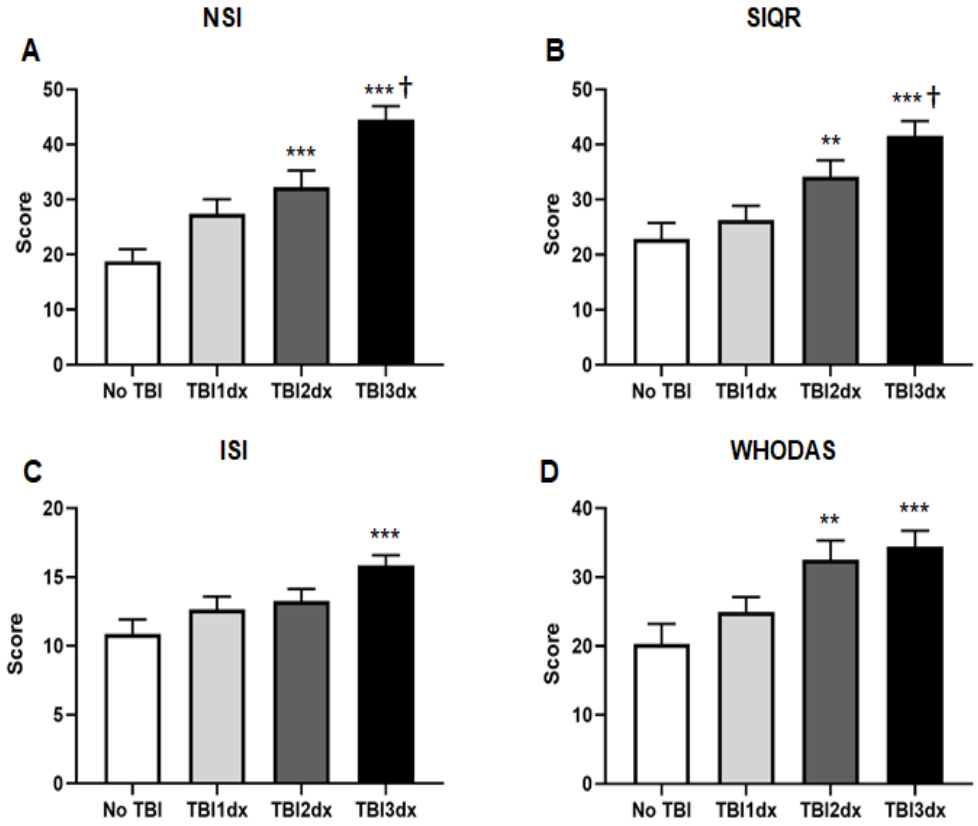

Figure 2.3. Symptom severity based on congruent TBI diagnosis
A) The TBI-2x and TBI-3dx groups had significantly higher NSI scores compared to the No TBI group. The effect size of the TBI-3dx was significantly higher than the effect size in the TBI-1dx group. **B)** TBI-2x and TBI-3dx had significantly higher SIQR scores compared to the No TBI group. The effect size of the TBI-3dx was significantly higher than the effect size in the TBI-1dx group. **C)** Only the TBI-3dx group scored significantly higher than the No-TBI group. No significant differences between TBI positive subjects. **C)** Both the TBI-2x and TBI-3dx had significantly higher WHODAS scores compared to the No TBI group. No significant differences between TBI positive subjects.** $p < 0.01$ vs No TBI, *** $p < 0.001$ vs No TBI, † $p < 0.05$ vs TBI-1dx

evaluation methods. As seen in **Figure 2.4A**, when predicting a positive diagnosis in the HTEC our model had an AUC of 0.73 (95% CI [0.64, 0.81]), which was almost identical to our models predicting self-reported TBI (0.73; 95% CI [0.65, 0.81]), and EMR-related TBI (0.72; 95% CI [0.64, 0.80]).

We performed a similar ROC curve analysis evaluating how NSI, WHODAS, SIQR, and ISI scores predicted a TBI diagnosis based on the number of the congruent positive diagnoses across all three types of TBI evaluation. As seen in **Figure 2.3B**, the model predicting subjects with in the TBI-3dx group had an AUC of 0.76 (95% CI [0.68, 0.84]). This was significantly larger than the AUC when predicting subjects in the TBI-2dx group (0.51; 95% CI [0.49, 0.61]; P

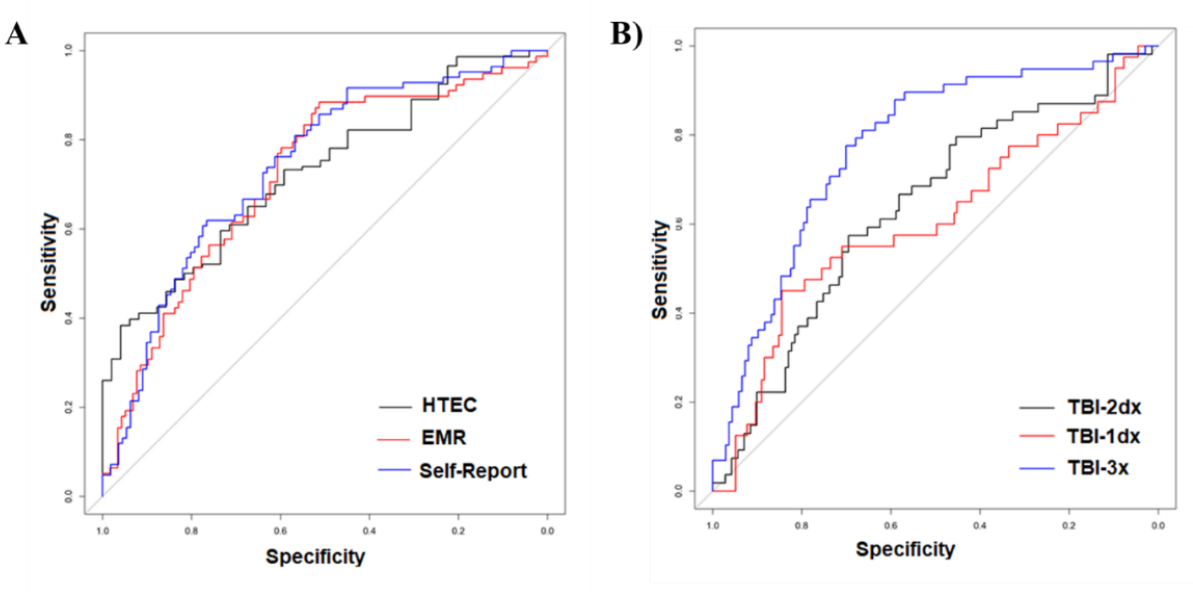

Figure 2.4 ROC curves predicting TBI diagnosis using self-reported symptom scores. **(A)** ROC curves using logistic models based on NSI, SIQR, ISI, and WHODAS scores to predict positive TBI diagnosis based on each of the 3 TBI evaluation methods. The AUC predicting HTEC (0.73), EMR (0.72), or self-report (0.73) TBI status, did not significantly differ from one another. **(B)** ROC curves using similar logistic models to predict congruent positive TBI diagnosis methods across evaluation methods. The AUC predicting TBI-1dx (0.59), or TBI-2dx (0.51) were nor significantly better than chance levels. The AUC predicting TBI-3dx (0.76) was significantly larger than both these models.

<0.001) or subjects in the TBI-1dx group (0.59; 95% CI [0.40, 0.61]; P = 0.01), both of which were not significantly better than chance levels.

Discussion

The results of this study suggest that the type of TBI evaluation method drastically changes the proportion of Veterans that are screened as TBI positive, with widely varying rates of post-concussive symptoms and sequelae. Surprisingly, using what many researchers consider the gold-standard of TBI evaluation methods, our clinical interview was most sensitive and resulted in the highest prevalence rate for TBI, with more than 75% of our sample receiving a positive diagnosis. This was considerable higher than the number of subjects who self-reported a TBI or had one documented in their EMR.

There are several possibilities for these discrepancies. For one, subjects are unlikely to fully understand the diagnostic criteria for a TBI and are therefore unlikely to endorse it on a self-report survey. It is possible that only those with the most severe head injuries would actually endorse our self-report question; however, there were no significant differences between groups in terms of moderate and severe TBI history, arguing against this possibility. And although the HTEC relied on self-report due to its interview structure, the clinician begins the consultation by asking about post-concussive symptoms ("Have you had an injury to your head that resulted in confusion, feeling dazed/stun, or see stars?"), rather than relying on subjects to have knowledge on what a TBI is. In ambiguous cases, the clinician is allowed to probe the subjects further, which may explain the higher rate of positive TBI diagnosis than self-report alone.

Secondly, our diagnostic interview screened our subjects' entire lifespan for possible head injuries, similar to the BAT-L and OSU TBI-ID (Corrigan & Bogner, 2007; Fortier et al., 2014). This possibly led to positive diagnoses of head injuries that were no longer present in the

EMR, or never recorded. EMR records are often incomplete and sometimes do not include medical notes from hospitalizations or clinic visits outside the VA system, and almost never include injuries prior to military enrollment.

Need for congruent diagnoses

Of our 200 subjects, only 102 (51.0%) had complete convergence across all three evaluation methods, either showing no evidence of ever sustaining a TBI, or receiving a positive diagnosis in every measure. These numbers are concerningly low considering that almost half our subjects could be considered either TBI positive or TBI negative if they participated in a different research study using only one TBI screening method. This result alone could help explain the extreme variance the prevalence of chronic post-concussive symptoms following a TBI that is reported in the field (Iverson, 2010; Karr et al., 2014).

These results argue that if researchers are interested in a complete TBI history from their subjects, a TBI clinical interview is necessary as this method has the highest diagnostic sensitivity. However, one of our more striking findings was the vast difference in post-concussive symptoms among subjects depending on the congruency between TBI many positive diagnoses. Our TBI-1dx had the highest proportion of asymptomatic subjects, which could explain inconsistent results in the literature examining long term symptoms following TBI.

Difference in TBI symptomology

It is still unclear if this prolonged symptomology is specificity linked to the original injury, or if these symptoms are related to some other mental health disorder. For example Iverson and Lange reported a high prevalence of post-concussive like symptoms in healthy controls, which were highly correlated with depressive symptoms (Iverson & Lange, 2003). Another study from King and colleagues found similar results using the NSI in a large group of Veterans (P. R. King et al., 2012). Subjects suffering from comorbid disorders with mTBI scored

the highest on the measure, suggesting that the NSI is a reliable and valid measure of post-concussive symptoms. However, subjects suffering from a wide range of mental health disorders, including anxiety, depression and post-traumatic stress disorder (PTSD), all had elevated NSI scores compared to controls without a history of TBI. These results suggest that the NSI is a reliable and valid measure of postconcussive symptoms, but other non-TBI disorders can inflate scores. This is true even in individuals without a history of TBI. Future longitudinal studies are needed to accurately track these symptoms from the acute stage to the chronic stage to better attribute their etiology to the actual injury.

Regardless, it is clear from our study that those who self-report a history of TBI, have documented records of one in their medical records, and are accurately screened using a clinical interview, are most likely to have chronic TBI symptoms.

Future directions and limitations

The HTEC is the clinically recommended VA/DoD guidelines for TBI diagnosis. Although the HTEC interview is similar to other TBI evaluation methods used by clinicians and researchers, including the Ohio State University TBI Identification Method (OSU TBI-ID) (Corrigan & Bogner, 2007) and the Boston Assessment of TBI-Lifetime (BAST-L) (Fortier et al., 2014), it may have subtle differences from these other research-grade tools that could lead to different rates in positive diagnoses. For example, when conducting the HTEC for this study, subjects were only asked about the most severe and most recent head injuries. The OSU TBI-ID requires interviewers to collect detailed information on any possible head injury, which is more time and labor intensive, but could result in an even higher rate of positive TBI diagnosis. It is also important to note that HTEC interviews were not done immediately after injury, and in some cases the injury was sustained several decades prior to assessment. Although we acknowledge this limitation, it is worth pointing out that this is a standard protocol in many TBI studies that

include a diagnostic interview. Retrospective studies such as these rely on firsthand accounts from subjects, and cannot be acquired directly after the injury. This may partially explain the high percentage of TBI-HTEC subjects yet with lower levels of chronic symptoms.

It is also important to point out that our EMR review was limited to VA databases and does not include records from active military members. Although we recognize this limitation, it is important to note that most studies using EMR are subject to this issue and many researchers will not have complete access to the entirety of a subject's medical records over their lifespan. Therefore, we believe that our conclusions are still valid as they pertain to differences in research results based on these screening tools.

Lastly, we recognize that our sample is extremely homogenous, with more than 80% of subjects identifying as white males. Previous research has shown that there are racial disparities in long-term outcomes following a TBI, which was primarily due to differences in socioeconomic status and access to healthcare (Shafi et al., 2007). There has been little research examining gender differences following TBI, but the few that have been conducted suggest that women may experience worse outcomes compared to males (Farace & Alves, 2000). The VAPORHCS has low rates of both minority and female patients and is not representative of the diversity of U.S. Military Veterans. Therefore, future studies should examine differences in chronic TBI symptoms based on evaluation methods with a wider range of participants.

Overall, we believe that our results clearly demonstrate the importance of TBI evaluation methods in research studies, which could explain discrepant TBI diagnostic rates, post-concussive symptoms, and recovery rates across studies.

Conclusions

We found wide discrepancies between the three diagnostic methods, which resulted in significant differences in TBI-related symptoms. Although we did not find significant differences

in self-reported post-concussive symptoms between TBI positive subjects across methods, subjects with congruent positive diagnosis across all three screening tools reported the highest severity of chronic TBI symptoms.

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Chapter 3: Photosensitivity Thresholds are Associated with Chronic Pain Complaints in Patients with and without Traumatic Brain Injury

Abstract

Chronic pain is a common clinical disorder that is driven by sensitization of pain-processing circuits in the central nervous system. Traumatic brain injury (TBI) is a neurobiological condition which is defined as a disruption of brain function due to an external blow to the head. A subset of individuals with a history of TBI will go on to develop long-term sequelae, including increased photosensitivity as well as widespread chronic pain. However, previous studies on this population have mostly relied on self-report measures to quantify levels of pain and light sensitivity, and few have utilized more objective or quantifiable measures. Previous research has also failed to examine the relationship between photosensitivity and chronic pain. The purpose of this study was to examine differences in chronic pain complaints, pressure pain levels, and light sensitivity in individuals with and without a history of TBI. We employed a variety of self-report surveys, as well as pressure algometry and an objective measure of visual photosensitivity thresholds (VPT) to quantify these differences.

Subjects were diagnosed as having a history of TBI by a neuropsychologist after undergoing a standardized structured TBI interview. Of the total sample (n = 395), 160 subjects were negative for a history of TBI and were classified as controls, while 235 screened positive for at least one TBI. Of those 235, 128 subjects were categorized as symptomatic TBI (sTBI) based on elevated levels of self-reported TBI symptoms, and 105 subjects were categorized as asymptomatic (aTBI).

Using the Symptom Impact Questionnaire (SIQR) as a measure of chronic pain severity, and the Michigan Body Map (MBM) to assess the degree of widespread pain, we found that the TBI group reported greater severity and more widespread chronic pain than controls (P <0.001). These results were mostly driven by the sTBI group, which reported significantly higher SIQR and MBM scores compared to controls and aTBI subjects. Despite these differences, we found no differences between groups in pressure algometry. However, TBI subjects did exhibit significantly lower VPTs compared to controls (P <0.001), which was again driven by the sTBI subjects. Lastly, VPTs were strongly correlated with SIQR scores across all groups and a multiple linear regression analysis found that VPTs were a better predictor of chronic pain complaints (β = -0.16, P = 0.01) than other diagnostic measures including pressure pain thresholds (β = 0.001, P = 0.98). Taken together, these results suggest that photosensitivity levels could be used as a marker for individuals in whom central sensitization drives chronic pain, and could be applied to other populations that suffer from chronic pain.

Introduction

Chronic pain, any pain persisting past the normal time of healing, typically three or more months, is estimated to impact over 50 million American adults (Merskey, 1986). One population disproportionately impacted by chronic pain is individuals with a history of traumatic brain injury (TBI) (Lew, Tun, & Cifu, 2009). TBI can be defined as an external force to the resulting in disrupted brain functioning (O'Neil et al., 2013). TBIs range in severity, and mild TBI (mTBI) make up 80% of all cases in the United States (Center for Disease Control and Prevention, 2016). Although many mTBI patients become asymptomatic within weeks or months following the injury (Cantu, 1998; McCrea et al., 2003; Merrett & McDonald, 1977), chronic pain that cannot be attributed to the original injury is prominent in a subset of these patients, with a significant

impact on psychological and physical function (Balba et al., 2018; Beetar et al., 1996; Faux & Sheedy, 2008; Seal et al., 2017).

Unlike *acute* pain, which is explained by activation of specific nociceptive pathways, *chronic* pain cannot always be tied directly to activation of these pathways. Chronic pain is instead thought to be due to altered processing in spinal cord and brain pain-transmission and pain-modulating circuits (Curatolo, Arendt-Nielsen, & Petersen-Felix, 2006; Heinricher, Tavares, Leith, & Lumb, 2009; Moeller-Bertram et al., 2014; Woolf, 2011). This plasticity involves changes at multiple levels and in multiple circuits, but is broadly described as "central sensitization." Under these conditions, spinal and supraspinal nociceptive circuits are abnormally responsive to non-injurious peripheral stimuli, and descending control serves to amplify sensory signals. As a consequence, normally innocuous inputs are experienced as painful. The concept of central sensitization is well supported in preclinical models of persistent pain, where invasive technologies can be used to document altered excitability of pain-transmitting and pain-modulating neurons (Cleary & Heinricher, 2013; Heinricher et al., 2009; Urban & Gebhart, 1999; Woolf, 2011).

Unfortunately, central sensitization cannot be demonstrated directly in humans. However, individuals that have sustained a TBI frequently complain of abnormal sensitivity to light (Callahan et al., 2016; Dikmen et al., 2010; J. E. Elliott et al., 2018; Goodrich et al., 2013). We showed recently that a specific population of brainstem pain-facilitating neurons, part of the circuitry of central sensitization, can respond to light under some conditions (Martenson et al., 2016). Because activation of these pro-nociceptive neurons, referred to as "ON-cells," causes the pain threshold to be lowered (Heinricher et al., 2009), recruitment of these neurons by light could cause normal somatic stimuli to be felt as painful, making light itself aversive. Consistent with the latter idea, individuals with a variety of chronic pain conditions complain of abnormal

photosensitivity, and we recently documented increased photosensitivity in patients with fibromyalgia (Friend & Bennett, 2011; Martenson et al., 2016). Further, light has been shown to activate a cortical structure considered to signal pain in a chronic pain population (Harte, Hoot, & Borszcz, 2004), very likely by recruiting these pro-nociceptive modulatory neurons. Collectively, these lines of evidence suggest that photosensitivity could be a useful marker for central sensitization in individuals with chronic TBI.

The goal of the present study was to quantify photosensitivity in individuals with and without TBI, and test the hypothesis that photosensitivity is associated with clinical pain status in these individuals.

Methods

The Oregon Health and Science University (OHSU) and VA Portland Healthcare System (VAPORHCS) institutional review boards approved this study (IRB #3988) and all subjects provided verbal and written informed consent prior to participation. Subjects were recruited through a variety of methods including online advertisements, clinical referral from VAPORHCS Sleep Clinic, flyers posted at OHSU and VAPORHCS, as well as flyers posted throughout the local community. Recruitment lasted from June 2018 through March 2020. Veterans with eye diseases (e.g. glaucoma, macular degeneration, etc.) or taking eye medications for eye health were excluded from the study. A total of 434 subjects were enrolled in the study. Thirty-nine subjects did not complete the TBI interview or could not be properly diagnosed for a history of TBI, therefore 395 were included in the analyses.

TBI diagnosis

All subjects underwent a modified version of the Head Trauma Event Characteristics (HTEC) interview (Management of Concussion/mTBI Working Group, 2009). HTEC interviews

were used to screen subjects for a history of TBI and were conducted in-person or over the phone by trained study personnel. This interview included questions on subjects' most severe and most recent head injuries, if they endorsed having had one. Details of the injury including how it happened, whether there was direct or indirect impact, skull fracture, presence of seizures, location of impact, recency of injury, post-concussive symptoms, duration of any potential loss of consciousness, and duration of any potential memory loss were elicited. All records were reviewed by a trained neuropsychologist who made a diagnosis of no, mild, moderate, or severe TBI based on the criteria laid out in US Veteran Affairs guidelines (Management of Concussion/mTBI Working Group, 2009).

Survey Instruments

Prior to any behavioral testing, subjects filled out the following battery of self-report surveys:

Neurobehavioral Symptom Inventory (NSI). A 22-item self-report assessment of post-concussive syndrome symptom. Each item is ranked on a 5-point Likert scale: 0 = "None", 1 = "Mild", 2 = "Moderate", 3 = "Severe", 4 = "Very Severe". We excluded a single question assessing light sensitivity from subsequent analyses as it directly related to our outcome measure. Total summed scores therefore range from 0-84 (Cicerone & Kalmar, 1995).

Symptom Impact Questionnaire-Revised (SIQR). A 21-item self-report assessment of overall chronic pain and its impact on function and disability over the previous 7 days. Each item is ranked on an 11-point Likert scale, with higher signifying greater levels of chronic pain and disability. The SIQR is broken down into three domains: Function (9-items; total score of 90/3 = 30), Overall Impact (2-items; total score of 20), and Symptoms (10-items; total score of 100/2 = 50). Total scores range from 0-100, with higher scores indicating greater symptom severity (Friend & Bennett, 2011).

Michigan Body Map (MBM). A self-report measure that assesses body areas in which subjects experience chronic pain over the past 3 months. The body map displays 35 different areas and by summing the number of body areas endorsed (0-35), the total score represents how widespread each subject's pain is. The MBM has been used to assess centralized pain features (Brummett et al., 2016).

PTSD Checklist for DSM-5 (PCL-5). A 20 item measure used for screening and provisionally diagnosing subjects for PTSD, as well as assessing PTSD symptom severity. Individual items are 5-point Likert scales: 0 = "Not at all", 1 = "A little bit", 2 = "Moderately", 3 = "Quite a bit", 4 = "Extremely. Total summed scored range from 0-80 with higher scores indicating greater PTSD symptom severity (Blevins, Weathers, Davis, Witte, & Domino, 2015). The total score can be subdivided into four subscales: Cluster B (intrusion; 1-5), cluster C (avoidance; 6-7), cluster D (mood/cognition; 8-14), and cluster E (arousal; 15-20). For diagnostic purposes, PTSD was determined by a total score ≥33 and meeting certain subscale criteria including endorsing at least one B item, one C item, two D items, and two E items as a 2 greater (Blevins et al., 2015).

Patient Health Questionnaire 9 (PHQ-9). A 9-item self-report assessment of depression severity. Each item is ranked on a 4-point Likert scale: 0="not at all," 1="several days," 2="more than half of the days," 3="nearly every day"; and items are summed together for a total score between 0-27, with higher scores representing higher depression severity (Kroenke, Spitzer, & Williams).

Insomnia Severity Index & Functional Outcomes of Sleep Questionnaire-10 (ISI). A 7-item measure assessing insomnia severity, including difficulty initiating and staying asleep. Individual items are 5-point Likert scales: 0 = "None", 1 = "Mild", 2 = "Moderate", 3 = "Severe", 4 = "Very severe". Total scores are calculated by summing all responses, resulting in a total score

ranging from 0-28, with higher scores indicating greater severity of symptoms (Bastien et al., 2001)

World Health Organization Disability Assessment Schedule 2.0 (WHODAS). A 12-item measure assessing activity limitations and disability severity. Each question assesses difficulty in performing a certain task using a 5-point Likert scale: 0 = "None", 1 = "Mild", 2 = "Moderate", 3 = "Severe", 4 = "Extreme or cannot do". Each question relates to one of the following domains:1) Understanding and communication; 2) Self-care; 3) Mobility; 4) Interpersonal relationships; 5) Work and household roles; and 6) Community and civic roles. This instrument produces a raw/simple score ranging from 0-48 (Üstün, Kostanjsek, Chatterji, & Rehm, 2010).

Behavioral Testing

Following the completion of the HTEC and self-report surveys, all subjects underwent behavioral testing which included pressure algometry to assess pressure-pain threshold and tolerance, and photosensitivity testing.

Pressure Algometry. After completion of the self-reported surveys, all subjects were tested for pressure pain sensitivity using an Algomed Computerized Pressure Algometer (Medoc Ltd. Advanced Medical Systems, Israel). This handheld pressure gauge consists of a 7.5 cm metal plunger with 1 cm^2 rubber tip that allows delivery of precisely controlled pressure ramp. Pressure was applied to the thumb of the non-dominant hand except when the subject reported a recent injury near that area. In that case, the dominant hand was used. During testing, the experimenter placed the rubber tip of the algometer at the base of the subject's thumbnail, and increased the pressure at a rate of 20 kPa/s second until subjects terminated testing using a hand-held button.

Pressure threshold and *pressure tolerance* were determined for each subject. All subjects were first tested for pressure threshold. During this test, subjects were told to press the button and

say “stop” at the point at which the pressure felt “mildly painful”. This test was repeated 3 times, with a 2-min inter-trial interval. After each trial, the threshold pressure was recorded and subjects were asked to rate the pain of the stimulus on a scale of 0-10, with 0 indicating “no pain” and 10 indicating “the worst pain imaginable”. Because previous studies have shown that threshold decrease with repeated testing (Lacourt, Houtveen, & van Doornen, 2012), the first trial was discarded and pressure thresholds were calculated by averaging the second and third trials. Subjects were next tested for their pressure tolerance. This test mirrored the pressure threshold test, except that subjects were asked to press the button when “the pressure becomes intolerable”. Again, the first trial was discarded and pressure tolerance levels were calculated by averaging the second and third trials. The maximum level of pressure used was 1000 kPa, any trial that reached that level before the subject responded was terminated and scored as 1000 kPa.

Photosensitivity. Visual Photosensitivity Thresholds (VPT) were determined using an Ocular Photosensitivity Analyzer (OPA; Bascom Palmer Eye Institute Photosensitivity; Miami, FL). This instrument produces light stimuli ranging from 4 to 32,000 lux using 210 light emitting diodes focused 50 cm away from the subject’s eyes. The protocol is similar to that described by Verriotto and colleagues (Verriotto et al., 2017). Briefly, subjects were dark adapted for 10 min with a background lighting of 4 lux, before being tested in the same environment. Subjects were seated in front of the LED light panel and asked to stare forward for the entirety of the test. A computer-generated voice from the OPA read test instructions to the subject, ensuring each subject was given the same instructions. Subjects were exposed to a light stimulus for 2 s and were asked to respond with a button press if the light was uncomfortable. There was a 4-s inter-stimulus interval. Stimulus intensity was adjusted using a Garcia-Perez staircase, with ascending

and descending steps depending on the subject's previous response. VPTs were based on the mean of 10 response reversals (**Figure 3.1).**

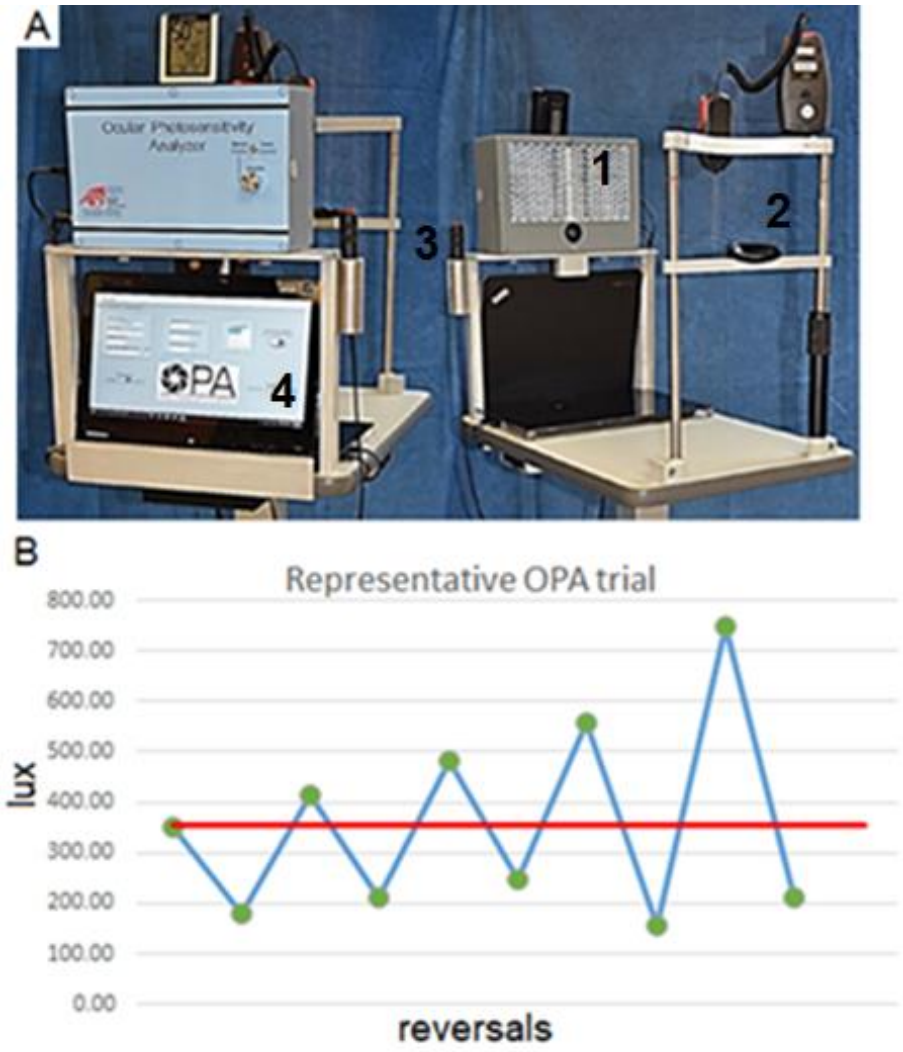

Figure 3.1. Ocular Photosensitivity Analyzer (OPA) and representative data
(A) OPA device. The LED array which produces the light stimuli is shown in (1), the chin-rest 50cm away from LED array (2), response button-press used by subjects (3), and attached laptop used to control software and record data (4)
(B) Representative data from one subject's trial illustrates calculation of their Visual Photosensitivity Threshold (VPT). Green dots represent response reversal, where subjects report that stimulus intensity was uncomfortable after previous stimuli was not, or where subjects report the stimulus was not uncomfortable when previous stimulus was. After 10 response reversals, VPT is calculated using their mean (represented by red line).

Statistical Analyses

All analyses were performed using R version 3.3.2 (R Development Core Team, 2016). For all tests, $p < 0.05$ was considered statistically significant unless otherwise noted in post-hoc comparisons. Differences in numerical variables between groups were assessed using Student's *t*-test or one-way analysis of variance (ANOVA) with Tukey's honestly significant difference post-hoc analysis, or a Kruskal-Wallis Test with Dunn's multiple comparison test, depending on the distribution of data. Categorical data were analyzed using a Chi-Square test with Bonferroni correction for multiple comparisons. Pearson's correlation coefficients of different groups were compared based on their confidence intervals using the open-source software R package cocor (Diedenhofen & Musch, 2015; Zou, 2007). A multivariate linear regression was employed to analyze demographic covariates.

Results

NSI scores and demographics

We first tested to see whether there were any significant differences between TBI severity in regards to chronic TBI symptomology. Subjects with mTBI ($n = 187$, $p < 0.001$), moderate TBI ($n = 35$, $p < 0.001$), and severe TBI ($n = 13$, $p < 0.001$) diagnoses, all scored significantly higher on the NSI than control subjects. However, we found no significant differences between our 3 TBI groups ($p > 0.05$). Since the severity of TBI had no effect on the severity of chronic post-concussive symptoms, and due to the low frequency of moderate and severe TBIs, we decided to group these subjects together into our TBI group (**Figure 3.2)**.

However, many subjects in this TBI group reported little or no post-concussive symptoms, which can be seen in the slightly skewed distribution of NSI scores (**Figure 3.3).** Therefore, we divided our TBI subjects into asymptomatic (aTBI) and symptomatic (sTBI). We

used a median split of the NSI scores to categorize these sTBI subjects as scoring greater than 23, and aTBI subjects as scoring 23 or lower. These scores are consistent with previous studies of this population (King et al., 2012).

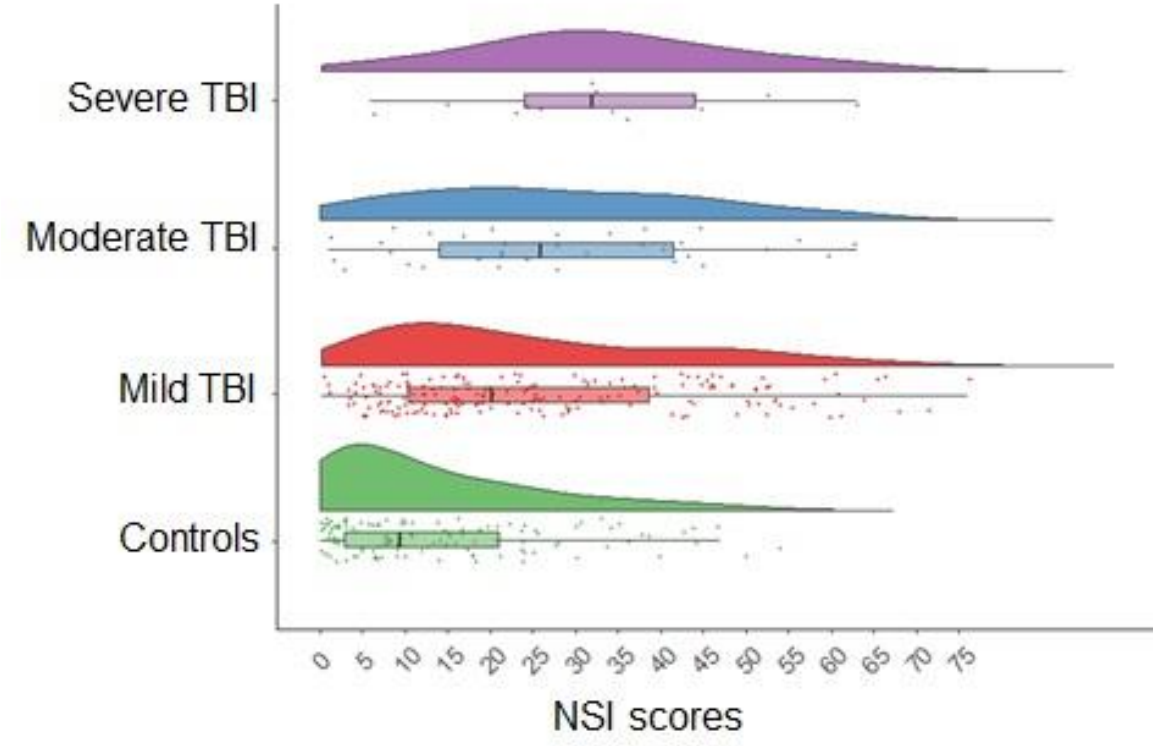

Figure 3.2. NSI Scores and TBI severity
Raincloud plots illustrating the distribution on NSI scores. Whisker plots mark the lowest/highest observations, upper/lower quartiles, and median scores within each group. All 3 TBI groups scored significantly greater than controls (p <0.001), but did not differ from one another. NSI, neurobehavioral symptom inventory, range 0-84.

The demographics of the aTBI and sTBI groups were similar, as they did not significantly differ in terms gender, age, or race (**Table 3.1).** Both groups did have a significantly higher proportion of male subjects than female subjects compared to our control group. In terms

of TBI characteristics, the aTBI group did have a greater ratio of mild TBI subjects than the sTBI group, but there was no difference in the number of moderate and severe TBIs, or in TBI recency. (**Table 3.1**).

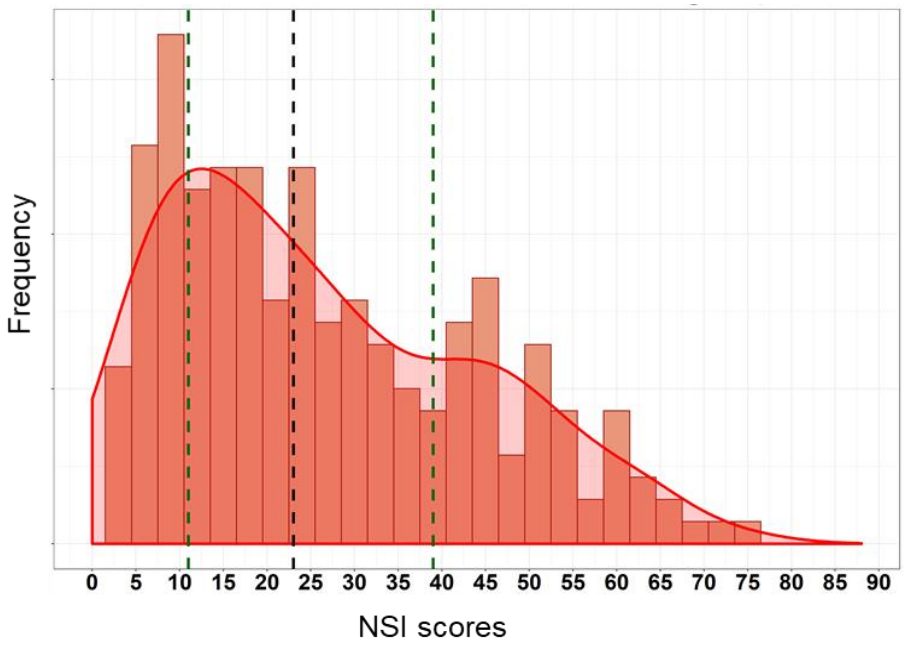

Figure 3.3. Chronic TBI symptoms across all TBI subjects
Frequency histogram depicting the range of NSI scores in subjects with confirmed TBI. Dashed green lines mark upper and lower quartiles, the black dashed line marks the median score. Due to the skewness of the distribution, TBI subjects were categorized as symptomatic or asymptotic using a median split.

TBI subjects self-report greater chronic pain complaints

To examine differences in chronic pain complaints between TBI and control subjects, we analyzed SIQR and MBM scores. TBI subjects had significantly higher SIQR (**Figure 3.4A**) and MBPM (**Figure 3.4B**) scores compared to controls. sTBI subjects scored significantly higher on both the SIQR (**Figure 3.4C**) and MBM (**Figure 3.4D**), compared to aTBI or control subjects.

These data demonstrate that the sTBI group not only had greater chronic pain complaints, but had more widespread pain compared to non-TBI and aTBI subjects.

Table 3.1. *Demographic information across groups.*

	Control	**aTBI**	**sTBI**	**Statistic**	**P-value**
Total subjects	160	105	128		
Gender				15.33	p <0.01
Male,n	83 (51.76%)*	75 (71.4%)	91 (71.1.1%)		
Female, n	35 (16.5%)	8 (18.6%)	10 (18.9%)		
Non-binary, n	3 (1.8%)	0 (0.0%)	1 (0.8%)		
Age, years	51.4 ± 14.6	51.4 ± 16.4	52.8 ± 14.3	0.36	p = 0.70
Race, white	129 (80.66%)	80 (76.19%)	94 (73.44%)	2.15	0.34
TBI Severity				8.30	p = 0.02
Mild, n	--	92 (87.6%)†	94 (73.5%)		
Moderate, n	--	11 (10.5%)	23 (18.0%)		
Severe, n	--	2 (1.9%)	11 (8.6%)		
TBI recency (years)		23.7 ± 18.4	19.5 ± 17.7%	1.76	p = 0.08

Data are presented as n (% total) or mean ± standard deviation. TBI, traumatic brain injury. Subjects endorsing more than one race were classified as 'Mixed'. Age was tested using a one-way ANOVA, TBI recency was tested using an unpaired t-test, all other variables were tested using Chi-Square test. *p < 0.01 vs aTBI and sTBI; † P < 0.05 vs sTBI

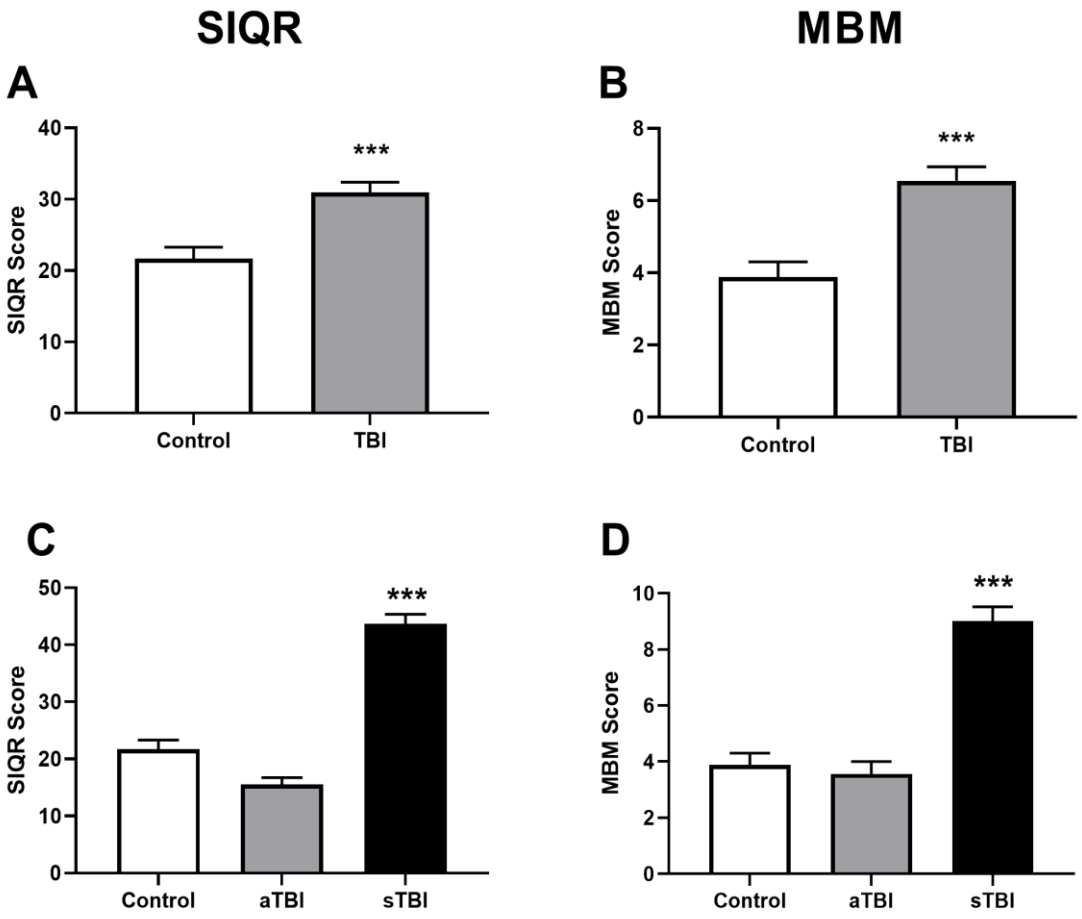

Figure 3.4 Symptomatic TBI group report greater levels of widespread chronic pain **(A)** Subjects in the TBI group reported significantly higher SIQR scores than controls (Controls N = 160, TBI N = 235; *** $p < 0.001$). **(B)** The TBI group also endorsed significantly more body areas affected by chronic pain (*** $p < 0.001$). When broken down into symptomatic (sTBI) and asymptomatic (aTBI) groups, we found the sTBI group scored significantly higher on the SIQR **(C)** and the MBM **(D)** than both the aTBI and control groups. Controls also scored higher than the aTBI on the SIQR, but not on the MBM (Controls N = 160, aTBI N = 105, sTBI N = 128; * $p < 0.05$ vs Controls, *** $p <$ 0.001 vs Controls and aTBI). Data are presented as mean + SE

No differences in pressure-pain threshold or tolerance

Despite differences in self-reported pain, there were no differences in pressure thresholds (Figure **3.5A**) or pressure tolerance among groups (**Figure 3.5B).** These was true even when we divided subjects into aTBI and sTBI groups (**Figure 3.5C/D**). We found no differences between TBI and control groups in self-reported pain ratings of pressure thresholds (p = 0.200) and pressure tolerance levels (p = 0.656). There were still no significant differences in self-reported pain ratings of pressure thresholds (p = 0.310) and pressure tolerance levels (p = 0.610) when subjects were categorized between the aTBI, sTBI, and control groups.

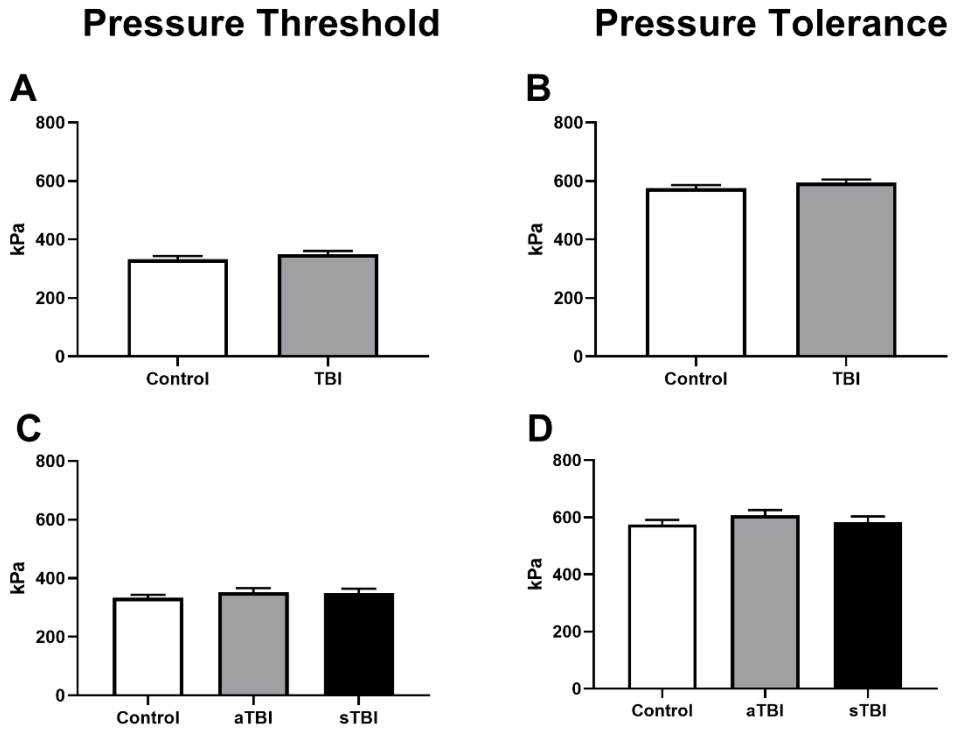

Figure 3.5 No differences in pressure algometry between TBI and controls
Despite the TBI group reporting significantly higher levels of chronic pain, we found no differences between groups on either their pressure pain thresholds (**A,** p = 0.239) or the pressure pain tolerance levels (**B,** p = 0.372). This was true even when we analyzed aTBI and sTBI groups separately on both measures (**C, p** = 0.516; **D,** p = 0.458).

Photosensitivity and associations with chronic pain

There were substantial differences in photosensitivity among groups. TBI subjects had significantly lowered VPTs compared to our control group (**Figure 3.6A).** When broken down based on NSI scores, this difference was almost entirely due to the sTBI subjects, as aTBI subjects showed no significant differences from controls (**Figure 3.6B**).

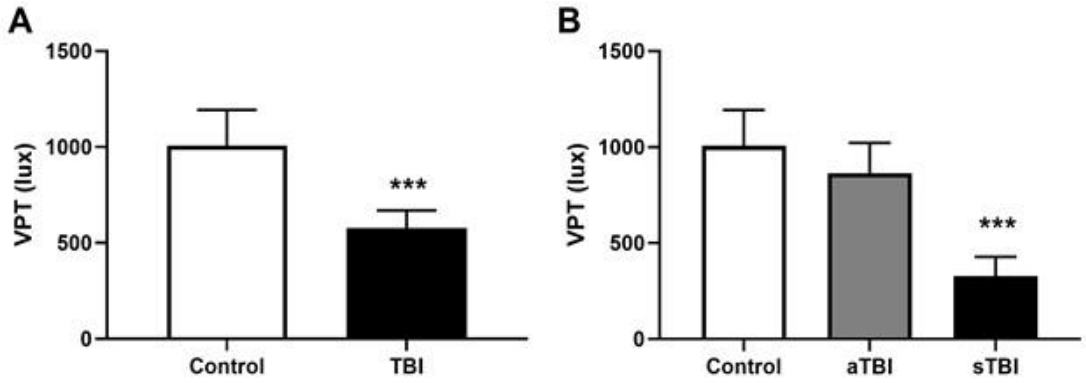

Figure 3.6. Symptomatic TBI subjects have lowered photosensitivity thresholds. **(A)** TBI subjects had significantly lowered VPTs compared to our control group (*** $p <$ 0.001). **(B)** This difference was almost entirely due to the sTBI subjects, which were significantly different from both the control group and the aTBI group (*** $p <$ 0.001). The aTBI subjects were not significantly different from controls ($p = 0.819$).

There was a strong association between photosensitivity and self-reported chronic pain across subjects in all groups (**Figure 3.7A**). Thus, regardless of TBI status, there was a significant negative correlation between VPT and SIQR scores ($R = -0.447$, $p < 0.001$) as well as between VPT and MBM scores ($R = -0.266$, $p < 0.001$). Comparing controls, aTBI, and sTBI subjects, all three groups showed a significant correlation between VPT and SIQR scores (Controls $R = -0.384$, $p < 0.001$; aTBI $R = -0.230$; $p < 0.05$; sTBI $R = -0.308$, $p < 0.001$, **Figure 3.7B**), and group correlations did not differ significantly differ ($p = 0.843$). When we analyzed the

relationship between VPTs and MBM scores in these groups, only the control group showed a significant correlation (R = -0.244, p <0.05), while the aTBI group (R = -0.117, p = 0.808) and

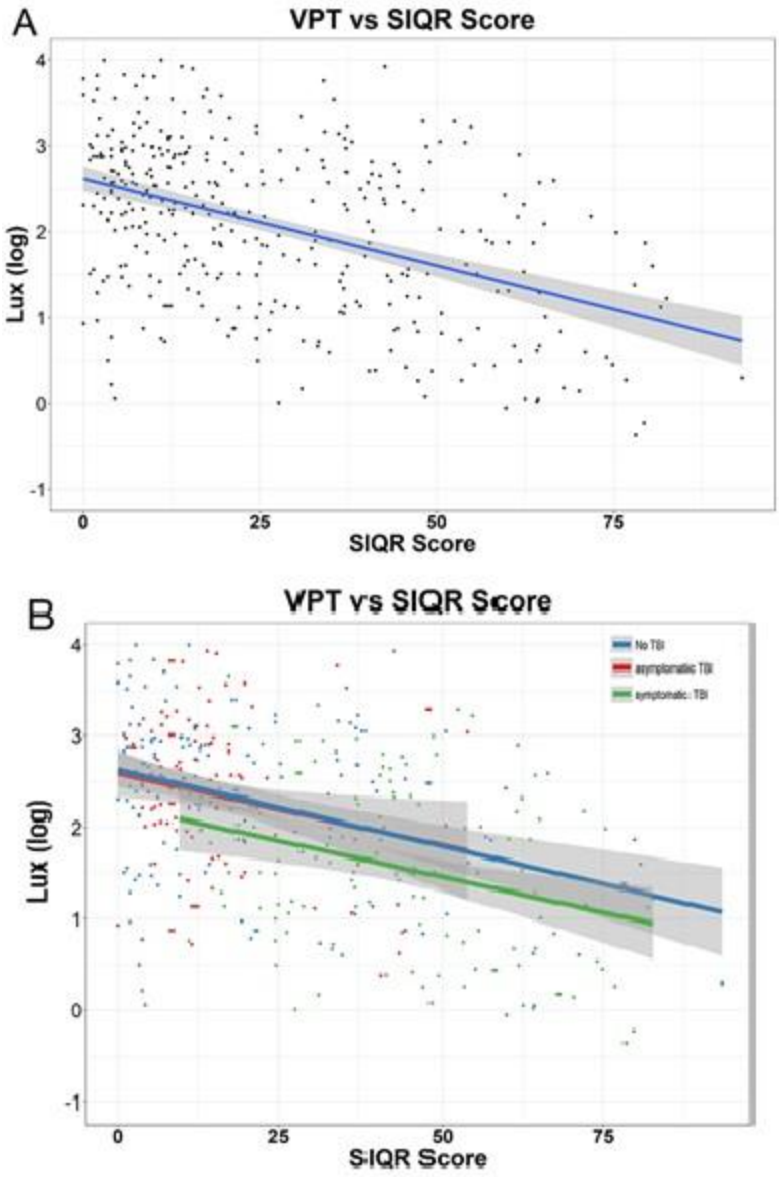

Figure 3.7. Strong correlation between photosensitivity and chronic pain complaints. **(A)** VPT levels were strongly correlated with SIQR scores (R = -0.447, P <0.001) across all subjects, regardless of TBI status. **(B)** When broken down by group, we found that controls (R = -0.384, P <0.001) and sTBI subjects (TBI R = -0.308, P <0.001) and aTBI subjects (aTBI R = -0.231, P <0.05) all displayed a strong negative correlation between VPT and SIQR scores which did not statistically differ from one another.

sTBI group did not (R = -0.242, p = 0.214). However, we did find a strong negative correlation when we collapse all TBI subjects (R = -0.231, p <0.001). Together, these results suggest that photosensitivity is strongly associated with widespread chronic pain independent of TBI status.

Multiple linear regression predicting chronic pain scores

In order to better explore the relationship between chronic pain as measured by the SIQR score and a variety of relevant variables, we employed a multivariate linear regression model. The model included several TBI characteristics (severity, recency, and number of TBIs). Demographic variables known to influence chronic pain and/or light sensitivity (age, sex, eye color, and PTSD diagnosis) were also included. Lastly, pressure-pain tolerance and VPT were included to determine whether either of these sensory tests was independently associated with chronic pain. This model accounted for more than 44% of the variance of SIQR scores, but only PTSD diagnosis and VPT were significant predictors (**Table 3.2**).

Table 3.2 *Multivariate Regression Analyses*

Outcome Variable	Predictor Variables	B	Beta	T-score	P-value	Adjusted R^2
SIQR Score					**<0.001**	**0.442**
	Age	0.218 ± 7.955	0.134	1.884	0.061	
	Sex	2.648 ± 0.116	0.05	0.796	0.427	
	TBI diagnosis (severity)	3.085 ± 2.528	0.098	1.344	0.181	
	TBI recency	-0.066 ± 0.093	-0.051	-0.708	0.48	
	TBI count	0.098 ± 0.138	0.043	0.709	0.479	
	Eye Color	0.007 ± 0.138	0.024	0.855	0.394	
	PTSD diagnosis	**21.591 ± 3.213**	**0.371**	**6.721**	**<0.001**	
	Pressure Tolerance level	0.002 ± 0.008	0.02	0.299	0.766	
	VPT	**-7.945 ± 1.65**	**-0.341**	**-4.815**	**<0.001**	

Differences in self-reported sleep disturbances, depression, disability, and PTSD symptoms

Chronic TBI sequelae are not limited to chronic pain, and include a variety of behavioral, functional, and mood related symptoms. We tested for differences in sleep disturbances using the

ISI, depressive symptoms using the PHQ-9, disability levels using WHODAS, and PTSD symptom severity using the PCL-5. We found that the sTBI group scored significantly higher on than both the control and aTBI groups on the ISI ($p < 0.001$), PHQ-9 ($p < 0.001$), WHODAS ($p < 0.001$), and PCL-5 ($p < 0.001$). The aTBI and control groups did not significantly differ on any of these measures (ISI, $p = 0.284$; WHODAS, $p = 0.0612$; PCL-5, $p = 0.228$). The radar plot in **Figure 3.8** represents these group differences, illustrating how the sTBI group is suffering from a range of chronic TBI sequelae.

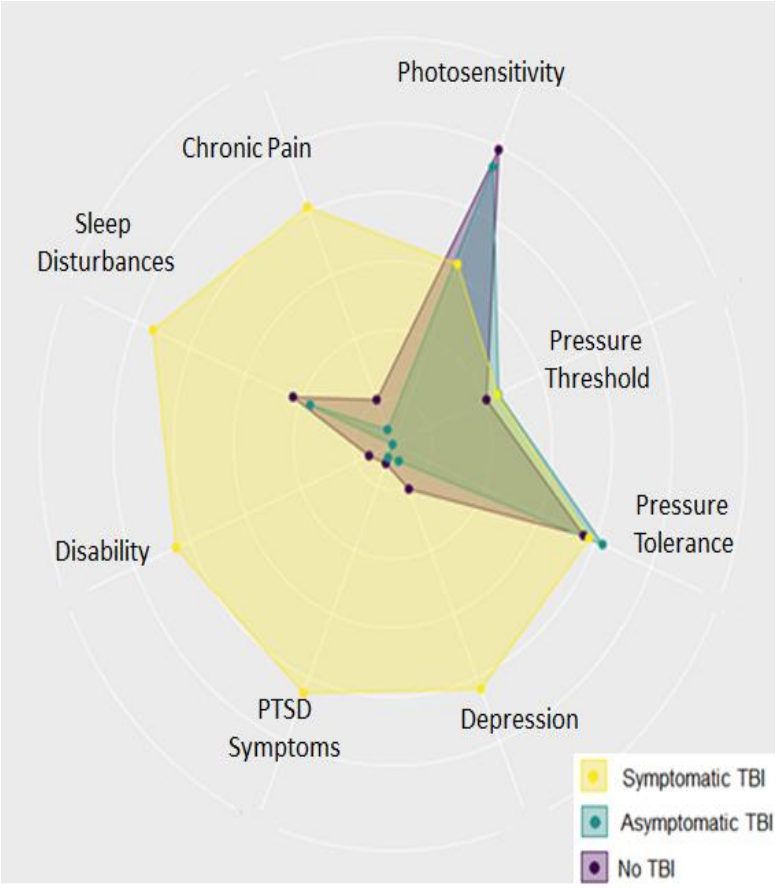

Figure 3.8. Radar plot depicting self-report and behavioral scores between groups. Points farther out from the center represent higher severity and high (worse) scores. The symptomatic TBI group has the highest severity in all measures, except for pressure pain threshold and tolerance levels. Visual Photosensitivity Threshold = VPT; Chronic Pain = SIQR scores; Sleep Disturbances = ISI scores, Disability = WHODAS scores; PTSD Symptoms = PCL-5 scores.; Depression = PHQ-9 scores.

Discussion

The purpose of the present study was to measure visual photosensitivity and pressure-pain responses using quantitative sensory testing in individuals with and without a history of TBI. We also aimed to directly examine the relationship between chronic pain complaints and photosensitivity, and to analyze the effect of other TBI symptomology on this relationship. The primary finding of the present study was that individuals with a history of TBI exhibit a significantly lower threshold for light-evoked discomfort and are less able to tolerate a light stimulus than healthy controls. Individuals who have sustained one or more TBIs also report higher levels of chronic pain compared to those with no history of TBI. These group differences were driven in large part by a subset of the TBI group that endorsed chronic symptomology, as determined using the NSI. This subset also reported higher levels of PTSD, depression, sleep disorders and disability.

We found no group differences in pressure-pain threshold or tolerance, whether comparing individuals with and without TBI or asymptomatic and symptomatic TBI. However, visual photosensitivity thresholds were strongly correlated with chronic pain self-report across individuals, regardless of TBI status. Taken together, these data suggest that a photosensitivity could represent a much-needed indicator of central pain mechanisms in individuals with TBI, and more generally, in individuals experiencing chronic pain.

Quantitative sensory testing

An association between multisensory hypersensitivity and chronic pain has been well established clinically (Friend & Bennett, 2011 et al., J Pain, 2008; Wilbarger & Cook, 2011). However, most investigators have relied on symptom-severity questionnaires or other self-report. Such approaches lack granularity and rely on non-explanatory questions to simply rank sensory sensitivity, which many subjects might not inherently understand. The use of standard stimuli and

stimulation protocols as applied here allowed us to quantify photosensitivity. Although these responses are subjective, this approach increases the reliability of this difficult-to-measure phenomenon (Verriotto et al., 2017). Moreover, the quantitative approach improves sensitivity, revealing a strong and statistically significant correlation between photosensitivity and chronic pain impact, as measured by the SIQR.

The present study did not directly analyze other sensory modalities, but sensitivity to other non-somatic stimuli is also likely to be associated with chronic pain. Individuals with fibromyalgia report aversion to sound and smells, and similar hypersensitivity is frequently seen associated with migraine headache (Goadsby et al., 2017; Schwedt, 2013). Multiple studies have found increased sensitivity to sound after TBI (Callahan et al., 2016; J. E. Elliott et al., 2018). It has been suggested that this sensory dysfunction is related not only to chronic pain, but to other dysfunctions, including cognitive decline and mental health (Callahan et al., 2016; Lin et al., 2011; Pinto et al., 2014). Although continued investigation of the relationships between pain and other sensory modalities is important for understanding chronic pain, photosensitivity testing is likely to prove simpler and more reliable.

By contrast with the strong association between photosensitivity and chronic pain, we found no group difference in pressure-pain threshold or tolerance and chronic pain impact, as measured by the SIQR. This differentiates chronic pain after TBI from chronic pain in fibromyalgia. Although individuals in both groups endorse significant chronic pain impact (as measured by the SIQR), individuals with fibromyalgia exhibit substantially greater sensitivity to pressure and pressure pain than healthy controls (Maquet, Croisier, Demoulin, & Crielaard, 2004; Tunks, Crook, Norman, & Kalaher, 1988).

Photosensitivity associated with "high-impact" chronic pain

Photosensitivity was greatest in the subset of the TBI subjects experiencing an array of chronic symptoms, as measured by the NSI ("symptomatic" TBI group). The symptomatic TBI group also scored high on the SIQR, our measure of chronic pain impact. In addition, these individuals also reported mood disorders, sleep disturbances and a low quality of life due to disability. These symptoms are inter-related, mutually reinforcing, and respond poorly to conventional treatments, and as a whole represent what is now referred to as "high-impact chronic pain" (Pitcher et al., 2019). By contrast, healthy controls and the "asymptomatic" TBI group had lower scores and less severe chronic pain, sleep disturbances, depression, and overall disability. Interestingly, photosensitivity, but not pressure-pain measures, discriminated between these groups. This again suggests that quantitative photosensitivity testing could be a useful marker for this population.

One striking finding was the increased report of PTSD in the symptomatic TBI group, which along with photosensitivity, was a significant predictor of SIQR scores in our multiple linear regression model. We were unable to directly analyze the association between PTSD and photosensitivity/pain, due to low sample size of subjects with pure PTSD without TBI. Since both TBI and PTSD are both independently linked to chronic pain and sensory sensitivity, future studies should examine PTSD-only and comorbid TBI+PTSD populations on these measures.

Potential mechanisms

The neurobiological basis for the high prevalence of chronic pain in individuals with chronic TBI symptomatology is unclear but is unlikely to be ongoing injury and tissue damage. Most importantly, although headaches and head pain are common after TBI, many individuals experience pain at multiple sites and at sites remote from the original injury (Defrin, Riabinin, Feingold, Schreiber, & Pick, 2015; Khoury & Benavides, 2017), which would be more consistent

with central sensitization as a critical mechanism. Evidence for altered activity and reduced connectivity among pain-related brain regions such as the thalamus, pons, prefrontal cortex, and anterior cingulate is (Leung et al., 2016) also points to central dysfunction as a major factor in chronic pain after TBI.

Animal work documents changes in pain-transmission and pain-modulation circuits following experimental TBI. Increases in glutamate, BDNF, serotonin, chemokines, and substance P have been documented (Feliciano et al., 2014; Irvine, Sahbaie, Ferguson, & Clark, 2020; Mustafa et al., 2017), which could contribute to synaptic plasticity throughout the central nervous system (Sandkühler, 2007). Loss of descending inhibition and enhanced descending facilitation (Irvine et al., 2020) have also been demonstrated. Either of these could amplify nociceptive transmission, and contribute to chronic pain (Heinricher et al., 2009). The potential for abnormal engagement of brainstem pain-facilitating neurons by light.

These changes may be triggered by the initial insult, but biopsychosocial elements associated with TBI are also likely to play a significant role. For example, an increase in the prevalence of insomnia and sleep disturbances following TBI, confirmed in the present study, has been associated with increased pain (Smith, Edwards, McCann, & Haythornthwaite, 2007; Smith & Haythornthwaite, 2004), as has depression and anxiety (Thieme, Turk, & Flor, 2004). Biological and psychosocial changes associated with TBI are likely mutually reinforcing and together contribute to the observed high prevalence of chronic pain after TBI.

Significance

These data indicate that photosensitivity is associated with high-impact chronic pain in individuals with chronic TBI symptomatology, and suggest that photosensitivity could be used as a much-needed index of central sensitization in these individuals. This marker is quantitative, non-invasive, easily measured, and could guide future treatment for pain in this vulnerable

population. Treatments that would be less effective in situations where central plasticity contributes to the pain state could also be avoided, for example, surgery directed at a site of perceived pain. These findings also suggest that modifications to the general light environment have the potential to reduce pain and enhance daily function in this population. These simple and inexpensive changes could easily be implemented at clinics treating this population and could provide an immediate benefit. Perhaps most important, the simple test utilized in this work could be extended to other populations with chronic pain. Finally, future studies should aim to understand neuronal processing of light in individuals with TBI, particularly those with high-impact chronic pain.

Future directions and limitations

One limitation of the current study is the lack of longitudinal data. Due to the cross-sectional design, we cannot directly attribute causality to the relationship between increased photosensitivity or chronic pain impact and TBI. Future research will aim to track individuals directly after TBI to see if lowered VPT is an early response to TBI, and whether it predicts subsequent development of chronic symptomatology, including high-impact chronic pain. These studies could also examine if photosensitivity is reduced with effective pain treatments in this population. Future studies will also aim to measure neurological markers of central sensitization using fMRI and electroencephalography to examine whether these neurobiological underpinnings are directly related to photosensitivity. Lastly, our sTBI group had a high prevalence of PTSD, which was also a significant predictor of SIQR scores in our multiple linear regression model. Due to the lack of subjects who had PTSD without TBI, we were underpowered and could not directly analyze the effect of post-traumatic stress on pain and photosensitivity on its own. Since both TBI and PTSD are both independently linked to chronic pain and sensory sensitivity, future studies should examine PTSD-only and comorbid TBI+PTSD populations on these measures.

Chapter 4: Increased sleep disturbances and pain in Veterans with co-morbid TBI and PTSD.

[This chapter has been reformatted for inclusion for this dissertation from: **Balba, N.M.*,** Elliot, J.E.*, Weymann, K.B., Opel, R.A., Oken, B.S., Heinricher, M.M., Lim, M.M. (2018). Sleep disturbances in TBI and PTSD: Associations with chronic pain. *Journal of Clinical Sleep Medicine,* 14(11), 1865-1857. (*Co-First Author)

]

Abstract

Study Objectives: Veterans are at an increased risk for traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD), both of which are associated with sleep disturbances and increased pain. Furthermore, sleep disturbances and pain are reciprocally related such that each can exacerbate the other. Although both TBI and PTSD are independently linked to sleep disturbances and pain, it remains unclear whether Veterans with comorbid TBI+PTSD show worse sleep disturbances and pain compared to those with only TBI or PTSD. We hypothesized Veterans with comorbid TBI+PTSD would demonstrate worse sleep disturbances and pain compared to Veterans with only TBI or PTSD.

Methods: Veterans (*n*=639) from the VA Portland Health Care System (VAPORHCS) completed overnight polysomnography and self-report questionnaires. Primary outcome variables were self-reported sleep disturbances and current pain intensity. Participants were categorized into four trauma-exposure groups: 1) “Neither”, without TBI or PTSD (*n*=383); 2) “TBI”, with only TBI (*n*=67); 3) “PTSD”, with only PTSD (*n*=126); and 4) “TBI+PTSD”, with both TBI and PTSD (*n*=63).

Results: Veterans with PTSD and TBI+PTSD reported the worst sleep disturbances. Veterans with TBI+PTSD reported the greatest pain intensity.

Conclusions: These data suggest that Veterans with TBI+PTSD experience the worst sleep disturbances and greatest pain intensity compared to those with only TBI or neither condition. Those with PTSD also reported the worst sleep disturbances despite not having as much pain. Thus, PTSD appears to be the primary contributor to developing sleep disturbances, and the comorbid condition of TBI appears to potentiate pain intensity in this population.

Current Knowledge/Study Rationale

Traumatic Brain Injury (TBI) and post-traumatic stress disorder (PTSD) are common in Veterans and are independently associated with sleep disturbances and pain, both of which can exacerbate the other and impede rehabilitation. Understanding the relationship between TBI, PTSD, sleep, and pain will help improve treatment and rehabilitation in this vulnerable population.

Study Impact

This study demonstrates that Veterans with PTSD and comorbid TBI+PTSD experience the worst sleep disturbances, but those with TBI+PTSD report significantly greater current pain intensity. These data add to our limited understanding of how Veterans with comorbid TBI+PTSD differ from Veterans with only TBI or PTSD and contribute to the development of improved therapeutic approaches for Veterans in this vulnerable population.

Introduction

Traumatic brain injury (TBI) is defined as a disruption in brain function, or other brain pathology, resulting from an external force (Wortzel & Arciniegas, 2014). The most recent estimate from the Centers for Disease Control and Prevention found that ~2.5 million people in

the United States sustain a TBI each year,(Center for Disease Control and Prevention, 2016) with a significantly higher incidence of TBI among Veterans. Although TBI severity can range from mild, moderate to severe, ~80% are classified as mild,(Okie, 2005)and are associated with a variety of sequelae as well as an increased risk of developing post-traumatic stress disorder (PTSD). Among the most prevalent, persistent and debilitating sequelae in both TBI and PTSD are sleep disturbances and increased pain. Importantly, sleep disturbances and pain also share a reciprocal relationship such that increases in either can independently exacerbate the other (Lautenbacher, Kundermann, & Krieg, 2006; Lewin & Dahl, 1999; Smith et al., 2007; Smith & Haythornthwaite, 2004).

It has been estimated that over 50% of people with TBI experience sleep disturbances,(Grima, Ponsford, Rajaratnam, Mansfield, & Pase, 2016; Mathias & Alvaro, 2012; Sandsmark et al., 2017) including insomnia,(Ouellet, Beaulieu-Bonneau, & Morin, 2006) hypersomnia,(Mathias & Alvaro, 2012) obstructive sleep apnea (OSA),(Grima et al., 2016) and circadian rhythm sleep disorders (Grima et al., 2016; Weymann & Lim, 2017). Furthermore, current evidence suggests these sleep disturbances can persist for several years post-injury (Kempf et al., 2010). Sleep disturbances are also a hallmark feature of PTSD with recurrent nightmares and difficulty sleeping being diagnostic symptoms for PTSD (American Psychiatric Association, 2013a). One study of Vietnam Veterans revealed that almost 91% of soldiers suffering from PTSD also experienced difficulties sleeping (Roszell, McFall, & Malas, 1991). Similar to TBI, individuals with PTSD experience a range of sleep problems,(Khazaie, Ghadami, & Masoudi, 2016) including insomnia,(Neylan et al., 1998; Ohayon & Shapiro, 2000) nightmares,(Neylan et al., 1998; Woodward, Arsenault, Murray, & Bliwise, 2000) sleep fragmentation,(Insana, Kolko, & Germain, 2012) OSA,(Williams, Collen, Orr, Holley, & Lettieri,

2015; Yesavage et al., 2012) and parasomnias (Husain, Miller, & Carwile, 2001; Mysliwiec et al., 2018; Mysliwiec et al., 2014).

Similar to sleep disturbances, both TBI and PTSD are also independently associated with increased pain (Asmundson, Coons, Taylor, & Katz, 2002; Beckham et al., 1997; Beetar et al., 1996; Bryant, 2001; Faux & Sheedy, 2008; Gironda et al., 2009; Hoge, Terhakopian, Castro, Messer, & Engel, 2007; Khoury & Benavides, 2017; Pitman, Altman, & Macklin, 1989; Seal et al., 2017; van Reekum, Cohen, & Wong, 2000). In fact, the combination of TBI, PTSD, and pain, referred to clinically as the "polytrauma clinical triad", (Dobscha et al., 2009; Gironda et al., 2009; Lew et al., 2009; Pugh et al., 2014) is very common among Veterans with recent work reporting a prevalence of ~42% from 340 Operation Enduring Freedom and Operation Iraqi Freedom (OEF/OIF) Veterans (Lew et al., 2009). Irrespective of TBI and PTSD, the presence of sleep disturbances are also independently associated with increased pain (D. Foley, Ancoli-Israel, Britz, & Walsh, 2004; Kaniecki & Lucas, 2004; Landy & Smith, 2004; Lautenbacher et al., 2006; Morin, Gibson, & Wade, 1998; Palermo & Kiska, 2005). Although the mechanism(s) linking sleep disturbances and pain are not fully understood, a bidirectional theory exists which acknowledges pain can interfere with sleep, while poor sleep can exacerbate pain. For instance, Lang and colleagues found that in Veterans with TBI, PTSD and pain (i.e., the polytrauma clinical triad), insomnia was a significant mediator of both pain severity and pain interference (Lang, Veazey-Morris, & Andrasik, 2014). Conversely, improving sleep quality in patients with TBI and/or PTSD can ameliorate pain and thereby improve the efficacy of rehabilitative strategies (Gironda et al., 2009; R. L. Ruff, Riechers II, & Traci Piero NP-C, 2012). Understanding the link between these disorders and sleep disturbances is therefore highly relevant and important for developing more effective treatment options for Veterans.

Although there is a considerable literature describing the association between TBI and PTSD with increased sleep disturbances and pain, few studies have explored how comorbid TBI and PTSD might potentiate this relationship. Thus, the purpose of this study was to determine whether Veterans with comorbid TBI and PTSD exhibit a higher prevalence of sleep disturbances (determined via self-report and objective polysomnography) and pain compared to Veterans with only TBI or PTSD. Pain was primarily assessed via self-reported current pain intensity, and secondarily via the prevalence of headache and sensory (light and noise) sensitivity. We hypothesized that Veterans with comorbid TBI and PTSD would report worse sleep disturbances and pain compared to Veterans with only TBI or PTSD.

Methods

Overview.

The VA Portland Healthcare System (VAPORHCS) institutional review board approved this study (MIRB #3641) and all subjects provided verbal and written informed consent prior to participation. Veterans referred to the VAPORHCS Sleep Disorders Clinic between May 2015 and November 2016 were recruited for participation in a cross-sectional study design (n = 639). Participants provided self-report data on sleep quality, pain, and symptom severity relating to TBI and PTSD, as well as completed an overnight polysomnography (PSG) study at the VAPORHCS Sleep Clinic.

Subject grouping.

Veterans were assessed for a prior history of TBI via a retrospective medical record review (see below), and for the presence of PTSD via the PTSD Checklist for DSM-5 (see below). Based on their prior history of trauma exposure, participants were grouped into the

following four trauma-exposure categories: “Neither”, no history of TBI or PTSD (*n* = 383); “TBI”, at least one instance of TBI documented in the medical record, but no PTSD (*n* = 67); “PTSD”, meeting diagnostic criteria for PTSD, but no medical record documented TBI (*n* = 126); “TBI+PTSD”, both a medical record documented TBI and meeting diagnostic criteria for PTSD (*n* = 63). Subjects in the “Neither” group, i.e., those that did not have a history of TBI or PTSD constituted the control group in the present manuscript and analyses. Demographic data, including, age, sex, body mass index (BMI), race, education (self-reported highest level of completed education), and current exercise status (self-reported minutes of exercise/week) was also collected for all subjects.

Retrospective medical record review.

A retrospective medical record review was conducted to assess numerous metrics related to participants TBI(s) and general health. These included determining a) the number of TBIs; b) the recency of the TBI (determined from year of most recent TBI if >1 TBI was identified); c) whether or not the TBI was caused by blast exposure; d) whether the TBI caused loss of consciousness, confusion, post-traumatic amnesia, or post-concussive syndrome; e) if subjects now suffer from tinnitus or hearing loss; f) whether subjects were Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) Veterans; g) anxiety; h) diabetes; i) hypertension; j) heart disease; k) lung disease and current l) sleep medication; and m) pain medication usage. Sleep medication usage included any one of the following: Sedative-hypnotics, Benzodiazepines, Gamma-Hydroxybutyric Acid, Melatonin, Doxylamine, Trazadone, Quetiapine, Diphenhydramine, Mirtazapine, and over the counter herbs. Pain medication usage included any one of the following: Oxycontin, Hydrocodone, Morphine, Percocet, Vicodin, Fentanyl Patch, Methadone, Codeine, Naltrexone/Suboxone, and Lidocaine Patch. Items a through f were

obtained through manual review of relevant notes; items g through k were obtained through the VA CPRS Problem List (ICD-10 coded diagnoses) and were included only if there were active problems at or around the time of consent. Additionally, the presence of sleep apnea was extracted from subjects overnight PSG.

Survey Instruments.

TBI symptom severity: Rivermead Post Concussion Questionnaire. Subjects with a history of TBI were administered the Rivermead Post Concussion Questionnaire (RPQ) to assess post-concussive syndrome symptom severity, which asks subjects to rate 13 commonly occurring symptoms of TBI (N. King, Crawford, Wenden, Moss, & Wade, 1995). These include headaches, dizziness, nausea, noise sensitivity, sleep disturbance, fatigue, irritability, depression, frustration, forgetfulness, poor concentration, taking longer to think, blurred vision, light sensitivity, double vision, and restlessness. Each individual symptom is ranked on a 5-point Likert scale: 0 = "Not experience at all", 1 = "No more of a problem", 2 = "A mild problem", 3 = "A moderate problem", 4 = "A severe problem". Thus, total scores ranged from 0-52, with higher scores indicating greater severity of symptoms.

PTSD status and symptom severity: PTSD Checklist DSM-5. The PTSD Checklist for DSM-5 (PCL-5)(Blevins et al., 2015) is a 20 item measure used for screening and provisionally diagnosing subjects for PTSD, as well as for assessing PTSD symptom severity. Individual items are 5 point Likert scales: 0 = "Not at all", 1 = "A little bit", 2 = "Moderately", 3 = "Quite a bit", 4 = "Extremely". Thus, the total score ranges from 0-80. The survey questions are subdivided into four subscales, or "clusters": Cluster B (Intrusion; 1-5), Cluster C (Avoidance; 6-7), Cluster D (Mood and Cognition; 8-14), and Cluster E (Arousal Activity; 15-20). Cluster A, which was not administered in this study, is a structured clinical interview (e.g., Clinician-Administered PTSD

Scale) and is required for administering an official diagnosis of PTSD. Thus, subjects in the present study were categorized as having PTSD based on their PCL-5 cluster criteria, and total score (≥33) (Blevins et al., 2015). PCL-5 cluster criteria required subjects to rate 1 B item, 1 C item, 2 D items, and 2 E items as 2 (Moderately) or higher. Cronbach alpha in our sample was 0.97 [0.97 - 0.97], which is consistent with previously reported values (Weathers, Litz, Herman, Huska, & Keane, 1993).

Sleep: Insomnia Severity Index & Functional Outcomes of Sleep Questionnaire-10. The Insomnia Severity Index (ISI) is a 7-item measure assessing insomnia severity (i.e., difficulty initiating and staying asleep), with the total score ranging from 0-28 (Bastien et al., 2001). Individual items are 5-point Likert scales: 0 = "None", 1 = "Mild", 2 = "Moderate", 3 = "Severe", 4 = "Very severe". Cronbach alpha in our sample was 0.88 [0.87 - 0.90], which is consistent with previously reported values (Smith & Wegener, 2003).

The Functional Outcomes of Sleep Questionnaire (FOSQ-10) is a 10 item measure assessing quality of life due to sleep quality (Weaver et al., 1997). Individual items are 4 point Likert scales: 1 = "Yes, extreme difficulty", 2 = "Yes, moderate difficulty", 3 = "Yes, a little difficulty", 4 = "No difficulty". Half of the items include a rating of 0 = "I don't do this activity for other reasons", and items answered as a "0" are not used in determining total score (range 5-40). The survey has five subscales reflecting how their sleep quality affects different aspects of their lives: 1) *General Productivity*, indicating participant's inability to complete important daily tasks (2 items); 2) *Activity Level*, indicating participant's struggle to participate in normal physical activities (3 items); 3) *Vigilance*, indicating participant's inability to sustain attention during normal activities (1 item); 4) *Social Outcomes*, indicating participant's level of daily socialization (2 items); and 5) *Intimacy and Sexual Relationships*, indicating participant's level of sexual satisfaction (1 item) (Omachi, 2011). To obtain the total score, the mean of each subscale

was calculated, then summed, divided by the number of subscales with an answer, and then multiplied by five, for a total score of 5 to 20 (Chasens, Ratcliffe, & Weaver, 2009). The higher score indicates higher function. Cronbach alpha in our sample was 0.85 [0.83 - 0.87], which is consistent with previously reported values (Weaver et al., 1997).

Pain: NIH PROMIS Global Health survey. The National Institute of Health Patient Reported Outcome Measurement Information System (PROMIS) Global Health survey is a validated self-report that measures several domains related to the patient's overall health (Hays, Bjorner, Revicki, Spritzer, & Cella, 2009). For this study we used the Global Health Item 7 score, which rates the patient's overall level of pain on an 11-point Likert scale: 0 = "No Pain", 10 = "Worst Imaginable Pain" (Hays et al., 2009).

Overnight Polysomnography.

All subjects completed a clinically indicated in-laboratory, technician-attended overnight PSG (i.e. Type I sleep study). Clinically indicated PSG studies were either, 1) a full-night positive airway pressure (PAP) titration study, where participants wore a PAP mask throughout the night, 2) a split-night study, where participants wore a PAP mask through the second half of the night, or 3) a full-night diagnostic study where the participant did not wear a PAP mask. Of note, the statistical analysis of PSG related variables was done using a one-way analysis of covariance with PSG type as the covariate. All sleep studies were recorded using Polysmith® version 9.0 (Nihon Kohden; 2012). Sleep staging was performed by an AASM-certified sleep technician and verified by a board-certified sleep medicine physician. Standard parameters as specified by the AASM (Beetar et al., 1996) were captured in the PSG recordings, including electroencephalography (EEG), electromyography (EMG) of the mentalis muscle, electrooculography (EOG; left and right eyes), electrocardiography (EKG), peripheral blood-oxygen saturation (SpO_2), respiratory

movement/effort (thorax and abdominal), airflow (nasal and oral), auditory (snoring), and body positioning (right side, left side, supine, prone).

Individual PSG data were analyzed for total sleep time (TST), time spent in each sleep stage as a percent of TST, number of sleep stage transitions, sleep efficiency, sleep latency, wake after sleep onset (WASO), and body position transitions. Total sleep time was calculated by summing the total number of epochs scored as NREM or REM sleep and converting to minutes. Sleep stage transitions was determined by counting the number of times a patient changed from one sleep stage (wake, NREM 1, NREM 2, NREM 3, or REM) to another stage, with the tally beginning at lights off. Sleep efficiency was calculated as the percent of time a patient spent sleeping after initially falling asleep. Sleep latency was determined by counting the number of 30 second epochs between lights off and the initial onset of NREM sleep. WASO was determined to be the length of time in minutes a patient spent awake after initially falling asleep for the night. Finally, body position transitions were calculated similarly to sleep stage transitions; transitions that occurred before sleep onset were ignored.

Statistical Analyses.

All statistical analyses were performed using R version 3.3.2, (R Development Core Team, 2016) and alpha was set to $P = 0.05$ *a priori*. Differences in numerical variables between groups were assessed using either a Student's unpaired t-test or a one-way analysis of variance (ANOVA) or covariance (ANCOVA), where appropriate. When a significant omnibus test was observed, a Newman-Keuls or Tukey's Honestly Significant Difference *post hoc* test where appropriate, was performed to elucidate significant pairwise differences of interest. Differences in categorical data was performed using a Chi-Square test with a Bonferroni *post hoc* test if warranted (McDonald, 2009). If the expected value in the 2x2 contingency table was <5, Fisher's

exact test with a simulated *P*-value was used. Normality was assessed via the Shapiro-Wilk test, and although not all data sets were normally distributed, these analyses are relatively robust to the violation normality assumptions given the sample size. A multivariate linear regression analysis was used to examine the relationship between sleep disturbances and pain with respect to TBI and PTSD specific comorbidities.

Results

Demographic and general health parameters.

Demographic and general health parameters are shown in **Table 4.1**. The primary difference across groups was with respect to participants' age. Specifically, the TBI+PTSD group was younger than the PTSD (P <0.001), TBI (P = 0.047), and Neither groups (P <0.001). Additionally, although the age of the TBI and PTSD groups did not differ from each other (P = 0.628), they were also both younger than the Neither group (P <0.001 for both). No other differences were detected across groups with respect to BMI, sex, race, education level, or weekly exercise level.

There were also few differences across groups within general health parameters assessed via the retrospective chart review. No differences across groups were found in the rates of anxiety, hypertension, heart disease, lung disease, or obstructive sleep apnea. However, we did detect differences in the proportion of subjects with diabetes and tinnitus. With respect to diabetes, both the TBI and TBI+PTSD groups showed significantly lower rates compared to the Neither group (TBI+PTSD vs. Neither P = 0.002; TBI vs. Neither P = 0.006), while the PTSD group had significantly lower rates compared to the TBI group (P = 0.002). With respect to tinnitus, the TBI (P = 0.039), PTSD (P = 0.001), and TBI+PTSD (P <0.001) groups all showed significantly higher rates compared to the Neither group. However, the TBI+PTSD group

reported the highest prevalence, with it also being significantly higher than the TBI ($P = 0.008$) and PTSD ($P = 0.004$) groups.

Table 4.1. *Demographic and general health parameters in Veterans with TBI, PTSD, and TBI+PTSD.*

	Neither	TBI	PTSD	TBI+PTSD	Statistic	P-value
	n = 383	*n* = 67	*n* = 126	*n* = 63		
Age, years	58.4 ± 14.6	49.6 ± 16.0*	52.3 ± 15.3*	42.7 ± 14.8*†‡	25.16	**<0.001**
Sex, male	351 (91.9%)	62 (92.5%)	115 (91.3%)	58 (92.1%)	0.1	0.991
BMI, kg/m^2	33.0 ± 6.5	32.6 ± 6.5	32.8 ± 6.9	31.2 ± 6.2	1.34	0.262
Race, white	331 (86.4%)	59 (88.1%)	101 (80.2%)	50 (79.4%)	4.84	0.184
Education	289 (76.3%)	54 (81.8%)	95 (76.0%)	49 (79.0%)	1.2	0.753
Exercise	176 (46.0%)	43 (64.2%)	63 (50.0%)	36 (57.1%)	9.17	0.027
Anxiety	36 (9.4%)	14 (20.9%)	21 (16.7%)	11 (17.5%)	10.79	0.013
Diabetes	98 (25.6%)	6 (9.0%)*	34 (27.0%)†	4 (6.3%)*‡	20.17	**<0.001**
Hypertension	201 (52.5%)	23 (34.3%)	56 (44.4%)	23 (36.5%)	12	0.007
Heart disease	95 (24.8%)	11 (16.4%)	21 (16.7%)	8 (12.7%)	8.19	0.042
Lung disease	61 (15.9%)	6 (9.0%)	20 (15.9%)	9 (14.3%)	2.28	0.517
OSA	325 (84.9%)	55 (82.1%)	102 (81.0%)	47 (74.6%)	4.43	0.218
Tinnitus	125 (32.6%)	34 (50.7%)*	66 (52.4%)*	50 (79.4%)*†‡	56.93	**<0.001**
Sleep medication	88 (23.6%)	21 (31.8%)	51 (42.5%)*	23 (38.3%)	16.8	**<0.001**
Pain medication	107 (27.9%)	26 (38.8%)	43 (34.1%)	20 (31.7%)	4.17	0.243

Table 4.1 Data are mean ± standard deviation, or *n* (% of total). TBI, traumatic brain injury; PTSD, post-traumatic stress disorder; BMI, body mass index; Education, subjects with some college education or above; Exercise, subjects who reported >90 min of exercise/week; OSA, obstructive sleep apnea; Sleep medication usage includes any one of the following: Sedative-hypnotics, Benzodiazepines, Gamma-Hydroxybutyric Acid, Melatonin, Doxylamine, Trazadone, Quetiapine, Diphenhydramine, Mirtazapine, and over the counter herbs; Pain medication usage includes any one of the following: Oxycontin, Hydrocodone, Morphine, Percocet, Vicodin, Fentanyl Patch, Methadone, Codeine, Naltrexone/Suboxone, and Lidocaine Patch. Post hoc comparisons on continuous and categorical data were made using Tukey's HSD and Bonferroni, respectively. * P <0.05 vs. Neither; † P <0.05 vs. TBI; ‡ P <0.05 vs. PTSD.

TBI and PTSD parameters.

Characteristics and post-concussive symptomology related to participants TBIs are presented in **Table 4.2**. Although the TBI+PTSD group experienced a significantly higher number of TBIs compared to the TBI group (P = 0.030), there were no differences detected in the recency (measured in years) of subjects TBI between groups despite an overall difference in the proportion of subjects being OEF/OIF Veterans (P = 0.002). With respect to specific post-injury

Table 4.2. *TBI characteristics in Veterans with TBI and TBI+PTSD.*

	TBI	TBI+PTSD	Statistic	P-value
	n = 67	*n* = 63		
Number of TBIs	1.99 ± 1.65	2.94 ± 3.11*	2.2	**0.03**
TBI recency, years	23.27 ±19.02	18.86 ±14.56	1.41	0.16
Blast injury	16 (23.9%)	28 (44.4%)*	6.13	**0.013**
PCS	26 (38.8%)	36 (57.1%)*	4.37	**0.036**
LOC	31 (46.3%)	33 (52.4%)	0.48	0.486
Confusion	20 (29.9%)	30 (47.6%)*	2.08	**0.037**
PTA	11 (16.4%)	11 (17.5%)	0.16	0.874
Hearing loss	24 (35.8%)	29 (46.0%)	1.4	0.236
OEF/OIF	19 (28.4%)	35 (55.6%)*	9.89	**0.002**

Data are mean ± standard deviation, or *n* (% of total). TBI, traumatic brain injury; PTSD, post-traumatic stress disorder; PCS, post-concussive syndrome; LOC, loss of conscious; PTA, post-traumatic amnesia; OEF/OIF, Operation Enduring Freedom/Operation Iraqi Freedom. Post

characteristics, we found differences between groups in the proportion of subjects experiencing a blast related TBI (P = 0.013), post-concussive syndrome (P = 0.036), and post-injury confusion (P = 0.037). However, there were no differences in the distribution of subjects experiencing post-traumatic loss of consciousness (P = 0.486), post-traumatic amnesia (P = 0.874), or hearing loss (P = 0.236).

Sleep-wake disturbances.

Participants in the TBI+PTSD and PTSD groups had significantly worse ISI scores (i.e., higher) compared to both the TBI and Neither groups (P <0.001; all comparisons) (**Figure 4.1A**). Furthermore, participants in the TBI+PTSD and PTSD groups had significantly worse FOSQ-10 scores (i.e., lower) compared to both the TBI and Neither groups (P <0.001; all comparisons) (**Figure 4.1B**). However, in both cases, the no differences were detected between the Neither and TBI groups, as well as the PTSD and TBI+PTSD groups. There were also significant positive correlations between the RPQ and ISI (r = 0.53, P <0.001; **Figure 4.1C**) in participants with TBI, as well as between the PCL-5 and ISI (r = 0.46; P <0.001; **Figure 4.1D**) in participants with PTSD.

With respect to sleep medication usage, there were few overall differences observed across groups. The PTSD group reported a significantly higher usage of "any" sleep medication compared to the Neither group (P <0.001), but no differences were seen between the TBI, PTSD, and TBI+PTSD groups. There was a higher rate of sedative-hypnotic use in the PTSD and TBI-PTSD group compared to the Neither group, as well as a higher rate of quetiapine use in the TBI+PTSD group compared to the Neither, TBI, and PTSD groups (P <0.001; all comparisons).

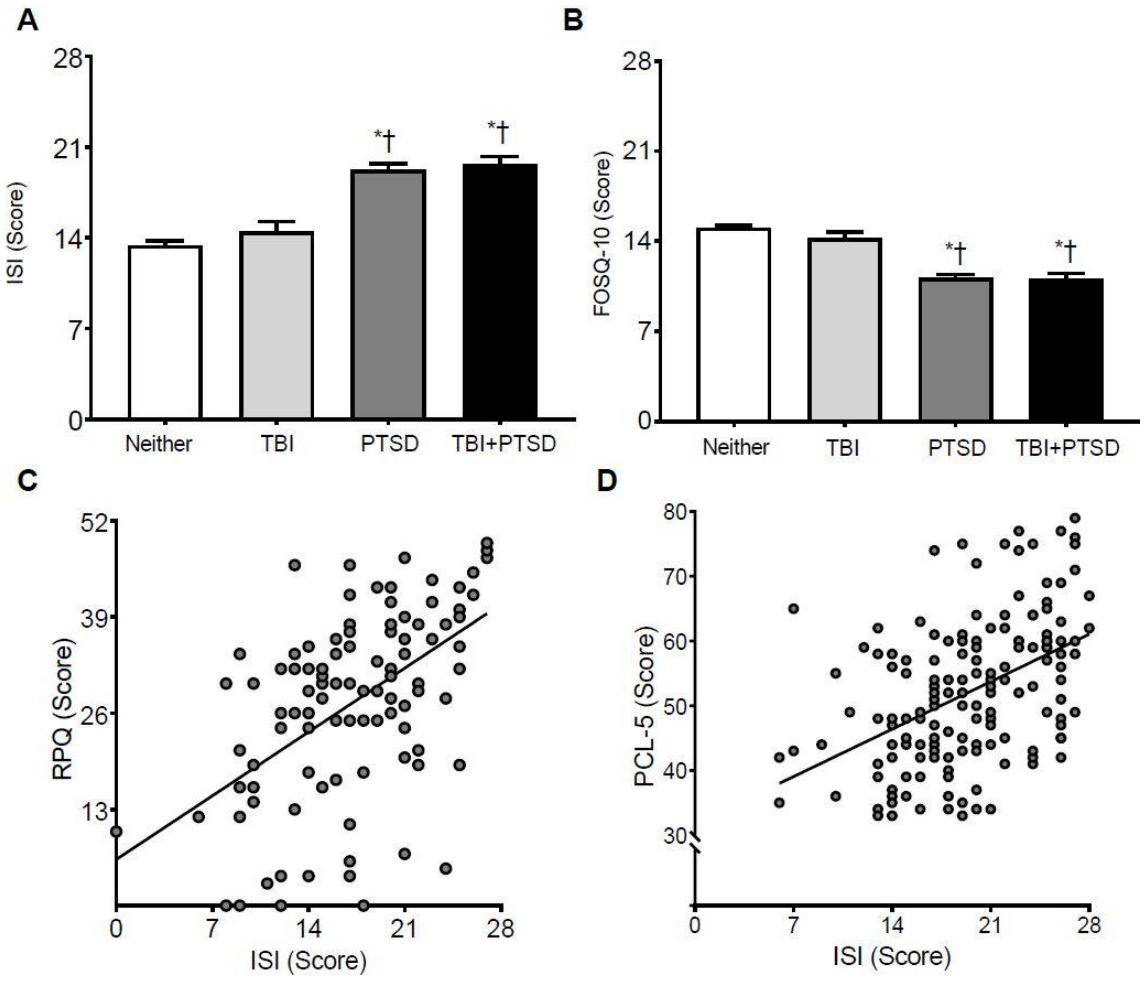

Figure 4.1. Sleep disturbances are associated with TBI, PTSD, and TBI+PTSD. **(A)** Symptom severity for insomnia determined by ISI scores (0-28, higher = worse insomnia); **(B)** Functional outcomes of sleep, determined by the FOSQ-10 (5-40, lower = worse outcomes); For both measures, participants with TBI+PTSD (black bar, n = 58) or PTSD (dark gray bar, n = 106) had significantly worst scores that participants with a TBI (light gray bar, n = 59) or Neither disorder (white bar, n = 326; * P <0.05 vs. Neither; † P <0.05 vs. TBI). **(C)** The correlation between ISI scores and post-concussive symptom severity determined by the RPQ (n = 106, r = 0.53, P <0.001)**,** and **(D)** PTSD symptom severity determined by the PCL-5 (n = 164, r = 0.46, P <0.001). Note, the n's for each group are slightly less than group totals presented elsewhere due to subjects not completing, or missing specific questions that preclude obtaining a meaningful total score.

Pain.

Self-reported pain was significantly higher in the TBI (P <0.05), PTSD (P <0.001) and TBI+PTSD (P <0.001) groups compared to the Neither group (**Figure 4.2A**). However, the TBI+PTSD group also reported significantly higher pain scores than both the TBI (P <0.001) and PTSD (P <0.05) groups. There were also significant positive correlations between the RPQ and pain scores (r = 0.42, P <0.001; **Figure 4.2B**) in participants with TBI, as well as between the PCL-5 and pain scores (r = 0.30; P <0.001; **Figure 4.2C**) in participants with PTSD.

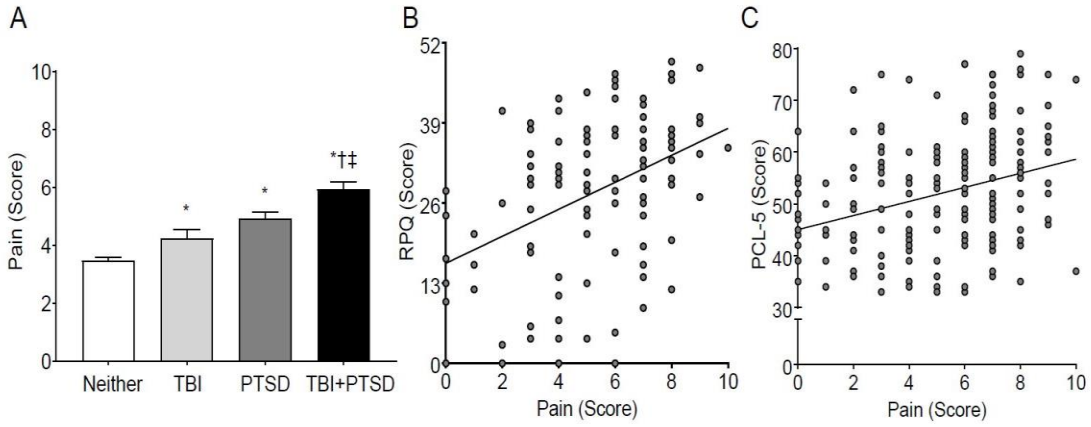

Figure 4.2. Pain is associated with TBI, PTSD, and TBI+PTSD.
(A) Current pain intensity determined by the PROMIS Global pain score (0-10, higher = worse pain); Participants with TBI+PTSD (black bar, *n* = 58) had significantly higher scores that participants in the TBI group (light gray bar, *n* = 64) or the Neither group (white bar, *n* = 356). Participants in the PTSD group (dark gray bar, *n* = 118) also scored higher than the Neither group (* *P* <0.05 vs. Neither; † *P* <0.05 vs. TBI; ‡ *P* <0.05 vs. PTSD). **(B)** The correlation between pain intensity and post-concussive symptom severity determined by the RPQ (*n* = 117, *r* = 0.42, *P* <0.001)**,** and **(C)** PTSD symptom severity determined by the PCL-5 (*n* = 188, *r* = 0.30, *P* <0.001). Note, the *n*'s for each group are slightly less than group totals presented elsewhere due to subjects not completing, or missing specific questions that preclude obtaining a meaningful total

With respect to pain medication usage, the only differences detected were a higher usage of oxycontin in the TBI group compared to the Neither group (P = 0.016), and a higher usage of topical lidocaine in the TBI group compared to the Neither group (P = 0.007).

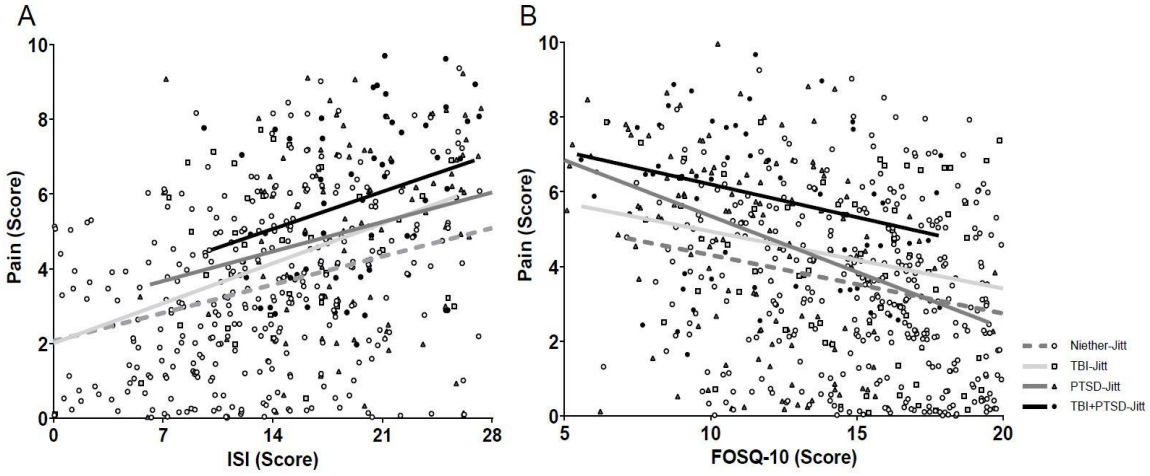

Figure 4.3. Sleep disturbances are significantly correlated with pain with TBI, PTSD, and TBI+PTSD.
Sleep disturbances, as measured by ISI and FOSQ-10 scores, plotted against pain scores (Neither = open symbols and dashed line, TBI = light gray shaded symbols and line, PTSD = dark gray symbols and line, TBI+PTSD = filled symbols and solid line). **(A)** ISI scores showed a statistically positive correlation with pain scores in all groups (Neither: $n = 324$, $r = 0.30$, $P < 0.001$; TBI: $n = 58$, $r = 0.37$, $P = 0.005$; PTSD: $n = 105$, $r = 0.22$, $P = 0.024$; TBI+PTSD: $n = 58$, $r = 0.30$, $P = 0.022$). **(B)** FOSQ-10 scores showed a statistically negative correlation in all groups (Neither: $n = 359$, $r = -0.22$, $P < 0.001$; TBI: $n = 64$, $r = -0.22$, $P = 0.076$; PTSD: $n = 123$, $r = -0.35$, $P < 0.001$; TBI+PTSD: $n = 60$, $r = -0.30$, $P = 0.021$). Random jitter between -0.25 and 0.25 was applied to pain and ISI data points for illustrative purposes to avoid overlapping data points. Note, the *n*'s for each group are slightly less than group totals presented elsewhere due to subjects not completing, or missing specific questions that preclude obtaining a meaningful total score.

The relationship between sleep-wake disturbances and pain.

The relationship between pain scores and ISI showed significant correlations within each group, albeit no differences were detected in the slopes of these relationships (**Figure 4.3A**): The TBI group had the highest correlation coefficient (r = 0.37, P = 0.005), followed by the TBI+PTSD group (r = 0.30, P = 0.022), the Neither group (r = 0.293, P <0.001), and the PTSD

group (r = 0.22, P = 0.024). Similarly, all groups showed a significant correlation between pain scores and the FOSQ-10, albeit without differences in the slopes of these relationships (**Figure 4.3B**): The PTSD group had the highest correlation coefficient (r = -0.35, P <0.001), followed by the TBI+PTSD group (r = -0.30, P = 0.021) the TBI group (r = -0.22, P = 0.076), and the Neither group (r = 0.22, P <0.001).

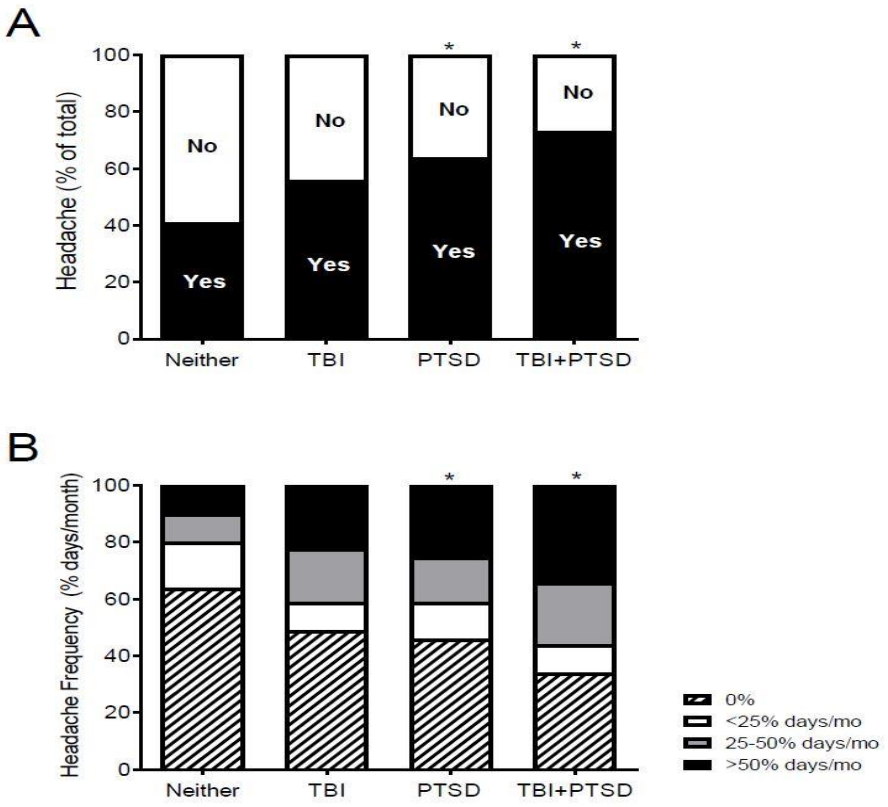

Figure 4.4. Prevalence of headaches in Veterans with TBI, PTSD, and TBI+PTSD.
(A) Proportion of participants who reported experiencing chronic headaches and (B) frequency of headache. PTSD (n = 109; X^2 = 10.61, P = 0.001) and TBI+PTSD (n = 59; X^2 = 20.89, P <0.001) groups reported significantly more headaches than the Neither group (n = 343). The TBI group (n = 59) did not significantly differ from any other group. Note, the n's for each group are slightly less than group totals presented elsewhere due to subjects not completing, or missing specific questions relating to their headache characterization.

Headache, photo- and phonosensitivity.

Although not a primary outcome variable, headaches are a very common form of pain post-TBI and we found significantly higher rates of self-reported headache in the PTSD (P = 0.007) and TBI+PTSD (P <0.001) groups compared to the Neither group (**Figure 4.4A**). Subjects in the PTSD (P = 0.016) and TBI+PTSD (P <0.001) groups also reported a significantly increased frequency of headache (in days/month) compared to the Neither group (**Figure 4.4B**).

Similarly, photo- (**Figure 4.5A**) and phonosensitivity (**Figure 4.5B**) are also common manifestations after TBI and may indicate lower pain thresholds in this population. These parameters (part of the RPQ) were assessed on a 0-4 Likert scale, and were phrased as "Light sensitivity, easily upset by bright light" and "Noise sensitivity, easily upset by loud noise". The TBI+PTSD group showed the worse (i.e., the highest) photosensitivity score compared to the PTSD, TBI and Neither groups (P <0.001; all comparisons). Furthermore, the PTSD group had significantly worse scores than the TBI and Neither groups, as well as the TBI group compared to the Neither group (P <0.001; all comparisons). A very similar pattern was observed with respect to phonosensitivity, with the PTSD and TBI+PTSD group reporting the higher scores compared to the Neither and TBI groups (P <0.001; all comparisons). Again, similar to the photosensitivity data, the TBI group reported higher phonosensitivity compared to the Neither group (P <0.001).

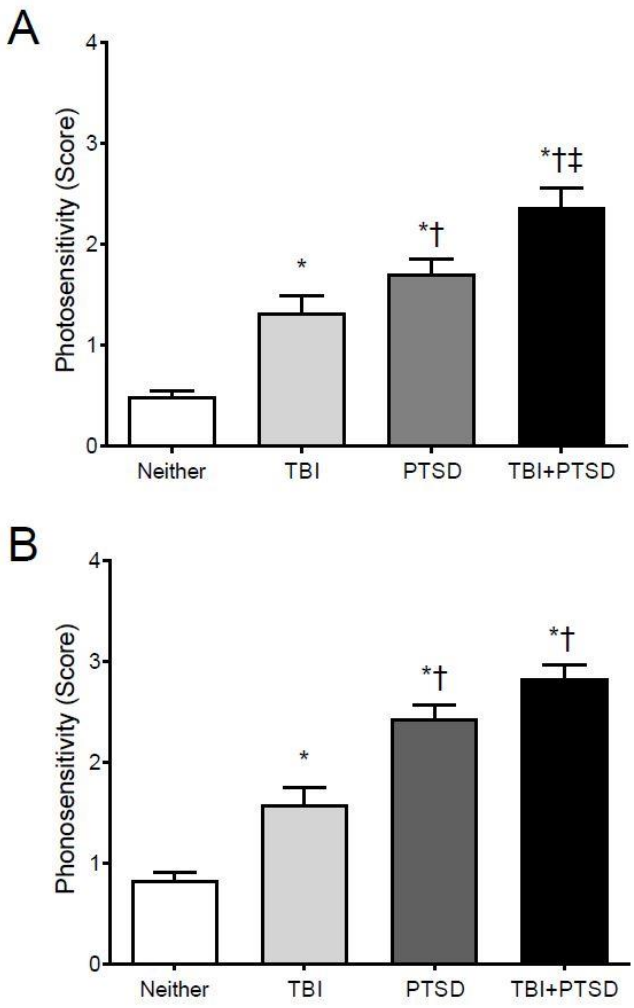

Figure 4.5. Photo- and phonosensitivity in Veterans with TBI, PTSD, and TBI+PTSD.

Participants self-reported **(A)** photo- (i.e., light) and **(B)** phonosensitivity (i.e., noise) scores (0-4, higher = greater sensitivity). Participants with TBI+PTSD (black bar, $n = 57$) had significantly higher light sensitivity scores than all other groups, and participants with PTSD (dark gray bar, $n = 88$) or TBI+PTSD had significantly higher noise sensitivity scores than the TBI (light gray bar, $n = 54$) and Neither groups (white bar, $n = 277$). * $P < 0.05$ vs. Neither; † $P < 0.05$ vs. TBI; ‡ $P < 0.05$ vs. PTSD. Note, the *n*'s for each group are slightly less than group totals presented elsewhere due to subjects not completing, or missing specific questions relating to their photo- and phonosensitivity

Polysomnography.

Overnight PSG data (**Table 4.5**) from each participant was analyzed using a one-way ANCOVA while controlling for age and PSG type (full-night diagnostic, split-night, or full-night PAP titration study). There were no statistically significant differences between groups in sleep latency, heart rate, sleep stage transitions, total sleep time, sleep efficiency, amount

Table 4.3. ***Polysomnography metrics in Veterans with TBI, PTSD, and TBI+PTSD.***

	Neither	TBI	PTSD	TBI+PTSD	Statistic	*P* -value
	n = 383	*n* = 67	*n* = 126	*n* = 63		
Total sleep time, min	298 ± 92	318 ± 70	319 ± 83	327 ± 97	3.75	0.011
Sleep latency, min	52 ± 56	56 ± 56	50 ± 53	46 ± 42	0.3	0.821
Sleep efficiency, %	70 ± 18	75 ± 15	74 ± 17	76 ± 18	4.2	0.006
WASO, min	26 ± 18	20 ± 13	22 ± 17	20 ± 17*	4.77	**0.003**
Heart rate, bpm	63 ± 11	61 ± 10	65 ± 12	62 ± 11	0.53	0.66
Sleep stage transitions	845 ± 133	853 ± 89	867 ± 102	839 ± 148	1.15	0.33
Sleep stage, %						
Wake	30 ± 18	25 ± 15	26 ± 17	23 ± 17*	4.45	**0.004**
REM	11.7 ± 7.1	12.5 ± 7.2	12.2 ± 7.5	14.1 ± 8.3	1.98	0.115
NREM	57 ± 15	61 ± 12	60 ± 14	60 ± 14	3.57	0.014
Stage 1	11.5 ± 5.5	11.0 ± 5.2	11.1 ± 6.1	9.9 ± 4.1	1.73	0.159
Stage 2	44 ± 16	48 ± 14	46 ± 15	47 ± 14	2.21	0.086
Stage 3	1.6 ± 4.2	2.7 ± 4.8	2.5 ± 5.0	4.0 ± 5.9*	6.38	**<0.001**

Data are mean ± standard deviation. TBI, traumatic brain injury; PTSD, post-traumatic stress disorder; WASO, wake after sleep onset; REM, rapid eye movement sleep; NREM, non-rapid eye movement sleep. All variables were tested using one-way ANCOVA with age and PSG type as covariates. Post hoc comparisons on continuous and categorical data were made using Tukey's HSD and Bonferroni, respectively. * *P* <0.05 vs. Neither.

of rapid eye movement (REM) sleep, total non-REM sleep, amount of NREM Stage N1 sleep, or amount of NREM Stage N2 sleep. There were significant group differences in wake after sleep onset (P = 0.006), with post-hoc tests revealing that the TBI+PTSD group was significantly lower than the Neither group (P = 0.039). We also found group differences in time spent awake (P = 0.004), with the TBI+PTSD group being significantly lower than the Neither group (P = 0.040). Lastly, while overall amounts of NREM Stage N3 were low, there was a significant difference (P <0.001) with the TBI+PTSD group being significantly higher than the Neither group (P <0.001).

Multivariate linear regression analyses.

In order to better explore the relationship between TBI, PTSD, sleep, and pain, multivariate regression models were employed. Three models were developed based on our primary outcome variables, including current pain intensity, ISI, and FOSQ-10 scores (**Table 4.4**). Predictor variables across all outcome variables included RPQ, PCL-5, sleep and pain medication usage, and number of TBIs sustained. Additional predictor variables depending on the outcome variable of interest included pain intensity, ISI scores and FOSQ-10 scores. While predicting current pain intensity based on ISI, FOSQ-10, RPQ, PCL-5, sleep and pain medication usage, and number of sustained TBIs, a significant regression equation was found ($F = 24.27$, $P <0.001$, $R^2 = 0.282$). We found that ISI ($P <0.01$) and RPQ scores ($P <0.01$) and pain medication usage ($P <0.001$) significantly contributed to the model, all of which increased predicted current pain intensity. When predicting ISI scores using variables of current pain intensity, RPQ, PCL-5, sleep and pain medication usage, and number of sustained TBIs, a significant regression equation was found ($F = 31.48$, $P <0.001$, $R^2 = 0.414$). PCL-5 score ($P <0.001$) was the largest contributors to this model, but pain intensity, RPQ score, and sleep medication usage all significantly contributed to the model as well ($P <0.01$). This same model was also used to

predict FOSQ-10 scores, and again a significant regression was found (F = 43.87, P <0.001, R^2 = 0.406). Pain, PCL-5, and RPQ scores all significantly contributed to the model (P <0.001) as did sleep medication usage albeit to a lesser extent (P <0.05).

Table 4.4. *Multivariate Regression Analyses.*

Outcome Variables	Predictor Variables	Beta ± SE	T-score	P-value	Adjusted R^2
Current Pain Intensity (0-10 scale)					0.282
	ISI (Total Score)	**0.072 ± 0.02**	**3.303**	**0.001**	
	FOSQ-10 (Total Score)	0.050 ± 0.03	1.426	0.154	
	RPQ (Total Score)	**0.031 ± 0.01**	**2.683**	**0.008**	
	PCL-5 (Total Score)	0.010 ± 0.01	1.117	0.282	
	Pain Medication usage	**1.421 ± 0.22**	**6.364**	**<0.001**	
	Sleep Medication usage	-0.057 ± 0.23	-0.243	0.808	
	Number of TBIs	0.013 ± 0.06	0.211	0.833	
ISI (Total Score: 0-28 range)					0.414
	Current Pain Intensity	**0.389 ± 0.11**	**3.422**	**0.001**	
	RPQ (Total Score)	**0.085 ± 0.03**	**3.223**	**0.001**	
	PCL-5 (Total Score)	**0.162 ± 0.02**	**5.896**	**<0.001**	
	Pain Medication usage	-0.723 ± 0.30	-0.944	0.346	
	Sleep Medication usage	**-2.663 ± 0.53**	**-2.575**	**0.01**	
	Number of TBIs	0.031 ± 0.15	0.028	0.978	
FOSQ-10 (Total Score)					0.406
	Current Pain Intensity	**0.429 ± 0.11**	**3.801**	**<0.001**	
	RPQ (Total Score)	**0.089 ± 0.03**	**3.443**	**<0.001**	
	PCL-5 (Total Score)	**0.107 ± 0.02**	**5.752**	**<0.001**	
	Pain Medication usage	0.298 ± 0.54	0.549	0.583	
	Sleep Medication usage	**1.218 ± 0.53**	**2.283**	**0.023**	
	Number of TBIs	-0.176 ± 0.15	-1.186	0.406	

ISI, insomnia severity index; FOSQ-10, functional outcomes of sleep questionnaire-10; RPQ, Rivermead Post-concussive Questionnaire; PCL-5, Post-traumatic stress disorder checklist-5; TBI, traumatic brain injury; Pain and sleep medications refer to Table 1 legend; SE, standard error.

Discussion

The primary outcome of the present study is that Veterans with comorbid diagnoses of TBI and PTSD report worse pain, headaches, and light/noise hypersensitivity compared to Veterans with a single or neither disorder. Furthermore, the present study shows that comorbid TBI+PTSD is not associated with exacerbation of SWD beyond that reported by Veterans with only PTSD. Taken together, these data suggest that PTSD is the primary contributor to self-reported SWD in this patient population. Nevertheless, we do present a strong correlation between post-concussive/PTSD symptom severity and SWD, which was independently found to be associated with chronic pain. Although previous research has documented a high prevalence of SWD and chronic pain co-occurring in Veterans with TBI and with PTSD,(Lang et al., 2014; Lew et al., 2010; Pugh et al., 2014) to our knowledge, previous research has not yet demonstrated how the comorbidity of TBI+PTSD can exacerbate or influence the persistence of these sequelae >10 years post-injury. Collectively, these results suggest that TBI and PTSD contribute independently to chronic pain, headache, and sensory sensitivity, and that Veterans suffering from comorbid TBI+PTSD show potentiation of these symptoms.

Comorbid TBI+PTSD is associated with worse sleep disturbances

Out of the four groups, Veterans with TBI+PTSD reported the most severe insomnia (i.e., highest ISI score) and the worst quality of life due to poor sleep (i.e., lowest FOSQ-10 score). However, the TBI+PTSD group did not differ statistically from the PTSD group, suggesting that PTSD is the primary contributor of SWD in Veterans with both TBI and PTSD. These results mirror several previous studies, including a recent one by Lew et al. examining sleep disturbances in a sample of 200 OEF/OIF Veterans (Lew et al., 2010). Lew et al. found that Veterans suffering from the polytrauma clinical triad (TBI, PTSD, and chronic pain) reported more sleep disturbances than Veterans diagnosed with a single disorder, and that PTSD was the most

significant predictor of sleep complaints. However, these authors also concluded that TBI and chronic pain, "were separately and independently interacting with PTSD or amplifying" its effect on sleep impairments. Their findings are consistent with our findings reported herein. While we found that the TBI group curiously did not show worse subjective or objective sleep compared to controls, this could be due to a number of factors specific to our population. The most likely explanation is that subjects in our Neither group were also recruited from the Sleep Clinic and were referred for evaluation of sleep complaints. Other potential contributors could be the chronic duration since last TBI (average ~21 years), as well as our focus on insomnia symptoms, compared to other more comprehensive sleep questionnaires. Nevertheless, we did find a strong correlation between RPQ (a measure of TBI post-concussive symptoms) and ISI scores in our sample of Veterans diagnosed with TBI. These results are in accordance with several previously published studies that found post-concussive symptoms are linked to a plethora of sleep disturbances (Beaulieu-Bonneau & Morin, 2012; J. L. Ponsford et al., 2013; Shekleton et al., 2010). We also found a strong correlation between PCL scores (a measure of PTSD severity) and ISI scores. This too mirrors several other studies demonstrating that PTSD symptom severity is associated with poor sleep (Lamarche & De Koninck, 2007; Mellman, Pigeon, Nowell, & Nolan, 2007; Pigeon, Campbell, Possemato, & Ouimette, 2013). It is important to note that PSG data did not reflect the high levels of SWD in the TBI+PTSD group, which on average had a lower wake after sleep onset (WASO) and more NREM stage N3 sleep. This could be due to the well documented paradoxical "first-night effect" in our population, where people with insomnia, unlike those without insomnia, have a tendency to sleep better during the first night in a sleep laboratory (Newell, Mairesse, Verbanck, & Neu, 2012). Due to the night-to-night variability seen in PSG data, consecutive overnight studies would be helpful to evaluate whether the first-night effect is contributing to group differences in sleep metrics in TBI+PTSD.

Comorbid TBI+PTSD is associated with worse chronic pain

The TBI+PTSD group also scored significantly higher in self-reporting pain compared to all other groups. This was not surprising, as there was a strong correlation between RPQ/PCL scores and pain scores suggesting both disorders are contributing to chronic pain complaints. Furthermore, both the TBI and PTSD groups scored significantly higher than the Neither group, suggesting that each of these disorders is independently contributing to increased pain. Although there were significant group differences in age, age was not applied as a covariate in our analyses. As age is known to be positively correlated with pain in the general population (Elliott, Smith, Penny, Smith, & Chambers, 1999; Foley, Monjan, Simonsick, Wallace, & Blazer, 1999; Johannes, Le, Zhou, Johnston, & Dworkin, 2010), the fact that we found an inverse relationship such that TBI+PTSD were the youngest group, but had the most pain complaints, suggests that the effect of trauma on pain is probably even more pronounced in spite of younger age. Similar results were obtained with headaches, with 73% of Veterans with TBI+PTSD self-reporting some incidence of headache in the previous 30 days, and 34% stating they suffered from headaches on more than half the days in the past month. Although previous research has reported similar findings, (Bryant, Marosszeky, Crooks, Baguley, & Gurka, 1999; Jaramillo et al., 2016; Nampiaparampil, 2008; Ruff, 2008; Stojanovic et al., 2016; Young, 2007) these data are the first to report the persistence of chronic pain in Veterans with TBI decades after injury (average duration since last TBI was 23.3 years in TBI group and 18.9 years in the TBI+PTSD group).

Sleep-wake disturbances are correlated with chronic pain.

It has been well established that SWD and chronic pain are inextricably linked. In the present study we found that Veterans with TBI or comorbid TBI+PTSD had the strongest correlation between ISI and pain scores, but there was also a significant positive correlation between these scores in the PTSD and Neither groups. We found similar results when correlating

FOSQ-10 and pain scores, with the PTSD and TBI+PTSD displaying the strongest correlations, followed by the Neither and TBI groups. Taken together, these results reaffirm the well-established connection between increased SWD and chronic pain,(Call-Schmidt & Richardson, 2003; Menefee et al., 2000) but also suggests that this link may be even stronger in those suffering from a TBI+PTSD. Although disentangling this relationship and determining cause and effect has been challenging for researchers, the current consensus explanation is a bidirectional relationship between SWD and pain. Several animal studies have shown that sleep deprivation and reduced REM stage sleep can induce hyperalgesia in mice and rats (Asakura, Matsumoto, Ohta, & Watanabe, 1992; Hicks, Coleman, Ferrante, Sahatjian, & Hawkins, 1979; Hicks, Moore, Findley, Hirshfield, & Humphrey, 1978). Studies on humans are consistent with this idea. For example, the subjective quality of sleep in patients suffering from severe burn injuries was a significant predictor for pain intensity the following day,(Raymond et al., 2001) which replicated a comparable study on patients suffering from rheumatoid arthritis (Stone et al., 1997). But the converse is also true: Pain can lead to poor sleep, with one study on fibromyalgia patients indicating that pain intensity predicted their quality of sleep and suggesting that this may be mediated by increased attention to pain (Affleck et al., 1996). Thus, a mutual potentiation exists in which one disorder increases the symptoms of the other, and this vicious cycle may be exceptionally severe in Veterans suffering from the polytrauma clinical triad (Lew et al., 2010).

Comorbid TBI+PTSD is associated with increased sensitivity to light and noise.

Light and noise sensitivity are known symptoms of TBI, and previous research has found that these symptoms can persist for several months after the initial injury (Bohnen, Twijnstra, Wijnen, & Jolles, 1991; Callahan et al., 2016; N. King et al., 1995). However, these symptoms have not been examined in Veterans suffering from chronic post-concussive symptoms decades

post-injury. We found that Veterans with TBI or PTSD reported higher levels of light and noise sensitivity, and that the comorbid TBI+PTSD group reported the highest levels (even being decades after their diagnosis). This is especially interesting because of the scarcity of research examining the relationship between PTSD and sensory sensitivity, although there have been other studies that suggest PTSD can exacerbate post-concussive symptoms in individuals with a history of TBI, which may include sensory hypersensitivity (Bryant et al., 1999). Of note, both chronic pain and increased light sensitivity are also common complaints of patients suffering from fibromyalgia (Geisser, Donnell, et al., 2008; Geisser, Glass, et al., 2008) and chronic migraines,(Burstein, Noseda, & Borsook, 2015; Goadsby et al., 2017) which have both been linked to the sensitization of pain-processing circuits (Martenson et al., 2016; Woolf, 2011). Further studies are needed to determine whether light and noise sensitivity could be a useful marker to predict central sensitization of pain in Veterans with TBI and PTSD.

Future directions and limitations.

The present study demonstrates strong evidence that Veterans suffering from both TBI+PTSD are at greater risk for chronic pain, SWD, and sensory sensitivity than Veterans with either TBI or PTSD. However, limitations of our study include caveats that come with any correlational study, including inference of causality between these variables. Our study is also reliant on self-reported data, rather than objective methods of quantifying sleep impairments and pain. Although both are relevant, self-reported data for these metrics is potentially of greater importance because ultimately it reflects how the individual patient perceives these symptoms. However, the ISI has been repeatedly validated as an accurate assessment to quantify insomnia severity by comparing results obtained from sleep diaries, observations from significant others and clinicians, and polysomnography (Bastien et al., 2001; Morin, Belleville, Bélanger, & Ivers, 2011; Savard, Savard, Simard, & Ivers, 2005). Other survey instruments used here have also been

well validated (Blevins et al., 2015; Chasens et al., 2009; Hays et al., 2009; N. King et al., 1995; Omachi, 2011; Savard et al., 2005). Nevertheless, in order to address the limitations of self-reported data, our future studies will be using objective pain testing combined with functional neuroimaging in our cohort of Veterans with TBI, PTSD, and TBI+PTSD to more precisely quantify pain threshold and sensory sensitivity.

It is also possible that a third independent variable, such as comorbid depression, could influence symptom severity and contribute to poor sleep and chronic pain (Fishbain, Cutler, Rosomoff, & Rosomoff, 1997; Nicassio, Moxham, Schuman, & Gevirtz, 2002; Nicassio & Wallston, 1992). Previous research has implicated that subjects suffering from chronic pain and depression may be excessively attending to external or internal stimuli,(Affleck et al., 1996; Gotlib, Krasnoperova, Yue, & Joormann, 2004) and mind-body interventions could be particular effective in treating these patients (Wahbeh, Elsas, & Oken, 2008). Future analysis could collect data on mood disorders and further explore potential mediators and moderators between these relationships.

Finally, regarding other factors that might potentially contribute to group differences in this study: We were unable to match groups on age, and the trauma-exposed groups (TBI, PTSD, and TBI+PTSD) were all significantly younger than the Neither group. However, because chronic pain and SWD are positively correlated with age (e.g., the opposite of our effect), using age-matched groups would likely show similar, if not more pronounced, results as the present study. It is also worth noting that our TBI+PTSD group experienced more TBIs than our TBI alone group (2.94 vs 1.99). Because number of TBI increases risk for comorbid PTSD, it would be difficult to dissociate this as an independent factor, although this could potentially contribute to our group differences.

Overall, we believe that our results, in combination with our planned future studies and basic science approaches to understanding the neurobiology underlying these phenomena (e.g., rodent models of TBI/PTSD conducted in parallel), will be critical to a better understanding and design of more effective interventions for sleep and pain problems after polytrauma.

Conclusions.

The present study demonstrates that Veterans suffering from comorbid TBI+PTSD report worse chronic pain than Veterans with a single or neither disorder, and their SWD and pain complaints are strongly correlated with TBI and PTSD symptom severity. Veterans with TBI+PTSD were especially vulnerable to common manifestations of chronic pain such as persistent headaches and light and noise sensitivity. Future research should examine how TBI and PTSD interact with one another to exacerbate these symptoms and develop more effective treatments for those suffering from TBI+PTSD.

Chapter 5: General Discussion

Summary of goals and results

This dissertation had three overarching aims: 1) Investigate differences in TBI evaluation methods on prevalence and severity of chronic TBI symptoms; 2) Characterize photosensitivity and pressure pain thresholds in subjects with and without TBI; 3) Examine the relationship between TBI incidence, chronic pain complaints, and photosensitivity thresholds; and 4) Determine the effect of comorbid TBI+PTSD on chronic pain complaints and photosensitivity compared to subjects with a single or neither disorder.

The findings in Chapter 2 demonstrated that the three most common TBI screening methods used by clinicians and researchers (clinical interview, medical chart review, and self-report) resulted in vastly different rates of positive TBI diagnoses in a sample of US Veterans at our single site. In terms of chronic TBI symptomology, we did not find differences between subjects who screened positive for a history of TBI across any single evaluation methods. However, we did find that subjects with congruent positive diagnoses across all three screening tools reported the highest severity of these symptoms. This subgroup of TBI subjects is potentially driving the elevated levels of chronic post-concussive symptoms in other TBI research.

The findings in Chapter 3 demonstrated that subjects with a history of TBI have more widespread chronic pain and display lower photosensitivity thresholds compared to subjects without a history of TBI. However, a subgroup analysis revealed that symptomatic TBI subjects (sTBI), reporting chronic post-concussive symptoms, were driving these results and that asymptomatic TBI (aTBI) subjects did not display any noticeable differences from control subjects. We also found that photosensitivity thresholds were strongly correlated with chronic pain scores, not only in sTBI subjects, but across all subjects. Photosensitivity was a strong

predictor of high impact chronic pain (HICP), even more so than the more commonly used pressure pain thresholds and could be a helpful marker of HICP.

Lastly, the findings in Chapter 4 revealed that Veterans with comorbid TBI+PTSD report greater levels of chronic pain, sleep disturbances, and multi-sensory sensitivity than subjects with only TBI. Although the TBI-only group did report higher pain, photo-, and phonosensitivity scores than controls, they did not report higher rates of sleep-wake disturbances or chronic headaches, while the TBI+PTSD scored high across all measures. Considering the results from Chapter 3, which revealed that a positive PTSD diagnosis was also a significant predictor of chronic pain, these results suggest that comorbid PTSD likely plays a major role in HICP following TBI.

Differences in TBI evaluation methods and symptomology

Perhaps one of the more surprising results from this set of experiments was the varying rates of TBI based on diagnostic methodology. Only half of the 200 subjects screened in Chapter 2 had congruent diagnoses across all three evaluation methods. We found exceedingly high rates of TBI using a clinical interview, which is often considered the gold standard TBI screening tool. The prevalence of TBI was almost doubled using this method, compared to chart reviews or self-report questionnaires. The fact that many subjects only screened positive in this one evaluation method, 50 out of the 53 subjects in our TBI-1dx group, suggests that the HTEC interview is the most sensitive TBI evaluation method and often includes subjects with low rates of post-concussive symptoms. This may explain the different rates of chronic TBI and post-concussive syndrome in the literature, as researchers lack a universally accepted TBI criteria and studies rely on different screening tools (Lannsjö, Geijerstam, Johansson, Bring, & Borg, 2009; Nampiaparampil, 2008; Voormolen et al., 2018).

Furthermore, subjects who received congruent positive diagnoses across all screening tools scored extremely high on the NSI and the SIQR, even compared to other TBI-positive subjects. This was not due to differences in TBI characteristics between groups such as recency or severity. However, the TBI-3dx group did have fewer subjects reporting only one lifetime head injury compared to other groups. This is likely due to the fact that subjects with multiple head injuries increase their chances of receiving a chart-confirmed diagnosis and are also more likely to confidently endorse a TBI themselves. This group also reported more deployments which could lead to higher levels of physical or emotional trauma. If researchers and clinicians want to use the most sensitive screening tool for the most accurate assessment of TBI history, a structured clinician interview is highly suggested.

Repeated TBI, post-concussion syndrome, and chronic traumatic encephalopathy

Other studies have found that repeated TBIs were a predictor for post-concussion syndrome (PCS), even when TBI severity and acute symptoms were not (Cnossen et al., 2017; J. Ponsford et al., 2000). This is distinctly different from research on chronic traumatic encephalopathy (CTE), which is another neurological disorder associated with repeated blows to the head. CTE is a neurodegenerative disease defined by its progressive tauopathy, and cannot be identified through clinical presentation like PCS, but instead can only be diagnosed post-mortem (Stern et al., 2011). And, although a TBI diagnosis is not necessary to develop CTE, it is still likely that the cases of CTE and PCS overlap in the chronic TBI population. Many of the neuropsychiatric symptoms associated with CTE are overlaid with PCS criteria, including headache, insomnia, and depression (Vasilevskaya & Tartaglia, 2018). It also makes sense neurobiologically, as TBIs are known to dramatically increase glutamate levels in the brain, which can cause chronic cognitive symptoms (Dorsett et al., 2017), and induce excitotoxicity

related to CTE (Blaylock & Maroon, 2011). We also see increased levels of neuroinflammation in rodent models of repeated TBI, which are strongly associated with behavioral changes mirroring PCS symptoms (Shultz et al., 2012), while amplified neuroinflammation is a hallmark marker of CTE (Cherry et al., 2016). Additionally, structural MRI demonstrated mTBI was related to decreased prefrontal grey matter and lower structural connectivity a full year post-injury and was correlated with greater PCS severity (Dean, Sato, Vieira, McNamara, & Sterr, 2015), which mirrors results in CTE patients. Regardless, it is currently impossible to directly tie chronic TBI to CTE, due to the heterogeneity of symptoms and a lack of in-vivo markers of CTE. Future longitudinal research will hopefully elucidate this relationship.

Photosensitivity and chronic pain following TBI

A central finding in Chapter 3 was the low photosensitivity thresholds in subjects with a history of TBI. The average TBI recency in this sample was ~20 years, which was similar to what we found in our Veteran-only sample from Chapter 2. Photosensitivity during the acute post-injury phase of TBI is extremely common, but only a few studies have demonstrated chronic sensory sensitivity lasting a decade after the initial insult (Balba et al., 2018; Callahan et al., 2016). This study was also the first to use an Ocular Photosensitivity Analyzer (OPA) to more accurately calculate visual photosensitivity thresholds (VPT) in this population, moving away from less granular self-report measures. This more precise and objective measure of photosensitivity, was strongly correlated with chronic pain complaints. Not only was it negatively correlated with the number of body regions subjects endorsed for chronic pain, it was also our strongest behavioral measure of chronic pain intensity and impact.

In our subgroup analysis, separating sTBI from aTBI subjects, we exposed the striking nature of disability and comorbidities in a subset of TBI positive individuals. These chronic sTBI

subjects scored extremely high on measures related to sleep disturbances, depression, disability, and PTSD. As noted earlier, this constellation of symptoms in relation to chronic pain has been coined HICP. It is impossible from this study to determine if the subjects' chronic pain directly caused these other symptoms; previous studies, however, have demonstrated that pain can result in poor sleep (Lang et al., 2014; Raymond et al., 2001), increase depressive symptoms (Von Korff & Simon, 1996), and increase disability (Janevic, McLaughlin, Heapy, Thacker, & Piette, 2017). Pitcher et al. suggested that high disability in a HICP population was not due to other comorbidities, as they controlled for over 15 other chronic health conditions in their analyses, but was instead directly related to their incidence of chronic pain (Pitcher et al., 2019).

This is a seminal study, as it demonstrates that simply categorizing chronic pain patients as those experiencing pain lasting more than 3 months, results in 2 separate subgroups: chronic pain without limitations (CPWL) and HICP. Although both groups experienced similar levels of pain intensity and duration, the CPWL group suffered lower rates of mental health disorders and cognitive impairments, while maintaining normal daily functioning. The HICP group not only suffered from greater levels of disability, including incapacity to work and lowered quality of life, also other suffered from similar comorbidities as our sTBI group. Pitcher and colleagues stressed the importance of identifying this group within the population, which they suggested accounts for less than a quarter of the all chronic pain patients in the United States. Although HICP patients are a smaller, more heavily burdened, subset of this population, some CPWL will likely progress into HICP in the future. If clinicians can identify these subjects early on, they can utilize precision medicine to better treat these patients and improve their quality of life.

This provides important context when interpreting our results in Chapter 3. Not only did these data demonstrate how VPTs are directly correlated with widespread chronic pain levels, but it also revealed they were a better predictor of HICP than pressure algometry and could be

potentially be used as behavioral marker. Widespread pain and HICP is likely due to dysfunction in the central nervous system pain system (Meeus & Nijs, 2007; Nijs, Malfliet, Ickmans, Baert, & Meeus, 2014). This includes central sensitization of nociceptive neurons in the spinal cord (Woolf, 2011), and changes in the brain's descending pain modulation circuits (Heinricher, 2009). Given the fact that light has already been shown to directly engage nociceptive-facilitating neurons in the brainstem (Martenson et al., 2016), it is likely that photosensitivity is also a result of maladaptive central pain circuity. This is reinforced by the fact that other chronic pain populations, including fibromyalgia (Harte et al., 2016; Watson et al., 2009) and chronic migraineurs (B. J. Katz & Digre, 2016; Noseda & Burstein, 2011; Noseda et al., 2010), also exhibit photosensitivity.

Potential mechanism of photosensitivity

Although this study did not aim to find the exact neurological mechanism of photosensitivity, future studies should examine the role of ocular and pupillary response in light aversion. Given that intrinsically photosensitive retinal ganglion cells (ipRGC) have been linked to photophobia (B. J. Katz & Digre, 2016; McAdams et al., 2020) and mediate the pupillary reflex (Pickard & Sollars, 2011), they potentially play a role in low VPTs following TBI. This could explain why blind patients sometimes experience photosensitivity (Amini et al., 2006; Loh et al., 2015), as the ipRGC are involved in irradiance detection system and non-image forming vision circuitry. It has also been shown that blocking the olivary pretectal nucleus (OPN), a brain region directly involved in the pupillary reflex receiving direct connections from ipRGCs, can inhibit brainstem nociceptive facilitating neurons from responding to a light stimulus (Martenson et al., 2016) Dysfunction of ipRGCs following TBI could also play a role in the high prevalence

of sleep disorders in this population, as they project to the suprachiasmatic nucleus (SCN) and facilitate circadian rhythms (Pickard & Sollars, 2011).

The impact of comorbid TBI+PTSD

Given the fact that PTSD was associated with chronic pain based on the multiple linear regression analysis used in Chapter 3, and that highly photosensitive sTBI also reported high levels of PTSD symptoms, an additional study was required to examine whether comorbid TBI+PTSD could exacerbate these effects. The TBI sample used in Chapter 2 had too few PTSD subjects without TBI to complete a proper analysis, but in Chapter 3 we discovered that PTSD was indeed one of the strongest predictors of photosensitivity and chronic pain. Our PTSD-only group reported higher levels of photo- and phonosensitivty than our TBI-only subjects, but the comorbid TBI+PTSD group was significantly higher than both. The same was true in regards to self-reported pain levels, with TBI+PTSD having an additive effect on this symptom. We also found that PCL-5 scores, measure PTSD symptom severity, were strongly correlated with self-reported sleep quality and pain levels.

There are several possible mechanisms linking PTSD, poor sleep, chronic pain, and photosensitivity. A well accepted theory of PTSD is that following the experience of a traumatic event, the altered responsiveness of the hypothalamic-pituitary-adrenal (HPA) axis can lead to elevated levels of cortisol. This dysfunction has been known to cause sleep disruptions (Khazaie et al., 2016; Ohayon & Shapiro, 2000; Shin, Rauch, & Pitman, 2006), impaired function of the medial prefrontal cortex (mPFC), and hyperactivity in the amygdala (AMY), insula (INS), and anterior cingulate cortex (ACC) all of which can partially explain the high prevalence of chronic pain (Garfinkel & Liberzon, 2009; Hamner, Lorberbaum, & George, 1999; Liberzon & Sripada, 2007). The AMY, INS, and ACC are all pain-facilitating brain region and major hubs in the

central nervous system pain pathway. Hyperactivation of these pain region has been associated with chronic pain disorder and central sensitization (Cottam, Iwabuchi, Drabek, Reckziegel, & Auer, 2018; Kissiwaa & Bagley, 2018; Zhuo, 2014). Meanwhile, the mPFC is an inhibitory upstream brain region in the descending modulatory pain system, and when impaired can also lead to greater levels of chronic pain. Add in the biosocial factor of poor sleep and its ability to further increase stress and cortisol, and it's clear that PTSD can create the perfect neurobiological setting for a sensitized central pain circuit. Based on data presented in Chapter 2, we believe that central sensitization is not only linked to chronic pain, but also photosensitivity, which could explain why our PTSD subjects reported high levels on both measures (**Figure 5.1**).

This study not only demonstrated the additive effect of TBI and PTSD on pain complaints, it also demonstrates the important role of sleep quality which was significantly correlated with self-reported pain. One surprising result from this study, was the incongruent findings between self-reported sleep quality in our PTSD and TBI+PTSD group and their polysomnography (PSG) data. Although these subjects scored significantly worse on sleep surveys than controls, we did not find any evidence of sleep disturbances during their overnight sleep study. Nightmares and sleep disturbances are hallmark characteristics of the disorder and is a part of its diagnostic criteria (American Psychiatric Association, 2013b), yet we found PTSD subjects had similar PSG metrics during our sleep study. We believe this discrepancy is likely due to the well documented "first-night effect", where patients with clinical sleep disorders often experience better sleep at sleep laboratory compared to healthy controls (Mendels & Hawkins, 1967; Newell et al., 2012). This effect usually disappears on the second night of sleep, however we were only able to collect one night worth of data in this experiment. Future studies will hopefully reexamine whether PSG markers, such as wake after sleep onset (WASO), sleep efficacy, and total sleep time are related to self-report chronic pain levels.

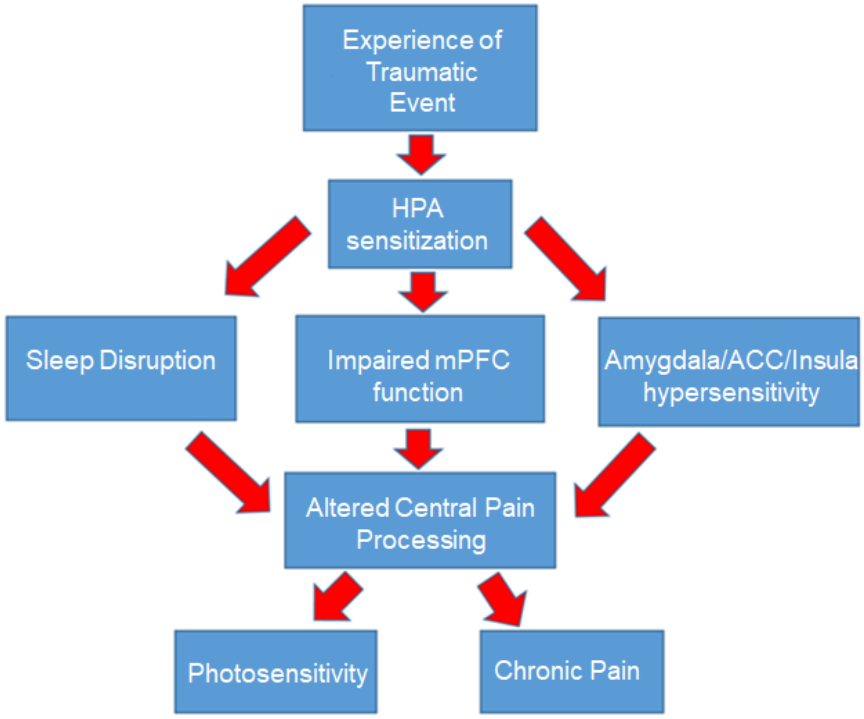

Figure 5.1. Hypothesized circuitry in PTSD
Previous research has shown that following a traumatic even, patients that that go on to develop PTSD are likely to experience HPA sensitization resulting in increased adrenocortical activity and chronically elevated levels of cortisol. This can lead to sleep disturbance, impaired mPFC functioning, and hyperactivity of pain-processing brain regions. All of these are independently linked to altered central pain circuitry, which will inevitably lead to chronic pain complaints and potentially increased photosensitivity

Implications

These results will hopefully have a positive impact in several research fields. The findings in Chapter 2 will hopefully inform researchers of the potential differences in TBI samples based on differing evaluation methods. These results suggest that researchers, and even clinicians, should be screening their patients for TBI with more than one evaluation method.

The findings from Chapter 3 reveal that photosensitivity could represent a much-needed marker for dysfunctional central pain processing in individuals sustaining a TBI, and could be

extended to other chronic pain populations suffering from HICP. This marker would be quantitative, non-invasive, easily measured, and could guide future treatment for chronic pain. For instance, using pharmacological treatments that act directly on brain mechanisms to treat patients with centralized pain syndromes, or other complementary medicines that be used for multidimensional HICP, would be more effective than using treatments targeting peripheral mechanisms,

Lastly the results in Chapter 4 suggest that comorbid TBI+PTSD subjects are especially vulnerable to HICP, with higher rates of pain, sleep disturbances, and multisensory sensitivity. This combination of disorders is particularly common in Veterans, and clinicians should be aware that this population is at risk for multiple disorders that can exacerbate one another.

Future Directions

This dissertation only marks the beginning of a new research field. We need to continue to add to these studies and push the field forward. There were several limitations that we could not overcome in these sets of experiments, and I hope future research will improve on our work.

For example, none of the work presented here directly examines the neuronal substrates of photosensitivity in TBI subjects with chronic pain. Ongoing studies are examining whether TBI subjects with chronic pain respond differently to light compared to subjects without TBI or chronic pain. Does exposure to a dim light activate nociceptive circuits in the brain? Can it activate somatosensory networks, or is its effect limited to normal light processing regions such as the thalamus and visual cortex? We aim to answer these questions in the near future using task-based fMRI experiments. We also hope to examine differences brain connectivity between TBI subjects with chronic pain and those without, using both resting-state fMRI and slow wave

coherence EEG analyses, both of which provide insights into how the brain is working at rest and/or during sleep.

One major limitation to the cross-sectional studies described in this dissertation, is that it is impossible to draw a direct connection from the TBI, photosensitivity, and the increased rates of chronic pain we report. The fact that our TBI group consistently scored higher in several of our measures compared to subjects without TBI, and that VPTs were strongly correlated with chronic pain scores, is evidence of this connection, but not proof. We hope to conduct a future longitudinal study that tracks subjects before and after sustaining a TBI, gathering measures on chronic pain and photosensitivity. If we see that these measures track longitudinal, it would provide further support to our hypothesis that photosensitivity is a marker of chronic pain in this population. Alternatively, photosensitivity could also be measured and tracked in other chronic pain populations, including pre/post-surgery. A subset of patients who undergo surgery will experience post-surgery pain and are eventually diagnosed with a chronic pain disorder (Kalso, 2013). Based on the findings presented here, subjects with higher photosensitivity are more likely to have altered central pain processing, possibly making them susceptible to this post-surgery pain.

Gender differences should also be further examined in another cohort. Data presented in Chapters 2-4 came from an overwhelming male population. These studies either focused exclusively on Veteran populations, or were conducted at a VA center, resulting in few female participants. Due to the fact that the prevalence of chronic pain conditions is significantly higher in women compared to men, previous studies validating SIQR across chronic pain disorders were mostly done using female subjects (Friend & Bennett, 2015; Tsang et al., 2008). Women tend to suffer from more comorbidities associated with chronic pain, such as depression and anxiety disorders (Tsang et al., 2008), and have a higher incidence rate of HICP (Pitcher et al., 2019).

This suggests that female chronic pain subjects are similar to our sTBI group, and would also exhibit the same increased photosensitivity that was presented in Chapter 3. The fact that our results were found in a male population, which have a much lower incidence rate of chronic pain syndromes than females, suggest that this result are likely to translate across genders and sexes, but further studies will be needed to test this hypothesis.

We also recognize that other non-somatic sensory sensitivity could also be directly related to chronic pain and perhaps central sensitization. Other chronic pain populations also suffer from phonosensitivity and olfactory sensitivity. We did not decide to purse these other potential markers in these sets of experiments because we did not have direct evidence of sound or smell stimuli directly activating or inhibiting on nociceptive neurons in the central nervous system like we did with light. Nor did we have access to an objective and quantifiable measure of either phonosensitivity or olfactory sensitivity, as we did with the OPA. However, we recognize that this population likely suffers from multisensory sensitivity, not just sensitivity to light, and further research aims to explore this further.

Lastly, my next goal is to try my best to directly help these TBI subjects suffering from high impact chronic pain by testing potential treatments. This multidimensional form of pain interferes with nearly every aspect of their lives. It has proven to be extremely difficult to treat, as their symptoms are heavily intertwined and can exacerbate one another. Conventional pharmaceutical treatments are often ineffective at treating this type of pain, so we aim to test whether a mindfulness-based intervention –which targets holistic healing by reducing chronic pain, improving sleep, and reducing stress– would be a more efficacious treatment in this population. This study will also allow us to test whether photosensitivity levels decrease in chronic pain patients after successful pain treatment, which would further support our thesis that VPT is a marker of central sensitization of pain.

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