PHOTOSENSITIVITY IN MILD TRAUMATIC BRAIN INJURY: EXPLORATION OF ASSOCIATED FACTORS AND A NOVEL TREATMENT APPROACH

A thesis presented to the graduate faculty of
New England College of Optometry in partial fulfillment
of the requirements for the degree of Master of Science

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Abstract:

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Jenalyn Jotie OD FAAO
New England College of Optometry, 2023

Background: Photosensitivity (PS) is one of the more common sequelae of mild traumatic brain injury (mTBI). The pathophysiology and visual sequelae of mTBI-related PS are not well understood. Studies in Post-9/11 Veterans have shown that both physical and psychiatric traumas can impact visual function, including PS. The first aim of this thesis was to understand how comorbidities that often occur with mTBI in Post-9/11 Veterans, such as posttraumatic stress disorder (PTSD), impact PS. Results from the first study of this thesis may guide novel therapeutic interventions, as there are currently few management options for PS beyond spectacle tints.

While spectacle tints are conventionally used to alleviate PS symptoms, they have been associated with lower recovery rates, underscoring the need to develop more effective, non-invasive treatment options that can reduce or eliminate PS. Recent work has shown that neurofeedback interventions, such as Low Intensity Pulse-Based Transcranial Electrical Stimulation (LIP-tES) may be effective in treating post-concussive symptoms, including PS. The second aim of this thesis was to investigate the treatment of mTBI-related PS using LIP-tES.

Methods: 641 Post-9/11 Veterans were included in Study 1. Existing data from the Translational Research Center for TBI & Stress Disorders (TRACTS) cohort study was analyzed including TBI history and PTSD clinical diagnostic interviews; sleep quality, anxiety, and depression symptoms self-report questionnaires; and PS severity self-report from the Neurobehavioral Symptom Inventory. Analysis of covariance and multiple ordinal regression models were used to assess associations between mTBI and common comorbidities with PS severity.

Study 2 was a case report investigating the effect of 12 sessions of LIP-tES on PS symptoms of a 49-year-old Post-9/11 Veteran male. Secondary outcomes on pupillary diameter, general post-concussive and headache symptoms were also investigated.

Results: Study 1 showed both mTBI and current PTSD diagnosis were independently associated with higher PS ratings compared to Veterans without either condition, with no interaction observed between these two conditions. Results of ordinal regression models demonstrated positive associations between degree of PS and the number of mTBIs during military service and current PTSD symptom severity, particularly hyperarousal symptoms, even when controlling for other factors. Additionally, sleep disturbances and current anxiety symptoms were both positively associated with PS ratings while depression symptoms, age, and gender were not.

Study 2 showed promising results. The Veteran initially reported moderate/severe PS symptoms (UPSIS-17 = 49), severe headaches (HIT-6 = 63), and post-concussive symptoms (RPCSQ = 37). After the intervention, the Veteran reported reductions across all three measures: UPSIS-17= 20 (59% reduction), HIT-6 = 40 (37% reduction), and RPCSQ = 14 (73% reduction). No systematic trend in pupil diameter was observed across sessions.

Conclusions: Repetitive mTBI and psychiatric comorbidities common after mTBI can significantly impact PS severity and are important clinical factors that eye care providers should consider when managing veterans with a history of deployment-related trauma reporting PS symptoms. A case report of one Post-9/11 Veteran after 12 sessions of LIP-tES showed significant reductions in PS, headaches, and other post-concussive symptoms. LIP-tES shows potential as a novel, non-invasive neurofeedback intervention for the treatment of PS following mTBI.

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1. Introduction

1.1. Overview of the Problem

Traumatic brain injury (TBI) is a major cause of disability and death in the U.S. and worldwide (Langlois et al., 2006; Capizzi et al., 2020). 80% of all TBIs are classified as mild (mTBI) (Wagner et al., 2021). This may be a misnomer as patients with mTBI may suffer from ongoing cognitive, psychological, behavioral, and sensory deficits that persist beyond the immediate post-concussive period (Kushner 1998). Given that 70% of the sensory input to the brain are from the eyes and half of the cranial nerves involve vision or oculomotor functioning, it is not surprising that even a "mild" TBI can lead to a constellation of visual and ocular deficits, including photosensitivity (Suter, 1995; Capó-Aponte et al., 2012).

Photosensitivity (PS) is defined as an aversion to a light source that normally does not provoke visual discomfort (Chang et al., 2007; Truong et al., 2014). PS has been used interchangeably in the literature with the terms "photophobia," "photo-oculodynia," (Digre et al., 2012) and "photoallodynia" (Matynia et al., 2013). Over half of patients with mTBI complain of PS (Capó-Aponte et al., 2012). PS may occur during the acute (3-10 days) [Dischinger et al., 2009] and subacute phases (7-19 days) after the initial insult [Waddell et al., 1984;]. While post-mTBI PS usually resolves within 6 months (Vos et al., 2002), one study reported that PS recovery appears to be a long-term process, for which 50% improve after the first year, while 43% remain stable and 3% worsen over time (Truong et al., 2014).

1.2. Pathophysiology of Photosensitivity

The pathophysiology of PS in mTBI is poorly understood. PS has been extensively studied in the field of migraine research, which may provide insights into mTBI-related PS. The high comorbidity of TBI with migraines suggests common underlying pathophysiological mechanisms (Diel et al., 2020; Mares et al., 2019; Lambru et al., 2020). There are at least four mechanisms of PS, three of which have been distinctly elucidated and a possible fourth pathway found in a rodent model (Digre and Brennan, 2012; Katz and Digre, 2016; Noseda et al., 2010; Noseda et al, 2019; Bernstein et al., 2019). Three PS circuits have been uniquely identified in the migraine literature: 1) Retino-midbrain-parasympathetic (superior salivatory nucleus [SSN]) (Okamoto et al., 2009; Digre et al., 2012; Cortez et al., 2017; Noseda et al., 2019) 2) Retino-thalamo-cortical (Digre et al., 2012; Noseda et al.,2016; Noseda et al, 2019); and 3) Retino-hypothalamic pathways (Noseda et al., 2017; Noseda et al., 2019; Burstein et al., 2019). A potential fourth PS pathway found in a rodent model involves intrinsically photosensitive iris melanopsin cells that can activate the pupillary light reflex (PLR) locally without involvement of the optic nerve or retina (Xue et al., 2011; Digre et al., 2012). Due to the redundancy of neural networks, it is likely that these pathways intersect and interact with each other and there may be other mechanisms yet to be discovered (Digre et al., 2012). The intrinsically photosensitive retinal ganglion cells (ipRGCs) are non-image forming photoreceptors that are involved in both the retino-midbrain-parasympathetic (SSN) and retino-thalamo-cortical pathways by contributing to the PLR response and mediate the nociceptive response to light via projections to dura-sensitive (trigeminovascular) nuclei in the thalamus (Noseda et al., 2010; Noseda et al., 2019). On a molecular level, calcitonin gene-related peptide (CGRP) is a key mediator of photophobia that underlies the pathologic central neuroplasticity of the trigeminothalamic pathway in dry eye, migraine and TBI, which are often comorbid with each other (Diel et al., 2020).

1.3. Assessment of Photosensitivity

The diagnosis of PS has been largely based on subjective reports, obtained either through the case history or questionnaires. Several PS questionnaires in the literature are specific to migraine-related PS such as the Visual Discomfort Scale [VDS] (Cucchiara et al., 2015), Migraine Photophobia Scale [MPS] (Cucchiara et al., 2015), Leiden Visual Sensitivity Scale [L-VISS] (Perenboom et al., 2018), Korean Photophobia Questionnaire [KUMC-8] (Choi et al., 2009), and the Utah Photophobia Symptom Impact Scale [UPSIS-17] (Cortez et al., 2019). The UPSIS-17, utilized in Study 2, was more correlated to light sensitivity thresholds and demonstrated better instrument targeting, including reliability and internal consistency, on Rasch analysis compared to the KUMC-8 (Cortez et al., 2019). Verriotto et al. (2017) developed the Visual Light Sensitivity Questionnaire (VSLQ-8) to broadly assess general PS symptoms for any condition of which PS is a prominent feature. The major limitations of the Verriotto et al. study (2017) were the narrow range of PS symptom levels in the study population and significant variability in the Pearson correlations between visual PS thresholds and individual VSLQ-8 items.

Light sensitivity threshold is a psychophysical assessment that quantifies the functional impairment of PS but is still based on subjective responses (Vanagaite et al., 1997; Adams et al., 2006; Cortez et al., 2017; Verriotto et al., 2017; Cortez et al., 2019). Electromyography (EMG), which records blink frequency, duration, and force, has been used objectively to measure light sensitivity thresholds in normal subjects (Stringham et al., 2003) and to evaluate the effectiveness of specific chromatic filters in benign essential blepharospasm (Blackburn et al., 2009). There are few distinctly objective measures of mTBI-related PS. The pupillary light response (PLR) may differentiate those with PS from those without PS in mTBI as well as from

visual normals (Truong et al., 2016; Yuhas et al., 2017; Ciuffreda & Joshi et al., 2017). In general, those with mTBI and PS exhibit larger pupillary diameters measured throughout the dynamic PLR profile over a 6-second period and show a more rapid return to baseline diameter (Truong et al., 2016). Truong et al. proposed that the 6-second post-stimulus pupillary diameter (6SPSD) to blue light, which mainly targets ipRGCs, could be a potential objective biomarker for mTBI-related PS (Truong et al., 2016).

The pattern reversal visual evoked potential (VEP) has been studied in the TBI population (Papathanasopoulos et al., 1994; Sarno et al., 2000; Gaetz et al., 2000; Yadav et al., 2013), which shows waveform abnormalities, such as a delayed P100 latency and decreased VEP amplitude, that can improve with vision rehabilitation (Freed et al., 1997) and optical treatments such as binasal occlusion (Padula et al., 1994; Yadav et al., 2014; Ciuffreda & Yadav et al., 2017) and base-in prism (Padula et al., 1994); however, it has not yet proven to be a differentiating test for mTBI-related PS (Fimreite et al., 2016). Electrophysiologic studies in migraineurs suggest other potential objective assessments of PS in mTBI. Noseda et al. (2016) showed single flash VEP responses and electroretinogram (ERG) changes in migraineurs that support the theory that migraine photophobia originates in the retina via cone-driven pathways that are relayed to light/pain sensitive neurons in the thalamus (most specifically the Lateral Posterior and Posterior nuclei) and are preserved in the cortex. One study in the TBI literature to investigate frequency specific PS demonstrated a change in single flash VEP responses in one post-concussion subject that correlated with relief or exacerbation of PS symptoms from specific spectacle tints (Clark et al., 2019). Questions that warrant further examination are if there are cone-driven pathways involved in the pathophysiology of mTBI-related PS and if frequency

specific PS symptoms are different for each post-mTBI individual. Through objective outcome measures that may explain the underlying pathophysiology of PS in mTBI, more effective treatments may be found and would allow for better quantification of PS changes over time.

1.4. Current Treatment of Photosensitivity

Spectacle tints are currently the main treatment of PS (Digre et al., 2012). While darkly tinted lenses provide immediate relief, the long-term consequences may be counterproductive to the recovery process in mTBI-related PS (Truong et al., 2014). Tint usage may inhibit the reduction of PS over time by interfering with the natural neural adaptation to normal light levels (Truong et al., 2014). Besides tint density, the frequency spectrum that provides the most relief or exacerbates PS may be unique to the individual (Digre et al., 2012; Wilkins et al., 1994; Jackowski et al, 1996; Riddell et al., 2006; Huang et al., 2011; Clark et al., 2017). Specific tints have been successful at reducing photophobia in various conditions. The FL-41 tint is a pink topaz-colored tint that blocks shorter wavelengths of light and decreases the sensation of flicker from fluorescent illumination sources (Wilkins et al., 1991) which is problematic for migraineurs (Karanovic et al., 2011). The FL-41 tint has been found to decrease PS in both migraines and benign essential blepharospasm (Good et al., 1991; Blackburn et al., 2009). Jackowski et al. (1996) found that Corning Photochromic Filters (CPF), most specifically the CPF 450-S (yellow) tint, controls PS symptoms and provides functional improvements in reading rate and contrast sensitivity in mTBI subjects. Other studies have supported the use of less common treatment modalities for PS such as broad-spectrum light therapy which has decreased photophobia in seasonal affective disorder (Gallin et al., 1995) and the use of targeted light frequencies in syntonic phototherapy (Stern, 2011).

Systemic medications that block CGRP (e.g., eptinezumab) [Scuteri et al., 2019; Diel et al., 2020] or block the CGRP receptor (e.g., erenumab and ubrogepant) are among current treatments for migraine (Scuteri et al., 2019; Dodick et al., 2020; Diel et al., 2020) and has been shown to reduce photosensitivity in a rodent TBI model (Daiutolo et al., 2016). Gabapentin and pregabalin have been used anecdotally to treat pain associated with photophobia (Digre et al., 2012) and neuropathic ocular symptoms, including PS, in dry eye (Small et al., 2020). More invasive treatments have been described such as botulinum toxin injections to reduce photophobia associated with chronic migraines (Diener et al., 2010), photo-oculodynia (Shoari et al., 2007), and neuropathic ocular pain without migraines (Venkateswaran et al., 2020). Superior cervical sympathetic ganglion blockade with lidocaine was found to decrease light sensitivity in three cases of photo-oculodynia, but the results were temporary, lasting only a few hours to days (Fine et al., 1995). There is a definite need for more effective, less invasive adjunctive therapies for PS in the mTBI population.

1.5. Non-invasive Treatment for Photosensitivity

Non-invasive neurostimulation techniques, such as transcutaneous electrical stimulation (TENS), transcranial magnetic stimulation (TMS) and low intensity pulse-based transcranial electrical stimulation (LIP-tES), are a promising class of treatments that address neural and cortically based networks involved in pain associated with various conditions and could potentially target the nociceptive cortical responses to light in PS.

TENS involves the transmission of electrical current to peripheral nerves via electrodes on the skin surface. It has shown effectiveness and is well tolerated for the treatment of migraine, but meta-analysis of randomized controlled studies indicates that the quality of evidence is still lacking (Tao et al., 2018). TENS has been investigated to treat neuropathic ocular complaints in dry eye, including photophobia, but the results are temporary as a standalone intervention, with overall ocular pain intensity returning to baseline within 24 hours (Sivanesan et al., 2018). A more recent retrospective study of 10 patients using TENS as a supplemental therapy integrated into their chronic ocular pain management showed a 27.4% reduction in overall ocular pain for a minimum of 3 months but did not specifically show a statistically significant reduction in photoallodynia (Zayan et al., 2020).

Transcranial magnetic stimulation (TMS) is another non-invasive neurotherapy that involves the use of wire coils to generate magnetic fields through the skull to induce electrical currents in the underlying cortex (Klomjai et al., 2015). The two main types of TMS differ in the application of pulses, delivered either in single pulses (sTMS) or in a series of repetitive pulses (rTMS) (Lipton et al., 2010). sTMS can be effective for acute migraine attacks, with amelioration of associated photophobia (Mohammad et al., 2006). rTMS has been extensively studied for the treatment of major depressive disorder (MDD) and research is emerging to support the use of rTMS for other conditions such as chronic pain, PTSD, and TBI (Anderson et al., 2020). A recent evidence brief prepared for the Veterans Health Administration showed that rTMS may improve symptoms after TBI, but the strength of evidence is limited due to inconsistent study findings, small sample sizes and methodological variations (Anderson et al., 2020). While TMS appears to be generally safe and well-tolerated, there have been a few case

reports of adverse ocular events following TMS treatment for depression, including retinal detachment in one patient with a known history of an atrophic retinal hole (Bloomquist et al., 2023). Staffing availability issues, cost, and accessibility barriers may limit the expansion of TMS for other conditions besides depression (Anderson et al., 2020).

Low intensity pulse-based transcranial electrical stimulation (LIP-tES) is a passive neurofeedback technique that combines electroencephalography (EEG) monitoring with the application of low-intensity electrical pulses to the scalp and has shown promise in treating TBI symptoms and PTSD (Schoenberger et al., 2001; Ochs, 2006; Larsen et al., 2006; Nelson et al., 2015; Huang et al., 2017). While LIP-tES devices on the market share similar hardware designs, they differ in their software protocols such as the Flexyx Neurotherapy System (FNS) (Schoenberger et al., 2001); Low Energy Neurofeedback System (LENS) (Ochs 2006), and IASIS (not an acronym, but is derived from the Greek word for healing or cure) Microcurrent Neurofeedback (Huang et al., 2017; Snook 2013). While LIP-tES has not been specifically used to treat mTBI-related PS, one pilot study conducted through the VA San Diego Healthcare System using magnetoencephalography (MEG) to investigate neuronal changes following LIP-tES treatment (IASIS Microcurrent Feedback) for mTBI and persistent post-concussive symptoms, found that 3 out of the 5 subjects who reported PS had a reduction in their PS symptoms by at least 50% (Huang et al., 2017).

While the mechanisms of LIP-tES are not completely understood, Huang et al. (2017) cited the theory of stochastic resonance (SR) proposed by Fertonani and Miniussi (2016) to explain the neuromodulatory effects of IASIS and other forms of LIP-tES. SR involves adding

an external signal (i.e., low-intensity electrical pulses) to enhance the endogenous oscillatory brain wave signal (Huang et al., 2017; Fertonani et al., 2016). Slow brain waves, specifically the delta frequency, which are normally present during deep sleep, are abnormal when present during wakefulness (Assenza et al., 2015). Abnormally slow brain waves present during wakefulness is a biomarker for mTBI and a sign of neuronal healing at the sites of brain injury (Assenza et al., 2015). SR via LIP-tES may potentiate slow-wave generation to promote neuronal plasticity and eventual cessation or reduction of slow waves during wakefulness (Assenza et al., 2015). For the mTBI subjects in the Huang et al. (2017) study who experienced a decrease in PS symptoms, there was a corresponding decrease in slow waves in cortical areas that corresponded to brain regions linked to pain (e.g., anterior cingulate cortex) (May et al., 2007) and photophobia (e.g., lingual gyrus) (Boulloche et al., 2010).

There have been minimal adverse side effects reported in the literature for the various LIP-tES devices, including a transient increase in symptoms, such as post-concussive symptoms, after 6-7 sessions for FNS [Schoenberger et al., 2001] and after 20-30 sessions for LENS [Larsen et al., 2006]. These symptoms typically cease within a few days (Schoenberger et al., 2001). Re-emergence of seizures and motor tics that were previously resolved lasted a few weeks before subsiding was reported for LENS in an unspecified number of patients (Ochs 2006). While no adverse events were reported in the Huang et al. study (2017), one subject dropped out for unspecified reasons, completing 4 out of the 12 treatment sessions with marginal positive outcomes in both abnormal MEG scores and post-concussive symptoms. The LIP-tES system that will be used Study 2 of this research project, Neurogen™ High-Performance Neurofeedback (HPN), utilizes an updated

software platform of the IASIS Microcurrent Neurofeedback used in the Huang et al. study (2017) (C. Snook, personal communication, April 16, 2021). The EEG interface device used in conjunction with both the Neurogen™ HPN, and the IASIS Microcurrent Neurofeedback systems has received 510(K) clearance through the FDA.

1.6. Personal Significance and Summary of Studies 1 and 2

The primary focus of the two studies conducted during my VA Boston Healthcare System Optometry Research Fellowship (2020-2022) was to understand the pathophysiologic mechanisms underlying mTBI-related PS and to explore novel, non-invasive treatment options for this debilitating condition. I was inspired to pursue this research because of a couple of patients who stood out during my time in the U.S. Navy and during my Brain Injury Vision Rehabilitation and Ocular Disease residency through the South Texas Veterans Healthcare System. These were individuals who suffered disabling light sensitivity and the only treatment option at my disposal at the time were sunglasses. One patient was an active-duty sailor with severe PS who sustained multiple concussions as a boxer prior to military service and requested a "chit" to be allowed to wear sunglasses in formation and indoors, which is generally prohibited. A "chit" in the military is a formal exception granted to the servicemember from having to follow a specific military regulation due to a medical or other permitted condition. The other individual who haunts me to this day was a former NATO officer whom I encountered during my residency. He was medically discharged after a blast-related injury that caused extreme, intractable headaches and severe light sensitivity. Unbeknownst to other management options for PS, I granted the chit to the former patient and prescribed sunglasses for them both. I

felt that I was doing a disservice to both the sailor and to the NATO veteran because sunglasses merely reduced their symptoms and did not get to the root cause of their PS issues. After my initial exam with each of them, I observed them both deteriorate over time, with minimal relief of their symptoms. These experiences fueled my determination to not allow future patients with PS to continue to suffer this way under my watch. Although I did not have the background knowledge at the time when they were under my care that I do now, I realized that not only did these patients suffer from the physical trauma of their brain injuries, but there were other psychiatric and social factors related to the physical trauma that contributed to their suffering. During the course of this research fellowship, I learned about how the psychiatric comorbidities commonly associated with mTBI can impact the severity of light sensitivity and negatively affect quality of life, which are explored in the first study of this thesis project. Study 1 addresses the effect of repetitive mTBI and PTSD on PS symptom severity in Post-9/11 Veterans. The impact of other common comorbidities on PS symptomology in this cohort, such as sleep disturbances and anxiety, were also investigated. This study provides insights into the multi-factorial pathways involved in post-mTBI PS and may possibly explain why many cases of mTBI-related PS remain chronic or worsen over time. Understanding the various neuro-psychiatric factors that affect post-concussive PS may also provide potential targets for therapeutic intervention. Study 2 investigates the use of LIP-tES as a novel, non-invasive treatment option for mTBI-related PS. Previous work has shown that LIP-tES can reduce post-concussive symptoms and symptomology related to post-traumatic comorbidities such as PTSD. Study 2 showed a significant reduction in PS and other mTBI-related symptoms in one Post-9/11 Veteran after 12 sessions of LIP-tES. The Veteran participant in Study 2 had many of the factors identified in Study 1 that impact PS severity, including multiple concussive events and chronic PTSD. Study

1 may provide insights into the mechanisms behind the positive effects of LIP-tES on post-mTBI PS in the case report outlined in Study 2. The two studies presented as part of this thesis project may help healthcare providers better understand and manage post-concussive light sensitivity and offer initial pilot data to explore other non-invasive treatment modalities beyond chromatic filters, such as LIP-tES, for mTBI-related PS.

2. Study 1: Association of Repetitive Mild Traumatic Brain Injury, Posttraumatic Stress Disorder, and other Comorbidities on Photosensitivity

2.1. Introduction

Although the wars in Iraq and Afghanistan are technically over, recovery from the physical and psychological traumas experienced during deployment is not over for many of our Post-9/11 Veterans. Both mild traumatic brain injury and posttraumatic stress disorder are considered the signature injuries of the recent Iraq and Afghanistan wars (Hayward 2008). Studies have shown that these physical and psychiatric traumas can impact visual function, including photosensitivity (Hayward 2008; Capó-Aponte et al., 2012; Goodrich et al., 2014; Trachtman 2010). Photosensitivity is defined as an aversion to a light source that normally does not provoke visual discomfort in the absence of an ocular cause (Chang et al., 2007; Stern 2011; Truong et al., 2014). While the term "photosensitivity" has been used interchangeably in the literature with the terms "photophobia," "photo-oculodynia" (Digre et al., 2012), and "photoallodynia" (Matynia et al., 2012), the nomenclature has been adopted in more recent studies to refer to light sensitivity following a traumatic brain injury (Truong et al., 2014; Balba et al., 2018; Balba et al., 2022; Ciuffreda et al., 2017; Silverberg et al., 2023).

The definition of mild traumatic brain injury varies across organizations and has evolved in the literature (Silverberg et al., 2023). The U.S. Department of Veterans Affairs (VA) and Department of Defense (DoD) evidence-based working group, which established clinical

practice guidelines for the management of concussion-mild traumatic brain injury for the Veterans Health Administration and Military Health System, defines mild traumatic brain injury as a physiological disruption of brain function by an external force accompanied by one or more of the following criteria: 1) normal structural imaging; 2) loss of consciousness of 30 minutes or less; 3) alteration of consciousness of up to 24 hours; 4) posttraumatic amnesia of up to 1 day; and 5) a Glasgow Coma Scale score of 13-15 within the first 24 hours of the injury (U.S. Department of Veterans Affairs and U.S. Department of Defense 2009). In Post-9/11 Veterans, the vast majority of traumatic brain injuries are classified as mild. It has been estimated that the prevalence of mild traumatic brain injuries in this population is 10-20% (Norris et al., 2014). Over half of patients with mild traumatic brain injury complain of photosensitivity (Capó-Aponte et al., 2012), which negatively affects rehabilitation outcomes (Lew et al., 2009) and quality of life (Shepherd et al., 2020). Post-concussive symptoms have been reported to typically resolve within 6 months after a mild traumatic brain injury, but remain chronic in 7-8% of these patients (Vos et al., 2002).

The current investigation explores how other commonly occurring comorbidities in Post-9/11 Veterans who have sustained a mild traumatic brain injury, most notably posttraumatic stress disorder, may affect the severity of photosensitivity. Posttraumatic stress disorder may occur following exposure to a traumatic event and is defined by a constellation of symptoms that are clustered into three general categories including intrusive thoughts/re-experiencing, avoidance and/or numbing behavior, and hyperarousal symptoms. Clinical diagnosis of posttraumatic stress disorder requires both exposure to a traumatic event and functionally disrupting symptom duration of 1 month or longer (Bell 1994). The prevalence of posttraumatic stress disorder in Post-9/11 Veterans ranges from 8-30% in the literature (Lippa et al., 2015;

Stein and McAllister 2009). Posttraumatic stress disorder is highly comorbid with mild traumatic brain injury in Post-9/11 Veterans. A systematic review found that 3 of the largest studies involving thousands of Veterans from the Iraq and Afghanistan conflicts reported the frequency of study participants with comorbid probable mild traumatic brain injury and probable posttraumatic stress disorder to be between 33-39% (Carlson et al., 2011). Schneiderman et al. (2008) found that posttraumatic stress disorder was 2.7-3.0 times more likely to occur in military personnel deployed to Iraq and/or Afghanistan who had sustained a mild traumatic brain injury than those who did not experience mild traumatic brain injury during deployment. The visual sequelae of posttraumatic stress disorder are not well understood. Photosensitivity, in particular, may be independently associated with posttraumatic stress disorder (Balba et al., 2018), and has been associated with higher self-reported symptoms of photosensitivity in a mixed sample of traumatic brain injury severity (Goodrich et al., 2014). There is, however, a research gap in terms of our understanding of both the independent effects of posttraumatic stress disorder and the potential interaction of posttraumatic stress disorder with mild traumatic brain injury on photosensitivity symptom severity ratings in Post-9/11 Veterans.

Commonly co-occurring diagnoses in Post-9/11 Veterans have led to the distinction of several clinical phenotypes, including the Deployment Trauma Phenotype of comorbid mild traumatic brain injury, posttraumatic stress disorder and depression, that are associated with significant disability (Lippa et al., 2015) and cognitive dysfunction (Esterman et al., 2019). While the relationship between photosensitivity and posttraumatic stress disorder have been previously described in this cohort, it is uncertain how other comorbidities, such as depression, sleep disturbances and anxiety, contribute to photosensitivity symptom intensity. One recent meta-analysis of 33 studies examining sensory processing difficulties in adults and adolescents

across different psychiatric categories found that sensory sensitivity, which includes sensitivity to light stimuli, might be a trans-diagnostic factor broadly associated with psychopathologies such as depression and trauma-related disorders (van den Boogert et al., 2022). While this meta-analysis did not specifically look at photosensitivity, sensory processing difficulties in general may warrant further consultation for a neuropsychiatric evaluation. Photosensitivity can also present as a diagnostic challenge to eye care providers, with a chart review in one clinic reporting that 26% of civilian patients with subjective complaints of photosensitivity left the clinic without an identified cause for their symptoms (Buchanan et al., 2022). Another diagnostic challenge is the management of chronic photosensitivity symptoms in the mild traumatic brain injury population, as 85% of mild traumatic brain injury patients who report photosensitivity have no change in the severity of their photosensitivity symptoms 1 year post-injury (Truong et al., 2014).

The primary goal of the study was to clarify the independent and potential dose-dependent effects of these signature injuries on the severity of photosensitivity ratings in Post-9/11 Veterans. Beyond the macro effects of mild traumatic brain injury and posttraumatic stress disorder diagnoses on subjective photosensitivity complaints, the present investigation explored the impact of the number of mild traumatic brain injuries sustained during military service and the intensity of posttraumatic stress disorder symptoms on photosensitivity severity. Additionally, we sought to examine how other common comorbidities in Post-9/11 Veterans may also play a role in photosensitivity rating severity. The current study may provide insights for those patients with photosensitivity without a readily identifiable cause and elucidate potential contributory etiologies for these challenging photosensitivity cases. The unique visual impairments of Post-9/11 Veterans will become an emerging public health burden for eye care

providers in the community as well as within the Veterans Health Administration, as 48% of these veterans will seek care outside the Veterans Health Administration (Epidemiology Program Post-Deployment Health Group 2012). While the present study focuses on the Post-9/11 Veteran population, the knowledge gained from analyzing the relationship between psychiatric comorbidities and photosensitivity in this cohort may broadly assist civilian providers in managing mild traumatic brain injury patients with persistent light sensitivity symptoms.

2.2. Methods

2.2.1. Participants: The sample of 641 Veterans was drawn from the Translational Research Center for Traumatic Brain Injury and Stress Disorders (TRACTS) study, which is a longitudinal cohort study of community-dwelling Post-9/11 Veterans enrolled at the Veterans Administration (VA) Boston and Houston Healthcare Systems (McGlinchey et al., 2017). This multidisciplinary study has been collecting data regarding deployment trauma in Post-9/11 Veterans and its consequences including biomedical function, lifetime head trauma, psychological and neurological functioning since 2010, with periodic releases of measurements. All data reported in the current study were collected as part of the standard TRACTS testing battery during the initial enrollment period. At the time of analyses for the current study, the available data repository included data from 808 participants who completed the initial enrollment testing session. Exclusion criteria for the current study included factors flagged during neurological and clinical assessments that affect neurologic (n=4), psychiatric (n=10), cognitive (n=4), or multiple areas of functioning (n=2), such as low estimated premorbid intelligence quotient, possible psychotic or personality disorder diagnoses, or congenital neurologic irregularities. An additional 36 participants were excluded due to history of

moderate/severe traumatic brain injury and 51 participants were excluded for missing data. Finally, an additional 54 participants were excluded for failing the effort/validity measure on the Medical Symptom Validity Test (MSVT) (McGlinchey et al., 2017; Green 2004). Participants were excluded based on performance validity testing to ensure validity of self-report measures of neurobehavioral symptoms. Thus, the final sample of 641 participants was included in the study. All participants provided informed written consent prior to any data collection. This research was reviewed by the VA Boston Healthcare System Internal Review Board and conforms to the principles and applicable guidelines for the protection of human subjects in biomedical research.

2.2.2. Measures & Procedures: The following assessments from the TRACTS data repository were examined: the Neurobehavioral Symptoms Inventory (NSI) (Cicerone and Kalmar 1995), Boston Assessment of TBI-Lifetime (BAT-L) (Fortier et al., 2014), Clinician-Administered PTSD Scale (CAPS) (Blake et al., 1995), Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989) and Depression Anxiety Stress Scales (DASS) (Lovibond and Lovibond 1995). Photosensitivity severity self-ratings were assessed using Question #7 of the NSI, which asks participants to rate their sensitivity to light over the last two weeks on a scale of 0-4, where a score of 0 indicates “None” or symptoms are rarely present, while a score of 4 indicates “Very Severe” disruption to daily activities (Cicerone and Kalmar 1995).

The number of lifetime traumatic brain injuries, including the number of mild traumatic brain injuries sustained during military service, were obtained from the BAT-L, a validated semi-structured clinical interview that used current VA and Department of Defense criteria for classification of traumatic brain injury severity (U.S. Department of Veterans Affairs and U.S. Department of Defense 2009). This clinical interview assesses a subject’s traumatic brain injury history during 3 time periods: before, during, and after military service (Fortier et al., 2014;

Fortier et al., 2015). The BAT-L also assesses mechanisms of traumatic brain injury (blast-related versus blunt force trauma) as well as exposure to blast events that may or may not result in a traumatic brain injury. Blast exposures are classified based on distance (close, medium, and far), with close-blast exposures defined as blast events that detonate within 10 meters of an individual. The presence and symptom severity of posttraumatic stress disorder was determined from the CAPS, which is 30-item clinician-administered interview that assesses symptoms based on the Diagnostic and Statistical Manual (4^{th} edition) definition of posttraumatic stress disorder (Blake et al., 1995). A total score is calculated that can range from 0-120 with higher scores indicating greater posttraumatic traumatic stress disorder symptom severity as well as subscale scores for three domains: Criterion B: Reexperiencing; Criterion C: Avoidance/Numbing; and Criterion D: Hyperarousal. All clinical interviews, including the BAT-L, were conducted by a doctoral level psychologist and diagnosis of traumatic brain injury, posttraumatic stress disorder, and other Axis I disorders were reviewed by at least three doctoral-level psychologists/psychiatrists at weekly diagnostic consensus meetings.

Sleep quality and disturbances over the preceding month were assessed using the PSQI self-report questionnaire. Seven component scores are tabulated to form the Global PSQI score which can range from 0-21, with higher scores indicating increased sleep disturbances and poorer sleep quality (Buysse et al., 1989). Depression and anxiety symptom severity were measured using the corresponding subscale scores from the DASS which can range from 0-21, with higher scores indicating greater symptom severity over the last week (Lovibond and Lovibond 1995). All measurements were collected as part of the standard TRACTS assessment battery during the enrollment visit.

2.2.3. Statistical Analyses: Comparisons of sample characteristics for participants with and without a history of mild traumatic brain injury during military service were calculated using two-sample t-tests for continuous variables or chi-square tests for categorical variables. As a first analysis, we sought to replicate the previous findings of Goodrich et al. (2014) that current posttraumatic stress disorder diagnosis is associated with higher photosensitivity ratings independent of mild traumatic brain injury status. For this analysis, a 2x2 univariate analysis of covariance (ANCOVA) was calculated comparing photosensitivity ratings on the NSI across individuals with and without a history of mild traumatic brain injury and those with or without a current diagnosis of posttraumatic stress disorder, adjusting for the age and gender of participants given the large age range in the current sample (range: 18-67 years) and differences seen in the proportion of males across the two groups. An additional set of analyses was then conducted to assess whether the number of mild traumatic brain injuries during military service and current posttraumatic stress disorder symptom severity were associated with photosensitivity severity when other common comorbidities were also considered (i.e., depression, anxiety, and sleep disturbances). For this analysis, a multiple ordinal regression model was calculated looking at the impact of several continuous measures on photosensitivity ratings. Additionally, we tested whether previous findings that the avoidance/numbing subscale of posttraumatic stress disorder measures would drive the association between posttraumatic stress disorder symptom severity and photosensitivity severity ratings (Callahan and Storzbach 2018). Four separate regression models were calculated. The initial model used the total posttraumatic stress disorder symptom severity score from the CAPS, while the three follow-up regression models used scores from the three posttraumatic stress disorder subscales instead of the total score (Criterion B: Reexperiencing; Criterion C: Avoidance/Numbing; Criterion D: Hyperarousal). Prior to

calculating each of the four models, checks were completed to ensure assumption of multiple ordinal regression were met. This included: 1) Preliminary multiple linear regression models were calculated before the ordinal regression model to test for collinearity of independent predictors, using a threshold of VIF = 2.5 for determining potential issues of multicollinearity. Inclusion of average pain ratings showed potential multicollinearity (VIF = 2.501). This, along with the fact that pain ratings were missing for 115 participants, led us to exclude this potential comorbidity as a predictor variable in the regression models. No other issues with multicollinearity were detected with the remaining 7 predictors (number of mild traumatic brain injuries, severity of current posttraumatic stress, depression, and anxiety symptoms, sleep disturbances, age, and gender). 2) Assumptions of proportional odds were assessed using the test of parallel lines for each model. All models met this assumption (all *Ps* > .74 for all models reported) and thus the assumptions required for use of ordinal regression models.

2.3 Results

2.3.1. Participant Demographics: The final sample of 641 participants had a mean age of 34.22 ± 8.98 years (range: 18-67 years) with the majority male (n=576; 89.9%) and Caucasian (n=453; 70.7%). Table 1 compares the demographic information between the no military mild traumatic brain injury group (mTBI-) (n=321), who had no previous history of mild traumatic brain injury during military service, and the military mild traumatic brain injury group (mTBI+) (n=320). Similar between group comparisons were completed looking at differences in the total number of participants with a history of mild traumatic brain injury across the lifespan, as well as before and after military service, and the number of close blast exposures during

military service (Table 2). We additionally examined the prevalence and severity of several common behavioral and psychiatric comorbidities seen in this veteran population (Table 3). As seen in Tables 2 and 3, participants with a history of military mild traumatic brain injury showed greater numbers of mild traumatic brain injuries across the lifespan, tended to have a mild traumatic brain injury more recently, and were exposed to a greater number of close blast exposures during military service compared to participants without a history of military mild traumatic brain injury. However, no difference was seen in the prevalence of mild traumatic brain injuries before and after military service for these two groups (Table 2). Participants with a history of mild traumatic brain injury during military service also showed significantly higher prevalence and severity of multiple behavioral and psychiatric comorbidities commonly seen in the Post-9/11 Veteran population compared to participants without a history of military mild traumatic brain injury. As seen in Table 3, these differences included higher prevalence and symptom severity of posttraumatic stress disorder, greater depression and anxiety symptom severity, poorer sleep quality and greater severity of chronic pain symptoms over the previous month. A greater proportion of participants with mild traumatic brain injury also reported having headaches. Of those who reported headaches, a greater proportion of participants with mild traumatic brain injury also reported having migraines. Collectively, these results illustrate the complex clinical picture that Post-9/11 Veterans with multiple deployments may present in clinical settings and highlight the need to consider these common comorbidities in analyses of photosensitivity symptoms.

Table 1: Sample demographic characteristics comparing those with and without a history of mild traumatic brain injury (mTBI) during military service.

	Military mTBI- Group (n= 321)				Military mTBI+ Group (n=320)				
Variable	***n***	***%***	***M***	***95% CI***	***n***	***%***	***M***	***95% CI***	**Statistical Test**
Age (years)			34.4	33.3-35.5			34.0	33.3-35.5	$t_{639} = 0.6$, $P = .55$
Male gender	279	86.9%			297	92.8%			$\chi^2_1 = 6.1$, $P = .01$
Education (years)			14.2	14.0-14.5			14.2	14.0-14.5	$t_{639} = 0.03$, $P = .98$
Race									
White	222	70.3%			231	74.8%			$\chi^2_1 = 1.6$, $P = .21$
Black	39	12.3%			42	13.6%			$\chi^2_1 = 0.2$, $P = .64$
Other	15	4.7%			23	7.2%			$\chi^2_1 = 1.8$, $P = .18$
Unknown/missing	52	16.2%			34	10.6%			$\chi^2_1 = 4.3$, $P = .04$
Service Branch									
Army	214	66.7%			219	68.4%			$\chi^2_1 = 0.2$, $P = .63$
Navy	17	5.3%			19	5.9%			$\chi^2_1 = 0.1$, $P = .72$
Air Force	36	11.2%			14	4.4%			$\chi^2_1 = 10.4$, $P = .001$
Marines	60	18.7%			76	23.8%			$\chi^2_1 = 2.4$, $P = .12$
National Guard/Reserves	180	56.1%			99	30.9%			$\chi^2_1 = 41.2$, $P < .001$
Deployments									
Number			1.5	1.4-1.6			1.9	1.7-2.0	$t_{639} = -4.3$, $P < .001$
Time (months)			14.6	13.5-15.8			17.9	16.6-19.2	$t_{639} = -3.7$, $P < .001$
Months since last deployment			52.0	47.1-56.9			68.5	63.4-73.6	$t_{639} = -4.6$, $P < .001$
Combat exposure[a]			12.8	11.7-14.0			22.3	20.9-23.8	$t_{639} = -10.3$, $P < .001$

Note: Comparisons across mild traumatic brain injury groups (mTBI) were calculated using chi-square tests for dichotomous variables and independent t-tests for continuous variables. (a) Combat exposure was measured using the Deployment Risk and Resilience Inventory (DRRI) combat exposure subscale.

Table 2. Sample characteristics of additional neurotrauma events comparing those with and without a history of mild traumatic brain injury (mTBI) during military service.

	Military mTBI- Group (n= 321)				Military mTBI+ Group (n=320)				
Variable	***n***	***%***	***M***	***95% CI***	***n***	***%***	***M***	***95% CI***	**Statistical Test**
Lifetime mTBI	129	40.2%			320	100%			$\chi^2_1 = 273$, $P < .001$
# Lifetime mTBI		0.67		.54-.80			2.58	2.34-2.83	$t_{484} = -13.45$, $P < .001$
Years Since Last mTBI			16.83	14.88-18.78			6.98	6.46-7.50	$t_{147} = 9.66$, $P < .001$
Pre-Military mTBI	121	37.7%			123	38.4%			$\chi^2_1 = 0.04$, $P = .871$
Post-Military mTBI	15	4.7%			25	7.8%			$\chi^2_1 = 2.70$, $P = .106$
# Close Blast Exposures			.74	.37-1.10			4.04	2.43-5.65	$t_{351} = -3.94$, $P < .001$

Note: Comparisons across mild traumatic brain injury groups (mTBI) were calculated using chi-square tests for dichotomous variables and independent t-tests for continuous variables. Lifetime mTBI is defined as any mild traumatic brain injury that occurred prior to, during, or after military service. The table also shows the number of mild traumatic brain injuries that specifically occurred prior to or after military service. The number of close blast exposures quantifies blast exposure that occurred within 10 meters of individual. To provide a metric for individuals this is further defined as “Approximately 32 feet or the length of 2 parking spaces”.

Table 3. Psychiatric and behavioral comorbidities in sample comparing those with and without a history of mild traumatic brain injury (mTBI) during military service.

	Military mTBI- Group (n= 321)				Military mTBI+ Group (n=320)				
Variable	***n***	***%***	***M***	***95% CI***	***n***	***%***	***M***	***95% CI***	**Statistical Test**
PTSD Diagnosis[a]	134	41.7%			200	62.5%			$\chi^2_1 = 27.6$, $P < .001$
PTSD severity			37.6	34.5-40.6			55.7	52.7-58.7	$t_{639} = -8.3$, $P < .001$
Reexperiencing			9.35	8.4-10.3			15.2	14.1-16.2	$t_{639} = -8.1$, $P < .001$
Avoidance/Numbing			13.8	12.4-15.2			20.5	19.1-21.9	$t_{639} = -6.7$, $P < .001$
Hyperarousal			14.4	13.4-15.5			20.0	19.0-20.9	$t_{639} = -7.8$, $P < .001$
Anxiety severity[b]			5.2	4.5-5.9			9.8	8.9-10.8	$t_{635} = -7.5$, $P < .001$
Depression severity[b]			7.2	6.2-8.2			11.8	10.7-13.0	$t_{635} = -5.9$, $P < .001$
Sleep quality[c]			8.9	8.4-9.4			11.7	11.2-12.1	$t_{626} = -7.5$, $P < .001$
Average pain[d]			27.3	24.5-30.2			39.4	36.0-42.7	$t_{524} = -5.4$, $P < .001$
Headaches[e]	197	61.8%			275	85.9%			$\chi^2_1 = 48.4$, $P < .001$
If so, migraines?	69	33.8%			134	60.1%			$\chi^2_1 = 29.5$, $P < .001$

Note: Comparisons across mild traumatic brain injury groups (mTBI) were calculated using chi-square tests for dichotomous variables and independent t-tests for continuous variables. All comparisons remain significant when using Bonferroni correction for multiple comparison with an adjusted critical $\alpha = .0045$. Available data is shown for all participants. (a) Posttraumatic stress disorder (PTSD) was measured using the Clinician Administered PTSD Scale (CAPS). This measure provides information for diagnosing current PTSD, current PTSD symptom severity through the total score, and measures of symptom severity for three subscales: reexperiencing (subscale B), emotional numbing/avoidance (subscale C), and hyperarousal (subscale D). (b)Anxiety and depression severity scores were measured from the Depression, Anxiety, and Stress Scale. Data was available for 637 participants. (c) Sleep quality was measured using the Pittsburgh Sleep Quality Index. Data was available for 628 participants. (d)Average pain over the last 30-days was measured using the McGill Pain questionnaire. Data was available for 526 participants. (e) Participants were asked to report yes/no whether they experienced headaches. If they responded in the affirmative, they were then asked if they experience migraines. Responses to the migraine question were available for 427 participants.

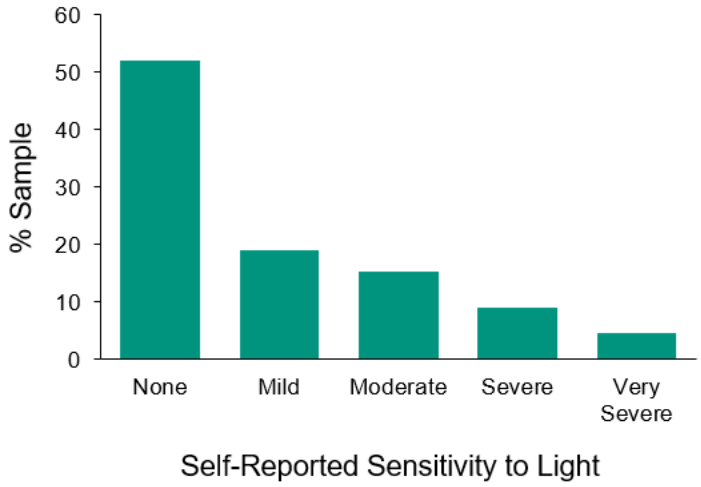


Figure 1. Histogram showing the distribution of photosensitivity severity rating scores from the Neurobehavioral Symptom Inventory Questionnaire.

2.3.2. Photosensitivity Ratings, Mild Traumatic Brain Injury, and Current Posttraumatic Stress Disorder Diagnoses:

Figure 1 shows the distribution of photosensitivity severity scores from the NSI questionnaire in the current sample. As seen in Figure 1, the distribution was positively skewed with most participants reporting little to no photosensitivity while 185 participants reported moderate to severe PS symptoms over the last two weeks. Results of the ANCOVA comparing photosensitivity ratings across mild traumatic brain injury and current posttraumatic stress disorder groups (Figure 2) showed that participants with a positive history of mild traumatic brain injury during military service reported increased photosensitivity ratings relative to those without a history of mild traumatic brain injury, $F_{1,634} = 50.56$, $P < .001$, as did participants with a current diagnosis of posttraumatic stress disorder compared to those without a current diagnosis of posttraumatic stress disorder, $F_{1,634} = 56.21$, $P < .001$. No interaction was seen between the mild traumatic brain injury and posttraumatic stress disorder factors, $F_{1,634} = 0.83$, $P = .414$. Indeed, as seen in Figure 2, an additive effect was seen across the two factors with each factor associated with a 0.50-0.53 point increase in age and gender-adjusted photosensitivity ratings compared to the 187 participants without posttraumatic stress disorder or a history of mild traumatic brain injury during military service. Individuals with both mild traumatic brain injury and posttraumatic stress disorder further showed a 0.65-0.68 point increase compared to those with a single condition. The same pattern of results was seen when a positive history of lifetime mild traumatic brain injury was used in the above analyses.

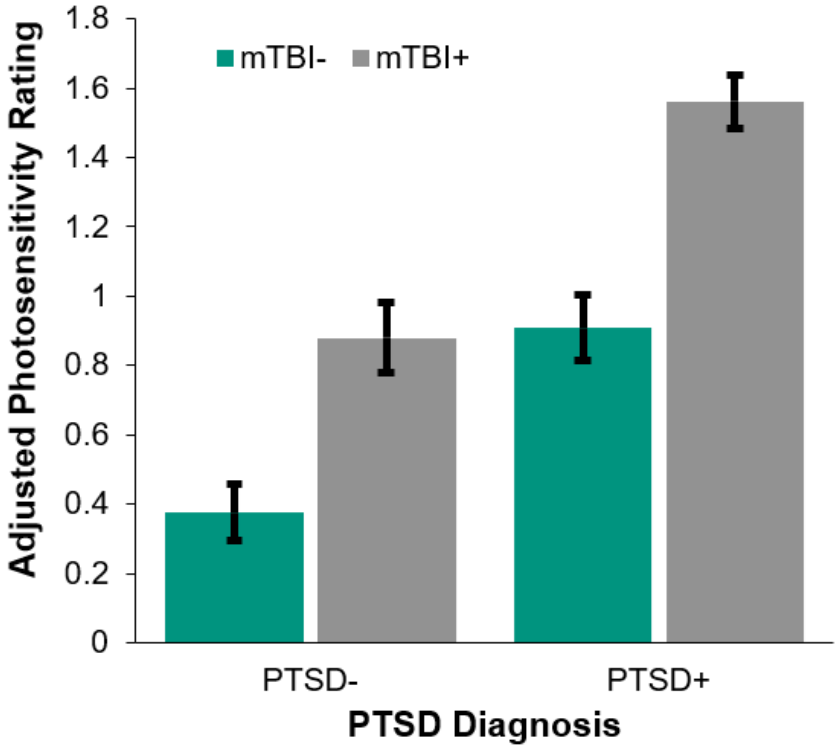


Figure 2. Age and gender-adjusted photosensitivity severity scores as a function of current posttraumatic stress disorder (PTSD) diagnosis and history of mild traumatic brain injury (mTBI) during military service. Results are shown for participants with no history of mild traumatic brain injury or current posttraumatic stress disorder diagnosis (n=187), only a positive history mild traumatic brain injury (n=120), only a current diagnosis of posttraumatic stress disorder (n=134), or both conditions (n=200). Error bars show ±1 Standard Error of the Mean (SEM).

While the main study focuses on the impact of mild traumatic brain injury during military service, an additional 129 participants were found to have experienced a mild traumatic brain injury either before or after military service. To determine if consideration of lifetime mild traumatic injury status would alter the relationship observed between current posttraumatic stress disorder (PTSD) diagnosis and mild traumatic brain injury on photosensitivity ratings, we re-ran the 2x2 ANCOVA including age and gender as covariates, with current PTSD diagnosis and lifetime mild traumatic brain injury as factors. Results mirror those seen in the manuscript. In comparison to participants without a history of lifetime mild traumatic brain injury or current

post-traumatic stress disorder diagnosis, a positive history of mild traumatic brain injury was associated with increased photosensitivity ratings, $F_{1,634} = 22.65$, $P < .001$, as was a current diagnosis of PTSD, $F_{1,634} = 49.39$, $P < .001$. No interaction was seen between the mild traumatic brain injury and post-traumatic stress disorder factors, $F_{1,634} = 1.04$, $P = .309$. Indeed, as seen in Figure 2, an additive effect was seen across the two factors with each factor associated with a 0.32-0.52 point increase in age and gender-adjusted photosensitivity ratings compared to those without post-traumatic stress disorder or a history of mild traumatic brain injury during military service. Individuals with both mild traumatic brain injury and post-traumatic stress disorder further showed a 0.53-0.72 point increase compared to those with a single condition.

2.3.3. Impact of Repetitive Mild Traumatic Brain Injury and Common Comorbidities on Photosensitivity Ratings:

While the previous analysis showed independent contributions of current posttraumatic stress disorder diagnosis and a history of military mild traumatic brain injury on increased photosensitivity symptom severity, TRACTS participants with mild traumatic brain injury showed not only a higher prevalence of posttraumatic stress disorder diagnoses but also greater symptom severity for multiple psychiatric and behavioral comorbidities as seen in Table 3. Multiple ordinal regression models were therefore calculated to examine the impact of multiple comorbidities along with the number of mild traumatic brain injuries on photosensitivity severity. All models in these analyses were found to provide a significantly better fit than the null model using chi-square tests ($P < .001$ for all), demonstrating a good fit for the omnibus test and allowing interpretation of individual predictor coefficients in the models. As a result, beta weights were converted to odds ratios and the significance of individual predictors in the models are discussed below (Table 4).

Table 4. Results from ordinal regression model showing coefficients for regressors in models.

	CAPS Total Score		CAPS Criterion B Reexperiencing		CAPS Criterion C Avoidance/Numbing		CAPS Criterion D Hyperarousal	
	Odds Ratio (95% CI)	*P*-value	Odds Ratio (95% CI)	*P*-value	Odds Ratio (95% CI)	*P*-value	Odds Ratio (95% CI)	P-value
Age	1.005 (.987-1.023)	.603	1.003 (.985-1.021)	.751	1.003 (.986-1.021)	.717	1.005 (.987-1.023)	.585
Gender	1.536 (.928-2.543)	.095	1.545 (.935-2.555)	.090	1.541 (.932-2.549)	.092	1.565 (.994-2.593)	.082
# mTBI	1.222 (1.093-1.366)	<.001***	1.224 (1.094-1.369)	<.001***	1.232 (1.102-1.377)	<.001***	1.219 (1.091-1.363)	<.001***
Anxiety	1.048 (1.020-1.078)	.001**	1.051 (1.021-1.081)	.001**	1.052 (1.024-1.082)	<.001***	1.047 (1.019-1.077)	.001**
Depression	1.021 (.998-1.044)	.072	1.026 (1.004-1.048)	.020*	1.020 (.997-1.044)	.090	1.024 (1.002-1.046)	.031*
Sleep Quality	1.060 (1.014-1.107)	.009**	1.071 (1.026-1.117)	.002**	1.070 (1.027-1.115)	.001**	1.049 (1.004-1.097)	.034*
PTSD[1]	1.008 (1.000-1.016)	.039*	1.011 (.989-1.032)	.328	1.012 (.996-1.029)	.127	1.033 (1.010-1.056)	.005**

Note: 1) Posttraumatic stress disorder (PTSD) severity scores used in each of the regression models are listed in the column title. For all models # mTBI reflects the number of mild traumatic brain injuries during military service. Anxiety, depression, and sleep quality scores are continuous measures described in Table 3. * Indicates $P < 0.05$, ** indicates $P < 0.01$, *** indicates $P < .001$.

As seen in the results of the main analysis in the left column of Table 4, both the number of military mild traumatic brain injuries and current posttraumatic stress disorder symptom severity using the total score on the CAPS interview were positively associated with photosensitivity severity ratings even when accounting for other common comorbidities in the same model. Thus, not only are yes/no diagnostic categories for mild traumatic brain injury and posttraumatic stress disorder differentially associated with photosensitivity severity (Figure 2), but a positive association was found between repetitive mild traumatic brain injuries during military service and current severity of posttraumatic stress disorder symptoms on photosensitivity (Table 4). Additionally, results show that poorer sleep quality and increasing anxiety symptoms were associated with increased photosensitivity severity, even when controlling for the number of mild traumatic brain injuries and current posttraumatic stress disorder symptom severity (Table 4). To assess if a specific subdomain of posttraumatic stress disorder symptom types was driving the association between posttraumatic stress disorder severity and photosensitivity symptoms, the ordinal regression models were recalculated using the CAPS subdomain scores. As seen in the three right columns of Table 4, when other common comorbidities were included in the model, we found that only the Hyperarousal subscale was associated with photosensitivity symptom severity. As previous work (Callahan and Storzbach 2018) linking avoidance/numbing symptoms with photosensitivity in Veterans only included participants with a history of blast exposure, we included additional exploratory analyses that recalculated the ordinal regression models substituting the number of blast-related mild traumatic brain injuries (Table 5) or the number of close blast exposures (Table 6) for the military mild traumatic brain injury measure used in the original regression models. In all cases the same

overall pattern emerged, with the hyperarousal subscale but not the avoidance/numbing subscale showing a significant association with photosensitivity symptom severity when other covariates such as sleep disturbances, anxiety and depression symptoms are included in the model (Tables 5-6).

Table 5. Results from follow-up ordinal regression model comparing association of Avoidance/Numbing versus Hyperarousal subscales for posttraumatic stress disorder severity when neurotrauma is modelled using the number of blast-related mild traumatic brain injuries. Analysis uses same approach outlined for Table 4 in the manuscript.

	CAPS Criterion C Avoidance/Numbing		**CAPS Criterion D Hyperarousal**	
	Odds Ratio (95% CI)	*P*-value	Odds Ratio (95% CI)	*P*-value
Gender	1.562 (.943-2.586)	.083	1.592 (.959-2.641)	.072
Age	1.004 (.987-1.002)	.638	1.006 (.989-1.024)	.486
Sleep Quality	1.068 (1.025-1.114)	.002**	1.045 (0.999-1.093)	.053
Anxiety	1.049 (1.020-1.079)	.001***	1.044 (1.015-1.074)	.003**
Depression	1.024 (1.00-1.048)	.046*	1.027 (1.005-1.050)	.015*
# Blast mTBI	1.483 (1.208-1.818)	<.001***	1.480 (1.207-1.817)	<.001***
PTSD[1]	1.012 (.996-1.028)	.154	1.035 (1.011-1.059)	.003**

Table 6. Results from follow-up ordinal regression model comparing association of Avoidance/Numbing versus Hyperarousal subscales for posttraumatic stress disorder severity when neurotrauma is modelled using the number of close blast exposures (<10 meters). Analysis uses same approach outlined for Table 4 in the manuscript.

	CAPS Criterion C Avoidance/Numbing		**CAPS Criterion D Hyperarousal**	
	Odds Ratio (95% CI)	*P*-value	Odds Ratio (95% CI)	*P*-value
Gender	1.408 (.854-2.319)	.181	1.439 (.871-2.377)	.155
Age	1.004 (.986-1.022)	.656	1.006 (.988-1.024)	.499
Sleep Quality	1.080 (1.037-1.125)	<.001***	1.057 (1.010-1.104)	.015*
Anxiety	1.058 (1.029-1.088)	<.001***	1.052 (1.023-1.082)	<.001**
Depression	1.016 (.993-1.040)	.169	1.020 (.999-1.043)	.068
# Close Blast Exposures	1.012 (.999-1.025)	.082	1.012 (.998-1.025)	.086
PTSD[1]	1.013 (.997-1.029)	.108	1.037 (1.013-1.060)	.002**

2.4. Discussion

The results of our preliminary analysis replicated and extended previous findings that comorbid traumatic brain injury and posttraumatic stress disorder potentiate photosensitivity symptoms compared to each diagnosis alone (Goodrich et al., 2014; Balba et al., 2018). While these earlier studies were in mixed samples of traumatic brain injury severity, our study excluded

participants with moderate and severe traumatic brain injuries and demonstrated that this pattern of results holds in a large sample of Veterans with mild traumatic brain injury. Results from the ordinal regression models showed that the number of military mild traumatic brain injuries had a significant impact on photosensitivity severity, which remained consistent across all posttraumatic stress disorder symptom clusters. Results also showed that current anxiety symptoms and sleep disturbances were associated with increased photosensitivity severity after controlling for military mild traumatic brain injury and posttraumatic stress disorder.

A notable and unique finding in the current study was that the hyperarousal component of posttraumatic stress disorder (CAPS Criterion D) was found to drive the increase in photosensitivity complaints attributed to posttraumatic stress disorder. In contrast to previous studies (Callahan and Storzbach 2018), we did not find the avoidance/numbing symptoms were associated with photosensitivity symptom severity when accounting for the number of mild traumatic brain injuries and other covariates. These findings conflict with a previous study of Post-9/11 Veterans with a history of blast-related mild traumatic brain injury and sensory sensitivity, which found that the avoidance cluster of posttraumatic stress disorder was significantly related to photosensitivity in blast-exposed mild traumatic brain injury subjects, while noise sensitivity was correlated to the hyperarousal criterion of posttraumatic stress disorder (Callahan and Storzbach 2018). Additional exploratory analyses showed the same pattern of results when the number of blast-related mild traumatic brain injuries or close blast exposures was included in the model. Thus, although our study did not specifically focus on blast-exposed Post-9/11 Veterans, the present analysis which included a much larger sample size (n=641 versus n=72 in the Callahan et al. study) (2018), may more accurately represent the broader population of Post-9/11 Veterans. Another study of veterans with mixed traumatic brain

injury severity did not find a posttraumatic stress disorder subscale that was predictive of photosensitivity, but found that the re-experiencing or intrusive thoughts criterion (cluster B) was trending, while the hyperarousal cluster was predictive of noise sensitivity (Elliott et al., 2018). While the literature regarding posttraumatic stress disorder symptom clusters and photosensitivity is mixed within the broader traumatic brain injury literature, the current finding that the hyperarousal component of posttraumatic stress disorder drives photosensitivity symptoms suggests an alternate pathway to the trigeminothalamic pathway previously described as central to the pathophysiology of photosensitivity in dry eye, traumatic brain injury and migraine, which are highly comorbid with each other (Diel et al., 2021).

Dysregulation of wide-spread cortical functional networks related to the perception of pain may provide a possible explanation for increased photosensitivity symptoms related to the hyperarousal subscale of posttraumatic stress disorder. A dynamic pain connectome has been defined that involves three areas: the Default Mode and Salience Networks along with the Anti-Nociceptive system which plays a role in the mind wandering away from pain (Kucyi and Davis 2015). There is evidence of atypical resting state functional network activity within these areas in both mild traumatic brain injury and posttraumatic stress disorder (Klimova et al., 2023; Philippi et al., 2021; Santhanam et al., 2019), which may explain overlapping symptomology in these conditions. In both Post-9/11 Veteran and civilian populations, altered connectivity within and between the default mode and salience networks has also been suggested to underlie the hypervigilance component in posttraumatic stress disorder (Sripada et al., 2012; van der Horn et al., 2016). Given these findings, it is possible that the resting state dysregulation of the default mode network and salience network that drives the hyperarousal symptoms in posttraumatic stress disorder affects the perception of pain related to light stimuli and may explain the

exacerbation of photosensitivity in this cohort, especially in the group with comorbid mild traumatic brain injury and posttraumatic stress disorder.

The potential role of hyperarousal in driving photosensitivity symptoms is further supported by evidence that the state of autonomic arousal in other neurologic or psychiatric conditions can affect sensory sensitivity. Insomnia is a hyperarousal state that can exacerbate photosensitivity symptoms. Our study found that greater sleep disturbances were associated with higher photosensitivity scores. This is consistent with a previous study of veterans with traumatic brain injury that found that those with light sensitivity only and light sensitivity combined with noise sensitivity (i.e., sensory sensitivity), had greater sleep disturbances compared to the groups without sensory sensitivity or noise sensitivity alone (Elliott et al., 2018). The same study found that veterans with traumatic brain injury, posttraumatic stress disorder and sensory sensitivity had a higher resting heart rate during both non-rapid eye movement (non-REM) and rapid eye movement (REM) sleep compared to the veterans with comorbid traumatic brain injury and posttraumatic stress disorder without sensory sensitivity, even after controlling for posttraumatic stress disorder diagnosis and medications that affect heart rate (Elliott et al., 2018). This finding suggests that individuals with sensory sensitivity have a higher basal level of sympathetic outflow compared to those without sensory sensitivity. Future studies should investigate the role of autonomic nervous system hyperarousal in the pathophysiology of photosensitivity independent of noise and/or sensory sensitivity. The current study also compares favorably to another investigation through the VA Portland Health Care System that found greater sleep disturbances in veterans with comorbid traumatic brain injury and posttraumatic stress disorder and veterans with posttraumatic stress disorder alone compared to the traumatic brain injury only

and non-traumatic brain injury groups, suggesting that posttraumatic stress disorder drives sleep disturbances in this cohort (Balba et al., 2018).

Documented photosensitivity related solely to depression is not well established. While some studies suggest a potential link between depression and photosensitivity (van den Boogert et al., 2022; Buchanan et al., 2022), our study did not find an association when other conditions were considered. This finding highlights the need to consider multiple potential comorbid conditions, such as sleep disturbances, in future work looking at the association between psychiatric disorders and sensory sensitivity (van den Boogert et al., 2022).

While photosensitivity was modeled as an outcome variable in the current study, it is important to note that photosensitivity may have a bidirectional relationship with certain mental health disorders, such as posttraumatic stress disorder, with posttraumatic stress disorder not only impacting light sensitivity but being influenced by photosensitivity itself (Callahan and Storzbach 2018; Bushnik et al., 2015). Sensory sensitivity has also been broadly discussed as a potential risk factor for other neuropsychiatric disorders such as anxiety (van den Boogert et al., 2022; Cicerone and Kalmar 1995). While the current study is unable to determine causal relationships in these associations, the current findings add to existing literature demonstrating that light sensitivity secondary to a mild traumatic brain injury is an important symptom that signals the need for earlier interdisciplinary collaboration to manage these patients, as photosensitivity may be a strong predictor for persistent postconcussive symptoms (Wojcik 2014), is associated with a higher disease burden in those with posttraumatic headache, and can lead to profound negative effects on health-related quality of life measures (Shepherd et al., 2020).

2.4.1. Study Limitations

There are several important limitations in the current study. First, given the retrospective nature of the study, we were limited in the measurement of photosensitivity to one item of the NSI questionnaire asking for self-reported photosensitivity ratings within the TRACTS database. While sensory sensitivity ratings from this questionnaire have been used in prior studies (Callahan and Storzbach 2018) of photosensitivity in Post-9/11 Veterans, and objective measurements of photosensitivity are limited, there are additional validated questionnaires such as the Utah Photophobia Symptom Impact Scale (Cortez et al., 2019) that provide more detailed information regarding photosensitivity, including the impact on specific activities of daily living. To address issues related to possible symptom exaggeration, the current study excluded participants who failed an embedded effort measure within the TRACTS testing battery. Regardless, incorporation of detailed questionnaires or objective measures of light-related pain thresholds in future studies may improve our understanding of the associations highlighted in this current study.

Secondly, the TRACTS cohort study was not designed to specifically focus on visual function and did not include eye exams as part of their testing battery, so ocular comorbidities such as dry eye, and other anterior and posterior segment conditions associated with photophobia were not assessed (Digre and Brennan 2012). Light sensitivity is a common symptom in dry eye, traumatic brain injury, and migraine which are highly comorbid with each other. Dry eye is also more prevalent in patients with depression, anxiety, sleep disturbances and posttraumatic stress disorder (Galor et al., 2012; Magno et al., 2021; Wan et al., 2016), which were more common in the military traumatic brain injury group.

Another study limitation is the confounding effect of migraine on photosensitivity symptomology in this cohort. While we were not able to collect headache data on every subject,

there was an increased prevalence of migraine in the mild traumatic brain injury group (64%), which is higher than previous estimations of 33%-50% of posttraumatic headache being classified as migraine (Mares et al., 2019). Due to incomplete data, we were unable to calculate the variance from migraine on photosensitivity severity in the current sample. However, the photosensitivity networks are well-characterized in the migraine literature, as it is one of the major diagnostic criteria for migraine (Digre and Brennan 2012). Of note, studies on migraines have shown intrinsic connectivity changes between the salience and primary sensory networks (Digre and Brennan 2012), overlapping with changes seen in the mild traumatic brain injury and posttraumatic stress disorder studies outlined above. Given that migraine and mild traumatic brain injury are highly comorbid, further investigation about the relationship between these resting state functional connectivity networks and visual and sensory processing areas in the cortex should be pursued. One final potential confounder that is not accounted for in this investigation are medications or illicit substances that may increase photosensitivity, dry eye or cause mydriasis (Capó-Aponte et al., 2012; Dhingra et al., 2019). Given the results of the present study, further work replicating the current findings and providing additional information about the nature of light sensitivity is warranted.

2.6. Conclusion

Photosensitivity in the context of a relatively normal eye exam warrants a detailed history and further investigation to rule out neurological and psychiatric conditions that are associated with PS as outlined in this study: mild traumatic brain injury, posttraumatic stress disorder, anxiety, and sleep issues. Our study shows the impact and interaction that both physical and psychiatric traumas can have on photosensitivity and may point towards multi-disciplinary and

novel therapeutic interventions. Current treatment options are limited, however, there is increasing awareness in the optometry community that behavioral and psychiatric factors may impact sensory processing (Buchanan et al., 2022). Given the high comorbidity of the behavioral and psychiatric issues examined in the current study with mild traumatic brain injury in Post-9/11 Veterans, and the fact that most veterans in this sample had not incurred a mild traumatic brain injury in several years, the present findings highlight the need for optometrists to consider the chronic impact of deployment related traumas on visual functioning. Future work integrating psychologists and polytrauma experts in developing a comprehensive clinical perspective may benefit many patients, both veteran and civilian, reporting photosensitivity but who show normal functioning on standard neuro-ophthalmic testing. The current results help to highlight some of the common issues that may be exacerbating photosensitivity symptoms in these patients.

3. Study 2: The Treatment of Photosensitivity After Mild Traumatic Brain Injury with Low-Intensity Pulse-Based Transcranial Electrical Stimulation: A Case Study

3.1. Introduction

Photosensitivity (PS) is one of the more common sequelae of mild traumatic brain injury (mTBI), with over 50% of mTBI patients reporting some level of PS in the acute and/or chronic stages (Capó-Aponte et al., 2012). PS can significantly impair social, physical, and cognitive functioning (Shepherd et al., 2020), as well as rehabilitation outcomes (Lew et al., 2009). When analyzing the independent effects of light and noise sensitivity on specific health related quality of life (HRQoL) domains, one study showed that PS might have the greatest overall impact on HRQoL, adversely affecting bodily pain perception and may induce negative emotional responses that are counterproductive to goal-driven behaviors (Shepherd et al, 2020). In the context of general rehabilitation outcomes for mTBI patients, PS may be a strong predictor for persistent postconcussive symptoms (PPCS), highlighting the need for earlier multi-specialty PPCS intervention in mTBI-related PS (Wojcik 2014).

While spectacle tints are conventionally used to alleviate symptoms, they have been associated with lower symptom recovery over time (Truong et al., 2014), underscoring the need to develop more effective, non-invasive treatment options that can reduce or eliminate PS.

Besides the commonly prescribed spectacle chromatic filters, there are currently few utilized treatments for mTBI-related PS. While darkly tinted lenses provide immediate relief, the long-term consequences may be counterproductive to the recovery process in mTBI-related PS (Truong et al., 2014). Tint usage may inhibit PS symptom recovery by interfering with the natural neural adaptation to normal light levels (Truong et al., 2014). Systemic medications that target nociceptive molecules in the trigeminovascular pathway (Diel et al., 2020; Scuteri et al., 2019; Dodick et al., 2020) and more invasive treatments, such as botulinum toxin injections (Venkateswaran et al., 2020), can reduce PS in migraine, but may be limited due to compliance issues and adverse side effects. There is a definite need for more effective, less invasive adjunctive therapies for PS in the mTBI population.

Non-invasive neurostimulation techniques, such as low intensity pulse-based transcranial electrical stimulation (LIP-tES), are a potential class of treatments that address the neural and cortically based pain networks associated with various conditions and could potentially target the nociceptive response to light in PS. LIP-tES is a passive neurofeedback technique that combines electroencephalography (EEG) monitoring with the application of low-intensity electrical pulses to the scalp and has shown promise in treating TBI symptoms and PTSD (Schoenberger et al., 2001; Ochs 2006; Larsen et al., 2006; Nelson et al., 2015; Huang et al., 2017). While LIP-tES has not been specifically used to treat mTBI-related PS, one VA San Diego pilot study using magnetoencephalography (MEG) to investigate neuronal changes following LIP-tES treatment (IASIS Microcurrent Feedback) for mTBI and persistent post-concussive symptoms, found a reduction in PS symptoms by at least 50% in 3 out of the 5 subjects who reported PS (Huang et al., 2017). The LIP-tES device used in this case report, Neurogen^{TM} High-Performance Neurofeedback (HPN), is a more advanced version of the IASIS Microcurrent Neurofeedback

device used in the Huang et al. study (2017) and has a similar safety profile (C. Snook, personal communication, April 16, 2021). LIP-tES may be a potential non-invasive, novel treatment for mTBI-related PS.

Study 1 illustrates how PTSD and other psychiatric comorbidities, such as anxiety and sleep disturbances, that are common in the Post-9/11 Veterans who have sustained an mTBI, contribute to the severity of PS symptoms and suggest underlying shared pathophysiologic mechanisms. LIP-tES has been shown to improve post-concussive complaints, PTSD symptoms, anxiety, sleep quality and pain in the VA San Diego pilot study (Huang et al., 2017) and previous work (Larsen et al., 2006; Nelson et al., 2015; Schoenberger et al., 2001; Ochs 2006), therefore, targeting the multiple factors found in Study 1 that exacerbate PS severity in post-concussive patients. Chronic and/or severe PS symptoms in post-mTBI patients with neuro-psychiatric comorbidities may be responsive to LIP-tES treatment because it may target the underlying cortical pathways involved in nociception, which are likely interconnected with the PS neural networks.

3.2. Purpose

The primary aim of this case study was to investigate the effect of 12 LIP-tES treatment sessions on PS symptoms of a 49-year-old Hispanic male Veteran with a history of mTBI. Secondary outcomes on pupillary diameter, general post-concussive and headache symptoms were also investigated. Our main hypothesis was that the LIP-tES intervention would significantly improve mTBI-related PS symptoms. For the secondary outcomes, we predicted a smaller Mean Pupillary Diameter, and a significant reduction in both general post-concussive and headache symptoms after LIP-tES treatment.

3.3. Methods

3.3.1. Study Design

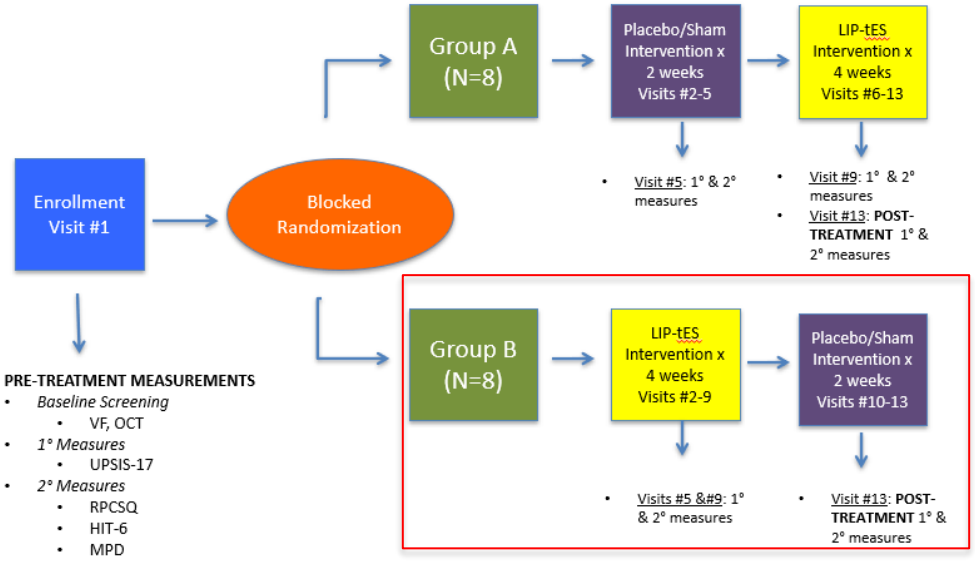


Figure 3 Original Study 2 Design. The participant of the current case report followed the study design of the Group B arm outlined in red.

The original project design was intended to be a prospective, double-cross over interventional study of 16 participants with a documented history of mTBI and PS complaints block randomized into 2 study groups, with each study group receiving a total of 4 sham/placebo treatments and 8 LIP-tES treatments over 6 weeks (Figure 3); however, due to the COVID-19 pandemic, all VA Boston Healthcare System research studies were paused for 6 months, and recruitment was limited when the COVID shutdown was lifted. One participant was successfully recruited, met all the study inclusion criteria (Table 7), did not meet the exclusion criteria (Table 8), and completed all 13 study visits, including the initial enrollment visit and subsequent visits as outlined (in red) under the Group B arm of the research protocol workflow illustrated in Figure 3, which is presented here as a case report. The participant received 8 LIP-tES treatments for the first 4 weeks (2 LIP-tES treatment sessions/week) followed by 4 sham/placebo treatments for the final 2 weeks and was blinded to the order of the active and sham/placebo treatment arms. Primary and secondary outcome data

was collected at the following four time points: 1) Pre-treatment at enrollment (Visit #1/2); 2) Mid-treatment point of the LIP-tES intervention arm (Visit #5); 3) Post-treatment at the end of the LIP-tES intervention arm (Visit #9); and 4) Final session of the Placebo/Sham intervention arm (Visit #13). Enrollment Visit #1 was combined with Visit #2, which was the first LIP-tES treatment session.

Inclusion Criteria
Ages 18-65
Documented history of mTBI without LOC or mTBI with LOC ≤30 minutes as determined by a medical provider
History of mTBI ≥6 months from the time of initial study visit
Documented PS symptoms in medical record
Documented optometric eye exam ≤ 12 mos of initial study visit to include baseline VF and RNFL and Macular OCT testing
BCVA ≤20/20 in each eye
Normal pupillary function; no APD in both eyes
Normal color vision in both eyes
No abnormalities on Macular OCT in both eyes
Normal RNFL OCT in both eyes
Normal Humphrey VF test in both eyes (VF 24-2 or 30-2)

APD= afferent pupillary defect; BCVA = best corrected visual acuity; LOC= loss of consciousness; mTBI = mild traumatic brain injury; OCT = optical coherence tomography; PS = photosensitivity; RNFL = retinal nerve fiber layer; VF = visual field

Table 7. Inclusion Criteria for Study 2.

Exclusion Criteria
History of strabismus or amblyopia
Visually significant ocular media opacity (e.g., cataract or corneal opacity) that could reduce amount of light entering pupil in one or both eyes
Previous or current history of retinal or optic nerve pathology in one or both eyes
History of stroke and/or visual neglect
History of neurodegenerative disease (e.g., Parkinson's, multiple sclerosis)
History of motor tics
Current use of medications or substances that may severely affect pupillary response and/or increase PS
Individuals with impaired decision-making capacity, including illiterate or no English language proficiency
Prisoners
Pregnancy
Inability to commit to all interventional/study visits
Injury or open sores at the sites of LIP-tES electrode placement that do not resolve within 1 week
Allergy to conducting paste and/or exfoliating gel used in preparing electrode sites for the LIP-tES procedure

Table 8. Exclusion Criteria for Study 2.

3.3.2. Outcome Measures

3.3.2.1. Primary Outcome Measure: Utah Photophobia Symptom Impact Scale (UPSIS-17)

The primary outcome measure was the change in total score on the Utah Photophobia Symptom Impact Scale (UPSIS-17), which is a 17-item questionnaire designed to quantitatively assess PS symptoms and their impact on activities of daily living (Cortez et al., 2019). UPSIS-17 uses a combination of Likert scale questions and yes/no response items, with a total possible score range of 0-80. Questions 1-15 are scored on a 0-5 point Likert scale. Items 6-15 refer to PS during the headache free (interictal) period, where 0 = ”no limitation,” 3 = ”moderate limitation,” and 5 = ”marked limitation.” Items 16 and 17 are yes/no response questions. For item 16A, 1 point is given for “Yes.” For item 16B, if the answer is “Yes” to item 16A, then 1 point is given for either A or B responses and 2 points if the subject reports “Both.” For item 17, 1 point is assigned for every “Yes” answer. The minimum score on the UPSIS-17 is zero (no photophobia and the maximum score is 70 (severe photophobia).

3.3.2.2. Secondary Outcome Measures

3.3.2.2.1. Rivermead Post-Concussion Symptoms Questionnaire (RPCSQ)

The Rivermead Post-Concussion Symptoms Questionnaire (RPCSQ) is a 16-item questionnaire that assesses post-concussive symptoms (King et al., 1995). Each item is scored on a 5-point scale, where 0 = “Not experienced at all”, 1 = “no more of a problem,” 2 = “a mild

problem," 3 = "a moderate problem," and 4 = "a severe problem." Scores for Items #1-16 were summed to calculate the RPCSQ Total Score. RPCSQ Total Scores can range from 0 to 80.

3.3.2.2.2. Headache Impact Test Questionnaire (HIT-6)

The Headache Impact Test Questionnaire (HIT-6) is a 6-item questionnaire that assesses the impact of headaches on activities of daily living (ADLs) (Kosinski et al., 2003). Responses to each item are based on the frequency of experiencing a particular feature of headache-related disability and are given relative weights as listed accordingly and summed to give a total score: "Never" = 6, "Rarely" = 8, "Sometimes" = 10, "Very Often" = 12, and "Always" = 14. HIT-6 scores can range between 36 to 78, with higher scores indicating greater impact on ADLs. (Yang et al., 2011; Bayliss et al., 2002)

3.3.2.2.3. Median Pupil Diameter (MPD)

Median pupil diameter (MPD) was measured using the Oculus Pentacam HR (Wetzlar, Germany). All Pentacam scans were performed on both eyes in dim illumination. Three Pentacam scans were taken per eye and the pupil diameter was noted from the Holladay report and averaged. The MPD was utilized to investigate static pupil responses as a potential objective measure of PS. The original Master's thesis proposal for this project included the aims of collecting dynamic pupillary responses and electrophysiological measurements, such as the pattern reversal VEP (Visual Evoked Potential), single flash VEP and single flash Cone ERG (electroretinogram) to various

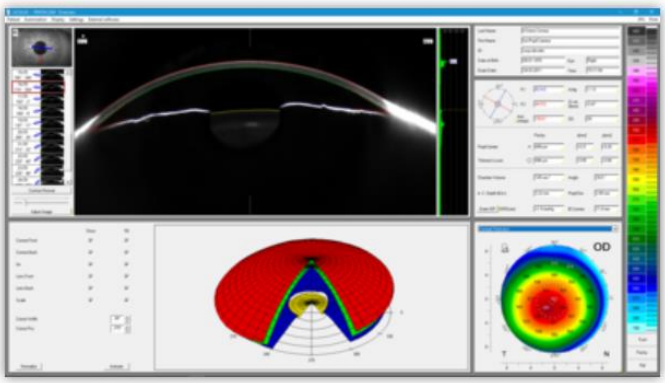


Figure 4: Oculus Pentacam HR summary screen of scan results.

light frequencies; however, the electrophysiology unit (RETI-port/scan 21) that also included a pupillometry program to measure the pupillary light reflex response, was not available for use during the duration of the research fellowship due to equipment issues. Although the literature has shown variability amongst the various Scheimpflug imaging devices for pupillary diameter measurements (Domínguez-Vicent et al., 2014; Yazici et al., 2010), one study found that although these differences were statistically significant, they may not be clinically significant with regards to refractive surgery considerations (Yazici et al., 2010). The Pentacam and other Schiempflug imaging devices typically measure corneal topography and other anterior segment parameters utilized in the assessment of anterior segment disorders, such as keratoconus, or are used to perform pre-operative measurements for refractive surgery. These imaging devices are more commonly available in primary care optometric practices than visual electrophysiology instruments, which are typically found in neuro-ophthalmic or retinal specialty ophthalmology practices. The hypothesis is that the MPD may potentially be used as an objective screening measure for mTBI-related PS.

3.3.3. Low Intensity Pulse-Based Transcranial Electrical Stimulation (LIP-tES) Treatment Procedure

Neurogen^{TM} High Performance Neurofeedback is the LIP-tES system used in this study which combines passive neurofeedback with EEG monitoring. Figure 5 depicts the general set-equipment set-up for the LIP-tES procedure. This passive neurostimulation intervention involves administration of low-intensity electrical pulses through electrodes progressively moved to different areas on the scalp, stimulating und7erlying cortical areas.

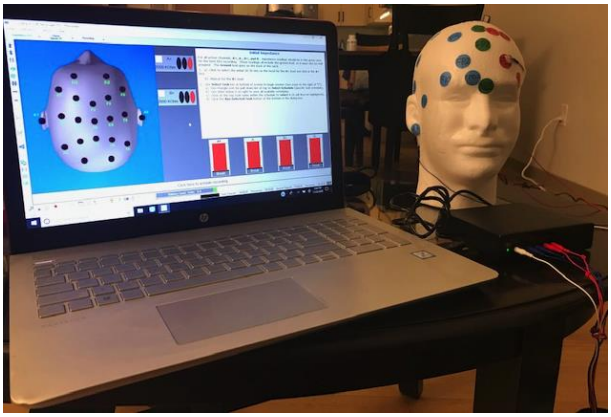


Figure 5: General setup for the LIP-tES system (Neurogen™). The leads are connected to the EEG interface/amplifier (small black box to the right). The Neurogen™ High Performance Neurofeedback (HPN) software both monitors the EEG and delivers the LIP-tES treatment.

The Neurogen™ device uses five EEG electrodes. The EEG interface device used in this study is the I-330 C2+ manufactured by Synaptic Tech, LLC, which is comparable to the EEG interface device used in the Huang et al. 2017 study and the software used was Neurogen™ 8.0. The LIP-tES neurofeedback was delivered through four EEG leads (A+, A-, B+, B-). For each treatment session, the positive leads (Fig. 6) were placed in a sequential order of 16 site pairs according to the International 10-20 sites and sequence configuration corresponding to underlying frontal, temporal, parietal and occipital regions which was comprised of the following three protocols (Table 9): 1) Full-24 protocol; 2) Migraine protocol; and 3) Uplifting protocol based on established Neurogen™ Brain Balancing, Inc. protocols proposed for PS.

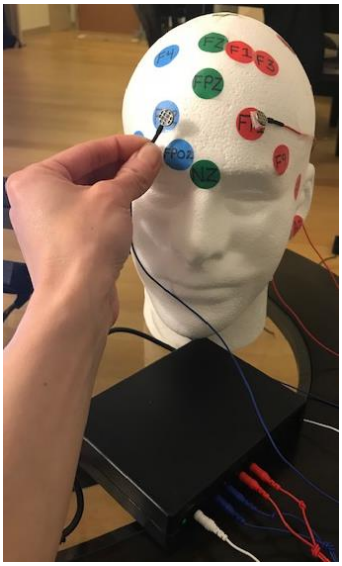


Figure 6: Simulation of positive lead placement. The positive leads are placed on various sites corresponding to different brain areas (designated by the stickers on the Styrofoam head).

Full-24 Protocol		Migraine Protocol
1. F3/F4	7. Fz/Pz	13. T3/T4
2. C3/C4	8. Cz/FPz	14. T4/P4
3. P3/P4	9. F7/F8	15. FPO2/P4
4. O1/O2	10. FP1/FP2	
5. T5/T6	11. F9/F10	**Uplifting Protocol**
6. T3/T4	12. Nz/Oz	16. F3/F7

Table 9: LIP-tES (Neurogen™) Treatment Intervention Protocol for PS

The positive electrodes both record EEG activity and deliver the electrical pulse trains based on the spectrogram reading from all five electrodes (Figure 6), measuring and delivering electrical pulses to reduce dominant brainwave oscillations at each location. The Neurogen™ software system simultaneously monitors EEG activity and calculates the spectrogram with a sliding window of 2 seconds. The amplitude distribution of frequencies in the range of 2.5 – 12.5 Hz is calculated, and an adaptive algorithm is used to determine the feedback signal based on the distribution of amplitudes across the five electrodes (Snook 2013). The negative leads, which were attached to the participant's right and left mastoid processes, and the ground electrode, which was positioned on the neck approximately 1.5 inches above the C7 vertebra, remained stationary throughout the procedure. The negative leads and the ground serve as receivers that continuously record the EEG activity.

The neurofeedback task schedule determines the wave forms, stimulation offsets and the stimulation duration at any given electrode site. There are 6 pre-programmed task schedules in the Neurogen™ software (Levels 1-6). The task schedule for the LIP-tES case report intervention was modeled after the graduated IASIS protocol of the Huang et al. study (2017) and was recommended per email correspondence with the software inventor IASIS and Neurogen™ HPN (C.Snook, personal communication, February 4, 2021), to minimize possible negative side effects and facilitate adaptation to the neurostimulation over time. Level 2 "Auto Basic" was chosen for study visits #2-3 and Level 4 "Up-Ramp" was chosen for study visits #4-9 (Table 10).

Table 10. Neurogen™ Task Schedules for LIP-tES Treatment Study

Study Visits	Task Schedule Name	Task Schedule Points	Time (seconds)	Offset (Hz)
Visits #2-3	Level 2 Auto-Basic	Start	2	14
		FB1	5	7
		FB2	5	3.3
		FB3	5	6.6
		FB4	5	10
		FB5	5	7
Visits # 4-9	Level 4 Up-Ramp	Start	3	14
		FB1	4	7
		FB2	3	7.8
		FB3	2	14
		FB4	2	3.9
		FB5	1	5
		FB6	1	6
		FB7	1	7
		FB8	1	8
		FB9	1	9
		FB10	1	10
		FB11	1	11
		FB12	1	12
		FB13	1	13
		FB14	1	14
		FB15	1	7

The subject was positioned facing away from the laptop monitor display during each procedure. For the LIP-tES intervention sessions, the electrode cables were plugged into the EEG interface box, allowing for delivery of electrical stimulation and simultaneous monitoring of the EEG, Frequency Band and Myoelectrical Activity displays (Figure 7). For the Placebo/Sham Intervention sessions, the electrode cables were not plugged into the EEG interface box, preventing administration of electrical stimulation. From the participant's perspective, the Placebo/Sham Intervention sessions mirrored the stimulation sessions in all

observable procedural aspects. The electrodes were still placed in sequential order in the sites listed in Table 9 as they were for the LIP-tES intervention sessions.

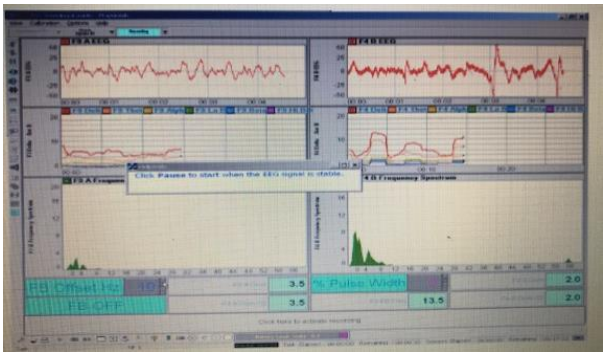


Figure 7: Neurogen™ HPN recording screen. Top graphs are the EEGs. The middle graphs (Frequency Bands Display) show the various brainwave frequencies and the bottom graphs (Frequency Spectrum) show the myoelectrical activity going from the brain to the spinal cord.

3.4. Case History

A 48-year-old Hispanic male was referred by his physical medicine rehabilitation provider for a neuro-optometric examination in January 2022 for "poor vision and photosensitivity when he has headaches." At the initial presentation, his chief complaint was light sensitivity both indoors and outdoors for several years. His PS was so severe that he had to keep the blinds closed at home and was especially bothered by fluorescent lighting. He reported having a pair of non-prescription sunglasses with a dark gray tint but was unsure if they were fully adequate for outdoor use and sometimes wore them indoors.

Medical history was significant for headaches, not classified as migraine, occurring a few times a week, located frontal and on both temples for several years. Light exacerbated his headaches. Other systemic conditions that he was treated for were hypertension, depression, lower back pain and chronic PTSD. The only medication he was taking was Amlodipine for hypertension. He did not report tobacco, recreational or illicit drug use, but did drink between 6 to 12 beers per day on the weekends. The Veteran sustained multiple mTBIs between 2006 to

2019; at least four occurred during military service, both blast-related and non-blast related injuries. He had at least two concussive events before his military career as a teenager, "getting his bell run 8 times" while playing football and being struck on the head with an aluminum bat. The most recent concussive event occurred post-military in 2018 or 2019 when he hit his head on the counter in the garage.

Ocular history was significant for physiologic optic nerve head cupping with normal intraocular pressures and open angles without recession on gonioscopy. Retinal nerve fiber layer (RNFL) optical coherence tomography (OCT) imaging and Humphrey 24-2 visual fields were normal in both eyes performed in 2019.

Best corrected visual acuities were 20/20 for the right and left eyes at both distance and near. Extraocular motilities, confrontation visual fields, color vision and pupillary responses were normal in both eyes. Binocular vision testing was relatively normal. He exhibited a receded near point of convergence (10 cm break/12 cm recovery) but was asymptomatic for diplopia while reading and near eye posture was within normal limits (1 Δ esophoria) on near cover testing. His convergence ranges at near were also normal (14 Δ blur/20 Δ break/18 Δ recovery). Macular OCT imaging was normal in both eyes. RNFL OCT imaging showed normal RNFL thickness for all sectors in the right eye and borderline RNFL thickness in the temporal (53 μm) and inferior temporal sectors (107 μm) in the left eye. A tint evaluation was performed, and the Veteran was prescribed a 30% absorption FL-41 tint for indoor use and an 80% absorption brown tint with a wrap-around frame for outdoors. Anti-reflective coatings were added to both pairs of tints for additional glare control. Due to his severe PS, we discussed the opportunity to participate in the LIP-tES study and he expressed interest in participating. To determine his eligibility for the study, a follow-up visit was scheduled to perform visual field

testing, to repeat the RNFL OCT imaging due to the borderline findings in the left eye and complete a dilated fundus examination to rule out peripheral posterior segment pathology.

On the second visit, the Veteran reported being satisfied with both 30% FL-41 and 80% brown tints. Dilated fundus examination revealed large optic discs with distinct margins for both eyes. Optic nerve cupping was 0.6 H/0.6V and 0.65H/0.65V for the right and left eyes respectively with laminar dots. Macula and vessels were normal in both eyes. There were no detachments, tears or holes seen in the peripheral fundus in both eyes. Repeated RNFL OCT imaging remained normal for all sectors in the right eye. The inferior temporal sector of the left eye was still borderline, maintaining stable thickness (107 μm), indicating no progressive RNFL loss in the left eye. Humphrey 24-2 visual field testing showed non-specific scattered defects on pattern deviation, which were non-neurological, in both eyes. Based on the results of this follow-up visit, the Veteran met the inclusion criteria and failed to meet the exclusion criteria, qualifying his eligibility to participate in the LIP-tES study.

The participant provided informed written consent prior to any data collection. This research was reviewed by the VA Boston Healthcare System Institutional Review Board and conformed to the principles and applicable guidelines for the protection of human subjects in biomedical research.

3.5. Results

3.5.1. Primary Outcome Measure: Utah Photophobia Symptom Impact Scale (UPSIS-17)

The Veteran initially reported moderate/severe PS symptoms (UPSIS-17=49) that reduced by 59% (UPSIS-17=20) after 12 LIP-tES sessions (Figure 8). The greatest relative

reduction occurred at Visit #5 (-36% change from the initial) and tapered off between the end of the treatment arm and the end of the sham/placebo arm (-9% between visits #9 and #13).

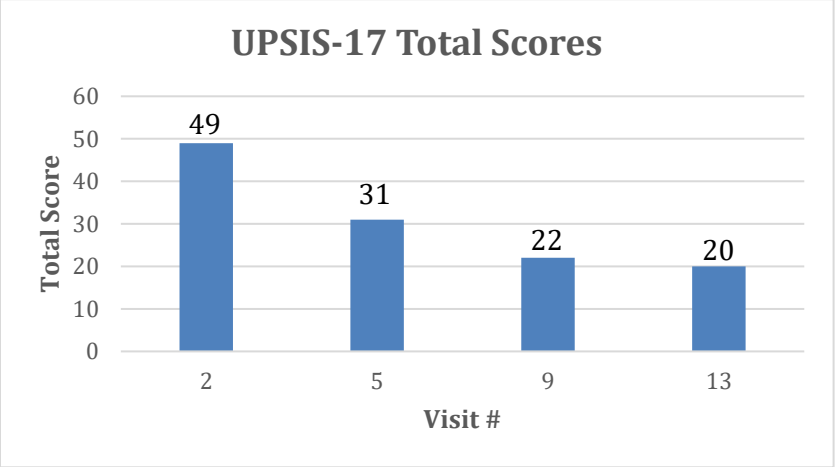


Figure 8. Change in UPSIS-17 Total Scores from Pre-Treatment (Visit #2), Mid-Treatment (Visit #5), End of Treatment arm (Visit #9) and End of Sham/Placebo Arm (Visit #13).

3.5.2. Secondary Outcome Measures

3.5.2.1. Rivermead Post-Concussion Symptoms Questionnaire (RPCSQ)

The severity of post-concussive symptoms reduced by 73% from the 85th percentile of males between 41-64 years old with at least one chronic health condition (Zeldovich et al. 2022) (RPCSQ=37) to below the 50th percentile (RPCSQ=10) at the end of 12 LIP-tES sessions (Figure 9). The sharpest reduction in symptoms occurred at Visit #5 and was stable from middle of the treatment arm to the end of the Sham/Placebo arm (Visits #5-13). RPCSQ Item #14 refers to the symptom of "light sensitivity, easily upset by bright light." The Veteran had a 67% reduction in PS symptoms from a "moderate problem" (RPCSQ Item #4=3) to "no more of a problem" (RPCSQ Item #4=1) at the end of the study. He had the greatest symptom reduction

for RPCSQ Item #7, “Being irritable, easily angered,” from 4 (“severe problem”) to 1 (“no more of a problem”) at the end of 12 LIP-tES sessions.

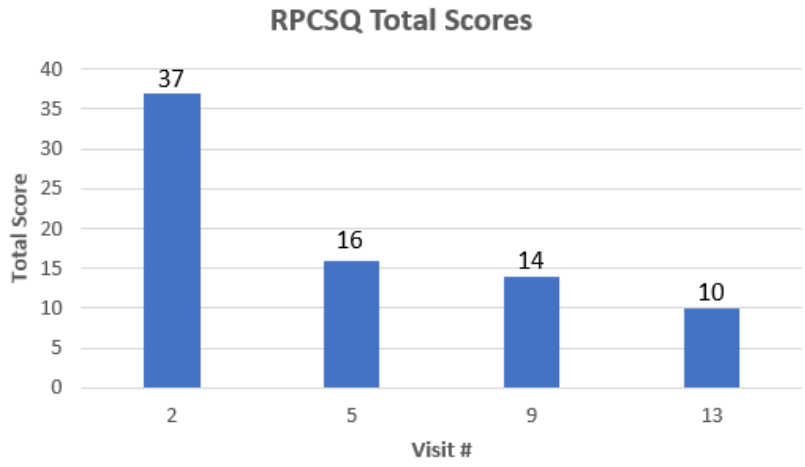


Figure 9: Change in RPCSQ Total Scores from Pre-Treatment (Visit #2), Mid-Treatment (Visit #5), End of Treatment arm (Visit #9) and End of Sham/Placebo Arm (Visit #13).

3.5.2.2. Headache Impact Test (HIT-6)

The Veteran experienced a 37% reduction in headache symptoms from severe headaches (HIT-6=63) before LIP-tES treatment to minimal or no impact (HIT-6=40) at the end of 12 LIP-tES sessions (Figure 10). HIT-6 scores of >60 are classified as “severe”; “substantial” for scores between 56-59; having “some impact” for scores between 50-55 and scores of <49 are considered to have little or no impact on ADLs (Yang et al., 2011; Bayliss et al., 2002).

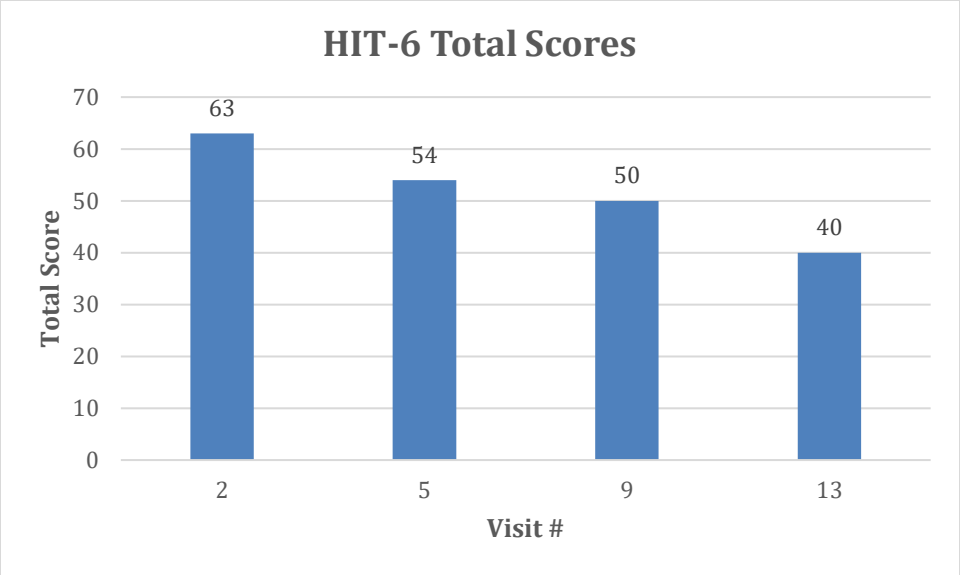


Figure 10: Change in HIT-6 Total Scores from Pre-Treatment (Visit #2), Mid-Treatment (Visit #5), End of Treatment arm (Visit #9) and End of Sham/Placebo Arm (Visit #13).

3.5.2.3. Median Pupil Diameter (MPD)

There was no systematic change in Median Pupil Diameter for either eye before the LIP-tES and after 12 LIP-tES sessions. Data was incomplete for Visits #2 and #13. Post-Treatment MPD was not obtained for Visit #2 and Pre-Treatment MPD was not obtained for Visit #13 due to technical issues with the Pentacam HR. The left pupil was smaller compared to the right pupil both pre-treatment and post-treatment throughout the study, but these differences were not clinically significant.

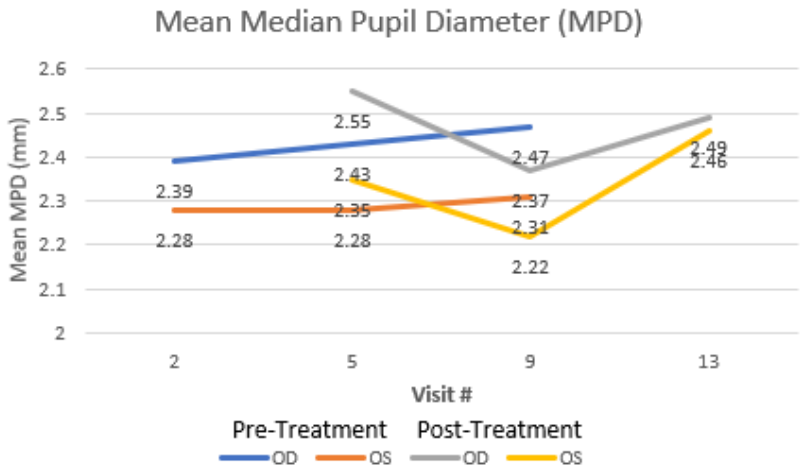


Figure 11: Mean Median Pupil Diameter (MPD). Pre-treatment MPD for OD and OS is in blue and brown respectively. Post-treatment MPD measurements for OD and OS are in green and purple respectively.

3.6. Discussion

This case report is the first study to investigate the use of LIP-tES as a potential treatment for post-mTBI PS. Previous studies have shown positive effects of LIP-tES to treat general post-concussive symptoms and PTSD but have not specifically looked at treating mTBI-related PS (Schoenberger et al., 2001; Ochs, 2006; Larsen et al., 2006; Nelson et al., 2015; Huang et al., 2017). The 59% reduction in PS symptoms on the UPSIS-17 and the 67% reduction of light sensitivity on the RPCSQ (Item #17) compares favorably to one pilot study conducted through the VA San Diego Healthcare System that found that 3 out of the 5 subjects who reported PS had at least a 50% reduction in their PS symptoms on the RPCSQ (Item #17) (Huang et al., 2017).

The 73% improvement of the Veteran's overall post-concussive symptoms on the RPCSQ after 12 sessions of LIP-tES (8 active and 4 placebo/sham sessions) is higher than the 53% reduction in RPCSQ total score in the Huang et al. (2017) study, which may not be solely due to

placebo effect, but rather due to a couple of differences in study methods. The Neurogen™ protocol used in this case report utilized more site pairs (16 total compared to the 10 site pairs activated in the UCSD pilot study) (Huang et al., 2017), thereby delivering stimulation across more cortical areas and included site pairs (i.e., Migraine protocol in Table 9) that experienced Neurogen™ Brain Balancing, Inc. practitioners found effective for PS. Another study difference is that the task schedule used in this case report went from Level 2 immediately to Level 4 after the second study visit and remained at Level 4, which is more aggressive than Level 2, for the last 6 LIP-tES treatment intervention sessions. In contrast, the Huang et al. pilot study was more graduated, starting from the IASIS task schedule "Genesis," which corresponds to the Neurogen™ Level 2 protocol, for the first two visits, to the "Balanced Energy" protocol, which corresponds to the Neurogen™ Level 3 task schedule for visits 3 and 4, then the IASIS "Activation protocol", which corresponds to the Level 4 Neurogen™ task schedule, for the remainder of their study (visits #5-12) . Although the Neurogen™ treatment protocol used in this case report had less total active treatment sessions (8 stimulation sessions) than the Huang et al. study, more site pairs were utilized, and a more aggressive task schedule was used earlier in the intervention. The observation that there was still a 30% relative reduction in the total RPSCQ score from the end of the active treatment session arm (visit #5) to the final placebo/sham session (visit #13) suggests either a placebo effect or continuing neural plasticity after cessation of the active treatment sessions and supports sustainability of the LIP-tES treatment effects for at least 2 weeks after the end of the active intervention. Lasting results have been anecdotally observed by experienced NeurogenTM practitioners after 10 sessions and may take up to 20-24 sessions for severe or repetitive head trauma (G. Gillespie, personal communication, January 11, 2021; C. Snook, personal communication, February 4, 2021).

Further research is needed to determine the most effective LIP-tES treatment protocols using functional neuro-imaging analysis both pre- and post-LIP-tES treatment and to ascertain the ideal number of LIP-tES treatment sessions to achieve maximum results in the shortest amount of time for mTBI-related PS.

Changes in post-concussive and headache symptoms were included as secondary outcomes to examine if the LIP-tES treatment for post-mTBI PS would exacerbate other comorbid symptoms. Both RPCSQ and HIT-6 Total Scores reduced (73% and 37% reduction respectively) from baseline pre-treatment levels after 8 active treatment sessions and remained below baseline after the 4 placebo/sham sessions. The Veteran reported one instance of increased sleep latency after a treatment session (visit #4) and fatigue after a couple of treatment sessions that resolved after taking a nap or resolved the next day after a night of sleep (visits #3 and 5). He did not report any other negative side effects for the remaining visits #6-12, suggesting that there is a temporary neural adaptation process to the LIP-tES sessions, which is not uncommon as observed by experienced Neurogen™ practitioners and the inventor of Neurogen™ (Mind-Brain Training Institute, 2018a; G. Gillespie, personal communication, January 11, 2021). Potential negative side effects of the Neurogen™ LIP-tES treatment are exceedingly rare (3% of clients), include hyperactivity/hypervigilance, fatigue, disorientation, dizziness/nausea, headache, and vivid dreams. When reported, these side effects are usually temporary and transient, lasting less than 24 hours with a typical duration of less than one hour with the longest reported effect lasting a couple of hours (Mind-Brain Training Institute, 2018a; G. Gillespie, personal communication, January 11, 2021). This case report provides initial data supporting that the LIP-tES Neurogen™ treatment is a relatively safe procedure with minimal temporary adverse effects.

Although the hypotheses that LIP-tES would demonstrate significant reductions in subjective measures of mTBI-related PS, post-concussive and headache symptoms were supported by the results of this case report, there were no systematic changes in Mean Pupillary Diameter as initially predicted and showed weak evidence supporting the use of MPD measurements via the Oculus Pentacam HR (Wetzlar, Germany) or other commercial Scheimpflug imaging devices as an objective screening measure for post-mTBI PS. This was not an unexpected result given that the environmental lighting conditions were not controlled (the instrument was in an open equipment room used by other providers) and the participant was not dark adapted for a standard period prior to each series of measurements. More research is needed to investigate the effect of LIP-tES on static pupillary measures. One study investigated dynamic pupillary responses to light of various light frequencies in mTBI and visual normal subjects both with and without PS and found that the maximum and minimum diameters in the pupillary light response profile to white and red light stimulus conditions for mTBI subjects with PS were larger than mTBI subjects without PS (Truong et al., 2016). There was no difference between the mTBI PS and non-PS groups in the blue stimulus conditions for maximum and minimum pupillary diameters in this study (Truong et al., 2016). The Oculus Pentacam HR (Wetzlar, Germany) used in this case report utilized a blue light to illuminate the eye for the measurement and it is uncertain where the MPD fits in the overall pupillary light response profile, as it is the mid-point of the series of Schiempflug images captured for any given Pentacam measurement. It cannot be assumed that the MPD is the average between the maximum and minimum diameters of the dynamic pupillary light response to the instrument stimulus.

Outside the structured questionnaires, the Veteran had subjective improvements in his quality of life. After several LIP-tES sessions, he noted that he was outdoors doing yardwork one day and did not realize that he had forgotten his sunglasses. Besides the significant reduction in PS symptoms, which was his chief complaint upon initial presentation and the reason for referral to the polytrauma eye clinic, the Veteran also observed a positive turn from a reported history of anger management issues stating that, "Little things no longer bother me." This observation had a major impact on how he interacted with his family and correlated with the RPCSQ item that exhibited the greatest reduction of all his post-concussive RPCSQ symptoms, (Item #7), "Being irritable, easily angered," (75% reduction, from 4 ["severe problem"] to 1 ["no more of a problem]).

The Veteran had multiple factors that may have exacerbated his PS symptoms, including repetitive concussive events in his lifetime and comorbidities commonly found in Post-9/11 Veterans with a history of mTBI, including pain issues (i.e., headaches and lower back pain) and chronic PTSD. Study 1 showed that the number of mTBIs, pain issues and the severity of PTSD are factors that increase PS symptoms. One possible mechanism for the effect of LIP-tES on PS and other post-concussive symptoms is that LIP-tES alters endogenous brain wave activity in cortical areas and functional networks related to pain perception that were described in Study 1. LIP-tES was previously shown to reduce abnormal Delta brain waves in areas related to pain and PS, corresponding to PS symptom reduction on the RPCSQ (Huang et al., 2017). Delta waves are typically present during the deep stages of sleep, but if present during wakefulness, are a sign of neuronal abnormalities in areas of brain injury (Kandel et al., 2013). Enhancing slow-wave sleep acutely after TBI in one rat model showed a significant reduction in diffuse axonal injury (DAI) in the cortex and hippocampus and preservation of cognitive abilities two weeks after

trauma (Morawska et al., 2016). Studies in rodents (Xie et al., 2013) and Alzheimer's disease subjects (Mander et al., 2015) support the role of slow-wave sleep in the clearance of neuro-toxic waste products via glymphatic pathways from the brain, such as β-amyloid, which appears to be central to the pathogenesis of Alzheimer's disease (Chen et al., 2017), and amyloid precursor protein, which is an immunological marker for DAI (Gentleman et al., 1993) . One possible mechanism of LIP-tES on post-concussive symptom reduction proposed by the authors of the UC San Diego 2017 pilot study is that LIP-tES potentiates slow-wave generation immediately after treatment, that then resolves upon completion of the healing process, corresponding to slow-wave reduction on magnetoencephalography and improvement in post-concussive symptoms (Huang et al., 2017). The electrical engineering signal theory concept of stochastic resonance (SR) has been proposed to explain the general neuromodulatory effects of transcranial electrical stimulation (tES) (Fertonani et al., 2017) and may also explain how LIP-tES alters cortical pathways. SR involves delivering an external signal (i.e., low-intensity electrical pulse trains) to modify endogenous brain waves. The goal of the LIP-tES neurofeedback is to rebalance frequency spectrums across cortical regions by reducing asymmetry in the distribution of the various brain wave frequencies at each treatment site, which may reflect neuronal signal dysfunction in underlying cortical networks (Snook 2013; C. Snook, personal communication, February 9, 2022). Based on the electrical brain wave pattern detected by the Neurogen™ software, the LIP-tES neurofeedback hardware system delivers a series of low-intensity electrical pulses at a frequency that is slightly offset from the dominant frequency detected a given electrode until the frequency spectra corresponding to that underlying cortical area becomes symmetrical (Snook 2013). More recent work has discovered cortical areas implicated in PS that LIP-tES could potentially target and may explain the effects of LIP-tES on PS symptom

reduction in Study 2. Initial pilot data from the Translational Research Center for TBI and Stress Disorders (TRACTS) cohort of Post-9/11 Veterans identified a functional connectome including regions in the visual, somatosensory, cerebellar, default mode network and salience cortical areas that predict PS with 72.06% Mean Accuracy (monte-carlo $p<0.002$) (Fortenbaugh, 2022). Study 1 and 2 findings in this thesis, combined with this recent work by Fortenbaugh et al. were used as supporting evidence for the Small Projects in Rehabilitation Research (SPiRE) grant, which I assisted in writing during my research fellowship, to fund a two year pilot study to further investigate the use of LIP-tES to treat mTBI-related PS, which was awarded to the Cognitive and Sensory Systems Laboratory (CASSL) after the completion of my fellowship.

3.7. Study Limitations and Future Directions

The biggest study weakness was that this was a single subject case report, limiting generalizability of results. Further research investigating the feasibility and effectiveness of LIP-tES to treat post-mTBI PS in a larger study population is forthcoming with the SPiRE pilot project, which will attempt to enroll 28 veterans with a history of mTBI randomized into two study groups A and B (at least n=10 per group), with one group receiving 12 active LIP-tES treatment sessions and the other group receiving 12 sham LIP-tES treatment sessions for 6 weeks. The active treatment arm of the SPiRE pilot study mirrors the number of active sessions in the Huang et al. pilot study, in contrast to this case report, which had 8 active treatment sessions. The SPiRE pilot study design better assesses placebo effects, which was another limitation of this case report.

Although the majority of the outcome measures were subjective (i.e., UPSIS-17, RPCSQ, and HIT-6 questionnaires), the MPD was attempted as a potential objective measurement of

post-mTBI PS, which did not show any systematic change after LIP-tES treatment in this case report. The original study 2 proposal included the following potential objective measures for post-mTBI PS that are not well-studied and should be further investigated: 1) frequency specific visual electrophysiologic responses (e.g., single flash VEP and single flash ERG to various wavelengths of light) and 2) dynamic pupillary responses to blue light. Single flash VEP and ERG changes in migraineurs supports the retino-thalamo-cortical theory that PS secondary to migraine originates in the retina via cone-driven pathways that are relayed to light sensitive and nociceptive neurons in the thalamus, which is then communicated to sensory areas in the cortex (Noseda et al., 2016). There is one case study of a post-concussion subject with PS that demonstrated changes in single flash VEP responses that correlated with changes in PS symptoms from specific spectacle tints (Clark et al., 2019). Future studies are warranted to determine if cone-driven pathways are involved in the pathophysiology of post-mTBI PS and how frequency specific PS symptoms vary with each individual. The 6-second post-stimulus pupillary diameter (6SPSD) to blue light, which is the light frequency that mainly targets ipRGCs, was proposed as a potential objective biomarker for post-concussive PS (Truong et al., 2016). Finding more objective measures for mTBI-related PS will further expand our understanding of the pathophysiology of post-mTBI PS, allowing for concrete means of tracking PS changes over time and leading to more effective and targeted treatment options.

3.8. Conclusion

LIP-tES shows potential as a novel, non-invasive neurofeedback intervention for the treatment of PS following mTBI. This case report of a Post-9/11 Veteran after 12 sessions of LIP-tES demonstrated significant reductions in PS, headaches other post-concussive symptoms

and provides initial pilot data supporting the need for further studies to examine the effectiveness and feasibility of LIP-tES and other non-invasive options for the treatment of post-mTBI PS.

4. General Conclusions

PS is a common symptom following a mild TBI (Capó-Aponte et al., 2012), which negatively impacts rehabilitation outcomes (Lew et al., 2009) and quality of life (Shepherd et al., 2020). Besides the commonly prescribed spectacle tints, there are currently few utilized non-invasive treatments for mTBI-related PS. The pathophysiology of mTBI-PS is poorly understood. Study 1 elucidates neuro-psychiatric factors that negatively affect mTBI-related PS, which may guide potential targeted treatment strategies for PS and possibly explain why some severe and/or chronic cases of post-mTBI PS are intractable to current treatments. Study 1 investigated how PTSD and other common comorbidities in Post-9/11 Veterans who have sustained an mTBI contribute to the severity of PS symptoms. Not only do the diagnoses of mTBI and PTSD predict higher PS ratings, with comorbid mTBI and PTSD predicting even higher PS ratings, the number of mTBIs and the severity of PTSD is positively correlated with more severe PS symptoms. Anxiety and sleep issues were other factors that exacerbate post-mTBI PS. The finding that the hypervigilance subdomain of PTSD drives post-mTBI PS symptoms in the Study 1 cohort suggests shared neurophysiologic pathways involving dysfunction of cortical networks involved in pain perception and the potential role of autonomic nervous system dysregulation imbalanced toward hyperarousal states. Study 2 investigated LIP-tES as a potential novel non-invasive treatment for post-mTBI PS. The Veteran participant in Study 2 had several of the factors outlined in Study 1 that exacerbate mTBI-related PS, including

multiple mTBIs, pain issues, and chronic PTSD. Study 2 provided initial pilot data showing the effectiveness of LIP-tES on subjective measures of PS, general post-concussive and headache symptomology. While the MPD did not show systematic changes after LIP-tES treatment in Study 2, more research is needed to investigate other objective measures for post-concussive PS. Further studies are also warranted to explore the effectiveness and long-term sustainability of effect for LIP-tES and other non-invasive treatment options for post-mTBI PS in larger study populations. Both studies in this Master's thesis project demonstrate the clinical complexity of PS after mTBI and the importance of interdisciplinary collaboration between eyecare providers and other healthcare professionals in the treatment and management of mTBI-related PS.

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