ABSTRACT

Title of Dissertation:	THE IMPACT OF MILD TRAUMATIC BRAIN INJURY ON TIME-FREQUENCY ERP MEASURES AND NEUROPSYCHOLOGICAL FUNCTIONING: A LONGITUDINAL STUDY OF ACUTELY INJURED SERVICE MEMBERS
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Traumatic Brain Injury (TBI) is the most common injury in recent military conflicts, with nearly 500,000 service members sustaining a TBI since 2000. Mild TBI (mTBI), or concussion, is by far the most common type of TBI and has been associated with long-term cognitive complaints and functional impairment. While clinical assessment of mTBI (i.e., MRI and performance-based cognitive testing) occasionally captures subtle abnormalities in the acute period following mTBI, these measurements lack the sensitivity to assess the time course of cognitive recovery from mTBI. The current study assessed cognitive changes from the acute to chronic period following mTBI using advanced time-frequency event-related potential (ERP) analysis, which isolates rapid regional brain activity and measures the functional communication within and between brain networks in response to varying task stimuli. The validity of these ERP biomarkers was evaluated with correlations between abnormal ERP findings and widely used clinical measures of cognitive

functioning (i.e., neuropsychological tests and self-reported cognitive symptoms). Differences between mTBI caused by blast explosion versus impact to the head were also evaluated. A sample of 173 service members, comprising an mTBI group, an orthopedically-injured control group, and a healthy control group, completed ERP, neuropsychological, and self-report assessments within weeks following injury and again six months later. Results suggested that mTBI leads to cognitive changes that persist in the acute to post-acute period following injury (i.e., up to 12 weeks). These cognitive changes were reflected by alterations in ERP time-frequency amplitude and functional connectivity measures, and they remained apparent even when controlling for psychiatric symptoms. ERP differences were also evident between blast-related and impact-related mTBI. Conversely, neuropsychological test performance was not sensitive to mTBI. Abnormal ERP time-frequency measures were related to self-reported cognitive symptoms, suggesting these ERP measures are valid biomarkers of cognitive difficulties following mTBI. Critically, cognitive functioning as assessed by ERP measures returned to a level indistinguishable from controls 7-9 months following mTBI, even though more than a third of mTBI patients continued to report cognitive symptoms. These persistent cognitive complaints were more related to post-injury psychiatric symptoms than to the direct effects of brain injury.

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by

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Chapter 1: Introduction

In 2014, about 2.87 million traumatic brain injury (TBI) related emergency department (ED) visits, hospitalizations, and deaths occurred in the United States (Peterson et al., 2019). TBI is the most common injury in the recent Iraq and Afghanistan military conflicts, with 413,858 active duty service members sustaining TBI since 2000 (Defense and Veterans Brain Injury Center, http://www.dvbic.org/TBI-Numbers.aspx). The most common type of TBI, among civilians and the military, is mild TBI or concussion (Cassidy et al., 2004; LaChapelle et al., 2008). A mild TBI (mTBI) occurs when there is a blow or jolt to the head that results in loss of consciousness of less than thirty minutes, alteration of consciousness of less than 24 hours, and/or posttraumatic amnesia of less than 24 hours. Clinical neuroimaging methods like CT are typically negative for mTBI patients (Hughes & Shin, 2011), leading researchers and clinicians to conclude that mTBI does not result in frank neuronal pathology. However, much research has documented long-term post-concussion symptoms and functional impairment in about a third to half of individuals who experience mTBI (Dikmen et al., 2016; Iverson, 2005; Levin & Diaz-Arrastia, 2015; McMahon et al., 2014; Meares et al., 2011; van der Naalt et al., 2017). Post-concussion symptoms following mild TBI fall into three categories: cognitive (e.g., forgetfulness, difficulty concentrating, slowed thinking), physical (e.g., headaches, vertigo, sleep disturbance) and emotional/behavioral (e.g., depression, anxiety, PTSD, irritability) (Iverson & Lange, 2011). Sustaining a mild TBI in the recent military conflicts is associated with increased risk of developing PTSD (Hoge et al., 2008; Yurgil et al., 2014), and co-occurring mTBI and PTSD is associated with more chronic cognitive difficulties (Brenner et al., 2010).

With the recent advancement of neuroimaging modalities that assess brain function through measurement of physiological activity, researchers are beginning to discover the neural underpinnings of post-concussion symptoms. Neuropsychological tests, or performance-based cognitive tasks that are known to be related to specific brain structures or circuits, may capture cognitive difficulties initially following mTBI, but these measures typically return to pre-morbid levels of functioning before neuroimaging measures of brain functioning (Belanger et al., 2007; Bigler, 2013; Mayer et al., 2011; Segalowitz et al., 2001; Slobounov et al., 2011). In fact, neuropsychological assessment in the chronic stage following mTBI has been criticized as insensitive and non-specific (Iverson, 2005; McCrea et al., 2008). Thus, the use of neuroimaging methods, such as electroencephalography (EEG) and functional magnetic resonance imaging (fMRI), is critical to understanding the cognitive consequences of mTBI and the time course of recovery.

In addition, the majority of mild TBIs in the recent military conflicts resulted from blasts caused by improvised explosive devises (Benzinger et al., 2009; Hoge et al., 2008; Ling et al., 2009; Stansbury et al., 2008). In fact, blast-related mTBI has been described as the "signature wound of the war on terror" (Rosenfeld & Ford, 2010). Individuals who sustained blast-related TBI report more cognitive and affective disturbances compared to civilians who experience TBI (Belanger et al., 2005). However, more research is needed to determine if blast-induced TBI has a differential effect on the brain relative to impact-induced TBI.

The current study aims to assess cognitive changes over a six month period (from the acute to chronic phase) following blast- and impact-related mTBI using advanced time-frequency event-related potential (ERP) analysis, which isolates rapid regional brain activity and measures the functional communication within and between brain networks in response to varying task stimuli.

In addition, this study will compare ERP measures to widely used objective and subjective measures of cognitive functioning, (i.e., neuropsychological tests and self-reported cognitive symptoms, respectively). These comparisons are critical for establishing the convergent and predictive validity of ERP indicators of impairment following mTBI.

Event-Related Potential Analysis of Traumatic Brain Injury

Compared to standard clinical EEG and evoked potentials, event-related potentials (ERPs) have demonstrated sensitivity to mTBI (see Gaetz & Bernstein, 2001 for a review). ERPs are the electrophysiological response to a specific stimulus presentation in a cognitive task, and thus may be better suited than other EEG methods for detecting subtle cognitive impairment following mTBI. The most widely studied ERP component is the P3, which was first reported over 50 years ago (Sutton et al., 1965). The P3, as well as the N2 component, are commonly elicited in an oddball paradigm, a discrimination task involving two or three categories of randomly presented stimuli (Donchin et al., 1978; Pritchard, 1981). Participants are instructed to classify the stimuli by either pressing a button or counting one type of stimulus (i.e., the "target" stimulus) and doing nothing for the other types of stimuli. When target and non-target stimuli occur infrequency (i.e., the "oddballs"), they elicit N2 and P3 components. The lower the probability of a given stimulus type, the larger the amplitude of the N2 and P3 (Duncan-Johnson & Donchin, 1977). These components are thought to reflect the cognitive processing involved in stimulus discrimination and categorization (Clark et al., 1992; Courchesne et al., 1977; Duncan et al., 2003, 2009; Duncan-Johnson & Donchin, 1977, 1982; Ritter et al., 1982). The N2 is a negative-going deflection occurring around 200 milliseconds after stimulus onset, while the P3 is a positive-going deflection that generally peaks 300 milliseconds or later after stimulus onset.

The majority of research investigating alterations in these ERP components following TBI has reported reductions in P3 amplitude (Campbell et al., 1990; Dautricourt et al., 2017; Gosselin et al., 2006; Lachapelle et al., 2008; Lew et al., 2004, 2007; Naito et al., 2005; Rugg et al., 1988; Solbakk et al., 2000, 2002) and longer P3 latency (Duncan et al., 2003, 2005; Gosselin et al., 2006; Lachapelle et al., 2008; Lew et al., 2004, p. 20, 2007; Naito et al., 2005; Nandrajog et al., 2017; Solbakk et al., 2002; Spikman et al., 2004). Some research has also shown diminished N2 amplitude (Clark et al., 1992; Duncan et al., 2005; Lachapelle et al., 2008; Solbakk et al., 1999), as well as delayed N2 latency (Duncan et al., 2003, 2005; Lachapelle et al., 2008; Rugg et al., 1988; Spikman et al., 2004) in individuals with TBI compared to controls. Early sensory components, like N1 and P2, have been found to be less sensitive to TBI than cognitive components like N2 and P3 (Duncan et al., 2005). However, while these N2 and P3 findings have been seen across many studies, there are several studies that have not found these effects (Bernstein, 2002; Duncan et al., 2003, 2005; Lew et al., 2007; Potter, Jory, Bassett, Barrett, & Mychalkiw, 2002; Rugg et al., 1988; Cavanagh 2019). Several factors may have influenced the variability in these findings, including variations in TBI severity, varying levels of task difficulty, differing task domains (e.g., auditory vs. visual), a wide range of elapsed time since injury, and time-domain ERP quantification approaches.

TBIs range in severity from mild, to moderate, to severe, with severe TBIs involving loss of consciousness and/or alterations of consciousness of more than 24 hours, as well as possible post-traumatic amnesia of more than seven days. Thus, the range in TBI severity is substantial, and the degree and duration of cognitive impairment is correlated with severity level (Dikmen et al., 1995; Rabinowitz & Levin, 2014). Much of the ERP research on TBI has been conducted on moderate to severe TBI patients, while more recent research has begun to focus on mild TBI given

its prevalence and association with long-term functional impairment (Iverson & Lange, 2011; McMahon et al., 2014; van der Naalt et al., 2017). Indeed, although mTBI is the least severe form of brain injury, research has demonstrated significant ERP differences between mTBI patients and controls (Nandrajog et al., 2017; Potter et al., 2001, 2002; Solbakk et al., 1999, 2000). Furthermore, variations in impairment seems to exist even within the mild TBI population (Iverson & Lange, 2011). Research has shown a relationship between mTBI severity and resting state functional connectivity (Gilmore et al., 2016), as well as neuropsychological functioning (Dikmen et al., 2016).

The ERP literature includes participants with a wide range of time elapsed since TBI, which has been shown to influence the consistency of results (Folmer et al., 2011). While some research has shown no relationship between time since injury and ERP measures (Sarno et al., 2006), other work has found a correlation between reduced P2/N2 amplitude and shorter time since injury (Clark et al., 1992). Some cross-sectional studies have shown reductions in ERP amplitudes from six months to six years following mTBI (Gosselin et al., 2011; Segalowitz et al., 2001). Longitudinal work has produced mixed findings, with some research showing normalization of P3 latency in mTBI subjects over 1-3 months post-injury (Lew et al., 2007; Nandrajog et al., 2017), and other work showing no ERP changes from shortly after mTBI to 3-7 months later (Sivák et al., 2008). Cavanagh and colleauges (2019) revealed that individuals with acute mTBI (< 2 weeks post-injury) showed a significant correlation between more symptoms of frontal lobe injury (i.e., apathy, disinhibition, executive dysfunction) and lower P3a amplitude. In addition, P3b amplitude predicted symptom recovery after mTBI from the acute (< 2 weeks) to post-acute period (2 months post-injury), above and beyond demographic predictors (Cavanagh et al., 2019). While this research is promising, more longitudinal work following mTBI patients from the acute to chronic

period is needed to assess the trajectory of cognitive recovery and the utility of biomarkers for predicting symptom recovery.

Research has also shown that task difficulty may play a role in the ERP effects observed following TBI. For example, Duncan and colleagues (2005) demonstrated that P300 amplitude reduction was detected only when task demands increased. Alternatively, Lew and colleagues (2007) found no difference in P300 amplitude between TBI participants and controls on a complex auditory task compared to a simpler one. On a similar note, variations in the ERP literature have been observed in relationship to task domain, namely visual vs. auditory discrimination tasks. Several studies have suggested that, compared to visual ERP components, auditory ERPs are more impacted by TBI (Duncan et al., 2003, 2005 for a review), although the samples in these studies consist of moderate to severe TBI. In contrast, Gaetz and Bernstein (2001) reviewed electrophysiological studies and found that visual P3 latency was the most sensitive measure in mild TBI studies specifically.

Finally, variations in ERP quantification approach likely play a role in the inconsistencies in the TBI literature. The oddball N2 is commonly quantified using a difference wave approach, where ERPs to frequent stimuli are subtracted from oddball stimuli to create a difference waveform for each subject. Thus, discrepancies in N2 results may be partially explained by the utilization of a difference wave approach, which complicates inferences about frequent vs. oddball activity. With respect to the P3, mounting evidence suggests that this component contains a mixture of processes that require specialized analytic approaches to isolate. A common distinction in oddball paradigms classifies the P3 into sub-components: an earlier P3a component evoked by novel stimuli and a later P3b component (i.e., the classic P3) elicited by target stimuli (Polich, 2007). Not only are these sub-components typically classified by differing stimulus types, but they also

reflect different processes and topographic distributions. P3a is thought to reflect a bottom-up orienting response that is localized to the anterior cingulate cortex, and this orienting response is believed to serve as an alarm to signal the need for cognitive control (Barceló et al., 2002; Friedman et al., 2001; Kopp et al., 2006; Nieuwenhuis et al., 2011; Wessel & Aron, 2013; Wienke et al., 2018). The P3b is thought to reflect a top-down process of cognitive categorization and context updating and has been localized to the posterior temporo-parietal junction and dorsolateral frontal cortex (Gaeta et al., 2003; He et al., 2001; Linden, 2005; Polich, 2007; Soltani & Knight, 2000; Spencer et al., 2001; Yago et al., 2003). While these sub-components have important distinctions, several studies have found that they may be more similar than initially thought. Spatial-temporal principal component analysis and independent component analysis of the P3a and P3b have revealed that both components contain frontocentral and centroparietal contributions, which are weighted differently depending on the stimulus context (Debener et al., 2005; Spencer et al., 1999, 2001). Thus, the P3a and P3b are present in processing both novel and target stimuli, but their relative magnitude and topographical distribution depend on the stimulus type. These findings suggest that quantifying P3 as a singular process will neglect the distinct underlying processes.

Time-frequency Analysis

Most ERP research employs time-domain quantification approaches for measuring the N2, P3, and other components. These approaches typically involve either measuring the peak or mean amplitude of a component within a specific time range. However, many common ERP components, such as the N2, P3a, and P3b, overlap in time and contain mixtures of separable processes that are confounded with conventional time-domain analysis. More recent work from our group and others has demonstrated that time-frequency analysis is effective for separating

activity that overlaps in time but is distinct in frequency. Several studies have shown that time-domain ERP components can be well-represented as separable processes occurring in the delta (< 3 Hz) and theta (3-7 Hz) frequency bands (Başar et al., 2001; Bernat et al., 2007; Cavanagh et al., 2012; M. X. Cohen et al., 2007; Demiralp, Ademoglu, Istefanopulos, et al., 2001). More specifically, several studies have demonstrated that the majority of variance in the oddball P3 is explained by centroparietal delta and frontocentral theta (Bachman & Bernat, 2018; Başar et al., 2001; Demiralp, Ademoglu, Comerchero, & Polich, 2001; Demiralp, Ademoglu, Istefanopulos, et al., 2001; S. Karakaş, Erzengin, & Başar, 2000; Sirel Karakaş, Erzengin, & Başar, 2000; Kolev, Demiralp, Yordanova, Ademoglu, & Isoglu-Alkaç, 1997; Spencer & Polich, 1999; Yordanova, Devrim, Kolev, Ademoglu, & Demiralp, 2000).

The majority of research utilizing time-frequency analysis has applied wavelet time-frequency transforms, which is not optimal for capturing low frequency activity, like delta, or high frequency activity (Bernat et al., 2005). Wavelet transforms smear activity in time in the lower frequencies and smear activity in frequency in the higher frequencies. However, recent work from our group has employed the reduced interference distribution (RID) from Cohen's class of time-frequency transforms, which provides uniform time and frequency resolutions at both low and high frequencies (Bernat et al., 2005). Utilizing the RID approach, our group and collaborators have demonstrated separable theta and delta activity underlying many common ERP components, including oddball P3 (Bachman & Bernat, 2018), go/no-go N2 and P3 (Harper et al., 2014, 2016), gambling feedback negativity (FN) and feedback-P3 (Bernat, Nelson, & Baskin-Sommers, 2015; Bernat, Nelson, Steele, Gehring, & Patrick, 2011; Foti, Weinberg, Bernat, & Proudfit, 2015; Watts, Bachman, & Bernat, 2017; Watts, Tootell, Fix, Aviyente, & Bernat, 2018; Watts & Bernat, 2018); and error-related negativity (ERN; Bernat et al., 2005; Hall, Bernat, & Patrick, 2007). This

research has shown that delta and theta contribute unique variance to these ERP components when analyzed in regression models, demonstrating the utility of time-frequency analysis for isolating distinct processes underlying ERPs. More specifically, Bachman & Bernat (2018) demonstrated that centroparietal delta and frontocentral theta contribute unique sources of variance to the P3 elicited by visual oddball target and non-target stimuli. Additionally, centroparietal delta contributed more variance than frontocentral theta in both target and non-target regression models. This study replicated similar work employing auditory oddball tasks (Demiralp, Ademoglu, Comerchero, et al., 2001; Demiralp, Ademoglu, Istefanopulos, et al., 2001; S. Karakaş et al., 2000; Sirel Karakaş et al., 2000; Kolev et al., 1997; Spencer & Polich, 1999; Yordanova et al., 2000). Furthermore, these underlying processes have been shown to be functionally distinct, where frontocentral theta reflects salience processing and centroparietal delta reflects more complex cognitive processing (Bachman & Bernat, 2018; Bernat et al., 2015; Harper et al., 2014; A. T. Watts et al., 2017). Taken together, these findings provide strong support for the use of time-frequency analysis for investigating oddball ERP activity.

In addition to deriving time-frequency surfaces using the RID, several studies have shown the utility of applying principal component analysis (PCA) to the time-frequency surfaces in order to isolate unique activity. Other approaches include assessing each frequency time series separately, using peak and mean measurement, or evaluating single bins from the wavelet transformations. However, these approaches are simpler data representations and do not assess the entirety of the energy in the signal at once. One common method of analyzing complete, high-resolution time-frequency surfaces is to use a region of interest approach, where time and frequency ranges are "cut out" based on a priori knowledge of the time and frequency characteristics of the ERP components of interest. However, because the time and frequency

characteristics of common ERP components are not well-established, a data driven approach like PCA is useful for decomposing time-frequency surfaces into distinct components that best represent the underlying activity. Time-frequency PCA was developed by Bernat and colleagues (2005) and has since been successfully implemented in a variety of datasets and tasks (Bernat et al., 2007, 2015, 2011; Ellis, Watts, Schmidt, & Bernat, 2018; Foti et al., 2015; Harper et al., 2014; Watts et al., 2017, 2018; Watts & Bernat, 2018).

Other Neuroimaging Findings

While ERP research has been important for understanding the pathophysiology of brain injury, other neuroimaging advances, like magnetoencephalography (MEG), functional magnetic resonance imaging (fMRI), and diffusion tensor imaging (DTI), have proven instrumental in characterizing specific brain regions and networks impacted by TBI. MEG research utilizing resting state connectivity has revealed that mTBI patients have weak local connectivity and strong long-range connectivity compared to controls (Dimitriadis et al., 2015). Work with MEG has also shown that functional connectivity patterns provide between 85-100% classification accuracy for mTBI patients vs. controls (Dimitriadis et al., 2015; Zouridakis et al., 2012).

fMRI research on mTBI has assessed both regional activation and functional connectivity in resting state and task-based paradigms (see Mayer et al. (2015) for a review). The majority of fMRI research has evidenced reduced activity in anterior brain regions and increased activity in posterior regions in mTBI patients compared to controls (Eierud et al., 2014). More specifically, Eierud and colleagues's (2014) meta-analysis revealed reduced activity in the dorsal lateral prefrontal cortex (dlPFC), right medial frontal gyrus (MFG), anterior cingulate cortex (ACC), and the right precentral gyrus. Reduced activity in the prefrontal cortex has been shown to be related to severity of post-concussive symptoms (Jen-Kai Chen et al., 2007; J.-K. Chen et al., 2004) and

TBI severity (Matthews et al., 2011). Posterior regions that showed increased activity included two coordinates in the cerebellum, two insula regions, and two foci in the parietal lobe (Eierud et al., 2014). On the other hand, some studies have cited hyperactivity in the dlPFC (Dettwiler et al., 2014; McAllister et al., 1999, 2001), but these results seem to be limited to tasks that required continuous vs. discrete periods of working memory. In fMRI studies employing tasks of auditory attention orienting, results have demonstrated widespread reductions in activity in both anterior and posterior regions (Mayer et al., 2009; Witt et al., 2010). The fMRI literature to date has included a wide range of time since injury, which likely accounts, at least in part, for variability in the results. Indeed, the most recent meta-analysis by Eierud and colleagues (2014) notes that there are too few fMRI studies to assess effects of time post-injury.

Resting state fMRI studies, in which participants are awake and not engaged in a task, typically assess activity and connectivity within the default mode network (DMN). The DMN is primarily composed of the posterior cingulate cortex (PCC), precuneus, and medial prefrontal cortex (mPFC), and is more active during wakeful rest than goal-oriented tasks. Several studies have revealed reduced activation and functional connectivity in the DMN following TBI (Han et al., 2014; Mayer et al., 2012; Palacios et al., 2017; K. Zhang et al., 2012; Zhou et al., 2012). Additionally, a number of studies have observed a failure of the DMN to deactivate during tasks, perhaps due to the reduced functional connectivity between task-based salience and control networks and the DMN leading to a failure of these networks to down-regulate the DMN (Mayer et al., 2012; Sharp et al., 2014; Stevens et al., 2012). This failure of the DMN to deactivate has been shown to be associated with worse cognitive functioning in patients with mTBI (Sharp et al., 2014). Disrupted functional connectivity in mTBI has also been demonstrated in other brain networks in both resting-state and task-based designs; these networks include the visual system,

executive/cognitive control networks, frontoparietal network, orbitofrontal network, motor regions, and limbic circuits (Gilmore et al., 2016; Palacios et al., 2017; Shumskaya et al., 2012; Slobounov et al., 2011; Stevens et al., 2012; Vakhtin et al., 2013; Zhou et al., 2014). In general, studies have found that alterations in functional connectivity either improve slightly or remain stable 5-12 months post-injury, and group differences are still observed during this follow-up window (Han et al., 2014; Mayer et al., 2011; Messé et al., 2013). Palacios and colleagues (2017) found that resting-state functional connectivity in the acute stage following mTBI was related to post-concussion symptoms and neuropsychological test performance 6 months later. More specifically, reduced functional connectivity in posterior brain regions, as well as the ACC, was related to post-concussion symptoms 6 months after mTBI. In addition, enhanced functional connectivity in the DMN, salience network, and dorsal attention network was correlated with performance on tests of attention, processing speed, and executive functioning at the six month follow-up.

DTI has also proven to be a sensitive tool for measuring structural connectivity changes following mTBI. DTI measures the diffusion of water molecules along axons, which can reveal microscopic changes in white matter (axon) integrity. In their meta-analysis, Eierud and colleagues (2014) discovered that elevated anisotropy values (a measure of diffusion) are more frequently reported in studies of acute mTBI (<2 weeks post-injury), whereas depressed anisotropy values are commonly reported in studies of post-acute to chronic mTBI (2 weeks to several years post-injury). Of note, one DTI study showed that functional outcome (i.e., severity of disability) after six months was related to severity of white matter injury within one to two weeks following mTBI (Yuh et al., 2014).

Neuroimaging of Blast-related mTBI

Given the prevalence of blast injuries in the recent military conflicts (Benzinger et al., 2009; Hoge et al., 2008; Ling et al., 2009; Stansbury et al., 2008), research over the past decade has begun to focus on the unique effects of blast-related mTBI on the brain. Preliminary research has suggested that blast-related TBI leaves a unique neural signature (Magnuson et al., 2012). The majority of neuroimaging research on blast-related mTBI has investigated structural and functional connectivity using DTI and fMRI. Fischer and colleagues (2014) showed that blast- and impact-related mild to moderate TBI showed decreased activation in the amygdala and DMN to correct responses on inhibitory trials. During unsuccessful inhibition, however, brain regions associated with the cognitive and emotional interpretation of negative feedback (i.e., the left caudate nucleus and left posterior lobe of the cerebellum) demonstrated hyperactivation in the blast-related TBI group relative to military controls, whereas the impact-related TBI group showed hypoactivation in these regions relative to the civilian controls (Fischer et al., 2014). fMRI studies of blast-related mTBI have also revealed reduced functional connectivity in several networks, including frontal, default mode, sensory, and motor networks (Gilmore et al., 2016; Han et al., 2014; Robinson et al., 2015; Sponheim et al., 2011; Vakhtin et al., 2013). One study demonstrated that disruptions in functional connectivity improved over a six month follow-up window, although differences between mTBI and control groups remained significant at follow-up (Han et al., 2014). DTI studies have shown widespread disruptions in white matter integrity (Davenport et al., 2012; Magnuson et al., 2012). Davenport and colleagues (2012) demonstrated a more diffuse pattern of axonal injury in blast-related mTBI vs. impact-related mTBI, but other research directly comparing blast and impact mTBI is limited. With respect to the relationship between EEG and DTI measures, Sponheim and colleagues (2011) demonstrated a correlation between reduced EEG time-frequency

phase-synchrony in frontal regions and the structural integrity of white matter tracts in the frontal lobe. These results provide support for the utility of EEG measures of neural communication in detecting damaged white matter tracts following blast-related mTBI.

EEG/ERP Phase Synchrony Measures

While the majority of research on functional and structural connectivity has been conducted using MRI measures, a growing line of research has developed EEG measures for assessing the connections within and between neural populations. Compared to fMRI, EEG connectivity measures are beneficial because they provide the excellent temporal resolution (on the scale of milliseconds) necessary for capturing rapid information processing. There is mounting evidence that EEG phase dynamics are fundamental to neural communication (Fries, 2005; Varela et al., 2001). Two measures have been developed to examine the phase synchrony within and between neural populations in response to a specific event (e.g., target stimulus). Intertrial phase synchrony (ITPS) is measured as the degree of phase alignment of frequency-specific event-related activity between trials, and is thought to be an index of the consistency of neural responding to a specific event type. Several studies have demonstrated that ITPS is closely related to modulations in ERP amplitude and is important for functional communication with other brain regions (Burwell et al., 2014; Cavanagh et al., 2009; Sauseng et al., 2007; A. T. Watts et al., 2018).

A primary view proposes that ITPS reflects encoding of new task-relevant information and the integration of prior knowledge, which promotes behavioral adaptation (Fries, 2005). Thus, ITPS reflects a state of neural readiness, with more ITPS within a region facilitating new information gathering and the subsequent integration with linked networks. In support of this view, empirical work has shown that information valuable for learning, such as negative feedback and error trials, elicits increased medial frontal theta amplitude and ITPS (Cavanagh et al., 2009, 2010;

M. X. Cohen et al., 2008; M. X. Cohen & Cavanagh, 2011; van Noordt et al., 2017; A. T. Watts et al., 2018). Additionally, blocks of trials that are more cognitively demanding have been shown to produce more ITPS (Papenberg et al., 2013). Furthermore, research has shown that more ITPS, especially in the mPFC, is linked to more adaptive task performance (Burwell et al., 2014; Cavanagh et al., 2009; M. X. Cohen & Cavanagh, 2011; Marco-Pallares et al., 2008, p.; A. T. Watts et al., 2018). Finally, ITPS within a particular region has also been found to augment neural plasticity for the formation of new connections (Fell & Axmacher, 2011).

Interchannel phase synchrony (ICPS), a measure of the degree of phase alignment between two electrode sites, is also a new and promising method for studying information processing between brain regions (Cohen et al., 2011). Medial prefrontal theta activity and theta ICPS between medial and bilateral PFC have been widely utilized as measures of cognitive control. The anterior cingulate cortex, located in the medial PFC, has long been considered the alarm signal of the performance monitoring system because it recruits control-related resources (e.g., in the bilateral PFC) that are necessary for the adaptation of behavior in pursuit of goals (Miller & Cohen, 2001). In addition to facilitating connectivity with control regions of the PFC, the ACC also promotes behavioral adaptation through integration with sensorimotor regions and structures important for memory in the temporal and parietal lobes (Holroyd & Coles, 2002). In support of this theory, research has shown that information valuable for learning, such as trials that are more conflicting, surprising, or negative, elicit greater ICPS between the ACC, the lateral PFC, and other related brain regions (Aviyente et al., 2017; M. X. Cohen et al., 2011; Hanslmayr et al., 2007; Luft, 2014; Smith et al., 2015; Van de Vijver et al., 2011; Watts et al., 2018). Time-frequency phase dynamics in motor and visual regions have been linked with medial-frontal theta amplitude (Cavanagh & Frank, 2014; Luu et al., 2004; Luu & Tucker, 2001; Makeig et al., 2002), consistent with the

involvement of visual and motor processing areas involved in goal-directed tasks. Taken together, these results suggest that ICPS is a valuable measure for indexing functional connectivity in goal-directed tasks.

To our knowledge, only a few studies have investigated functional connectivity abnormalities following mTBI using EEG measures during a cognitive task (Kumar et al., 2009; Reches et al., 2017; Smith & Allen, 2019). These studies show reduced functional connectivity following mTBI in frontal brain regions associated with cognitive control. In perhaps the closest to ours methodologically, Smith and Allen (2019) demonstrated reduced theta-band inter-site phase synchrony between mPFC and dlPFC electrode sites during error trials on a flanker task, and number of sports concussions was negatively correlated with this medial-lateral connectivity. While these three studies differ from the current study in several ways (e.g., non-military samples, different cognitive tasks, and different EEG methods), these findings mirror other neuroimaging results of military mTBI as described above. Thus, in the current study we hypothesize reduced theta-band ITPS and ICPS between medial and bilateral frontal electrodes in the mTBI group.

Neuropsychological Functioning Following mTBI

Much research has investigated the neuropsychological sequelae of mTBI. Common findings in the acute period following mTBI include deficits in processing speed, attention, working memory, executive functioning, and memory recall (Belanger et al., 2005; Binder et al., 1997; Frencham et al., 2005; Ponsford et al., 2000; Rohling et al., 2011). Deficits in executive functioning have also been observed in blast-related mTBI specifically (see Karr et al. (2014) for a meta-analysis). Most research has found that these impairments resolve within three months following mTBI (Belanger et al., 2005; Binder et al., 1997; Frencham et al., 2005; Ponsford et al., 2000; Rohling et al., 2011), but some studies suggest cognitive difficulties three months post-

injury and beyond (Pertab, James, & Bigler, 2009; Vanderploeg, Curtiss, & Belanger, 2005; Ponsford et al., 2011). Several moderating variables have been shown to contribute to the chronicity of neuropsychological deficits, including sampling methods (i.e., clinic-based and litigation-based vs. community samples), complicated mTBI (i.e., those with mild TBI that have positive neuroimaging findings on clinical CT or MRI), and comorbid psychopathology (Belanger et al., 2005; Borgaro et al., 2003).

Neuropsychological assessment has been shown to be less sensitive to cognitive impairment following mTBI compared to neuroimaging methods (Belanger et al., 2007; Bigler, 2013; Mayer et al., 2011; Slobounov et al., 2011). Additionally, the positive predictive value, or likelihood of a pathological condition given an abnormal test result, of neuropsychological assessment for mTBI has been found to be less than 50% (Binder et al., 1997). However, as Belanger and colleauges (2007) and others have highlighted, understanding the relationship between an abnormal neuroimaging finding (e.g., a significant difference in EEG ICPS between mTBI patients and controls) and functional status (e.g., neuropsychological testing results or symptom presentation) is important for interpreting the meaning of abnormal neuroimaging findings. Not only is establishing this relationship important for the interpretation of neuroimaging findings, but also for determining the clinical utility. That is, an abnormal neuroimaging finding is not clinically useful if there is no report or other evidence of cognitive difficulties. Furthermore, a clinically useful next step is determining the predictive validity of neuroimaging methods. For example, does blunted delta P3 activity during the post-acute period following mTBI predict post-concussion symptoms and/or neuropsychological functioning six months later?

Several studies have attempted to link brain measurements to neuropsychological assessments with some promising results. These studies have connected ERP, fMRI, and DTI

abnormalities to performance on neuropsychological tests of attention, memory, processing speed, and executive functioning (Belanger et al., 2007; Eierud et al., 2014; Geary et al., 2010; Potter et al., 2002). Eierud and colleagues' (2014) meta-analysis on mTBI revealed that poor performance on neuropsychological measures was associated with elevated anisotropy (a DTI measure) in the acute phase (<2 weeks post-injury) and reduced anisotropy in the chronic phase (2 weeks to several years post-injury). While this meta-analysis is promising for demonstrating a link between neuroimaging and neuropsychological findings in both the acute and chronic phases following mTBI, prospective longitudinal research is needed to assess the utility of biomarkers for predicting cognitive recovery and the sensitivity of neuroimaging vs. neuropsychological assessment for measuring persistent cognitive deficits.

Current Study

In summary, the current study aims to address several scientific gaps in an effort to improve the diagnosis and management of cognitive concerns following military mTBI. This study focuses on several areas of recommended future research as proposed by the VA/DoD Clinical Practice Guideline for the management of Concussion-Mild Traumatic Brain Injury (Department of Veterans Affairs, 2016). Relevant recommendations include:

1. Long-term outcome studies with a focus on the role of laboratory, imaging or physiologic testing in the management of and clinical decision making with a patient more than seven days following concussion.
2. Research to improve the diagnostic accuracy of tests for concussion/mTBI in the post-acute period.

3. Studies that acknowledge the lack of validation of existing case definitions of mTBI and examine diagnostic accuracy of cognitive and neuropsychological tests for concussion/mTBI.
4. Examine mechanism-specific physiologic response and associated pathophysiology for which specific treatment and predictive outcome measures may be of value. (p. 43)

With a focus on these recommendations, the current study aims to assess cognitive changes over a six month period following blast-and impact-induced mTBI using advanced time-frequency event-related potential (ERP) analysis. Much neuropsychological research suggests cognitive recovery from mTBI within three months, but a substantial subset of these individuals experience persistent post-concussive symptoms and functional impairment (Dikmen et al., 2016; Iverson, 2005; Levin & Diaz-Arrastia, 2015; McMahon et al., 2014; Meares et al., 2011; van der Naalt et al., 2017). Advancements in EEG/ERP methodology may be useful in understanding the etiology of these chronic cognitive complaints relative to other known risk factors (e.g., co-occurring PTSD or other psychiatric disorders and mTBI). In addition, few studies have assessed the relationship between ERP/EEG measures, neuropsychological tests, and post-concussion symptoms over time, which is critical for establishing the convergent and predictive validity of ERP biomarkers of impairment following mTBI.

The current study will employ time-frequency principal component analysis (PCA) of ERP data. Time-frequency PCA analysis overcomes several methodological limitations of traditional time-domain ERP methods. In addition, recent advances have led to the development of time-frequency phase synchrony measures, which index functioning communication within and between brain regions. These EEG methods have important methodological and practical advantages over MRI methods, namely, high temporal resolution and low financial cost. In

addition, EEG systems are available at most hospitals in the Unites States. DTI and fMRI measure are more advanced than EEG in terms of measuring network connectivity across the entire brain. However, EEG phase synchrony measures have shown promise in assessing rapid connectivity within and between salience and cognitive control networks.

The present study has three primary aims. The first aim is to evaluate the cognitive effects of military mTBI from the acute/post-acute to chronic period using EEG/ERP measures and neuropsychological (NP) tests. The terminology used to define the time periods following mTBI is based on the VA/DoD Clinical Practice Guidelines for the Management of Concussion-Mild Traumatic Brain Injury Version 2.0 (Department of Veterans Affairs, 2016). These terms include the immediate period (0-7 days post-injury), the acute period (1-6 weeks post-injury), the post-acute period (7-12 weeks post-injury) and the chronic period (>12 weeks post-injury). Comparisons will be conducted among three groups in the acute to post-acute period (i.e., baseline or approximately 4-11 weeks post-injury): 1) injured service members who sustained a mild TBI (i.e., the mTBI group), 2) injured service members who did not sustain a TBI (i.e., the IC group), and 3) healthy service members with no injuries or TBI (i.e., the HSM group). The duration of these cognitive effects will also be evaluated longitudinally by comparing the mTBI and IC groups at six months following the baseline assessment. Because PTSD symptoms are common in injured service members and can influence cognitive functioning, PTSD symptom severity will be included as a covariate in EEG/ERP and NP analyses. Given previous neuroimaging and neuropsychological research on mTBI, the following hypotheses are made for the mTBI relative to the control groups at baseline:

1a. N2 and P3 amplitude will be reduced

1b. N2 and P3 latency will be delayed

1c. Delta and theta amplitude underlying N2/P3 will be reduced

1d. Theta ITPS will be reduced

1e. Theta ICPS from medial prefrontal to bilateral prefrontal electrodes will be reduced

1f. Performance on NP tests will be worse in the areas of processing speed, working memory, sustained attention, and response inhibition

After six months, we expect neuropsychological functioning in the mTBI group to return to a level indistinguishable from controls. Improvements in EEG/ERP measures are also expected in the mTBI group after six months, but we expect significant differences between the mTBI and IC groups to remain.

The second aim is to evaluate the convergent and predictive validity of abnormal EEG/ERP findings. Correlations between abnormal EEG/ERP measures, NP measures, and cognitive post-concussion symptoms will be assessed. In addition, regressions with EEG/ERP measures predicting cognitive post-concussion symptoms at baseline and six months later will be assessed, as well as the relationship between psychiatric symptoms and persistent post-concussion symptoms. The following hypotheses will be tested:

2a. mTBI-related changes in EEG/ERP measures will be significantly correlated with worse NP performance and more post-concussion symptoms.

2b. Both EEG/ERP and psychiatric symptoms will predict cognitive post-concussion symptoms at baseline and follow-up.

The third aim is to compare the electrophysiological and neuropsychological effects of blast-related mTBI vs. impact-related mTBI at baseline. Because few studies have investigated differences between these subgroups, this aim is exploratory.

Chapter 2: Method

Participants

The present study was a secondary data analysis project. The primary study investigated predictors of PTSD in service member who had recently sustained a mTBI (*Brain Indices of Risk for Posttraumatic Stress Disorder after Mild Traumatic Brain Injury*: Connie C. Duncan, PI). In the current study, participants (n = 173) were active duty service members who were recruited from Walter Reed National Military Medical Center (WRNMMC) or Fort Belvoir Community Hospital (FBCH). The mTBI group (n = 87) comprised service members who recently sustained a mTBI, the injured control group (IC; n = 32) included service members who were recently injured but screened negative for TBI, and the healthy service members group (HSM; n = 54) comprised service members with no recent injuries or history of TBI. Of the two injured groups, 70% were injured while deployed in a combat zone in Iraq or Afghanistan, 4% were injured while deployed to a non-combat zone, and 26% were injured stateside.

All participants provided informed consent and were not compensated for their participation. Inclusion criteria for the mTBI group were: 1) 18 – 50 years of age; 2) inpatient or outpatient treatment at WRNMMC or FBCH; 3) Defense Enrollment Eligibility Reporting System eligible; 4) mTBI status as verified by a licensed medical practitioner using DOD criteria (Management of Concussion/mTBI Working Group, 2009)**.** Criteria for mTBI included loss of consciousness (LOC) of less than 30 minutes, post-traumatic amnesia (PTA) for less than 24 hours following the event, alteration of consciousness (AOC; e.g., being dazed or confused, "seeing stars") for less than 24 hours following the event, and no positive neuroimaging findings (on CT or MRI). Table 1 displays the TBI characteristics for the mTBI group.

Table 1

TBI Characteristics of the mTBI group

		Count
LOC	Yes	49
	No	34
	Unknown	4
LOC Time	Less than 5 min.	31
	Between 5-30 min.	9
	Unknown	9
PTA	Yes	41
	No	43
	Unknown	3
AOC	Yes	73
	No	11
	Unknown	3

Note. $n = 87$

Exclusion criteria for the mTBI group included: 1) penetrating brain injury; 2) significant neurological conditions, undergoing treatment for an illness that could affect brain function, or abuse of or dependence on alcohol or drugs in the previous six months as assessed by medical chart review; 3) history of a major psychiatric disorder as assessed by the Structured Clinical Interview for DSM-IV; 4) history of PTSD before the most recent deployment; 5) MRI contraindications such as metallic fragments or claustrophobia (because MRI was collected as a part of the primary study). Participation by service members taking intravenous medications for pain was delayed until such medications were discontinued.

The inclusion and exclusion criteria for the IC group were the same, with a few exceptions: 1) negative TBI status; 2) no history of TBI either during training or deployment; and 3) no history as a specialist in explosive ordnance disposal. In addition to these exceptions, the HSM group had no history of combat-related injuries or other recent traumatic injuries, and HSM participants were not required to be in treatment at WRNMMC or FBCH.

Of the 173 participants, 173 completed the visual oddball task, and 170 completed the auditory oddball task. Two participants were excluded from the visual and auditory analyses due to an excessive number of EEG artifacts. Thus, the final sample for all three groups (mTBI, IC, and HSM) included 171 participants for the visual analyses and 168 participants for the auditory analyses at baseline. At the six month follow-up assessment, some participants were lost to follow-up and the final sample for the two groups (mTBI and IC) included 94 participants for the visual analyses and 93 participants for the auditory analyses.

Table 2

Demographic Characteristics by Group

	mTBI (*n* = 87)	**IC (*n* = 32)**	**HSM (*n* = 54)**
Age (yrs)	27.8	28.0	33.7
Males (%)	77 (89%)	29 (91%)	37 (69%)
Education (yrs)	13.9	13.9	16.5
Race/Ethnicity			
Caucasian/White	74	29	42
African American	8	1	5
Asian American	3	2	5
Native American	2	0	1
Other	0	0	1
Duty Status			
Active Duty	81	30	47
Reserve	4	1	0
National Guard	2	1	7
Most Recent Rank			
Junior Enlisted	10	2	5
Non-Comm. Officer	56	24	23
Officer	16	4	23
Injury Mechanism			
Impact	44	-	-
Blast	43	15	-
Non-blast	-	17	-
Time Since Injury	59	52	-
Mean PCL-C Score	29.2	29.4	19.7

Note. Time Since Injury units are days from injury to baseline ERP assessment. The PCL-C (PTSD Checklist Civilian Version) measures PTSD symptom severity.

Demographic information is presented in Table 2. The mTBI and IC groups did not differ on any demographic variables. However, these groups differed from the HSM group on age (mTBI vs. HSM: $t = 4.01$, $p < .001$; IC vs. HSM: $t = 3.22$, $p = 0.002$), education (mTBI vs. HSM: $t = 5.13$, $p < .001$; IC vs. HSM: $t = 4.50$, $p < .001$), sex (mTBI vs. HSM: $\chi_2 = 7.89$, $p = .02$; IC vs. HSM: $\chi_2 = 7.29$, $p = .03$), and PTSD symptom severity (mTBI vs. HSM: $t = 6.76$, $p < .001$; IC vs. HSM: $t = 3.71$, $p < .001$), but not on race/ethnicity. Therefore, age, education, and PTSD symptom severity (i.e., PCL-C total score) were included as covariates in all analyses involving the HSM group. Sex was not included as a covariate because there were only three female participants in the injured control group.

Procedures

EEG/ERP and neuropsychological data were collected at baseline (as soon as possible following injury and study enrollment) and six months later. All three groups were included in the baseline analyses, while only the mTBI and IC groups were included in the six month follow-up analyses[1].

EEG data were recorded in a sound-attenuated, dimly lit room. Experimental stimuli were presented on a DELL computer monitor, centrally placed at a viewing distance of 100 cm. Compumedics Neuroscan's STIM2 program and response pad were used to present the stimuli and collect responses during the tasks.

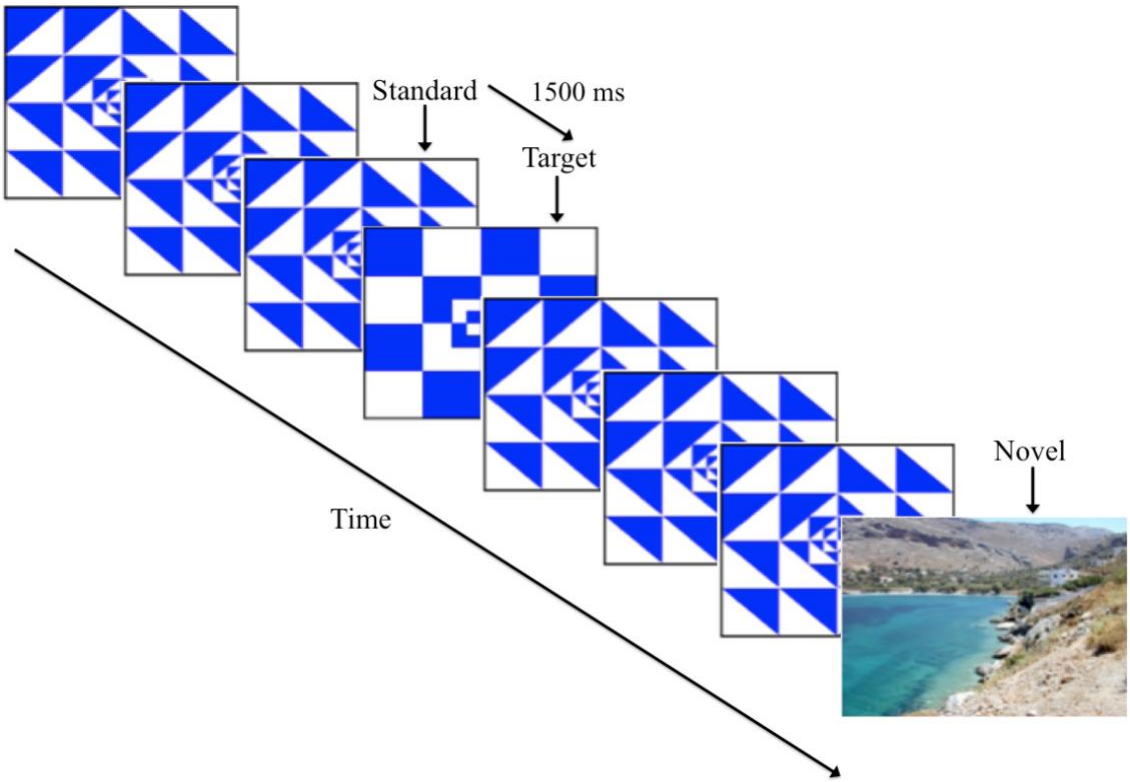
Participants performed two tasks, a visual novelty oddball task (displayed in Figure 1) and an auditory novelty oddball task. Each task had three types of stimuli. Visual stimuli were two

[1]The primary study (*Brain Indices of Risk for Posttraumatic Stress Disorder after Mild Traumatic Brain Injury*) ended before completion of the six month follow-up assessment for the HSM group. ERP data was collected for only nine HSM participants at follow-up; thus, the HSM group was not included in the follow-up analyses.

geometric figures, one composed of squares and one composed of triangles. Participants were instructed to respond by pressing a button with the thumb of their dominant hand when the figure of squares appeared (i.e., the target stimulus), and to not respond to the figure of triangles (i.e., the standard stimulus). In addition, novel stimuli were images from the International Affective Picture System (IAPS). Four pictures types were presented with an equal probability: 1) low arousal, negative valence images, 2) low arousal, positive valence images, 3) high arousal, negative valence images, and 4) and high arousal, positive valence images. Target, standard, and novel stimuli were presented in a random order, with probabilities of .60 for standards, .20 for targets, and .20 for novels. All stimuli were 700 ms in duration with a stimulus onset asynchrony of 1,500 ms. The task was 640 trials total separated into four equal blocks.

Figure 1

Visual Novelty Oddball Task



For the auditory task, standard stimuli (p=.60) were 1000-Hz tones and target stimuli (p=.20) were 2000-Hz tones; both tones were 336 ms in duration. Novel stimuli (p=.20) were 36 unique novel environmental sounds taken from a larger set of 96 sounds obtained from the New York State Psychiatric Institute (Fabiani et al., 1996). The mean duration of the 36 sounds was 347 ms (SD=53). All stimuli were presented binaurally with Neuroscan Earphone Insert 10Ω 1/4 Stereo with Etymotic foam ear inserts at the rate of one stimulus per second. The task comprised a single block of 180 trials.

Neurophysiological Data Acquisition

Data were recorded using an Electro-Cap International (ECI) 62-channel EEG cap (sintered Ag-Ag/Cl; 10-20 layout), as well as a SynAmps RT 64-channel amplifier. Horizontal electrooculogram activity was recorded from electrodes placed on the outer canthus of both eyes, while vertical electrooculogram activity was recorded from electrodes placed above and below the left eye. Impedances were kept below 10 kΩ. All electrodes were referenced during recording (to a nose electrode), and re-referenced to averaged mastoid signals offline. EEG signals were collected using an analog 0.05 to 100 Hz bandpass filter and digitized at 500 Hz using Neuroscan Acquire (Neuroscan, Inc.).

Data Preprocessing

Epochs of three seconds were taken from 1000 ms pre- to 2000 ms post-stimulus onset with a -500 ms to -100 ms pre-stimulus window used for baseline correction. Ocular artifacts were corrected with a regression-based algorithm developed by (Gratton et al., 1983) and downsampled to 256 Hz using the EEGLAB resample function (Delorme & Makeig, 2004), which utilizes an anti-aliasing filter before resampling. Then, several criteria were used to identify EEG channels with large artifacts. First, noisy electrodes were identified if 1) the mean amplitude of any electrode

was greater than three standard deviations away from the mean amplitude of all of the electrode, 2) the standard deviation of the mean of any electrode was greater than three standard deviations away from the standard deviations of all electrodes, 3) kurtosis of the amplitude distribution of any electrode was more than five standard deviations away from the mean kurtosis value of all electrodes, and 4) the probability of the amplitude of any electrode was greater than five standard deviations away from the mean probability distribution of all electrodes. Next, the identified channels were interpolated using spline interpolation. Channels within each epoch were then assessed for large artifacts using a threshold of ±150 μV, and a maximum of ten channels were interpolated per epoch before removal of the epoch from the data. EEGLAB functions were used for bad channel identification, interpolation, and trial rejection (Delorme & Makeig, 2004). During the visual task, 4% of all electrodes across subjects were interpolated, and an average of 1.7 electrodes were interpolated per subject. A total of 4% of all trials were removed from the visual analyses. For the auditory task, 5% of all electrodes across subjects were interpolated, and an average of 1.7 electrodes were interpolated per subject. A total of 5% of all trials were removed from the auditory analyses.

Data Averaging

Although data cleaning improves the quality of the data, the removal of trials leaves an uneven number of trials across participants. Resampling and bootstrapping methods are well-defined and widely implemented techniques for estimating population parameters (Efron, 1982). While an important benefit of resampling techniques in general are the improved estimates of population parameters, the primary purpose of implementing these techniques was to remove any bias associated with uneven trials counts by equating the number of trials in each subject-electrode-condition average. Indeed, previous research has shown that the number of trials used in each

average affects the reliability of the measures extracted from ERPs (J. Cohen & Polich, 1997; Olvet & Hajcak, 2009; Pontifex et al., 2010; Steele et al., 2016). Thus, in the current study, resampling and bootstrapping methods used in previous research (Watts et al., 2017) were employed. Subsets of five trials for each stimulus type were subsampled 50 times with replacement. Next, these sets of 50 resampled averages for each stimulus type were bootstrapped 500 times. Integrity of each waveform was preserved during this process by retaining all time points together in each step of the resampling and bootstrapping process.

Data Reduction

Visual Oddball Time-domain Components

Time-domain (TD) amplitude and latency measures were extracted for N1, P2, N2, P3, and slow wave (SW) elicited by target and novel stimuli. The target N1 was defined as the maximum negative deflection ranging between 5 and 25 sampling bins post-stimulus onset (or about 40 to 195 milliseconds). The target P2 was defined as the maximum positive deflection ranging from 18 to 32 sampling bins post-stimulus onset (or about 140 to 250 milliseconds). The target N2 was defined as the maximum negative deflection ranging between 25 and 56 sampling bins post-stimulus onset (or about 195 to 438 milliseconds). The target P3 was defined as the maximum positive deflection ranging from 38 to 76 sampling bins post-stimulus onset (or about 297 to 594 milliseconds). The target SW was defined as the maximum positive deflection ranging from 76 to 128 sampling bins post-stimulus onset (or about 594 to 1000 milliseconds). The novel N1 was quantified between 5 and 20 bins (or about 40 ms to 156 ms); the novel P2 was quantified between 15 and 33 bins (or about 117 ms to 258 ms); the novel N2 was quantified between 20 and 50 bins (or about 156 ms to 391 ms); the novel P3 was quantified between 33 and 64 bins (or about 258

ms to 500 ms); and the novel SW was quantified between 62 and 128 bins (or about 484 ms to 1000 ms).

Auditory Oddball Time-domain Components

For the auditory task, the target N1 was quantified between 1 and 22 bins post-stimulus onset (or about 8 ms to 172 ms); the target P2 was quantified between 13 and 30 bins (or about 102 ms to 234 ms); the target N2 was quantified between 22 and 50 bins (or about 172 ms to 391 ms); the target P3 was quantified between 36 and 66 bins (281 ms to 516 ms); and the target SW was quantified between 64 and 128 bins (or about 500 ms to 1000 ms). The novel N1 was quantified between 1 and 25 bins (or about 8 ms to 195 ms); the novel P2 was quantified between 20 and 38 bins (or about 156 to 297 ms); the novel N2 was quantified between 32 and 42 bins (250 ms to 328 ms); the novel P3 was quantified between 38 and 58 bins (297 ms to 453 ms); and the novel SW was quantified between 58 and 128 bins (or about 453 ms to 1000 ms).

For both the auditory and visual components, these latency windows were fitted to the edges of the peaks in target and novel grand average waveforms. A peak measurement approach was used for the amplitude and latency analyses. For statistical analyses, these components were reduced to a group of three central midline electrodes for targets (FCz, Cz, and CPz) and three frontocentral midline electrodes for novels (Fz, FCz, and Cz).

Time-frequency Amplitude

Time-frequency (TF) decompositions were performed on condition averages. The goal in starting with condition averages is to use the same ERP activity conventionally studied using time-domain components. This approach has been used in previous work (Bernat et al., 2011, 2015; Foti et al., 2015; Harper et al., 2014, 2016; Nelson et al., 2011; A. T. Watts et al., 2017, 2018). First, 3rd order Butterworth filters were used to isolate activity within delta and theta frequency

ranges. A 4 Hz lowpass filter was employed to isolate delta, and a 2 Hz highpass filter in conjunction with an 8 Hz lowpass filter was used for theta. Overlapping filters were used to allow the principal components analysis (PCA) approach to define the division between the delta and theta activity. TF transforms were produced using a binomial reduced interference distribution (RID) variant of Cohen's class of time-frequency transformations, using the full epoch of the filtered signals (-1 s to 2 s, relative to stimulus onset), using 32 time bins per second and 2 frequency bins per Hz. Principal component analysis (PCA) was then applied across the full set of TF representations of the condition averages, following methods previously presented (Bernat et al., 2005). PCA was applied to a post-stimulus time window of 0-1000 ms and a 0-12 Hz frequency window. PCA solutions were chosen separately for visual and auditory targets and novels based on the scree plots. The mean PC-weighted TF evoked energy was narrowed down to clusters of electrodes based on the topographical center of activity during target and novel stimulus processing.

Time-frequency ITPS

Average inter-trial phase synchrony (ITPS) was computed separately for target and novel trials. Creating these averages involved taking a set of trials, computing the phase difference between each trial and the average phase across trials, and then averaging the phase differences to create a phase locking value (PLV) across the trials (Aviyente et al., 2011). This process was conducted iteratively using the same subsampling and bootstrapping approach defined above. This process produced condition average ITPS surfaces of the same dimensions as the amplitude measures, for each electrode within participant. The PC solutions extracted for amplitude were then applied to the ITPS computation (as a filter, or mask), extracting ITPS activity directly corresponding to the amplitude measure TF regions defined by the TF-PCA. Components below

2 Hz were not included in statistical analyses for ITPS or ICPS. At this low frequency, there are not multiple oscillations within the 1000 Hz epoch with which to correlate across trials or electrodes; thus, the validity of phase synchrony measures below 2 Hz is questionable and warrants further development in a separate report.

Time-frequency ICPS

Salience and control-related functional network activity was assessed as the phase synchrony between medial prefrontal and bilateral prefrontal regions (cf. dorsolateral PFC) consistent with our previous work (Aviyente et al., 2017; Moran et al., 2015) and others (Cavanagh et al., 2009). Theta-band functional connectivity was calculated between the medial prefrontal region (i.e., electrode FCz) and two bilateral prefrontal electrodes (i.e., F3 and F4). Theta ICPS was calculated through phase synchrony computations based on Cohen's class of time-frequency distributions (Aviyente et al., 2011). Consistent with our previous work, data were transformed using current source density (CSD) before deriving PLV values, to minimize volume conduction effects by source localizing activity toward the cortical surface (Tenke & Kayser, 2012). As with ITPS computation, the PC solutions from theta amplitude were applied to the ICPS measure, targeting phase synchrony within the N2/P3 time window.

Neuropsychological Measures

Neuropsychological functioning was assessed at baseline and six months later. The primary domains of interest given previous literature on the neuropsychological effects of mTBI included processing speed, working memory, sustained attention, and response inhibition. Processing speed was measured with the Wechsler Adult Intelligence Scale Fourth Edition (WAIS-IV) processing speed index (PSI; Wechsler, Coalson, & Raiford, 2008). The PSI is a composite score composed of two timed subtests, coding and symbol search, that measure visual psychomotor processing

speed. Working memory was assessed with the n-back computer task (Gevins & Cutillo, 1993). Participants were asked to respond whenever a stimulus was the same as the one presented n trials previously, where n is a pre-specified integer. Conditions were divided into four blocks ranging from the 0-back to the 3-back condition, and the primary outcome measure was number of omissions. The continuous performance test (CPT) was administered to measure sustained attention. Specifically, participants were instructed to monitor a series of letters and respond when the letter X appeared after the letter A (AX-CPT, Rosvold, Mirsky, Sarason, Bransome Jr, & Beck, 1956). Sustained attention was measured by the percent of correct responses. Finally, the reverse CPT, a go/no-go task, was administered to index response inhibition and sustained attention. Participants were instructed to respond after the presentation of every letter except for the letter X (Not-X CPT; Conners, 1995). The number of commissions was utilized as the outcome measure for response inhibition and the number of omissions was utilized as outcomes measure of sustained attention.

Self-report Measures

Self-report measures of post-concussive symptoms and psychiatric symptoms were collected at baseline and six months later; self-report of PTSD symptoms was administered at baseline only. PTSD symptoms were evaluated with the PTSD Checklist Civilian Version (PCL-C). The PCL-C is a 17-item questionnaire that assesses the specific symptoms of PTSD based on the DSM-IV. Participants were asked to rate how much the problem described in each statement has bothered him or her over the past month on a five-point scale ranging from 1 (not at all) to 5 (extremely). This measure has been shown to have excellent reliability and validity (Blanchard et al., 1996; Weathers et al., 1993). The total score of PCL-C was used as the measure of interest in the current study.

Psychiatric symptoms were measured with the Brief Symptom Inventory 18 (BSI-18), an 18-item self-report questionnaire designed to assess current psychological distress (Derogatis, 1992). The BSI-18 is an abbreviated version of the 90-item Symptom Checklist and 53-item Brief Symptom Index. Respondents are instructed to rate their level of distress over the past 7 days using a 5-point scale ranging from 0 (not at all) to 4 (extremely often). This questionnaire contains three clinical subscales (i.e., somatization, depression, and anxiety) and a total based on all items called the Global Severity Index (GSI). The reliability and validity of the BSI-18 has been well-established in community and clinical samples, including a sample of patients with moderate to severe TBI (Meachen et al., 2008).

Post-concussive symptoms were assessed using the Rivermead Post-Concussion Symptoms Questionnaire (RPQ; King et al., 1995). The RPQ is a 16-item questionnaire that evaluates how much of a problem post-concussion symptoms are now (i.e., the past 24 hours) compared with before the injury on a five-point scale: 0 (not experienced at all), 0 (no more of a problem), 2 (a mild problem), 3 (a moderate problem), and 4 (a severe problem). Questions assess somatic, emotional, and cognitive symptoms associated with concussion. Factor analysis has shown goodness-of-fit for a three-factor model with the existence of separate cognitive, emotional, and somatic factors (Potter et al., 2006). Because the present study is most interested in cognitive problems following mTBI and we wanted to avoid overlap between psychological symptoms reported on the Rivermead and the PCL-C and BSI-18, only the cognitive cluster of symptoms was utilized. This included three symptoms: 1) forgetfulness, poor memory; 2) poor concentration; and 3) taking longer to think.

Data Analysis Plan

For the first aim, several ERP measures were analyzed for the visual and auditory tasks: 1)

target and novel time-domain N1, P2, N2, P3, and slow wave (SW) components, 2) target and novel time-frequency delta and theta PCs, 3) target and novel time-frequency theta ITPS, and 4) and target and novel time-frequency theta ICPS between medial prefrontal and bilateral prefrontal electrode sites. First, each of these measures was analyzed in separate ANCOVAs of group (mTBI vs. IC vs. HSM) with age, education, and PTSD symptom severity included as covariates to assess baseline differences between the mTBI and control groups. These measures were then assessed in 2 X 2 ANOVAs of group (TBI vs. IC) by time (baseline vs. six months later) to evaluate change in brain functioning over time. Next, to replicate previous work and to validate the present TF measures, multiple regression models with simultaneous entry of predictors were used to show the contributions of delta and theta to the time-domain components. To assess neuropsychological functioning, measures indexing working memory, processing speed, sustained attention, and response inhibition were analyzed in separate ANCOVAs of group (mTBI vs. IC vs. HSM) with age, education, and PTSD symptom severity included as covariates. These measures were then assessed in 2 X 2 ANOVAs of group (mTBI vs. IC) by time point (baseline vs. six months later).

Prior to conducted the above analyses, each of these measures were assessed for normality using visual inspection of histograms and the Shapiro-Wilks test. Variables that violated the assumption of normality, namely the neuropsychological measures and time-frequency amplitude measures, were transformed using the TransformTukey function in R (*TransformTukey Function | R Documentation*, n.d.). This function uses Tukey's Ladder of Powers to conduct all common transformations for each variable and select the one that maximizes the Shapiro-Wilks W statistic.

Analyses for the second aim included assessing the convergent validity of ERP measures by conducting spearman correlations between abnormal ERP measures (i.e., measures that showed significant differences between the mTBI and control groups at baseline), NP measures, and

cognitive post-concussion symptoms. To evaluate ERP measures and psychiatric symptoms as risk factors for cognitive post-concussion symptoms in the mTBI group, a few types of analyses were conducted. First, spearman correlations were assessed between psychiatric symptoms and post-concussion symptoms at baseline and follow-up. In addition, logistic regressions were conducted to assess the power of baseline abnormal ERP measures and psychiatric symptoms to predict the presence of cognitive post-concussion symptoms in the acute period (baseline) and chronic period (six months later).

Finally, to evaluate the third aim, a series of t-tests were conducted between blast and impact mTBI subgroups at baseline on the ERP and neuropsychological measures previously described.

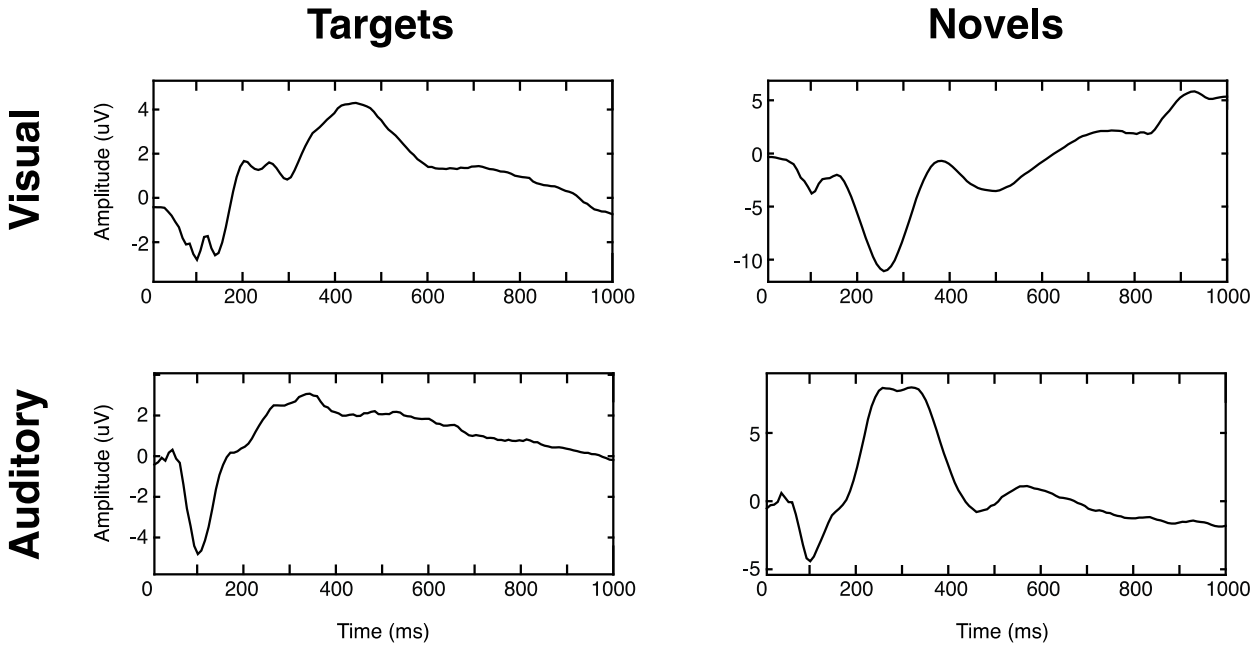
Chapter 3: Results

Time-Domain Amplitude and Latency

Figure 2 displays the average time-domain waveforms for visual oddball targets and novels. Targets are plotted at a cluster of three midline electrodes, FCz, Cz, and CPz, while novels are plotted at Fz, FCz, and Cz. The N2 and P3 are the primary components of interest in our analyses, although the N1, P2, and slow wave (SW) components were also assessed.

Figure 2

Grand Average Time-Domain Waveforms



Note. Grand average time-domain waveforms elicited by visual and auditory oddball target and novel stimuli. Targets are plotted at the mean of FCz, Cz, and CPz, and novels are plotted at the mean of Fz, FCz, and Cz.

Visual Targets

To test for the effects of mTBI on these components, ANCOVAs were performed comparing the three groups at baseline, with age and education included in the model as covariates.

For visual targets, a main effect of group was observed for P3 amplitude ($F(2,163) = 3.33$, $p = 0.04$) but not for N2 amplitude ($F(2,163) = 1.69$, $p = 0.19$). P2 amplitude also differed significantly between groups ($F(2,163) = 3.83$, $p = 0.02$), while N1 and SW amplitudes showed trend-level group effects (N1: $F(2,163) = 2.54$, $p = 0.08$; SW: $F(2,163) = 2.77$, $p = 0.07$). Many of these effects diminished when controlling for PTSD symptom severity, and only the effect of group on P3 amplitude remained significant ($F(2,153) = 3.40$, $p = 0.04$). Pairwise comparisons of marginal means revealed significantly reduced P3 amplitude for the mTBI group relative to the IC group ($t(156) = -2.38$, $p = 0.049$). Marginal means of P3 amplitude by group are presented in Table 3.

ANOVAs of group (mTBI vs. IC) by time (baseline vs. six months), to index change over time, revealed a main effect of time for P2 amplitude ($F(1,86) = 4.29$, $p = 0.04$) and N2 amplitude ($F(1,86) = 4.99$, $p = 0.03$), where P2 amplitude decreased with time and N2 amplitude increased with time (i.e., became more negative). Results also showed a main effect of group for P3 amplitude ($F(1,119) = 4.21$, $p = 0.04$) and a trend-level effect of group for SW amplitude ($F(1,119) = 3.72$, $p = 0.06$). Pairwise comparisons revealed no group differences at the six month follow-up for any components (N1: $t(92) = -0.80$, $p = 0.43$; P2: $t(92) = 1.22$, $p = 0.23$; N2: $t(92) = -1.18$, $p = 0.24$; P3: $t(92) = -1.02$, $p = 0.31$; SW: $t(92) = -0.92$, $p = 0.36$).

ANCOVAs were also performed on the latency of visual target N1, P2, N2, P3, and SW at baseline, and results showed a trend-level effect of group on P3 latency when controlling for age and education ($F(2,163) = 2.51$, $p = 0.08$). The effect of group on P3 latency strengthened with the addition of PTSD symptom severity as a covariate in the model ($F(2,153) = 3.12$, $p = 0.048$). Pairwise comparisons of marginal means demonstrated a significantly longer P3 latency for the mTBI group relative to the HSM group ($t(156) = 2.48$, $p = 0.04$). Marginal means are presented in Table 3. ANOVAs of group (mTBI vs. IC) by time (baseline vs. six months) on the latency of

visual target components revealed no significant effects, and pairwise comparisons showed no significant group differences at the six month follow-up for any components (N1: $t(92) = -0.43$, $p = 0.67$; P2: $t(92) = -1.00$, $p = 0.32$; N2: $t(92) = 0.69$, $p = 0.49$; P3: $t(92) = -1.08$, $p = 0.29$; SW: $t(92) = 1.89$, $p = 0.06$).

Table 3

Marginal Means of Visual Oddball Target P3

	Marginal Means	
Group	P3 Amplitude (uV)	P3 Latency (sec.)
TBI	6.56	440
IC	9.07	436
HSM	8.56	400

Visual Novels

To assess the effects of group in response to visual novel stimuli, ANCOVAs were conducted comparing the three groups at baseline and controlling for age and education. Significant main effects of group were observed for N2 amplitude ($F(2,163) = 3.43$, $p = 0.03$), P3 amplitude ($F(2,163) = 3.86$, $p = 0.02$), and SW amplitude ($F(2,163) = 3.85$, $p = 0.02$). After controlling for PTSD symptoms severity, the effect of group on N2 and SW amplitudes remained significant (N2: $F(2,153) = 4.70$, $p = 0.01$; SW: $F(2,153) = 3.14$, $p = 0.046$) but reduced to trend-level for P3 amplitude (P3: $F(2,153) = 2.58$, $p = 0.08$). Pairwise comparisons of marginal group means revealed enhanced N2 and SW amplitudes for the IC group relative to the HSM group (N2: $t(156) = -3.06$, $p = 0.008$; SW: $t(156) = 2.50$, $p = 0.04$), and reduced P3 amplitude for the mTBI group relative to the HSM group ($t(156) = -2.24$, $p = 0.07$). Marginal means of visual novel N2, P3, and SW amplitudes are presented in Table 4.

To evaluate the effect of group (mTBI vs. IC) and time (baseline vs. six months) on visual novels, 2 X 2 ANOVAs were conducted. Results revealed a main effect of time for SW amplitude ($F(1,86) = 4.52$, $p = 0.04$), with reductions in amplitude with time. A trend-level interaction between group and time was observed for N2 amplitude ($F(1,86) = 3.30$, $p = 0.07$), where N2 amplitude decreased with time for the IC group and remained relatively stable for the mTBI group. Pairwise comparisons revealed no significant group differences at the six month follow-up for any of these components.

ANCOVAs were performed on the latency of visual novel components at baseline, and results indicated a significant effect of group for N2 latency ($F(2,163) = 4.19$, $p = 0.02$) and P3 latency ($F(2,163) = 7.92$, $p = 0.001$). These effects remained significant after controlling for PTSD symptom severity (N2: $F(2,153) = 4.85$, $p = 0.009$; P3: $F(2,153) = 3.78$, $p = 0.03$). Pairwise comparisons of marginal means showed delayed latencies for the mTBI relative to the HSM group (N2: $t(156) = 2.44$, $p = 0.04$; P3: $t(156) = 2.74$, $p = 0.02$) and for the IC relative to the HSM group (N2: $t(156) = 3.10$, $p = 0.007$; P3: $t(156) = 2.10$, $p = 0.09$). These marginal latency means are presented in Table 4. ANOVAs of group (mTBI vs. IC) by time (baseline vs. six months) on the latency of visual novel components revealed no significant effects, and pairwise comparisons revealed no significant group differences at the six month follow-up.

Table 4

Marginal Means of Visual Oddball Novel Time-Domain Components

	Marginal Means				
Group	N2 Amplitude	P3 Amplitude	SW Amplitude	N2 Latency	P3 Latency
TBI	-12.45	1.03	7.61	261	407
IC	-14.55	1.15	8.63	268	403
HSM	-9.59	3.99	6.13	245	380

Note. Amplitude is in microvolts (uV) and latency is in seconds.

Auditory Targets

Figure 2 displays the average time-domain waveforms for auditory oddball targets and novels. As with the visual oddball data, the N2 and P3 were the primary components of interest in our analyses, although the N1, P2, and slow wave components were also assessed. The effect of mTBI on the amplitude and latency of auditory target components was assessed using ANCOVAs (i.e., controlling for age and education). Results revealed no significant effects of group on N2 or P3 amplitudes or latencies, but there was a significant effect of group on N1 amplitude ($F(2,161) = 4.69$, $p = 0.01$) and latency ($F(2,161) = 3.11$, $p = 0.047$). These effects remained significant when controlling for PTSD symptom severity (Amplitude: $F(2,152) = 4.22$, $p = 0.02$; Latency: $F(2,152) = 4.71$, $p = 0.01$). Pairwise comparisons of marginal means revealed that N1 amplitude was significantly larger and N1 latency was significantly longer for the HSM group compared to the mTBI group (Amplitude: $t(155) = 2.89$, $p = 0.01$; Latency: $t(155) = -2.61$, $p = 0.03$). In addition, N1 latency was longer for the IC relative to the mTBI group at a trend-level ($t(155) = -2.15$, $p = 0.08$). Table 5 displays the marginal means of N1 amplitude and latency by group. ANOVAs of group (mTBI vs. IC) by time (baseline vs. six months) indicated no significant changes over time, and pairwise comparisons at the six month assessment revealed no significant group differences.

Table 5

Marginal Means of Auditory Oddball Target N1

	Marginal Means	
Group	N1 Amplitude (uV)	N1 Latency (sec.)
TBI	-5.50	102
IC	-6.12	111
HSM	-7.72	114

Auditory Novels

The same analyses were conducted on auditory novel components. Results revealed no significant group difference for the amplitude and latency of any of the components. In addition, analysis of change over time indicated no significant effects.

Time-Frequency Amplitude

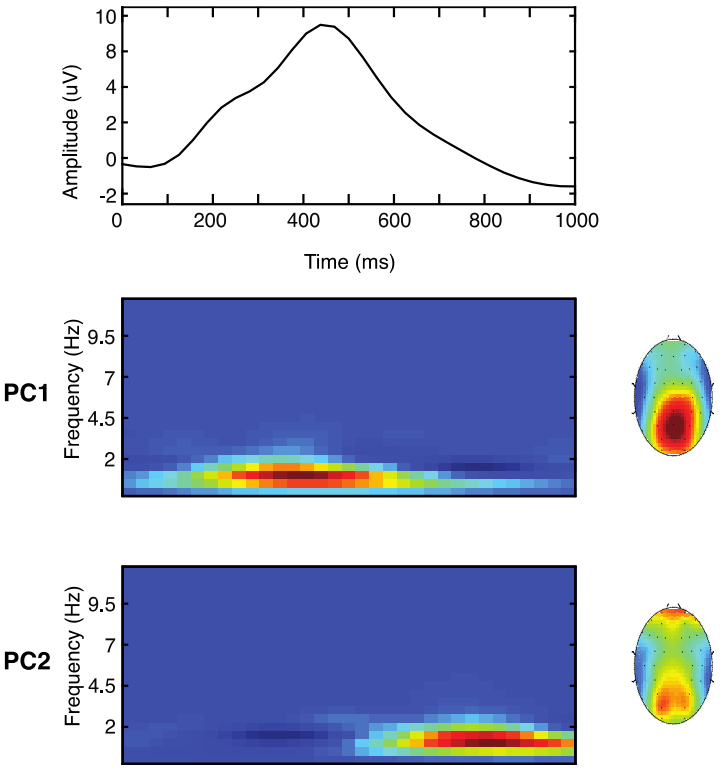
Visual Targets - Delta

Figures 3 and 4 depict the time-frequency average waveform and PCA decomposition for the visual target stimulus-locked ERPs for delta and theta. A two factor PCA solution explaining 44% of the total variance was selected based on the scree plot as the best representation of delta activity to target stimuli. PC1 represented delta activity during the P3 time range (i.e., 250 ms – 600 ms) while PC2 reflected late delta activity (i.e., after 600 ms). Electrode Pz was chosen for further analysis of PC1 based on the topographical center of maximal target stimulus activation, and a cluster of parietal electrodes (PO3, P3, PO4, P4) was chosen similarly for further analysis of PC2.

To evaluate the effects of mTBI on these components, ANCOVAs were performed comparing the three groups at baseline, with age and education included in the model as covariates. Results showed no significant effect of group for PC1 ($F(2,163) = 1.55$, $p = 0.22$) or PC2 ($F(2,163) = 1.15$, $p = 0.34$). Group effects remained non-significant when controlling for PTSD symptom severity. Analyses of group (mTBI vs. IC) by time (baseline vs. six months) showed trend-level main effects of time for both PC1 ($F(1,86) = 3.63$, $p = 0.06$) and PC2 ($F(1,86) = 3.67$, $p = 0.06$), where delta amplitude decreased with time for both groups. Pairwise comparisons revealed no significant differences at six months for PC1 ($t(92) = -0.05$, $p = 0.96$) and PC2 ($t(92) = 0.78$, $p = 0.44$).

Figure 3

Time-Frequency PCA Decomposition of Delta Activity to Visual Oddball Targets



Note. The grand average delta waveform and two time-frequency principal components are displayed.

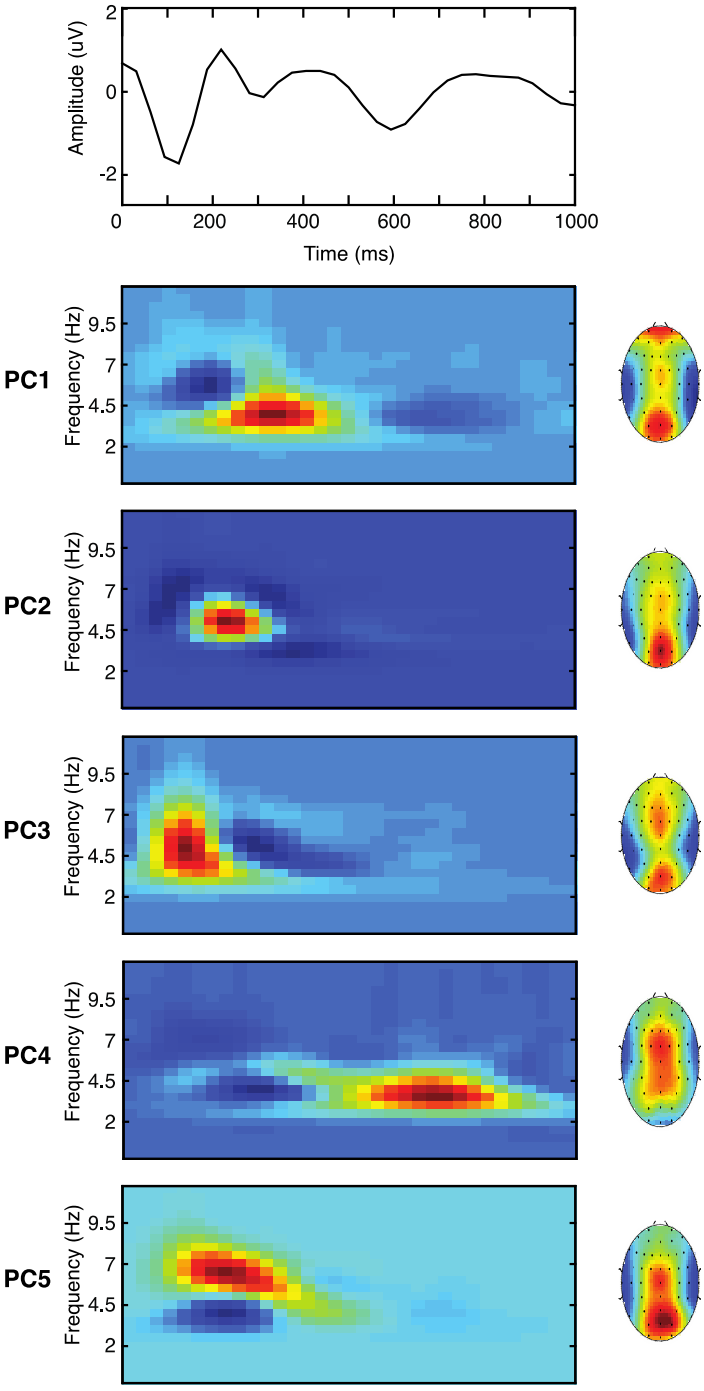
Visual Targets - Theta

For theta activity in response to visual targets, a five factor PCA solution explaining 32% of the variance was selected as the best representation of the data based on the scree plot. PC1 represented activity in the N2/P3 time window (i.e., 200 ms – 500 ms), PC2 reflected activity around P2 (i.e., 125 ms – 300 ms), PC3 represented activity in the N1 window (i.e., 50 ms – 200 ms), PC4 reflected the negative deflection following P3 (i.e., 500 ms – 800 ms), and PC5 represented high theta activity during the P2/N2 (i.e., 125 ms – 400 ms). A cluster of frontocentral electrodes (i.e., Fz, FCz, and Cz) was selected for further analysis of all PCs based on the topographical center of maximal target activity.

ANCOVAs of group differences at baseline revealed a significant effect for PC4 ($F(2,163) = 5.34$, $p = 0.01$), and this effect strengthened when controlling for PTSD symptom severity ($F(2,153) = 7.06$, $p = 0.001$). Pairwise comparisons of marginal means revealed significantly reduced theta activity for the mTBI group compared to the IC group ($t(156) = -3.09$, $p = 0.007$) and the HSM group ($t(156) = -2.78$, $p = 0.02$). No other group differences were observed at baseline for the other theta PCs. ANOVAs of group (mTBI vs. IC) by time (baseline vs. six months) revealed a significant interaction for PC4 ($F(1,86) = 6.15$, $p = 0.01$), where theta decreased over time for the IC group and increased for the mTBI group. Pairwise comparisons indicated no significant difference in theta between the mTBI and IC groups at six months ($t(92) = -1.46$, $p = 0.15$). Group by time effects for the other theta PCs were not statistically significant.

Figure 4

Time-Frequency PCA Decomposition of Theta Activity to Visual Oddball Targets



Note. The grand average theta waveform and five time-frequency principal components are displayed.

Visual Novels

Figure 5 displays the time-frequency average waveform and PCA decomposition for visual novel stimulus-locked ERPs. A six factor unfiltered PCA solution explaining 35% of the total variance was selected as the best representation of the data, with components in both the theta and delta frequency ranges. Because some PCs were a reflection of novel activity spanning both frequency ranges, an unfiltered approach was more appropriate than a filtered approach that divided cohesive components into multiple components based on frequency. The unfiltered solution consisted of the following: 1) PC1 reflected delta activity during the P3 time window (i.e., 275 ms – 450 ms), 2) PC2 represented delta activity during N2 (i.e., 100 ms – 350 ms), 3) PC3 consisted of theta activity around P2/N2 (i.e., 150 ms – 275 ms), 4) PC4 reflected late slow wave activity (i.e., around 700-1000 ms), 5) PC5 represented theta activity during N2/P3 (250 ms – 350 ms), and 6) PC6 reflected delta activity after P3 (i.e., around 350-650 ms). Electrode clusters for analysis were selected based on the topographical center of maximal activation to novel stimuli, including Cz and CPz for PC1, Fz and FCz for PC2 and PC4, and FCz and Cz for PC3, PC5, and PC6.

ANCOVAs assessing group differences at baseline with age and education as covariates revealed significant effects of group on delta N2 (PC2: $F(2,163) = 3.43$, $p = 0.03$) and the late slow wave component (PC4: $F(2,163) = 8.13$, $p < 0.001$). In addition, a trend-level effect of group on delta P3 was observed (PC1: $F(2,163) = 2.92$, $p = 0.06$). The addition of PTSD symptom severity as a covariate strengthened the effect of group on visual novel PCs in most cases. Namely, significant group effects were found for delta P3 (PC1: $F(2,153) = 3.42$, $p = 0.04$), the late slow wave component (PC4: $F(2,153) = 7.73$, $p < 0.001$), and theta N2/P3 (PC5: $F(2,153) = 4.15$, $p = 0.02$). In addition, results showed trend-level effects of group on delta N2 (PC2: $F(2,153) = 2.83$,

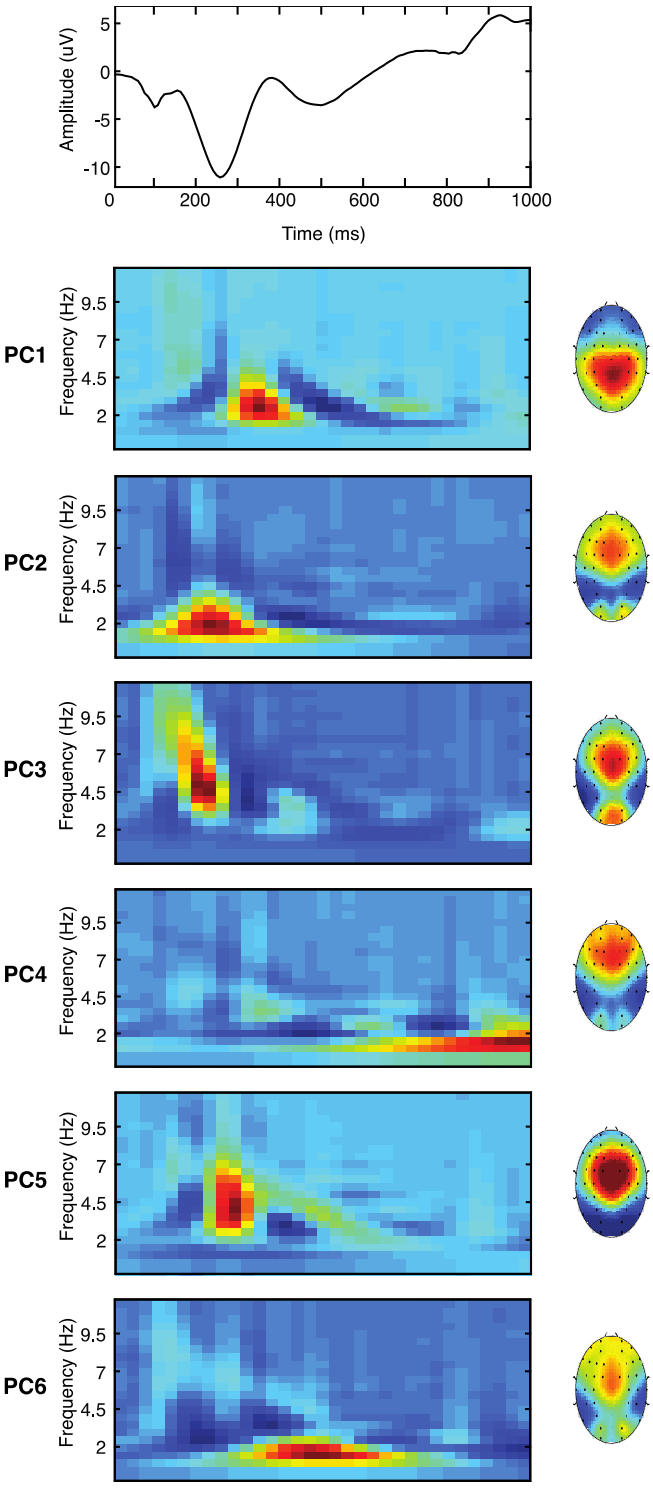
$p = 0.06$) and theta P2/N2 (PC3: $F(2,153) = 2.59$, $p = 0.08$).

Pairwise comparisons of marginal means showed larger delta P3 activity (PC1: ($t(156) = 2.57$, $p = 0.03$), delta N2 activity (PC2: $t(156) = 2.33$, $p = 0.06$), and theta N2/P3 activity (PC5: $t(156) = 2.85$, $p = 0.01$) for the IC group relative to the HSM group, with mTBI group means somewhere in the middle of the two control groups. In addition, late slow wave activity was greater for the IC group than the mTBI group (PC4: $t(156) = -2.75$, $p = 0.02$) and HSM group (PC4: $t(156) = 3.84$, $p < 0.001$) and somewhat heightened for the mTBI group relative to the HSM group (PC4: $t(156) = 2.13$, $p = 0.09$). Finally, a trend-level increase in theta P2/N2 activity was observed for the mTBI relative to the IC group (PC3: $t(156) = 2.25$, $p = 0.07$).

ANOVAs of group (mTBI vs. IC) by time (baseline vs. six months) revealed significant main effects of time for delta P3 (PC1: $F(1,86) = 6.54$, $p = 0.01$), late slow wave activity (PC4: $F(1,86) = 5.86$, $p = 0.02$), and theta N2/P3 (PC5: $F(1,86) = 6.64$, $p = 0.01$), where amplitude decreased with time across groups. Pairwise comparisons between the mTBI and IC groups at the six month follow-up revealed no significant differences (PC1: $t(92) = -0.98$, $p = 0.33$; PC2: $t(92) = -0.79$, $p = 0.43$; PC3: $t(92) = 1.42$, $p = 0.16$; PC4: $t(92) = -0.46$, $p = 0.65$; PC5: $t(92) = -1.65$, $p = 0.10$; PC6: $t(92) = 0.66$, $p = 0.51$).

Figure 5

Time-Frequency PCA Decomposition of Visual Oddball Novels



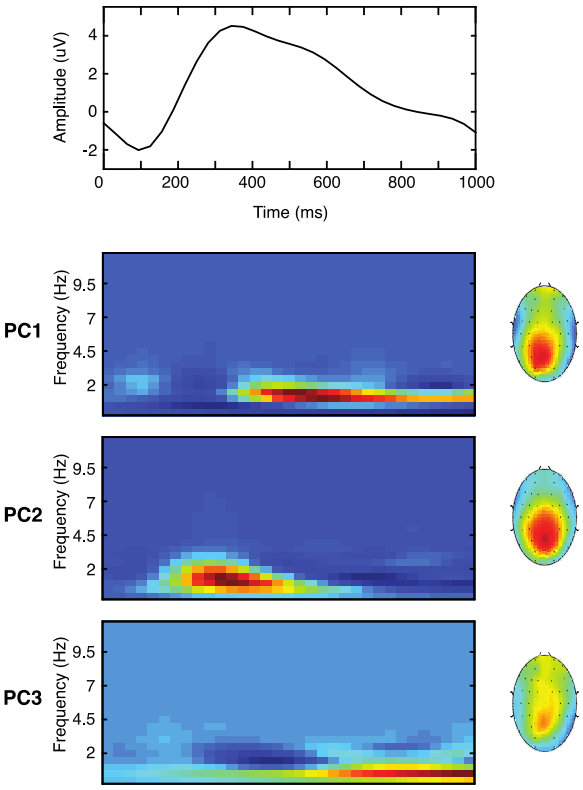
Note. The grand average unfiltered waveform and six time-frequency principal components are displayed.

Auditory Targets - Delta

Figures 6 depicts the time-frequency average waveform and PCA decomposition for the auditory target stimulus-locked ERPs for delta. A three factor PCA solution explaining 42% of the total variance was selected based on the scree plot as the best representation of delta activity to target stimuli. PC1 represented delta activity following the P3 peak (i.e., after 375 ms), PC2 reflected delta activity during the P3 time window (i.e., 200 ms – 450 ms), and PC3 reflected late slow wave activity (i.e., after 500 ms). A central-parietal cluster of electrodes (i.e., Cz, CPz, and Pz) was chosen for further analysis based on the topographical center of maximal auditory target stimulus activation.

Figure 6

Time-Frequency PCA Decomposition of Delta Activity to Auditory Oddball Targets



Note. The grand average delta waveform and three time-frequency principal components are displayed.

To assess the effects of mTBI on delta activity to auditory targets, ANCOVAs controlling

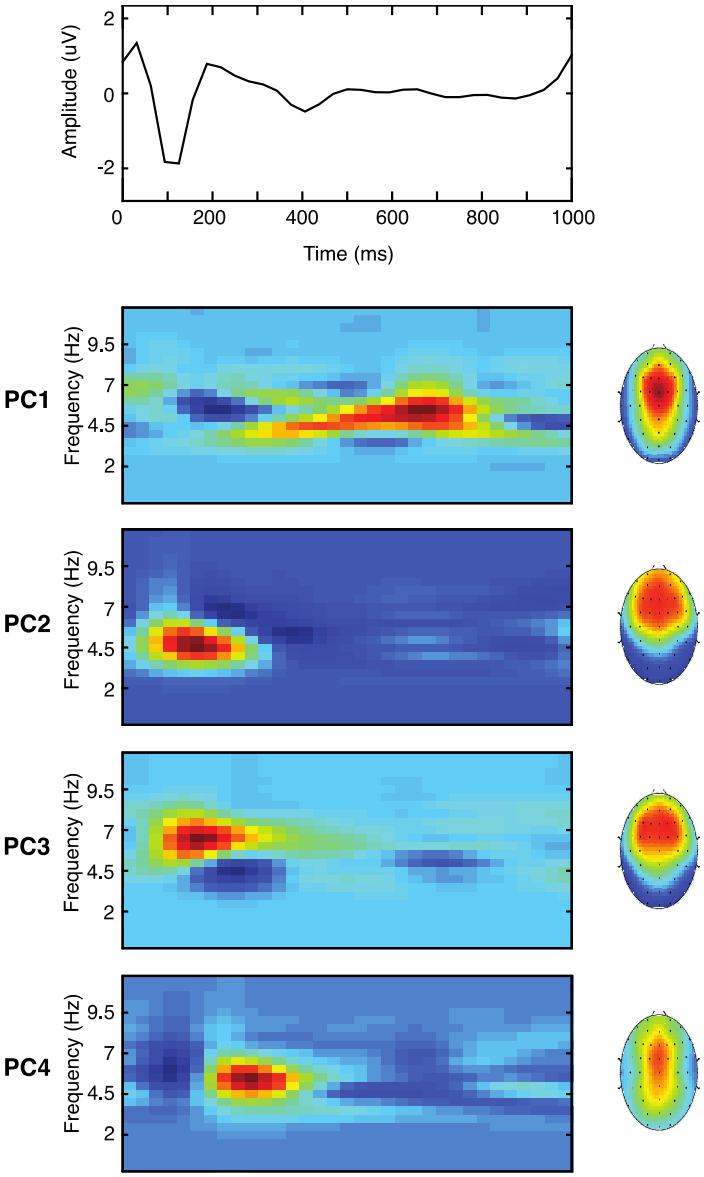
for age and education were performed. No significant group differences were observed for any of the PCs for the central-parietal region of interest. However, a significant group effect was found in P3 delta for a frontocentral cluster of electrodes around FCz (PC2: $F(2,161) = 5.22$, $p = 0.006$), and this effect remained significant after controlling for PTSD symptoms (PC2: $F(2,152) = 5.39$, $p = 0.006$). Pairwise comparisons revealed significantly larger delta P3 amplitude for the IC group relative to the mTBI group at baseline (PC2: $t(155) = -3.10$, $p = 0.007$). ANOVAs of group (mTBI vs. IC) by time (baseline vs. six months) showed a main effect of time for PC1 ($F(1,87) = 4.17$, $p = 0.04$) such that both groups decreased in amplitude with time. In addition, a main effect of group was observed for the frontocentral region of P3 delta (PC2: $F(1,115) = 7.41$, $p = 0.01$). Pairwise comparisons revealed no significant group differences for any of the components at six months (PC1: $t(91) = 0.60$, $p = 0.55$; PC2: $t(91) = -0.98$, $p = 0.33$; PC3: $t(91) = 0.72$, $p = 0.48$).

Auditory Targets - Theta

Figures 7 depicts the time-frequency average waveform and PCA decomposition for the auditory target stimulus-locked ERPs for theta. For theta activity to auditory targets, a four factor solution explaining 23% of the total variance was selected based on the scree plot and best representation of the data. PC1 represented theta activity following the P3 (i.e., 350 ms – 750 ms), PC2 reflected theta activity during the N1/P2 window (i.e., 50 ms – 250 ms), PC3 reflected higher theta activity during the same N1/P2 time range, and PC4 represented theta activity during the N2/P3 time range (i.e., 200 ms – 375 ms). Two frontal electrodes (i.e., Fz and FCz) were chosen for further analysis based on the topographical center of maximal theta activity during target stimulus processing.

Figure 7

Time-Frequency PCA Decomposition of Theta Activity to Auditory Oddball Targets



Note. The grand average theta waveform and four time-frequency principal components are displayed.

ANCOVAs assessing group differences at baseline revealed a significant effect for high theta during N1/P2 (PC3: $F(2,161) = 3.64$, $p = 0.03$) but no other components, and this effect remained significant after controlling for PTSD symptom severity ($F(2,152) = 3.69$, $p = 0.03$). Pairwise comparisons of marginal means showed that the IC group had significantly more early theta activity than the mTBI group (PC3: $t(155) = -2.57$, $p = 0.03$). ANOVAs of group (mTBI vs. IC) by time (baseline vs. six months) revealed a significant interaction for PC3 ($F(1,87) = 6.78$, p

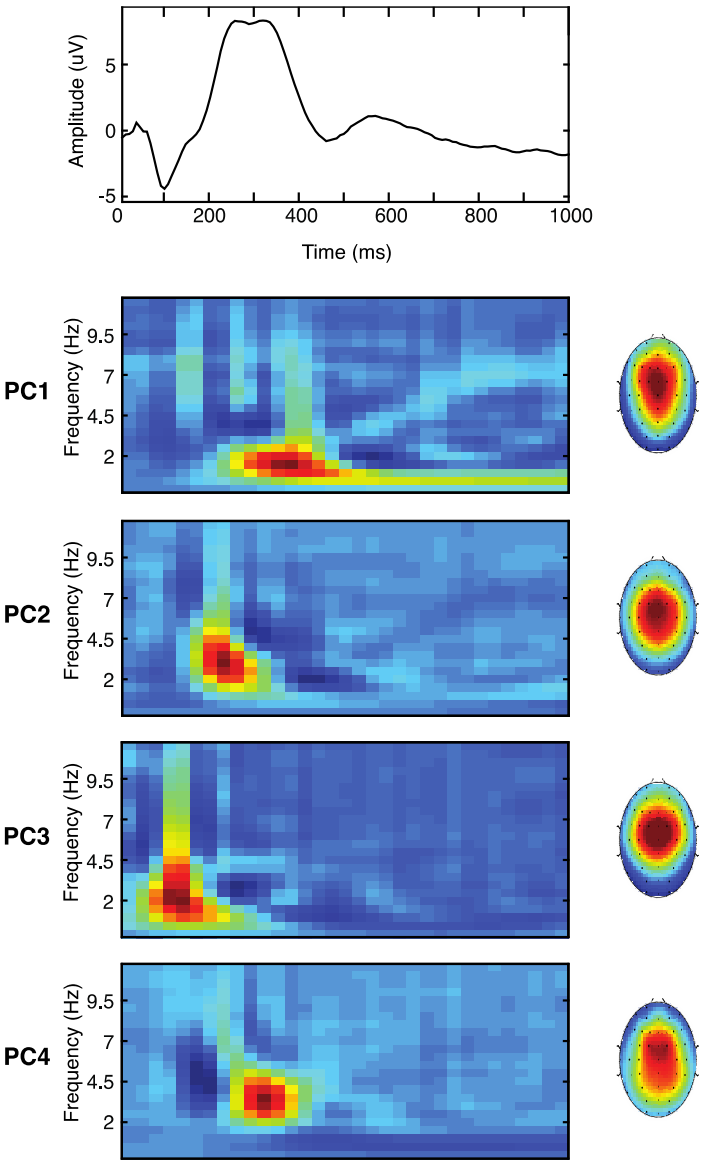
= 0.01), where early theta amplitude decreased with time for the IC group but remained relatively stable for the mTBI group. In addition, a main effect of time was observed for PC1 ($F(1,87) = 9.58$, $p = 0.003$), such that theta amplitude decreased with time for both groups. No group differences were observed at the six month assessment (PC1: $t(91) = 1.26$, $p = 0.21$; PC2: $t(91) = -1.62$, $p = 0.11$; PC3: ($t(91) = -0.60$, $p = 0.55$; PC4: ($t(91) = -0.13$, $p = 0.90$).

Auditory Novels

Figure 8 displays the time-frequency average waveform and PCA decomposition for auditory novel stimulus-locked ERPs. A four factor unfiltered PCA solution explaining 25% of the total variance was selected as the best representation of the data, with components in both the theta and delta frequency ranges. As with the decomposition of visual novels, some PCs were a reflection of auditory novel activity spanning both frequency ranges. Thus, an unfiltered approach was more appropriate that a filtered approach that divided cohesive components into multiple components based on frequency. PC1 reflected delta activity during the P3 time window (i.e., 250 ms – 475 ms), PC2 represented high delta/low theta activity during the P2 window (i.e., 175 ms – 300 ms), PC3 reflected high delta/low theta activity during N1 (i.e., 50ms – 200 ms), and PC4 reflected high delta/low theta activity during P3 (i.e., 250 ms – 400 ms). A cluster of two electrodes, FCz and Cz were chosen based on the topographical center of maximal auditory novel activity.

Figure 8

Time-Frequency PCA Decomposition of Auditory Oddball Novels



Note. The grand average unfiltered waveform and four time-frequency principal components are displayed.

ANCOVAs controlling for age and education were conducted to assess the effects of mTBI on auditory novel stimulus processing. No significant effects of group were observed at baseline. ANOVAs of group (mTBI vs. IC) by time (baseline vs. six months) revealed a significant interaction for PC3 ($F(1,87) = 7.36$, $p = 0.01$), where N1 activity increased for the mTBI group

with time and decreased for the IC group. Pairwise comparisons revealed no significant differences between the mTBI and IC groups at six months.

Time-frequency delta and theta predicting time-domain components

To replicate previous work and validate the present TF measures, multiple regression models with simultaneous entry of predictors were used to show the contributions of delta and theta to the time-domain N2 and P3 components (see Table 6). For visual targets, theta and delta components during the time range of N2 and P3 were included as independent variables in a multiple regression model predicting time-domain N2 and P3 components. For visual targets, results revealed that delta and theta uniquely predicted N2 amplitude but only delta predicted P3 amplitude. For visual novels, delta and theta components significantly predicted N2 amplitude. Only one component for visual novels, spanning delta and theta frequencies, was in the time range of the P3, and this component significantly predicted P3 amplitude. For auditory targets, delta and theta components predicted N2 and P3 amplitude. Finally, for auditory novels, only theta predicted P3 amplitude at a trend-level. The novel N2 component is not apparent in the time-domain waveform, which may explain why delta and theta were not significant predictors.

Table 6

Multiple Regression of Delta and Theta Predicting Time-Domain Components

		Delta		Theta		Overall
		Beta	T	Beta	T	Adj. R2
Visual Targets	N2	0.46	6.64***	-0.20	-2.94**	0.21***
	P3	0.70	12.84***	0.05	0.88	0.51***
Visual Novels	N2	-0.61	-20.51***	-0.50	-16.68***	0.88***
	P3	0.38	5.26***	--	--	0.14***
Auditory Targets	N2	0.22	2.78**	-0.19	-2.49*	0.05**
	P3 (early theta)	0.69	12.50***	0.10	1.88+	0.53***
	P3 (late theta)	0.72	14.80***	0.30	6.24***	0.61***
Auditory Novels	N2	-0.08	-0.98	-0.10	-1.18	0.01
	P3	0.05	0.58	0.16	1.86+	0.02+

Note. Multiple regressions of theta and delta components predicting time-domain N2 and P3 components. Only one component for visual novels, spanning delta and theta frequencies, was in the time range of the P3, so the statistics for that component are presented under the Delta column. +$p < 0.10$; *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$

Inter-trial phase synchrony

Visual Oddball

The PC solutions extracted for amplitude were applied to the ITPS computation (as a filter, or mask), extracting ITPS activity directly corresponding to the amplitude measure TF regions defined by the TF-PCA. For visual targets, the five factor theta solution was applied to the ITPS computation, and ANCOVAs controlling for age and education were conducted. Results showed no significant effects of group; however, the effect of group on theta ITPS after P3 was trend-level after controlling for PTSD symptom severity (PC4: $F(2,152) = 2.84$, $p = 0.06$). Pairwise comparisons of marginal means demonstrated a trend-level difference between the mTBI and HSM group (PC4: $t(155) = -2.21$, $p = 0.07$), with less ITPS in the mTBI group relative to the HSM group. Group (mTBI vs. IC) by time (baseline vs. six months) analysis revealed no significant

effects, and pairwise comparisons revealed no significant differences between groups at six months.

For visual novels, the six factor unfiltered solution was applied to the ITPS computation, and ANCOVAs revealed no significant group differences in ITPS for any of the components at baseline. Group (mTBI vs. IC) by time (baseline vs. six months) analysis revealed no significant effects, and pairwise comparisons revealed no significant differences between groups at six months.

Auditory Oddball

For auditory targets, the four factor theta solution was applied to the ITPS computation, and ANCOVAs revealed no significant effects of group at baseline. Group (mTBI vs. IC) by time (baseline vs. six months) analysis revealed a significant interaction for theta N1/P2 ITPS (PC3: $F(1,86) = 5.96$, $p = 0.02$), where ITPS for the IC group decreased more than the mTBI group with time. No significant difference was observed for theta N1/P2 ITPS at six months (PC3: $t(91) = 0.52$, $p = 0.61$).

For auditory novels, the four factor unfiltered PCA solution was applied to ITPS, and ANCOVAs assessing group differences at baseline were conducted. Results revealed a significant difference in ITPS between groups for theta during N1 (PC3: $F(2,161) = 6.54$, $p = 0.002$). These effects remained significant after controlling for PTSD symptom severity (PC3: $F(2,152) = 7.18$, $p = 0.001$). Pairwise comparisons of marginal means showed significantly greater ITPS for the mTBI group versus the IC group (PC3: $t(155) = 2.61$, $p = 0.02$), and a trend-level increase in ITPS for the HSM group relative to the mTBI group (PC3: $t(155) = -2.10$, $p = 0.09$). Group (mTBI vs. IC) by time (baseline vs. six months) analysis revealed a significant interaction for ITPS during

the P2 time range (PC2: $F(1,87) = 4.74$, $p = 0.03$), such that ITPS for the IC group increased more than the mTBI group with time. In addition, a main effect of time on ITPS during the N1 time range was observed (PC3: $F(1,87) = 6.67$, $p = 0.01$), where ITPS increased over time. No significant group differences in ITPS were observed at six months (PC1: $t(91) = 0.28$, $p = 0.78$; PC2: $t(91) = -0.82$, $p = 0.42$; PC3: $t(91) = 1.07$, $p = 0.29$; PC4: $t(91) = -1.79$, $p = 0.09$).

Inter-channel phase synchrony

Visual Oddball

As with ITPS, the PC solutions extracted for amplitude were applied to the ICPS computation (as a filter, or mask), extracting ICPS activity directly corresponding to the amplitude measure time-frequency principal components. For visual targets, the five factor theta solution was applied to the ICPS computation, and no significant group differences were observed at baseline or follow-up.

For visual novels, the six factor unfiltered solution was applied to the ICPS computation, and ANCOVAs controlling for age and education were conducted to assess group differences. As described in the method section, ICPS was computed between a medial prefrontal reference electrode (FCz) and bilateral prefrontal electrodes (cf. F3 and F4). Results demonstrated a significant effect of group for low theta ICPS during the P3 time window (PC1: $F(2,163) = 3.59$, $p = 0.03$), which remained significant when PTSD symptom severity was added as a covariate (PC1: $F(2,153) = 3.63$, $p = 0.03$). Pairwise comparisons of marginal means revealed decreased ICPS for the IC group relative to the HSM group (PC1: $t(156) = -2.67$, $p = 0.03$). ICPS for the mTBI group was in between the two control groups and did not differ significantly from either of them. Group (mTBI vs. IC) by time (baseline vs. six months) showed no significant main effects or interactions, and there were no significant differences between groups at six months.

Auditory Oddball

For auditory targets, the four factor theta solution was applied to the ICPS computation. ANCOVAs controlling for age and education revealed several significant group differences, and these effects either remained stable or strengthened with the addition of PTSD symptoms severity as a covariate (see Table 7). In every case, marginal means showed that the mTBI group had the greatest ICPS, followed by the IC group, and then the HSM group. As shown in Table 7, pairwise comparisons revealed that group effects were mainly driven by significant differences between the mTBI and HSM groups. Group (mTBI vs. IC) by time (baseline vs. six months) ANOVAs revealed no significant effects, nor did pairwise comparisons between the mTBI and IC groups at six months.

Table 7

ANCOVA Results: Group Effects on Theta ICPS to Auditory Targets

		ANCOVA		mTBI vs. IC	mTBI vs. HSM	IC vs. HSM
DV	IV	*F*(2,161)	*p*	*p*	*p*	*p*
PC1	Group	4.21	0.02*	0.41	0.02*	0.29
	Covariates					
	Age	1.07	0.30			
	Education	0.44	0.51			
	PTSD	0.60	0.44			
PC2	Group	4.89	0.009**	0.94	0.007**	0.04*
	Covariates					
	Age	1.02	0.32			
	Education	0.23	0.64			
	PTSD	1.18	0.28			
PC3	Group	5.97	0.003**	0.38	0.003**	0.12
	Covariates					
	Age	2.20	0.14			
	Education	0.09	0.76			
	PTSD	0.11	0.74			
PC4	Group	4.37	0.01*	0.43	0.01*	0.24
	Covariates					
	Age	3.14	0.08			
	Education	0.05	0.83			
	PTSD	1.27	0.26			

Note. ANCOVAs of the effect of group (mTBI vs. IC vs. HSM) on theta ICPS to auditory targets, with age, education, and PTSD symptom severity included in each model as covariates. The four factor PCA solution was applied to the ICPS computation, and ICPS was assessed between medial prefrontal (FCz) and bilateral prefrontal (F3 and F4) electrodes. The p-values of pairwise comparisons of estimated marginal group means using Tukey's multiple comparison test are also presented.

For auditory novels, the four factor unfiltered solution was applied to the ICPS computation, and no significant group differences were found at baseline or follow-up.

Neuropsychological Functioning

Table 8

Descriptive Statistics of Neuropsychology Measures by Group and Time Point

		Mean (SD)		
		mTBI	IC	HSM
WAIS-IV PSI	T1	101 (13.6)	98.6 (11.9)	103 (12.2)
	T2	109 (12.2)	108 (13.4)	-
N-back Omis	T1	22.1 (10.5)	23.0 (9.88)	22.4 (9.70)
	T2	17.7 (9.83)	17.6 (8.32)	-
R-CPT Comm	T1	15.9 (4.91)	16.9 (4.35)	14.5 (4.87)
	T2	14.7 (5.24)	15.8 (5.39)	-
R-CPT Omis	T1	33.0 (34.6)	33.3 (35.3)	15.5 (10.4)
	T2	32.8 (38.6)	24.4 (29.3)	-
Visual CPT	T1	0.95 (0.07)	0.96 (0.05)	0.99 (0.02)
	T2	0.95 (0.07)	0.98 (0.04)	-

Note. Descriptive statistics for neuropsychological measures at baseline (T1) and six months (T2).

Descriptive statistics for each neuropsychological measure are presented in Table 8. Each of the four neuropsychological measures were analyzed in ANCOVAs controlling for age and education to assess group differences. Results revealed no significant differences between groups in processing speed (WAIS-IV PSI: $F(2,124) = 0.33$, $p = 0.72$) or working memory (N-back omissions: $F(2,129) = 0.22$, $p = 0.80$). Of note, the average PSI for all three groups was between the 45th and 58th percentiles compared to normative data. Results from the reverse CPT (R-CPT) were mixed, with no significant difference for number of commission ($F(2,124) = 0.58$, $p = 0.56$), which reflects response inhibition. However, a trend-level group effect was observed for number of omissions ($F(2,124) = 2.62$, $p = 0.08$), which reflect sustained attention. In addition, sustained attention as measured by percent correct on the visual CPT was significantly different between groups ($F(2,138) = 3.58$, $p = 0.03$). Pairwise comparisons of marginal means revealed worse sustained attention for the mTBI group relative to the HSM group as indexed by percent correct

on the visual CPT ($t(138) = -2.65$, $p = 0.02$) and omissions on the R-CPT ($t(124) = 2.21$, $p = 0.07$). However, group effects on sustained attention measures weakened and became non-significant when controlling for PTSD symptoms severity (R-CPT: $F(2,121) = 1.59$, $p = 0.21$; CPT: $F(2,128) = 1.89$, $p = 0.16$).

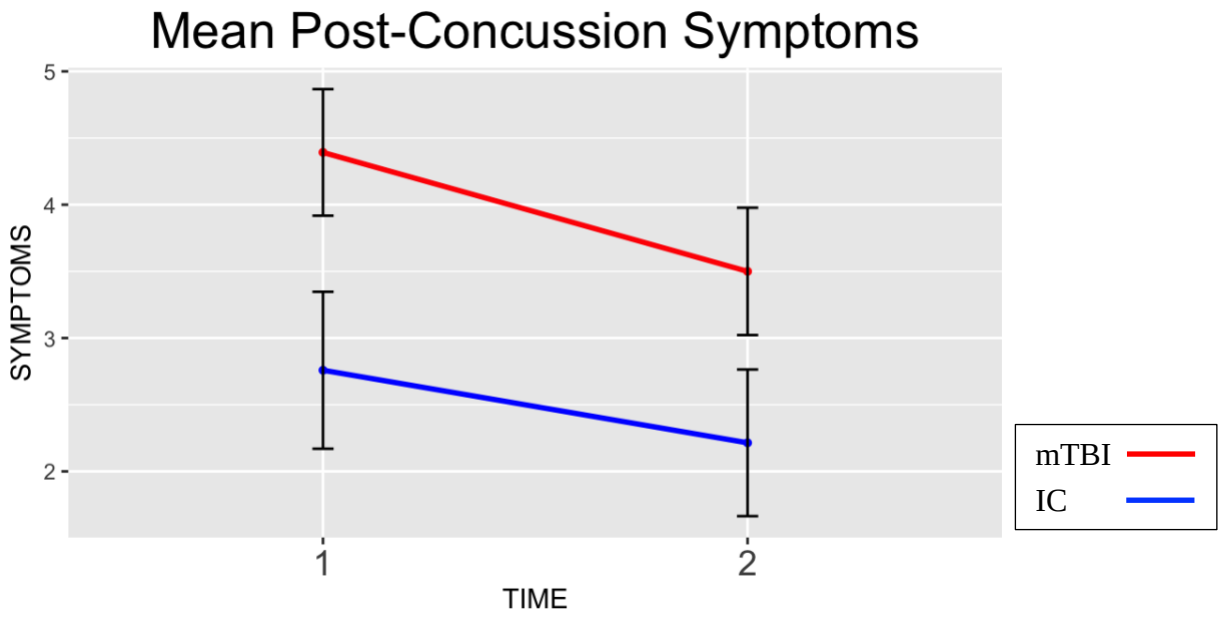
ANOVAs of group (mTBI vs. IC) by time (baseline vs. six months) were also conducted on the neuropsychological measures. Results showed a main effect of time for processing speed (WAIS-IV PSI: $F(1,78) = 82.44$, $p < 0.001$), working memory (N-back omissions: $F(1,86) = 12.94$, $p < 0.001$), and sustained attention as indexed by R-CPT omissions ($F(1,83) = 5.27$, $p = 0.02$). In all cases, performance for both groups improved with time. Pairwise comparisons revealed a significant difference in visual CPT performance between the mTBI and IC groups at six months ($t(83) = -2.27$, $p = 0.03$), but no other significant differences were observed at the six month time point.

Post-Concussion Symptoms

At baseline, 45% percent of mTBI patients and 14% of IC patients reported at least one cognitive post-concussion symptom (i.e., forgetfulness, poor concentration, and/or taking longer to think) that they did not have prior to the injury. At six months 38% of mTBI patients and 14% of IC patients endorsed at least one cognitive post-concussion symptom. A repeated-measures ANOVA of group (mTBI vs. IC) by time (baseline vs. six months) revealed significant main effects of group and time, where mean post-concussive symptoms were greater for the mTBI group than the IC group and both groups decreased with time (see Figure 9).

Figure 9

Post-Concussion Symptoms by Group and Time Point



Note. Mean cognitive post-concussion symptoms for the mTBI group vs. IC group at baseline (Time 1) and six months later (Time 2).

Correlations: EEG/ERP measures, NP tests, and post-concussion symptoms

Spearman rank-order correlations were computed between EEG/ERP measures, neuropsychological measures, and cognitive post-concussion symptoms at baseline. Only EEG/ERP measures that showed a significant difference between the mTBI group and at least one control group were included in the correlational analyses. Correlations are presented in Tables 9 and 10. In general, correlations between measures were small, with the strongest correlations observed between EEG/ERP measures and cognitive post-concussion symptoms.

Table 9

Spearman Correlations between Visual ERP Components, NP Measures, and PCS

Visual Oddball	PSI	N-Back Omis.	R-CPT Omis.	R-CPT Comm.	CPT % Correct	Cognitive PCS
Target P3 amplitude	-0.09	-0.13	0.01	0.02	0.05	-0.06
Target P3 latency	0.23*	-0.14	-0.03	-0.13	0.34*	-0.03
Novel N2 latency	-0.08	0.04	0.24*	-0.01	-0.23*	-0.14
Novel P3 amplitude	-0.06	0.11	-0.15	-0.08	0.06	0.09
Novel P3 latency	-0.02	-0.16	0.10	-0.22+	-0.13	0.12
Target theta PC4 ampl.	-0.19+	0.01	0.13	-0.18	0.10	-0.33*
Novel unfilt PC3 ampl.	0.06	-0.18	-0.11	-0.20+	0.13	0.00
Novel unfilt PC4 ampl.	-0.18	-0.01	-0.03	0.06	0.09	-0.39*
Target theta PC4 ITPS	-0.19+	0.04	0.00	-0.08	0.06	0.07

Note. Spearman correlations at baseline between visual oddball time-domain and time-frequency components, neuropsychological measures, and cognitive post-concussion symptoms.

Table 10

Spearman Correlations between Auditory ERP Components, NP Measures, and PCS

Auditory Oddball	PSI	N-Back Omis.	R-CPT Omis.	R-CPT Comm.	CPT % Correct	Cognitive PCS
Target N1 amplitude	-0.12	0.25*	0.06	0.07	0.06	-0.04
Target N1 latency	-0.12	0.04	0.03	0.08	-0.15	0.14
Target delta PC2 ampl.	0.32*	-0.09	0.11	0.03	-0.06	0.04
Target theta PC3 ampl.	0.09	-0.24*	-0.12	0.02	0.14	-0.07
Novel unfilt PC3 ITPS	0.22+	-0.05	-0.16	-0.07	0.13	0.11
Target theta PC1 ICPS	-0.09	-0.01	-0.19+	0.07	0.11	0.28*
Target theta PC2 ICPS	-0.08	-0.04	-0.15	0.03	0.07	0.23*
Target theta PC3 ICPS	-0.19+	0.05	-0.13	0.05	0.06	0.23*
Target theta PC4 ICPS	-0.08	0.02	-0.13	0.05	0.08	0.27*

Note. Spearman correlations at baseline between auditory oddball time-domain and time-frequency components, neuropsychological measures, and cognitive post-concussion symptoms. The four ICPS components reflect connectivity between medial and bilateral prefrontal electrodes.

Psychiatric Symptoms

Descriptive statistics for the Brief Symptom Inventory-18 (BSI-18) are presented in Table 11. A repeated-measures ANOVA of group (mTBI vs. IC) by time (baseline vs. six months) on the global severity index (GSI) revealed no significant effect of group but a main effect of time, where psychiatric symptoms decreased with time in both groups ($F(1,81) = 6.99$, $p = 0.01$).

Table 11

Descriptive Statistics of the Brief Symptom Inventory-18

		Mean (SD)	
BSI Scales		mTBI	IC
Somatization	T1	3.34 (3.27)	3.69 (4.40)
	T2	2.14 (2.92)	2.29 (3.36)
Depression	T1	2.27 (3.82)	2.90 (4.86)
	T2	2.21 (4.44)	1.61 (3.15)
Anxiety	T1	2.70 (3.81)	3.48 (5.02)
	T2	2.32 (3.90)	2.25 (3.18)
GSI	T1	8.30 (9.32)	10.10 (12.5)
	T2	6.67 (10.4)	6.14 (8.49)

Note. Means and standard deviations by group and time point (T1 = baseline; T2 = six months later) of the BSI-18 subscales, including somatization, depression, and anxiety, and the total score or global severity index (GSI).

Psychiatric and ERP Markers of Risk for Post-Concussion Symptoms

To evaluate psychiatric symptoms as a risk factor for post-concussion symptoms in the mTBI group, correlations were conducted between cognitive post-concussion symptoms and psychiatric symptoms at baseline and follow-up. Results showed a moderate correlation between post-concussion symptoms and psychiatric symptoms within the mTBI group at baseline ($rho = 0.57$, $p < 0.001$) and a strong correlation six months later ($rho = 0.73$, $p < 0.001$).

Next, logistic regression was employed to assess the power of psychiatric symptoms and ERP measures to predict whether service members in the mTBI group report cognitive post-

concussion symptoms or not. ERP measures were included in these regression analyses if they showed a significant difference between the mTBI and at least one of the control groups at baseline. One ERP measure and the global severity index (GSI) of psychiatric symptoms were included in each logistic regression model. Regressions assessed the predictive power of these baseline measures for cognitive post-concussion symptoms at baseline and at the six month follow-up. Positive beta coefficients and odds ratios over 1 indicate that an increase in the predictor variable is related to an increase in the odds of having cognitive post-concussion symptoms. Negative beta coefficients or odds ratios between 0 and 1 indicate that a decrease in the predictor variable is related to an increase in the odds of having cognitive post-concussion symptoms. For example, as seen in Table 12, a one-unit increase in psychiatric symptoms increases the odds of having cognitive post-concussion symptoms by a factor of 5.55 (the odds ratio), while a one-unit decrease in visual target theta amplitude increases the odds of having cognitive post-concussion symptoms by a factor of 2.04 (the inverse of the odds ratio of 0.49).

As demonstrated in Tables 12 and 13, both psychiatric symptoms and ERP measures were unique predictors of cognitive post-concussion symptoms at baseline. More specifically, while holding psychiatric symptoms constant, decreased visual target theta amplitude and visual novel slow wave amplitude increased the odds of experiencing cognitive post-concussion symptoms at baseline. In addition, more functional connectivity (ICPS) to auditory targets between medial and bilateral frontal electrodes also increased the odds of experiencing cognitive post-concussion symptoms at baseline. On the other hand, only baseline psychiatric symptoms and not ERP measures predicted cognitive post-concussion symptoms at the six-month follow-up (see Tables 14 and 15).

Table 12

Logistic Regressions Predicting Cognitive Post-concussion Symptoms at Baseline

Predictors	β	*SE* β	e_{β} (odds ratio)	*p*
GSI	1.57	0.55	4.80	0.004**
VIS Target P3 amplitude	0.11	0.27	1.12	0.67
GSI	1.57	0.55	4.79	0.004**
VIS Target P3 latency	-0.12	0.27	0.89	0.65
GSI	1.62	0.56	5.06	0.004**
VIS Novel N2 latency	-0.22	0.26	0.80	0.39
GSI	1.63	0.58	5.10	0.005**
VIS Novel P3 amplitude	0.29	0.27	1.34	0.28
GSI	1.49	0.55	4.42	0.007**
VIS Novel P3 latency	0.27	0.29	1.30	0.36
GSI	1.71	0.62	5.55	0.006**
VIS Target theta PC4 ampl.	-0.72	0.29	0.49	0.01*
GSI	1.57	0.55	4.83	0.004**
VIS Novel unfilt PC3 ampl.	0.05	0.26	1.05	0.85
GSI	1.57	0.57	4.79	0.006**
VIS Novel unfilt PC4 ampl.	-0.50	0.29	0.61	0.09+
GSI	1.56	0.54	4.77	0.004**
VIS Target theta PC4 ITPS	-0.05	0.27	0.95	0.86

Note. Logistic regressions of baseline psychiatric symptoms (GSI) and visual oddball ERP measures predicting baseline cognitive post-concussion symptoms vs. no cognitive post-concussion symptoms within the mTBI group (n = 77).

Table 13

Logistic Regressions Predicting Cognitive Post-concussion Symptoms at Baseline

Predictors	β	*SE* β	e^{β} (odds ratio)	*p*
GSI	1.50	0.53	4.50	0.005**
AUD Target N1 amplitude	0.02	0.25	1.02	0.93
GSI	1.52	0.53	4.55	0.004**
AUD Target N1 latency	0.15	0.25	1.17	0.55
GSI	1.60	0.55	4.95	0.003**
AUD Target delta PC2 ampl.	0.34	0.27	1.41	0.20
GSI	1.51	0.54	4.55	0.005**
AUD Target theta PC3 ampl.	-0.16	0.24	0.85	0.51
GSI	1.49	0.53	4.43	0.005**
AUD Novel unfilt. PC3 ITPS	0.32	0.26	1.38	0.22
GSI	1.57	0.56	4.81	0.005**
AUD Target theta PC1 ICPS	0.79	0.32	2.21	0.01*
GSI	1.47	0.54	4.33	0.006**
AUD Target theta PC2 ICPS	0.47	0.27	1.60	0.09+
GSI	1.55	0.57	4.72	0.006**
AUD Target theta PC3 ICPS	0.69	0.29	1.99	0.02*
GSI	1.56	0.56	4.74	0.006**
AUD Target theta PC4 ICPS	0.60	0.29	1.82	0.04*

Note. Logistic regressions of baseline psychiatric symptoms (GSI) and auditory oddball ERP measures predicting baseline cognitive post-concussion symptoms vs. no cognitive post-concussion symptoms within the mTBI group (n = 77).

Table 14

Logistic Regressions Predicting Cognitive Post-concussion Symptoms at Follow-up

Predictors	β	*SE* β	e^{β} (odds ratio)	*p*
GSI	0.88	0.42	2.41	0.03*
VIS Target P3 amplitude	0.29	0.30	1.34	0.33
GSI	0.83	0.41	2.30	0.04*
VIS Target P3 latency	0.21	0.29	1.23	0.47
GSI	0.82	0.41	2.28	0.04*
VIS Novel N2 latency	0.18	0.29	1.20	0.54
GSI	0.84	0.40	2.31	0.04*
VIS Novel P3 amplitude	-0.29	0.30	0.75	0.33
GSI	0.82	0.41	2.27	0.048*
VIS Novel P3 latency	0.13	0.30	1.14	0.65
GSI	0.83	0.42	2.29	0.047*
VIS Target theta PC4 ampl.	-0.19	0.29	0.83	0.52
GSI	0.82	0.41	2.26	0.048*
VIS Novel unfilt PC3 ampl.	-0.15	0.31	0.86	0.63
GSI	0.85	0.41	2.34	0.04*
VIS Novel unfilt PC4 ampl.	0.06	0.29	1.06	0.84
GSI	0.96	0.43	2.60	0.03*
VIS Target theta PC4 ITPS	-0.59	0.32	0.55	0.06+

Note. Logistic regressions of baseline psychiatric symptoms (GSI) and visual oddball ERP measures predicting cognitive post-concussion symptoms vs. no cognitive post-concussion symptoms within the mTBI group at the six month follow-up (n = 55).

Table 15

Logistic Regressions Predicting Cognitive Post-concussion Symptoms at Follow-up

Predictors	β	*SE* β	e^{β} (odds ratio)	*p*
GSI	0.87	0.41	2.39	0.04*
AUD Target N1 amplitude	-0.14	0.29	0.87	0.62
GSI	0.86	0.42	2.36	0.04*
AUD Target N1 latency	-0.33	0.31	0.72	0.29
GSI	0.89	0.42	2.43	0.03*
AUD Target delta PC2 ampl.	0.13	0.28	1.14	0.64
GSI	0.89	0.41	2.43	0.03*
AUD Target theta PC3 ampl.	0.16	0.28	1.18	0.57
GSI	0.88	0.41	2.40	0.03*
AUD Novel unfilt. PC3 ITPS	0.20	0.28	1.22	0.49
GSI	0.87	0.41	2.39	0.04*
AUD Target theta PC1 ICPS	0.03	0.28	10.3	0.92
GSI	0.87	0.41	2.39	0.04*
AUD Target theta PC2 ICPS	0.06	0.28	1.06	0.84
GSI	0.88	0.42	2.40	0.03*
AUD Target theta PC3 ICPS	-0.05	0.28	0.95	0.86
GSI	0.88	0.42	2.41	0.03*
AUD Target theta PC4 ICPS	-0.07	0.28	0.93	0.80

Note. Logistic regressions of baseline psychiatric symptoms (GSI) and auditory oddball ERP measures predicting cognitive post-concussion symptoms vs. no cognitive post-concussion symptoms within the mTBI group at the six month follow-up (n = 55).

Blast vs. Impact mTBI

The final aim was to assess electrophysiological and neuropsychological differences between blast-related and impact-related mild TBI. T-tests were conducted to compare blast and impact mTBI subgroups on the ERP and neuropsychological measures previously presented. Results revealed a few notable differences between these groups. Specifically, the blast-related mTBI group (n = 43) showed larger amplitude than the impact-related mTBI group (n = 44) for

visual target delta P3 (PC1: $t(85) = 2.46$, $p = 0.02$), visual novel slow wave (PC4: $t(85) = 3.58$, $p < 0.001$), auditory target theta during N1/P2 (PC3: $t(84) = 2.38$, $p = 0.02$) and after P3 (PC1: $t(84) = 1.98$, $p = 0.04$), and auditory novel delta P3 (PC1: $t(84) = 2.58$, $p = 0.01$). Group comparisons of neuropsychological measures revealed a significant difference for the WAIS-IV PSI, where blast-induced mTBI demonstrated slower processing speed than impact-induced mTBI ($t(87) = -3.08$, $p = 0.002$). These group differences in time-frequency ERP measures and processing speed were present despite no difference between the blast-related and impact-related mTBI subgroups in self-reported post-concussion symptoms ($t(82) = -0.21$, $p = 0.83$). Finally, no significant group differences were observed for time-domain components, ITPS, or ICPS.

Chapter 4: Discussion

The current study assessed the time course of cognitive recovery from mild TBI. Mild TBI has been associated with long-term cognitive complaints, although neurophysiological evidence to assess the brain basis of such complaints is sparse. Our study used advanced time-frequency EEG/ERP methodology, which includes sensitive measures for isolating rapid regional brain activity and the functional communication within and between brain networks, to longitudinally assess cognitive changes after mTBI over a 7 to 9 month period. Cognitive functioning was also evaluated with objective neuropsychological tests. In addition, the relationships between abnormal ERP findings and objective and subjective measures of cognitive functioning (i.e., neuropsychological tests and self-reported cognitive symptoms, respectively) were evaluated to assess the validity of ERP biomarkers of impairment following mTBI. Next, given evidence demonstrating that psychiatric symptoms are a risk factor for cognitive complaints following mTBI, we also assessed the relative power of psychiatric symptoms versus abnormal ERP measures for predicting cognitive post-concussion symptoms. Finally, the differential effect of blast-related versus impact-related mTBI was evaluated with EEG/ERP and neuropsychological measures.

Results revealed significant differences between the mTBI group and the control groups across several ERP measures at baseline, or the acute to post-acute period (about 4-11 weeks after injury). Most group differences remained significant after controlling for PTSD symptoms severity. Neuropsychological test performance only differed between groups on measures of visual sustained attention, but these differences were not significant when accounting for PTSD symptom severity. Some abnormal ERP findings were significantly related to cognitive post-concussion symptoms and neuropsychological test performance, but these relationships were generally small.

Results also indicated that no group differences were observed across electrophysiological measures at the 6 month time point. Both abnormal ERP findings and psychiatric symptoms uniquely predicted the presence of cognitive post-concussion symptoms at baseline, but only psychiatric symptoms predicted these cognitive symptoms six months later. Finally, comparisons of blast-related vs. impact-related mTBI revealed a few significant differences in time-frequency amplitude measures, as well as significantly slower processing speed among the blast-related mTBI group.

These results provide strong evidence that mTBI leads to cognitive changes that persist in the acute to post-acute period. Furthermore, ERP time-frequency measures were more sensitive than neuropsychological tests for capturing these cognitive changes. Critically, cognitive functioning as assessed by ERP measures returned to a level indistinguishable from controls 7-9 months following mTBI, even though 38% of mTBI patients continued to report cognitive post-concussion symptoms. Our findings suggests that these persistent cognitive complaints are more related to psychiatric symptoms than to the direct effects of brain injury.

Neurophysiological Findings

As predicted, group comparisons of time-domain ERP components revealed several significant differences at baseline. Specifically, P3 amplitude to visual targets (i.e., P3b) and P3 amplitude to visual novels (i.e., P3a) were reduced in the mTBI group relative to controls; however, group differences in P3b amplitude remained significant when controlling for PTSD symptom severity while the group effect on P3a amplitude diminished to trend-level. In addition, N2 and P3 latency to visual novels was slower in the mTBI group compared to health service members, which suggests that delays in processing speed may be specific to emotionally salient stimuli. Blunted P3b amplitude following mTBI suggests alterations in the top-down process of

cognitive categorization and context updating. Several studies have reported reductions in P3b amplitude following TBI (Campbell et al., 1990; Cavanagh et al., 2019; Dautricourt et al., 2017; Gosselin et al., 2006; Lachapelle et al., 2008; Lew et al., 2004, 2007; Naito et al., 2005; Rugg et al., 1988; Solbakk et al., 2000, 2002), and this finding has been observed in other cases of neurological and psychiatric disease, such as dementia, PTSD, ADHD, substance abuse, psychopathy, and general externalizing psychopathology (Anderson et al., 2015; Bernat et al., 2011; Cecchi et al., 2015; Gilmore et al., 2010, 2018; Iacono et al., 2003). Thus, a diminished P3b amplitude represents a sensitive but not specific biomarker of mTBI and may be generic index of cognitive dysfunction.

On the other hand, analysis of auditory ERP components did not reveal significant group differences for the primary components of interest (i.e., N2 and P3), but early auditory sensory processing as indexed by N1 amplitude and latency was impacted in mTBI. The mTBI group showed reduced N1 amplitude and shorter N1 latency to target stimuli relative to controls. These findings are somewhat inconsistent with previous literature showing that auditory ERPs are more susceptible to TBI (Duncan et al., 2005); however, factors like TBI severity and time since injury may play a role in this discrepancy. In fact, studies with samples more closely matched to the current study sample in terms of TBI severity and time since injury have demonstrated similar differences in visual ERPs compared to controls (Gaetz & Bernstein, 2001; Lachapelle et al., 2008).

Group comparisons of time-frequency ERP components also revealed significant differences between the mTBI group and control groups. Unlike the time-domain ERP results, several group differences were observed across both the visual and auditory oddball time-frequency measures. More specifically, group differences in amplitude were observed in visual

target and novel delta and theta components as well as auditory target delta and theta components. In addition, group differences in ITPS were found in response to visual targets and auditory novels, and ICPS differences were observed in response to auditory targets.

As anticipated, reductions in frontocentral theta amplitude were observed in the mTBI group in response to visual and auditory target stimuli, and reductions in delta amplitude were found in response to auditory targets when a frontocentral cluster of electrodes was assessed. Reduced delta and theta activity in frontocentral areas in response to target stimuli suggest that mTBI affects salience and control processes supported by the frontal regions of the brain, such as the prefrontal cortex and ACC. These findings are consistent with fMRI research on mTBI showing reduced activity in frontal brain regions, including the dlPFC, right medial frontal gyrus, ACC, and the right precentral gyrus (Eierud et al., 2014; Mayer et al., 2015).

While target elicited time-frequency amplitude findings were consistent with our hypotheses, time-frequency amplitude findings in response to visual novels were not. Reductions in theta and delta amplitudes in response to novels were not observed in the mTBI group relative to controls. While this study did not include specific hypotheses on comparisons between the two control groups, a few interesting differences emerged in response to visual novels. Namely, the injured control group displayed heightened delta and theta amplitude during the N2/P3 time window and enhanced late slow wave amplitude relative to the health service member group, while the mTBI group showed mean amplitudes between these two groups but closer to the IC group. These findings were consistent with time-domain results showing larger N2 and SW amplitudes for the IC group relative to the HSM group. Thus, service members with recent trauma exposure, irrespective of brain injury, showed heightened responding to emotional stimuli (i.e., novel pictures). Increased amplitude during the N2/P3 time window to novel stimuli is associated with

the orienting response (Barceló et al., 2002; Friedman et al., 2001; Kopp et al., 2006; Nieuwenhuis et al., 2011; Wessel & Aron, 2013; Wienke et al., 2018) and the late slow wave (analogous to the late positive potential in picture viewing tasks) to visual emotional stimuli is related to enhanced sustained attention (Hajcak et al., 2009). Therefore, our results suggest that trauma survivors show heightened orienting and visual sustained attention to emotional salient stimuli. Of note, these findings were apparent even after controlling for PTSD symptom severity, suggesting that PTSD symptoms do not account for the heightened response to novel stimuli in trauma survivors. Therefore, trauma history alone, regardless of PTSD symptom severity, may be an important factor in attentional disturbances, as a few previous ERP studies have demonstrated (Wei et al., 2010; Y. Zhang et al., 2014).

In summary, the mTBI group showed reductions in target-elicited delta and theta amplitude components that reflect cognitive processes mediated by the prefrontal cortex, whereas trauma survivors displayed heightened orienting and visual sustained attention to emotionally salient novel stimuli. These effects were only seen at baseline, approximately 4-11 weeks post injury.

Time-frequency phase synchrony measures also revealed significant group effects at baseline. Results revealed a main effect of group for early theta ITPS to auditory novels, with reduced ITPS in the mTBI and IC groups relative to the HSM group. In addition, a trend-level reduction in late theta ITPS to visual targets was observed for the mTBI group relative to controls, mirroring theta amplitude findings. Taken together, these results suggest subtle abnormalities in the consistency of frontocentral neural responses in the mTBI group.

Contrary to our hypotheses, time-frequency ICPS results showed increased rather than reduced functional connectivity (FC) between the salience and control networks for the mTBI group relative to controls. More specifically, result revealed increased theta ICPS between medial

and bilateral prefrontal electrodes in response to auditory targets for the mTBI group compared to the HSM group, and significant differences were seen across all four principal components (PCs), which ranged from about 50 ms to 800 ms and 4 Hz to 7.5 Hz. ICPS for the IC group was significantly greater than the HSM group for one of these four PCs, but did not differ significant from the mTBI or HSM groups for the other three PCs. In addition, findings showed enhanced theta ICPS during the P3 time window to visual novels for the IC group relative to the HSM group, with mean ICPS for the mTBI in between the two control groups.

While our ICPS findings were not expected based on neuroimaging literature showing reduced FC in frontal brain regions (Gilmore et al., 2016; Han et al., 2014; Kumar et al., 2009; Mayer et al., 2012; Palacios et al., 2017; Reches et al., 2017; Slobounov et al., 2011; Sponheim et al., 2011; K. Zhang et al., 2012; Zhou et al., 2014), there is some evidence to support increased FC following mTBI (Iraji et al., 2015; Mayer et al., 2011; Messé et al., 2013; Shumskaya et al., 2012; Stevens et al., 2012; Zhou et al., 2012). Increased FC between the salience and control networks (ACC and dlPFC) may reflect a compensatory process in which the brain increases its coordination in order to maintain effective behavior in the face of reduced cognitive capacity, as has been suggested in previous literature (Mayer et al., 2011; Messé et al., 2013; Shumskaya et al., 2012; Stevens et al., 2012; Zhou et al., 2012). This compensatory process of abnormally greater top-down attentional control may help explain the excessive cognitive fatigue reported by mTBI patients (Mayer et al., 2011; Shumskaya et al., 2012), although more research is needed to elucidate this relationship. Studies that have found increased FC in frontal salience and control networks have assessed mTBI patients in the acute to post-acute period following injury (Iraji et al., 2015; Mayer et al., 2011; Messé et al., 2013; Shumskaya et al., 2012; Stevens et al., 2012; Zhou et al., 2012), and one longitudinal study showed that reduced FC in frontal regions develops later, in the

chronic period following mTBI (Messé et al., 2013). In addition, a meta-analysis of mTBI structural connectivity abnormalities using anisotropy values derived from DTI demonstrated elevated anisotropy values in the acute period and depressed anisotropy values in the chronic period following mTBI (Eierud et al., 2014). Thus, our results provide further evidence of a cognitive compensatory process that seems to be temporary and occur in the acute to post-acute period following mTBI.

Another common factor among the studies showing greater frontal FC following mTBI is the use of resting-state designs. To our knowledge, the current study is the first to show mTBI-related increases in event-related FC during a cognitive task. Event-related designs provide strong ecological validity: they capture dynamic functional changes during high-order cognitive tasks, mimicking the real-word circumstances in which patients experience cognitive symptoms. Patients with post-concussive symptoms complain of cognitive difficulties when they engage in a goal-directed task. On the other hand, resting-state designs involve no cognitive task and no control over the mental activities of participants. While our results of enhanced FC are consistent with studies using resting-state paradigms, a few studies using task-based EEG studies have found the opposite effect (i.e., reduced FC in frontal regions; Kumar et al., 2009; Reches et al., 2017; Smith & Allen, 2019). This discrepancy may be due to variety of factors, such as varying FC measures analytic approaches, and frontal electrodes assessed, different tasks, different samples (military vs. civilian) and variable time periods from injury to assessment, but more research is needed to elucidate the cause of this discrepancy.

One important and somewhat unexpected takeaway of the current study is that neurophysiological functioning in the mTBI group returned to a level indistinguishable from controls at the six-month follow-up assessment, or 7-9 months post-injury. No significant group

differences were found on any EEG/ERP measure at follow-up. A limitation of this study is that only the injured control group was included in follow-up analyses, not the healthy service members control group. Thus, group difference may have been observed at follow-up if the mTBI group was compared to the HSM group, especially on those measures that only showed significant differences between the mTBI and HSM groups and not the mTBI and IC groups at baseline. Nevertheless, significant differences between the mTBI and IC groups were observed in many cases at baseline, so the null effects at follow-up are notable. These findings help clarify inconsistent results in the literature regarding the chronicity of cognitive impairment following mTBI as indexed by ERP measures (Cavanagh et al., 2019; Clark et al., 1992; Folmer et al., 2011; Gosselin et al., 2011; Lew et al., 2007; Nandrajog et al., 2017; Segalowitz et al., 2001).

Neuropsychological Findings

No significant differences were observed between the mTBI and control groups at baseline on any of the neuropsychological measures, including tests of processing speed, working memory, response inhibition, and sustained attention. A few studies have demonstrated chronic neuropsychological differences between mTBI patients and controls (Pertab et al., 2009; Vanderploeg et al., 2005), but our results are consistent with research showing that neuropsychological functioning returns to baseline within three months following mTBI (Belanger et al., 2005; Binder et al., 1997; Frencham et al., 2005; Ponsford et al., 2000; Rohling et al., 2011). While several studies have demonstrated deficits in processing speed, attention, working memory, and executive functioning in the acute period following mTBI (Belanger et al., 2005; Binder et al., 1997; Frencham et al., 2005; Ponsford et al., 2000; Rohling et al., 2011), the time range of the baseline assessment from the acute to post-acute phase (about 4-11 weeks post-injury) may explain

the null baseline effects. That is, neuropsychological abnormalities in the mTBI group may have been observed if the baseline assessment was conducted in the acute phase (1-6 weeks) for all participants.

Of note, the mTBI group showed poorer sustained attention compared to the HSM group, but this difference was not statistically significant when accounting for PTSD symptom severity. These results suggest that PTSD symptoms may negatively impact sustained attention among individuals who recently sustained mTBI, as has been shown in previous work (Barlow-Ogden, 2012; Esterman et al., 2019).

Results also revealed that performance on neuropsychological tests improved with time in both groups. These improvements likely reflect practice effects rather than genuine improvements in cognitive functioning (Estevis et al., 2012).

In summary, although we expected some mTBI-related neuropsychological effects at baseline, the lack of group differences in neuropsychological performance compared to ERP measures is generally consistent with our hypotheses. These findings add to the growing body of literature demonstrating that neuroimaging methods (e.g., ERP/EEG measures in the current study) are more sensitive to the effects of mTBI than neuropsychological measures (Belanger et al., 2007; Bigler, 2013; Mayer et al., 2011; Slobounov et al., 2011).

Blast vs. Impact mTBI Findings

The current study also explored the differential effects of blast-related versus impact-related mTBI on neurophysiological and neuropsychological functioning. Results revealed significantly heightened delta and theta amplitude for participants who sustained a blast-related mTBI compared to those who sustained an impact-related mTBI. More specifically, the blast-related mTBI group showed enhanced delta P3 activity in response to visual targets and auditory

novels, and increased theta activity following P3 to auditory targets. Alternatively, no differences were observed for these components between the primary groups (i.e., mTBI, IC, and HSM).

Two components, however, showed significant differences between both the primary groups and the blast versus impact mTBI subgroups: theta N1 amplitude to auditory targets and slow wave amplitude to visual novels. The blast-related mTBI subgroup demonstrated increased activity in both of these components relative to the impact-related mTBI group. In the primary group comparisons, these components were reduced in the mTBI group relative to the IC group. Of note, the mean amplitudes of the blast-related mTBI subgroup were much closer to those of the IC group than the impact-related mTBI subgroup. Approximately half of the participants in the IC group were exposed to blast as their primary injury mechanism, so perhaps blast exposure alone, irrespective of brain injury, can lead to subtle neurophysiological changes as one study has demonstrated (Robinson et al., 2015). Statistical comparisons of the blast- and impact-related mTBI subgroups with the two control groups was beyond the scope of the current study, but future research assessing the differential effects of injury mechanism on brain functioning should include blast exposed and non-blast exposed control groups with special attention to the range or distance from the blast explosion.

To our knowledge, no studies have directly compared the effects of different mechanisms of recently sustained mTBI on brain functioning in a military sample. Most research to date has compared blast-related mTBI to controls, with the blast mTBI group showing diffuse axonal injury (measured with DTI) and reduced functional connectivity as measured by fMRI and EEG (Davenport et al., 2012; Fischer et al., 2014; Sponheim et al., 2011; Vakhtin et al., 2013). While the current study found disruptions in functional connectivity in the mTBI group overall, no

differences in functional connectivity were observed between blast- and impact-related mTBI subgroups.

In addition to these ERP differences, our results also revealed significantly slower processing speed in the blast-related mTBI group compared to the impact-related mTBI group, which is the first study to our knowledge to show such an effect. The hypothesized neuropathology of blast-related TBI is diffuse axonal injury or wide-spread disruption in white matter integrity (Davenport et al., 2012), which is known to be associated with processing speed deficits. Thus, relative to focal injury seen in impact-related brain injury, slower processing speed in the blast-related mTBI subgroup is consistent with the hypothesized neuropathology.

While this study found subtle differences in neurophysiological and neuropsychological measures between the blast-related and impact-related mTBI subgroups, self-reported post-concussion symptoms did not differ between subgroups. This suggests that the observed ERP and neuropsychological differences do not reflect differences in self-reported cognitive complaints.

Validity of Abnormal ERP Measures

At baseline, nearly half of mTBI patients reported at least one new cognitive post-concussion symptom (i.e., forgetfulness, poor concentration, and/or taking longer to think), whereas only 14% of IC patients reported these symptoms. After six months, 38% of mTBI patients were still suffering from at least one cognitive post-concussion symptom. These results are consistent with previous research showing that a substantial subset on individuals experience persistent cognitive post-concussion symptoms following mTBI (Dikmen et al., 2016; Iverson, 2005; Levin & Diaz-Arrastia, 2015; McMahon et al., 2014; Meares et al., 2011).

In order to evaluate the validity and clinical utility of ERP biomarkers of impairment following mTBI, correlations between abnormal ERP findings and objective and subjective measures of cognitive functioning within the mTBI group were assessed. Significant correlations were observed between self-reported cognitive post-concussion symptoms and time-frequency amplitude and phase synchrony measures. More specifically, reduced delta and theta amplitudes and increased functional connectivity between medial and bilateral prefrontal regions were associated with more severe cognitive post-concussion symptoms. In addition, several ERP measures were correlated with performance on neuropsychological tests, although no specific pattern emerged (i.e., significant correlations were distributed across ERP measures and neuropsychological tests). Although correlations were of small magnitude, our results provide the first evidence that ERP time-frequency amplitude and phase synchrony measures are valid biomarkers of cognitive impairment following military mTBI.

The predictive validity of abnormal ERP measures was also assessed relative to a known risk factor for persistent cognitive post-concussion symptoms, psychiatric symptoms. In the acute to post-acute period following mTBI (i.e., baseline), abnormal frontocentral theta amplitude and ICPS (i.e., functional connectivity between medial and bilateral prefrontal regions) significantly increased the odds of reporting cognitive post-concussion symptoms while holding psychiatric symptoms constant. In addition, more psychiatric symptoms significantly increased the odds of reporting cognitive post-concussion symptoms while controlling for abnormal ERP measures. These results demonstrate that both abnormal frontocentral theta activation and connectivity and psychiatric symptoms are independent predictors of cognitive post-concussion symptoms in the acute to post-acute period following mTBI. Thus, post-concussion symptoms in this time period seem to be the result of both the direct alteration of brain functioning caused by brain injury and

the symptoms of depression, anxiety, and somatization that may be related to difficulties coping with injury and trauma.

We also assessed the validity of baseline abnormal ERP measures and psychiatric symptoms for predicting persistent cognitive post-concussion symptoms in the chronic phase (i.e., 7-9 months following mTBI). Results revealed that only psychiatric symptoms significantly increased the odds of persistent cognitive post-concussion symptoms, not abnormal ERP measures. In addition, the relationship between psychiatric symptoms and cognitive complaints strengthened with time, from a moderate correlation at baseline to a strong correlation at follow-up. Taken together, our results suggest that cognitive complaints in the acute to post-acute period are best explained by abnormal neurophysiological *and* psychiatric functioning, whereas cognitive complaints in the chronic period are best predicted by psychiatric symptoms experienced early after injury. These findings are consistent with previous literature demonstrating that psychiatric symptoms are a significant risk factor for post-concussion symptoms in the chronic period following mTBI (Brenner et al., 2010; Ponsford et al., 2000; van der Naalt et al., 2017). Of note, several studies have identified pre-injury mental health problems as an important factor in incomplete recovery following mTBI; however, the current study excluded individuals with a history of psychiatric disorders. Thus, our findings demonstrate that even without a prior history of mental health problems, individuals who sustain an mTBI are at risk for persistent cognitive post-concussion symptoms if they develop psychiatric symptoms early after injury.

Methodological Utility of Time-Frequency Measures

To replicate previous work and to validate the present TF measures, multiple regression models were employed to show the contributions of delta and theta to the primary time-domain components of interest (i.e., N2 and P3). Results demonstrated that delta and theta components

contributed unique variance to the amplitude of N2 and P3 components across stimulus type. Although both frequencies contributed significant variance to the time-domain N2 and P3 amplitudes, delta accounted for more variance than theta across targets and novels, consistent with previous literature (Bachman & Bernat, 2018). These results add to the mounting body of evidence that distinct processes confounded in the time-domain can be well-represented in the delta and theta frequency bands (Bachman & Bernat, 2018; Başar et al., 2001; Bernat et al., 2011, 2015; Demiralp, Ademoglu, Comerchero, et al., 2001; Demiralp, Ademoglu, Istefanopulos, et al., 2001; Foti et al., 2015; Harper et al., 2014; S. Karakaş et al., 2000; Kolev et al., 1997; Spencer & Polich, 1999; Watts et al., 2018; Yordanova et al., 2000), and they demonstrate the utility of time-frequency PCA methods for novelty oddball tasks specifically (Bachman & Bernat, 2018). One exception was in the case of the N2 in response to auditory novels, where neither delta nor theta contributed unique variance. The N2 deflection was not apparent in the auditory novel time-domain waveform, which may explain why delta and theta oscillations in the time range of the N2 did not significantly explain variance in the amplitude of the time-domain N2 component.

This study demonstrates the utility of time-frequency analysis in several ways. First, while the group effects were similar between time-domain and time-frequency amplitude measures, there were a few notable differences. As discussed previously, P3b amplitude to visual targets was diminished in the mTBI group relative to controls. However, neither delta nor theta were reduced in the time range of the P3b for the mTBI group. Reductions in theta amplitude to visual targets were only seen in the time range following the P3b peak. In addition, important distinctions in group effects between time-domain and time-frequency measures were observed in response to visual novels. Time-domain results revealed enhanced N2 amplitude for the IC group, and to a lesser degree the mTBI group, relative to the HSM group. Findings also demonstrated reduced P3a

amplitude for the mTBI group, and to a less degree the IC group, relative to the HSM group. Alternatively, time-frequency results showed only enhanced (not reduced) delta and theta activity during the N2/P3 time range for the IC and mTBI groups relative to the HSM group. Thus, the P3a reduction effect in the time-domain is likely due to the overlap in time between the N2 and P3a components and the separable contributions of underlying activity in the delta and theta frequency bands. The 4 Hz theta oscillation is enhanced in a negative deflection around the time of the N2, but this enhanced negative oscillation occurs in the same time range as the start of the time-domain P3a, leading to the appearance of a reduced P3a amplitude in the time-domain. Thus, absent time-frequency analysis, we may have concluded that the mTBI group showed a blunted P3a response, but if fact the mTBI group showed enhanced activation in this time range compared to the HSM group.

In addition to the benefits of time-frequency amplitude measures relative to time-domain approaches, this study demonstrates the utility of phase synchrony measures for assessing disruptions within and between neural networks following mTBI. Our findings add to the growing body of literature showing that even mild TBI can result in disordered network communication, and they also provide the first task-based EEG evidence of a cognitive compensatory process in the acute to post-acute period following injury in a military sample.

A final notable strength of time-frequency measures apparent from the current study is the convergent validity with self-reported post-concussion symptoms. That is, only time-frequency amplitude and phase synchrony measures were related to post-concussion symptoms, time-domain amplitude and latency measures were not. Thus, time-frequency measures show great promise as a valid biomarkers of cognitive dysfunction following mTBI.

Clinical Utility of EEG/ERP Measures

EEG/ERP methods have important methodological and practical advantages over MRI methods, namely, high temporal resolution to capture rapid cognitive processes and low financial cost. Event-related potential methods are particularly useful as measures of brain function relative to structural neuroimaging and resting-state functional neuroimaging approaches. They capture dynamic functional changes during high-order cognitive and affective tasks, mimicking the real-word circumstances in which patients experience psychological and/or neurocognitive symptoms. Finally, EEG systems are already available and widely used at most hospitals in the Unites States. Thus, EEG/ERP measures have great potential as indicators of cognitive dysfunction and recovery, but there is a need to establish normative data and standardized analytic procedures before clinical application is feasible. Indeed, promising efforts in the sport concussion field have shown preliminary evidence for establishing the clinical utility of a standardized EEG-based measure that includes a normative reference group (Eckner et al., 2016; Kiefer et al., 2015; Kontos et al., 2016; Reches et al., 2017).

Strengths

The present study addressed many scientific gaps in the assessment of cognitive concerns following military mTBI as prioritized by the VA/DoD Clinical Practice Guideline for the Management of Concussion-Mild Traumatic Brain Injury (Department of Veterans Affairs, 2016). First, the current study evaluated participants longitudinally from the acute/post-acute to chronic period following mTBI, thus providing important information on the time course of recovery from military mTBI. Second, this study included a relatively large sample of service members, a significant improvement from prior neuroimaging studies, which increases the generalizability and accuracy of our findings. Third, baseline analyses utilized two control groups in order to account

for several potential confounds, such as recent trauma exposure, recent injury, blast exposure, and military service. Next, multiple methods of assessment were employed, which provided a comprehensive understanding of cognitive functioning following military mTBI and afforded the evaluation of the validity of EEG/ERP biomarkers of cognitive dysfunction as described above. Finally, this was the first study to assess mechanism-specific physiological responses between blast-related and impact-related military mTBI in the acute to post-acute period, thus providing initial evidence of a unique pathophysiology following blast-related mTBI.

Limitations & Future directions

As mentioned previously, the first limitation of this study is that only the injured control group was included in follow-up analyses, not the healthy service members control group. Thus, any effect of recent traumatic injury (shared by the mTBI and IC groups) could not be determined at the follow-up assessment.

Much of the ERP literature on mTBI has assessed patients in the chronic phase, with large variability in the time from injury to assessment. Given that cognitive symptoms tend to be heightened in the acute period and improve with time, cognitive assessment of mTBI from the acute to chronic period is critical. A primary strength of our study is the longitudinal assessment of patients with mTBI from the acute/post-acute to the chronic period. However, one limitation is the range of time from injury to baseline assessment (about 4-11 weeks), given that significant recovery is thought to occur in the first few weeks and months following injury. Although we aimed to assess individuals as soon as possible following mTBI, many of our participants had significant orthopedic injuries that required medical attention and hospitalization. The baseline assessment was delayed until patients were medically stable and no longer taking pain medication.

However, future work should attempt to narrow the time since injury assessment window, or assess whether time since injury had any impact on the primary effects.

As discussed previously, there is a need to establish normative data and standardized analytic procedures before clinical application of EEG/ERP indicators of cognitive dysfunction and recovery is possible. Promising efforts in the sport concussion literature have shown preliminary evidence for establishing the clinical utility of a standardized EEG-based measure that includes a normative reference group (Eckner et al., 2016; Kiefer et al., 2015; Kontos et al., 2016; Reches et al., 2017). One recent study on sports concussion demonstrated that EEG measurement was significantly more accurate in diagnosing concussion than a symptom questionnaire alone, and the authors presented a compelling argument for utilizing EEG measurement in the locker room to provide an immediate and objective mTBI assessment to determine if players can return to the field (McNerney et al., 2019). A similar assessment could be beneficial for return to duty decisions following mTBI in the military. But before such an application is possible, future work using time-frequency EEG/ERP measures should aim to establish a normative military reference group with a standard set of cognitive ERP tasks. The novelty oddball task is a relatively simple task of stimulus discrimination and categorization, and previous research has shown that task difficulty can impact the ability to detect TBI-related group differences (Duncan et al., 2005). Future studies, especially those aimed at developing normative data, should utilize tasks that index a range of cognitive functions that are commonly impacted in TBI. In addition, replication of our findings is necessary before clinical application is warranted, including establishing quantitative cutoffs for maximizing the sensitivity and specificity of ERP biomarkers.

Finally, given the limited research on blast-related mTBI, we explored the differential effects of blast versus impact mTBI on cognitive functioning. While our study showed subtle

differences in time-frequency amplitude components and processing speed between these mTBI subgroups, more research utilizing multiple methods of assessment is needed to better understand if blast-related mTBI has a unique neural signature and unique cognitive consequences. Future work should not only compare varying mTBI injury mechanisms but also include military control groups with and without blast exposure. In addition, researcher should consider distance from blast explosion in their analyses given research showing greater cognitive effects of close-range blasts (< 10 meters; Robinson et al., 2015).

Conclusions

In conclusion, this study provides compelling evidence that mTBI leads to cognitive changes that persist in the acute to post-acute period following injury (i.e., up to 12 weeks). These cognitive changes were reflected by alterations in ERP time-frequency amplitude and phase synchrony measures, and they remained apparent even when controlling for PTSD symptoms. Abnormal ERP time-frequency measures were related to self-reported cognitive complaints, suggesting that these ERP measures are valid biomarkers of cognitive dysfunction. Neuropsychological test performance, on the other hand, was not sensitive to mTBI. Critically, cognitive functioning as assessed by ERP measures returned to a level indistinguishable from controls 7-9 months following mTBI, even though more than a third of mTBI patients continued to report cognitive complaints. Our findings suggest that these persistent cognitive complaints are more related to psychiatric symptoms than to the direct effects of brain injury. Therefore, our findings have a few main clinical implications: 1) ERP time-frequency measures provide a valid and sensitive assessment of cognitive changes up to 12 weeks following mTBI, 2) military patients should be carefully screened for psychiatric symptoms following mTBI; and 3) these symptoms

should be addressed as soon as possible after injury in order to reduce the risk of persistent cognitive complaints.

Bibliography

Affairs, D. of V. (2016). VA/DoD Clinical practice guideline for the management of concussion-mild traumatic brain injury (version 2.0).

Anderson, N. E., Steele, V. R., Maurer, J. M., Bernat, E. M., & Kiehl, K. A. (2015). Psychopathy, attention, and oddball target detection: New insights from PCL-R facet scores. Psychophysiology, 52(9), 1194–1204.

Aviyente, S., Bernat, E. M., Evans, W. S., & Sponheim, S. R. (2011). A phase synchrony measure for quantifying dynamic functional integration in the brain. Human Brain Mapping, 32(1), 80–93.

Aviyente, S., Tootell, A., & Bernat, E. M. (2017). Time-frequency phase-synchrony approaches with ERPs. International Journal of Psychophysiology, 111, 88–97.

Bachman, M. D., & Bernat, E. M. (2018). Independent contributions of theta and delta time-frequency activity to the visual oddball P3b. International Journal of Psychophysiology, 128, 70–80. https://doi.org/10.1016/j.ijpsycho.2018.03.010

Barceló, F., Periáñez, J. A., & Knight, R. T. (2002). Think differently: A brain orienting response to task novelty. NeuroReport, 13(15), 1887–1892.

Barlow-Ogden, K. (2012). Mild traumatic brain injury and posttraumatic stress disorder: Investigation of visual attention in Operation Iraqi Freedom/Operation Enduring Freedom veterans. Journal of Rehabilitation Research and Development, 49(7), 1101.

Başar, E., Başar-Eroglu, C., Karakaş, S., & Schürmann, M. (2001). Gamma, alpha, delta, and theta oscillations govern cognitive processes. International Journal of Psychophysiology, 39(2–3), 241–248. https://doi.org/10.1016/S0167-8760(00)00145-8

Belanger, H. G., Curtiss, G., Demery, J. A., Lebowitz, B. K., & Vanderploeg, R. D. (2005). Factors moderating neuropsychological outcomes following mild traumatic brain injury: A meta-analysis. Journal of the International Neuropsychological Society, 11(3), 215–227.

Belanger, H. G., Vanderploeg, R. D., Curtiss, G., & Warden, D. L. (2007). Recent Neuroimaging Techniques in Mild Traumatic Brain Injury. The Journal of Neuropsychiatry and Clinical Neurosciences, 19(1), 5–20. https://doi.org/10.1176/jnp.2007.19.1.5

Benzinger, T. L., Brody, D., Cardin, S., Curley, K. C., Mintun, M. A., Mun, S. K., Wong, K. H., & Wrathall, J. R. (2009). Blast-related brain injury: Imaging for clinical and research applications: report of the 2008 St. Louis workshop. Journal of Neurotrauma, 26(12), 2127–2144.

Bernat, E. M., Malone, S. M., Williams, W. J., Patrick, C. J., & Iacono, W. G. (2007). Decomposing delta, theta, and alpha time–frequency ERP activity from a visual oddball task using PCA. International Journal of Psychophysiology, 64(1), 62–74.

Bernat, E. M., Nelson, L. D., & Baskin-Sommers, A. R. (2015). Time-frequency theta and delta measures index separable components of feedback processing in a gambling task. Psychophysiology, 52(5), 626–637. https://doi.org/10.1111/psyp.12390

Bernat, E. M., Nelson, L. D., Steele, V. R., Gehring, W. J., & Patrick, C. J. (2011). Externalizing psychopathology and gain–loss feedback in a simulated gambling task: Dissociable components of brain response revealed by time-frequency analysis. Journal of Abnormal Psychology, 120(2), 352.

Bernat, E. M., Williams, W. J., & Gehring, W. J. (2005). Decomposing ERP time–frequency energy using PCA. Clinical Neurophysiology, 116(6), 1314–1334. https://doi.org/10.1016/j.clinph.2005.01.019

Bernstein, D. M. (2002). Information processing difficulty long after self-reported concussion. Journal of the International Neuropsychological Society, 8(5), 673–682. https://doi.org/10.1017/S1355617702801400

Bigler, E. D. (2013). Neuroimaging Biomarkers in Mild Traumatic Brain Injury (mTBI). Neuropsychology Review, 23(3), 169–209. https://doi.org/10.1007/s11065-013-9237-2

Binder, L. M., Rohling, M. L., & Larrabee, G. J. (1997). A review of mild head trauma. part I: Meta-analytic review of neuropsychological studies. Journal of Clinical and Experimental Neuropsychology, 19(3), 421–431. https://doi.org/10.1080/01688639708403870

Blanchard, E. B., Jones-Alexander, J., Buckley, T. C., & Forneris, C. A. (1996). Psychometric properties of the PTSD Checklist (PCL). Behaviour Research and Therapy, 34(8), 669–673.

Borgaro, S. R., Prigatano, G. P., Kwasnica, C., & Rexer, J. L. (2003). Cognitive and affective sequelae in complicated and uncomplicated mild traumatic brain injury. Brain Injury, 17(3), 189–198.

Brenner, L. A., Ivins, B. J., Schwab, K., Warden, D., Nelson, L. A., Jaffee, M., & Terrio, H. (2010). Traumatic Brain Injury, Posttraumatic Stress Disorder, and Postconcussive Symptom Reporting Among Troops Returning From Iraq. The Journal of Head Trauma Rehabilitation, 25(5), 307. https://doi.org/10.1097/HTR.0b013e3181cada03

Burwell, S. J., Malone, S. M., Bernat, E. M., & Iacono, W. G. (2014). Does electroencephalogram phase variability account for reduced P3 brain potential in externalizing disorders? Clinical Neurophysiology, 125(10), 2007–2015.

Campbell, K. B., Suffield, J. B., & Deacon, D. L. (1990). Electrophysiological Assessment of Cognitive Disorder in Closed Head-Injured Outpatients. In P. M. Rossini & F. Mauguière (Eds.), New Trends and Advanced Techniques in Clinical Neurophysiology (pp. 202–215). Elsevier. https://doi.org/10.1016/B978-0-444-81352-7.50025-X

Cavanagh, J. F., Cohen, M. X., & Allen, J. J. (2009). Prelude to and resolution of an error: EEG phase synchrony reveals cognitive control dynamics during action monitoring. The Journal of Neuroscience, 29(1), 98–105.

Cavanagh, J. F., & Frank, M. J. (2014). Frontal theta as a mechanism for cognitive control. Trends in Cognitive Sciences, 18(8), 414–421. https://doi.org/10.1016/j.tics.2014.04.012

Cavanagh, J. F., Frank, M. J., Klein, T. J., & Allen, J. J. (2010). Frontal theta links prediction errors to behavioral adaptation in reinforcement learning. Neuroimage, 49(4), 3198–3209.

Cavanagh, J. F., Wilson, J. K., Rieger, R. E., Gill, D., Broadway, J. M., Story Remer, J. H., Fratzke, V., Mayer, A. R., & Quinn, D. K. (2019). ERPs predict symptomatic distress and recovery in sub-acute mild traumatic brain injury. Neuropsychologia, 132, 107125. https://doi.org/10.1016/j.neuropsychologia.2019.107125

Cavanagh, J. F., Zambrano-Vazquez, L., & Allen, J. J. (2012). Theta lingua franca: A common mid-frontal substrate for action monitoring processes. Psychophysiology, 49(2), 220–238.

Cecchi, M., Moore, D. K., Sadowsky, C. H., Solomon, P. R., Doraiswamy, P. M., Smith, C. D., Jicha, G. A., Budson, A. E., Arnold, S. E., & Fadem, K. C. (2015). A clinical trial to

validate event-related potential markers of Alzheimer's disease in outpatient settings. Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring, 1(4), 387–394.

Chen, Jen-Kai, Johnston, K. M., Collie, A., McCrory, P., & Ptito, A. (2007). A validation of the post concussion symptom scale in the assessment of complex concussion using cognitive testing and functional MRI. Journal of Neurology, Neurosurgery & Psychiatry, 78(11), 1231–1238. https://doi.org/10.1136/jnnp.2006.110395

Chen, J.-K., Johnston, K. M., Frey, S., Petrides, M., Worsley, K., & Ptito, A. (2004). Functional abnormalities in symptomatic concussed athletes: An fMRI study. Neuroimage, 22(1), 68–82.

Clark, C. R., O'hanlon, A. P., Wright, M. J., & Geffen, G. M. (1992). Event-related potential measurement of deficits in information processing following moderate to severe closed head injury. Brain Injury, 6(6), 509–520. https://doi.org/10.3109/02699059209008148

Cohen, J., & Polich, J. (1997). On the number of trials needed for P300. International Journal of Psychophysiology, 25(3), 249–255.

Cohen, M. X., & Cavanagh, J. F. (2011). Single-trial regression elucidates the role of prefrontal theta oscillations in response conflict. Frontiers in Psychology, 2.

Cohen, M. X., Elger, C. E., & Ranganath, C. (2007). Reward expectation modulates feedback-related negativity and EEG spectra. NeuroImage, 35(2), 968–978. https://doi.org/10.1016/j.neuroimage.2006.11.056

Cohen, M. X., Ridderinkhof, K. R., Haupt, S., Elger, C. E., & Fell, J. (2008). Medial frontal cortex and response conflict: Evidence from human intracranial EEG and medial frontal cortex lesion. Brain Research, 1238, 127–142.

Cohen, M. X., Wilmes, K. A., & van de Vijver, I. (2011). Cortical electrophysiological network dynamics of feedback learning. Trends in Cognitive Sciences, 15(12), 558–566.

Courchesne, E., Hillyard, S. A., & Courchesne, R. Y. (1977). P3 waves to the discrimination of targets in homogeneous and heterogeneous stimulus sequences. Psychophysiology, 14(6), 590–597.

Dautricourt, S., Violante, I., Mallas, E.-J., Daws, R., Ross, E., Jolly, A., Lorenz, R., Sharp, D., & Gorgoraptis, N. (2017). Reduced information processing speed and event-related EEG synchronization in traumatic brain injury (P6. 149). Neurology, 88(16 Supplement), P6–149.

Davenport, N. D., Lim, K. O., Armstrong, M. T., & Sponheim, S. R. (2012). Diffuse and spatially variable white matter disruptions are associated with blast-related mild traumatic brain injury. Neuroimage, 59(3), 2017–2024.

Debener, S., Makeig, S., Delorme, A., & Engel, A. K. (2005). What is novel in the novelty oddball paradigm? Functional significance of the novelty P3 event-related potential as revealed by independent component analysis. Cognitive Brain Research, 22(3), 309–321.

Delorme, A., & Makeig, S. (2004). EEGLAB: An open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. Journal of Neuroscience Methods, 134(1), 9–21. https://doi.org/10.1016/j.jneumeth.2003.10.009

Demiralp, T., Ademoglu, A., Comerchero, M., & Polich, J. (2001). Wavelet analysis of P3a and P3b. Brain Topography, 13(4), 251–267.

Demiralp, T., Ademoglu, A., Istefanopulos, Y., Başar-Eroglu, C., & Başar, E. (2001). Wavelet analysis of oddball P300. International Journal of Psychophysiology, 39(2–3), 221–227. https://doi.org/10.1016/S0167-8760(00)00143-4

Dettwiler, A., Murugavel, M., Putukian, M., Cubon, V., Furtado, J., & Osherson, D. (2014). Persistent differences in patterns of brain activation after sports-related concussion: A longitudinal functional magnetic resonance imaging study. Journal of Neurotrauma, 31(2), 180–188.

Dikmen, S., Machamer, J., & Temkin, N. (2016). Mild Traumatic Brain Injury: Longitudinal Study of Cognition, Functional Status, and Post-Traumatic Symptoms. Journal of Neurotrauma, 34(8), 1524–1530. https://doi.org/10.1089/neu.2016.4618

Dikmen, S. S., Machamer, J. E., Winn, H. R., & Temkin, N. R. (1995). Neuropsychological outcome at 1-year post head injury. Neuropsychology, 9(1), 80–90. https://doi.org/10.1037/0894-4105.9.1.80

Dimitriadis, S. I., Zouridakis, G., Rezaie, R., Babajani-Feremi, A., & Papanicolaou, A. C. (2015). Functional connectivity changes detected with magnetoencephalography after mild traumatic brain injury. NeuroImage: Clinical, 9, 519–531.

Donchin, E., Ritter, W., & McCallum, W. C. (1978). Cognitive psychophysiology: The endogenous components of the ERP. Event-Related Brain Potentials in Man, 349–411.

Duncan, C. C., Barry, R. J., Connolly, J. F., Fischer, C., Michie, P. T., Näätänen, R., Polich, J., Reinvang, I., & Van Petten, C. (2009). Event-related potentials in clinical research: Guidelines for eliciting, recording, and quantifying mismatch negativity, P300, and N400. Clinical Neurophysiology, 120(11), 1883–1908.

Duncan, C. C., Kosmidis, M. H., & Mirsky, A. F. (2003). Event–related potential assessment of information processing after closed head injury. Psychophysiology, 40(1), 45–59.

Duncan, C. C., Kosmidis, M. H., & Mirsky, A. F. (2005). Closed head injury-related information processing deficits: An event-related potential analysis. International Journal of Psychophysiology, 58(2–3), 133–157.

Duncan-Johnson, C. C., & Donchin, E. (1977). On quantifying surprise: The variation of event-related potentials with subjective probability. Psychophysiology, 14(5), 456–467.

Duncan-Johnson, C. C., & Donchin, E. (1982). The P300 component of the event-related brain potential as an index of information processing. Biological Psychology, 14(1–2), 1–52.

Eckner, J. T., Rettmann, A., Narisetty, N., Greer, J., Moore, B., Brimacombe, S., He, X., & Broglio, S. P. (2016). Stability of an ERP-based measure of brain network activation (BNA) in athletes: A new electrophysiological assessment tool for concussion. Brain Injury, 30(9), 1075–1081.

Efron, B. (1982). The jackknife, the bootstrap, and other resampling plans (Vol. 38). Siam.

Eierud, C., Craddock, R. C., Fletcher, S., Aulakh, M., King-Casas, B., Kuehl, D., & LaConte, S. M. (2014). Neuroimaging after mild traumatic brain injury: Review and meta-analysis. NeuroImage: Clinical, 4, 283–294.

Ellis, J. S., Watts, A. T. M., Schmidt, N., & Bernat, E. M. (2018). Anxiety and feedback processing in a gambling task: Contributions of time-frequency theta and delta. Biological Psychology, 136, 1–12. https://doi.org/10.1016/j.biopsycho.2018.05.001

Esterman, M., Fortenbaugh, F. C., Pierce, M. E., Fonda, J. R., DeGutis, J., Milberg, W., & McGlinchey, R. (2019). Trauma-related psychiatric and behavioral conditions are uniquely associated with sustained attention dysfunction. Neuropsychology, 33(5), 711.

Estevis, E., Basso, M. R., & Combs, D. (2012). Effects of Practice on the Wechsler Adult Intelligence Scale-IV Across 3- and 6-Month Intervals. The Clinical Neuropsychologist, 26(2), 239–254. https://doi.org/10.1080/13854046.2012.659219

Fabiani, M., Kazmerski, V. A., Cycowicz, Y. M., & Friedman, D. (1996). Naming norms for brief environmental sounds: Effects of age and dementia. Psychophysiology, 33(4), 462–475.

Fell, J., & Axmacher, N. (2011). The role of phase synchronization in memory processes. Nature Reviews Neuroscience, 12(2), 105–118. https://doi.org/10.1038/nrn2979

Fischer, B. L., Parsons, M., Durgerian, S., Reece, C., Mourany, L., Lowe, M. J., Beall, E. B., Koenig, K. A., Jones, S. E., & Newsome, M. R. (2014). Neural activation during response inhibition differentiates blast from mechanical causes of mild to moderate traumatic brain injury. Journal of Neurotrauma, 31(2), 169–179.

Folmer, R. L., Billings, C. J., Diedesch-Rouse, A. C., Gallun, F. J., & Lew, H. L. (2011). Electrophysiological assessments of cognition and sensory processing in TBI: Applications for diagnosis, prognosis and rehabilitation. International Journal of Psychophysiology, 82(1), 4–15.

Foti, D., Weinberg, A., Bernat, E. M., & Proudfit, G. H. (2015). Anterior cingulate activity to monetary loss and basal ganglia activity to monetary gain uniquely contribute to the feedback negativity. Clinical Neurophysiology. http://www.sciencedirect.com/science/article/pii/S1388245714005148

Frencham, K. A., Fox, A. M., & Maybery, M. T. (2005). Neuropsychological studies of mild traumatic brain injury: A meta-analytic review of research since 1995. Journal of Clinical and Experimental Neuropsychology, 27(3), 334–351.

Friedman, D., Cycowicz, Y. M., & Gaeta, H. (2001). The novelty P3: An event-related brain potential (ERP) sign of the brain's evaluation of novelty. Neuroscience & Biobehavioral Reviews, 25(4), 355–373.

Fries, P. (2005). A mechanism for cognitive dynamics: Neuronal communication through neuronal coherence. Trends in Cognitive Sciences, 9(10), 474–480. https://doi.org/10.1016/j.tics.2005.08.011

Gaeta, H., Friedman, D., & Hunt, G. (2003). Stimulus characteristics and task category dissociate the anterior and posterior aspects of the novelty P3. Psychophysiology, 40(2), 198–208.

Gaetz, M., & Bernstein, D. M. (2001). The current status of electrophysiologic procedures for the assessment of mild traumatic brain injury. The Journal of Head Trauma Rehabilitation, 16(4), 386–405.

Geary, E. K., Kraus, M. F., Pliskin, N. H., & Little, D. M. (2010). Verbal learning differences in chronic mild traumatic brain injury. Journal of the International Neuropsychological Society, 16(3), 506–516. https://doi.org/10.1017/S135561771000010X

Gevins, A., & Cutillo, B. (1993). Spatiotemporal dynamics of component processes in human working memory. Electroencephalography and Clinical Neurophysiology, 87(3), 128–143.

Gilmore, C. S., Camchong, J., Davenport, N. D., Nelson, N. W., Kardon, R. H., Lim, K. O., & Sponheim, S. R. (2016). Deficits in Visual System Functional Connectivity after Blast-Related Mild TBI are Associated with Injury Severity and Executive Dysfunction. Brain and Behavior, 6(5).

Gilmore, C. S., Malone, S. M., Bernat, E. M., & Iacono, W. G. (2010). Relationship between the P3 event-related potential, its associated time-frequency components, and externalizing

psychopathology. Psychophysiology, 47(1), 123–132. https://doi.org/10.1111/j.1469-8986.2009.00876.x

Gilmore, C. S., Marquardt, C. A., Kang, S. S., & Sponheim, S. R. (2018). Reduced P3b brain response during sustained visual attention is associated with remote blast mTBI and current PTSD in US military veterans. Behavioural Brain Research, 340, 174–182.

Gosselin, N., Bottari, C., Chen, J.-K., Petrides, M., Tinawi, S., de Guise, É., & Ptito, A. (2011). Electrophysiology and Functional MRI in Post-Acute Mild Traumatic Brain Injury. Journal of Neurotrauma, 28(3), 329–341. https://doi.org/10.1089/neu.2010.1493

Gosselin, N., Thériault, M., Leclerc, S., Montplaisir, J., & Lassonde, M. (2006). Neurophysiological Anomalies in Symptomatic and Asymptomatic Concussed Athletes. Neurosurgery, 58(6), 1151–1161. https://doi.org/10.1227/01.NEU.0000215953.44097.FA

Gratton, G., Coles, M. G., & Donchin, E. (1983). A new method for off-line removal of ocular artifact. Electroencephalography and Clinical Neurophysiology, 55(4), 468–484.

Hall, J. R., Bernat, E. M., & Patrick, C. J. (2007). Externalizing psychopathology and the error-related negativity. Psychological Science, 18(4), 326–333.

Han, K., Mac Donald, C. L., Johnson, A. M., Barnes, Y., Wierzechowski, L., Zonies, D., Oh, J., Flaherty, S., Fang, R., & Raichle, M. E. (2014). Disrupted modular organization of resting-state cortical functional connectivity in US military personnel following concussive ‘mild’blast-related traumatic brain injury. Neuroimage, 84, 76–96.

Hanslmayr, S., Pastötter, B., Bäuml, K.-H., Gruber, S., Wimber, M., & Klimesch, W. (2007). The Electrophysiological Dynamics of Interference during the Stroop Task. Journal of Cognitive Neuroscience, 20(2), 215–225. https://doi.org/10.1162/jocn.2008.20020

Harper, J., Malone, S. M., Bachman, M. D., & Bernat, E. M. (2016). Stimulus sequence context differentially modulates inhibition-related theta and delta band activity in a go/no-go task. Psychophysiology. http://onlinelibrary.wiley.com/doi/10.1111/psyp.12604/full

Harper, J., Malone, S. M., & Bernat, E. M. (2014). Theta and delta band activity explain N2 and P3 ERP component activity in a go/no-go task. Clinical Neurophysiology, 125(1), 124–132.

He, B., Lian, J., Spencer, K. M., Dien, J., & Donchin, E. (2001). A cortical potential imaging analysis of the P300 and novelty P3 components. Human Brain Mapping, 12(2), 120–130.

Hoge, C. W., McGurk, D., Thomas, J. L., Cox, A. L., Engel, C. C., & Castro, C. A. (2008). Mild traumatic brain injury in US soldiers returning from Iraq. New England Journal of Medicine, 358(5), 453–463.

Holroyd, C. B., & Coles, M. G. (2002). The neural basis of human error processing: Reinforcement learning, dopamine, and the error-related negativity. Psychological Review, 109(4), 679.

Hughes, K. C., & Shin, L. M. (2011). Functional neuroimaging studies of post-traumatic stress disorder. Expert Review of Neurotherapeutics, 11(2), 275–285.

Iacono, W. G., Malone, S. M., & McGue, M. (2003). Substance use disorders, externalizing psychopathology, and P300 event-related potential amplitude. International Journal of Psychophysiology, 48(2), 147–178.

Iraji, A., Benson, R. R., Welch, R. D., O'Neil, B. J., Woodard, J. L., Ayaz, S. I., Kulek, A., Mika, V., Medado, P., & Soltanian-Zadeh, H. (2015). Resting state functional

connectivity in mild traumatic brain injury at the acute stage: Independent component and seed-based analyses. Journal of Neurotrauma, 32(14), 1031–1045.

Iverson, G. L. (2005). Outcome from mild traumatic brain injury. Current Opinion in Psychiatry, 18(3), 301. https://doi.org/10.1097/01.yco.0000165601.29047.ae

Iverson, G. L., & Lange, R. T. (2011). Mild Traumatic Brain Injury. In The Little Black Book of Neuropsychology (pp. 697–719). Springer, Boston, MA. https://doi.org/10.1007/978-0-387-76978-3_22

Karakaş, S., Erzengin, Ö. U., & Başar, E. (2000). A new strategy involving multiple cognitive paradigms demonstrates that ERP components are determined by the superposition of oscillatory responses. Clinical Neurophysiology, 111(10), 1719–1732.

Karakaş, Sirel, Erzengin, Ö. U., & Başar, E. (2000). The genesis of human event-related responses explained through the theory of oscillatory neural assemblies. Neuroscience Letters, 285(1), 45–48.

Karr, J. E., Areshenkoff, C. N., Duggan, E. C., & Garcia-Barrera, M. A. (2014). Blast-Related Mild Traumatic Brain Injury: A Bayesian Random-Effects Meta-Analysis on the Cognitive Outcomes of Concussion among Military Personnel. Neuropsychology Review, 24(4), 428–444. https://doi.org/10.1007/s11065-014-9271-8

Kiefer, A. W., Barber Foss, K., Reches, A., Gadd, B., Gordon, M., Rushford, K., Laufer, I., Weiss, M., & Myer, G. D. (2015). Brain network activation as a novel biomarker for the return-to-play pathway following sport-related brain injury. Frontiers in Neurology, 6, 243.

Kolev, V., Demiralp, T., Yordanova, J., Ademoglu, A., & Isoglu-Alkaç, Ü. (1997). Time–frequency analysis reveals multiple functional components during oddball P300. NeuroReport, 8(8), 2061–2065.

Kontos, A. P., Reches, A., Elbin, R. J., Dickman, D., Laufer, I., Geva, A. B., Shacham, G., DeWolf, R., & Collins, M. W. (2016). Preliminary evidence of reduced brain network activation in patients with post-traumatic migraine following concussion. Brain Imaging and Behavior, 10(2), 594–603.

Kopp, B., Tabeling, S., Moschner, C., & Wessel, K. (2006). Fractionating the neural mechanisms of cognitive control. Journal of Cognitive Neuroscience, 18(6), 949–965.

Kumar, S., Rao, S. L., Chandramouli, B. A., & Pillai, S. V. (2009). Reduction of functional brain connectivity in mild traumatic brain injury during working memory. Journal of Neurotrauma, 26(5), 665–675.

Lachapelle, J., Bolduc-Teasdale, J., Ptito, A., & McKerral, M. (2008). Deficits in complex visual information processing after mild TBI: Electrophysiological markers and vocational outcome prognosis. Brain Injury, 22(3), 265–274.

Levin, H. S., & Diaz-Arrastia, R. R. (2015). Diagnosis, prognosis, and clinical management of mild traumatic brain injury. The Lancet Neurology, 14(5), 506–517. https://doi.org/10.1016/S1474-4422(15)00002-2

Lew, H. L., Lee, E. H., Pan, S. S. L., & Date, E. S. (2004). Electrophysiologic Abnormalities of Auditory and Visual Information Processing in Patients with Traumatic Brain Injury. American Journal of Physical Medicine & Rehabilitation, 83(6), 428.

Lew, H. L., Thomander, D., Gray, M., & Poole, J. H. (2007). The Effects of Increasing Stimulus Complexity in Event-Related Potentials and Reaction Time Testing: Clinical

Applications in Evaluating Patients with Traumatic Brain Injury. Journal of Clinical Neurophysiology, 24(5), 398. https://doi.org/10.1097/WNP.0b013e318150694b

Linden, D. E. (2005). The P300: Where in the brain is it produced and what does it tell us? The Neuroscientist, 11(6), 563–576.

Ling, G., Bandak, F., Armonda, R., Grant, G., & Ecklund, J. (2009). Explosive blast neurotrauma. Journal of Neurotrauma, 26(6), 815–825.

Luft, C. D. B. (2014). Learning from feedback: The neural mechanisms of feedback processing facilitating better performance. Behavioural Brain Research, 261, 356–368.

Luu, P., & Tucker, D. M. (2001). Regulating action: Alternating activation of midline frontal and motor cortical networks. Clinical Neurophysiology, 112(7), 1295–1306.

Luu, P., Tucker, D. M., & Makeig, S. (2004). Frontal midline theta and the error-related negativity: Neurophysiological mechanisms of action regulation. Clinical Neurophysiology, 115(8), 1821–1835.

Magnuson, J., Leonessa, F., & Ling, G. S. (2012). Neuropathology of explosive blast traumatic brain injury. Current Neurology and Neuroscience Reports, 12(5), 570–579.

Makeig, S., Westerfield, M., Jung, T.-P., Enghoff, S., Townsend, J., Courchesne, E., & Sejnowski, T. J. (2002). Dynamic brain sources of visual evoked responses. Science, 295(5555), 690–694.

Management of Concussion/mTBI Working Group. (2009). VA/DoD clinical practice guideline for management of concussion/mild traumatic brain injury, Version 1.0. https://www.healthquality.va.gov/guidelines/Rehab/mtbi/concussion_mtbi_full_1_0.pdf

Marco-Pallares, J., Cucurell, D., Cunillera, T., García, R., Andrés-Pueyo, A., Münte, T. F., & Rodríguez-Fornells, A. (2008). Human oscillatory activity associated to reward processing in a gambling task. Neuropsychologia, 46(1), 241–248.

Matthews, S. C., Strigo, I. A., Simmons, A. N., O'connell, R. M., Reinhardt, L. E., & Moseley, S. A. (2011). A multimodal imaging study in US veterans of Operations Iraqi and Enduring Freedom with and without major depression after blast-related concussion. Neuroimage, 54, S69–S75.

Mayer, A. R., Bellgowan, P. S., & Hanlon, F. M. (2015). Functional magnetic resonance imaging of mild traumatic brain injury. Neuroscience & Biobehavioral Reviews, 49, 8–18.

Mayer, A. R., Mannell, M. V., Ling, J., Elgie, R., Gasparovic, C., Phillips, J. P., Doezema, D., & Yeo, R. A. (2009). Auditory Orienting and Inhibition of Return in Mild Traumatic Brain Injury: A FMRI study. Human Brain Mapping, 30(12), 4152–4166. https://doi.org/10.1002/hbm.20836

Mayer, A. R., Mannell, M. V., Ling, J., Gasparovic, C., & Yeo, R. A. (2011). Functional Connectivity in Mild Traumatic Brain Injury. Human Brain Mapping, 32(11), 1825–1835. https://doi.org/10.1002/hbm.21151

Mayer, A. R., Yang, Z., Yeo, R. A., Pena, A., Ling, J. M., Mannell, M. V., Stippler, M., & Mojtahed, K. (2012). A functional MRI study of multimodal selective attention following mild traumatic brain injury. Brain Imaging and Behavior, 6(2), 343–354. https://doi.org/10.1007/s11682-012-9178-z

McAllister, T. W., Saykin, A. J., Flashman, L. A., Sparling, M. B., Johnson, S. C., Guerin, S. J., Mamourian, A. C., Weaver, J. B., & Yanofsky, N. (1999). Brain activation during

working memory 1 month after mild traumatic brain injury A functional MRI study. Neurology, 53(6), 1300–1300.

McAllister, T. W., Sparling, M. B., Flashman, L. A., Guerin, S. J., Mamourian, A. C., & Saykin, A. J. (2001). Differential working memory load effects after mild traumatic brain injury. Neuroimage, 14(5), 1004–1012.

McCrea, M., Pliskin, N., Barth, J., Cox, D., Fink, J., French, L., Hammeke, T., Hess, D., Hopewell, A., & Orme, D. (2008). Official position of the military TBI task force on the role of neuropsychology and rehabilitation psychology in the evaluation, management, and research of military veterans with traumatic brain injury: APPROVED by: American Academy of Clinical Neuropsychology (AACN) American Psychological Association Division 40 (Neuropsychology) American Psychological Association Division 22 (Rehabilitation Psychology) National Academy of Neuropsychology (NAN). The Clinical Neuropsychologist, 22(1), 10–26.

McMahon, P. J., Hricik, A., Yue, J. K., Puccio, A. M., Inoue, T., Lingsma, H. F., Beers, S. R., Gordon, W. A., Valadka, A. B., & Manley, G. T. (2014). Symptomatology and functional outcome in mild traumatic brain injury: Results from the prospective TRACK-TBI study. Journal of Neurotrauma, 31(1), 26–33.

McNerney, M. W., Hobday, T., Cole, B., Ganong, R., Winans, N., Matthews, D., Hood, J., & Lane, S. (2019). Objective classification of mTBI using machine learning on a combination of frontopolar electroencephalography measurements and self-reported symptoms. Sports Medicine-Open, 5(1), 1–8.

Meachen, S.-J., Hanks, R. A., Millis, S. R., & Rapport, L. J. (2008). The reliability and validity of the Brief Symptom Inventory- 18 in persons with traumatic brain injury. Archives of Physical Medicine and Rehabilitation, 89(5), 958–965.

Meares, S., Shores, E. A., Taylor, A. J., Batchelor, J., Bryant, R. A., Baguley, I. J., Chapman, J., Gurka, J., & Marosszeky, J. E. (2011). The prospective course of postconcussion syndrome: The role of mild traumatic brain injury. Neuropsychology, 25(4), 454.

Messé, A., Caplain, S., Pélégrini-Issac, M., Blancho, S., Lévy, R., Aghakhani, N., Montreuil, M., Benali, H., & Lehéricy, S. (2013). Specific and Evolving Resting-State Network Alterations in Post-Concussion Syndrome Following Mild Traumatic Brain Injury. PLOS ONE, 8(6), e65470. https://doi.org/10.1371/journal.pone.0065470

Miller, E. K., & Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. Annual Review of Neuroscience, 24, 167–202. https://doi.org/10.1146/annurev.neuro.24.1.167

Moran, T. P., Bernat, E. M., Aviyente, S., Schroder, H. S., & Moser, J. S. (2015). Sending mixed signals: Worry is associated with enhanced initial error processing but reduced call for subsequent cognitive control. Social Cognitive and Affective Neuroscience, nsv046.

Naito, Y., Ando, H., & Yamaguchi, M. (2005). Assessment of traumatic brain injury patients by WAIS-R, P300, and performance on oddball task. Kobe Journal of Medical Sciences, 51(5/6), 95.

Nandrajog, P., Idris, Z., Azlen, W. N., Liyana, A., & Abdullah, J. M. (2017). The use of event-related potential (P300) and neuropsychological testing to evaluate cognitive impairment in mild traumatic brain injury patients. Asian Journal of Neurosurgery, 12(3), 447–453. https://doi.org/10.4103/1793-5482.180921

Nelson, L. D., Patrick, C. J., Collins, P., Lang, A. R., & Bernat, E. M. (2011). Alcohol impairs brain reactivity to explicit loss feedback. Psychopharmacology, 218(2), 419–428. https://doi.org/10.1007/s00213-011-2323-3

Nieuwenhuis, S., De Geus, E. J., & Aston-Jones, G. (2011). The anatomical and functional relationship between the P3 and autonomic components of the orienting response. Psychophysiology, 48(2), 162–175.

Olvet, D. M., & Hajcak, G. (2009). The stability of error-related brain activity with increasing trials. Psychophysiology, 46(5), 957–961.

Palacios, E. M., Yuh, E. L., Chang, Y.-S., Yue, J. K., Schnyer, D. M., Okonkwo, D. O., Valadka, A. B., Gordon, W. A., Maas, A. I., & Vassar, M. (2017). Resting-state functional connectivity alterations associated with six-month outcomes in mild traumatic brain injury. Journal of Neurotrauma, 34(8), 1546–1557.

Papenberg, G., Hämmerer, D., Müller, V., Lindenberger, U., & Li, S.-C. (2013). Lower theta inter-trial phase coherence during performance monitoring is related to higher reaction time variability: A lifespan study. NeuroImage, 83, 912–920.

Pertab, J. L., James, K. M., & Bigler, E. D. (2009). Limitations of mild traumatic brain injury meta-analyses. Brain Injury, 23(6), 498–508. https://doi.org/10.1080/02699050902927984

Peterson, A. B., Xu, L., Daugherty, J., & Breiding, M. J. (2019). Surveillance report of traumatic brain injury-related emergency department visits, hospitalizations, and deaths, United States, 2014.

Polich, J. (2007). Updating P300: An integrative theory of P3a and P3b. Clinical Neurophysiology, 118(10), 2128–2148.

Ponsford, J., Willmott, C., Rothwell, A., Cameron, P., Kelly, A.-M., Nelms, R., Curran, C., & Ng, K. (2000). Factors influencing outcome following mild traumatic brain injury in adults. Journal of the International Neuropsychological Society, 6(5), 568–579.

Pontifex, M. B., Scudder, M. R., Brown, M. L., O'Leary, K. C., Wu, C.-T., Themanson, J. R., & Hillman, C. H. (2010). On the number of trials necessary for stabilization of error-related brain activity across the life span. Psychophysiology, 47(4), 767–773.

Potter, D. D., Bassett, M. R. A., Jory, S. H., & Barrett, K. (2001). Changes in event-related potentials in a three-stimulus auditory oddball task after mild head injury. Neuropsychologia, 39(13), 1464–1472. https://doi.org/10.1016/S0028-3932(01)00057-4

Potter, D. D., Jory, S. H., Bassett, M. R. A., Barrett, K., & Mychalkiw, W. (2002). Effect of mild head injury on event-related potential correlates of Stroop task performance. Journal of the International Neuropsychological Society, 8(6), 828–837. https://doi.org/10.1017/S1355617702860118

Pritchard, W. S. (1981). Psychophysiology of P300. Psychological Bulletin, 89(3), 506.

Rabinowitz, A. R., & Levin, H. S. (2014). Cognitive Sequelae of Traumatic Brain Injury. The Psychiatric Clinics of North America, 37(1), 1–11. https://doi.org/10.1016/j.psc.2013.11.004

Reches, A., Kutcher, J., Elbin, R. J., Or-Ly, H., Sadeh, B., Greer, J., McAllister, D. J., Geva, A., & Kontos, A. P. (2017). Preliminary investigation of Brain Network Activation (BNA) and its clinical utility in sport-related concussion. Brain Injury, 31(2), 237–246.

Ritter, W., Simson, R., Vaughan, H. G., & Macht, M. (1982). Manipulation of event-related potential manifestations of information processing stages. Science, 218(4575), 909–911.

Robinson, M. E., Lindemer, E. R., Fonda, J. R., Milberg, W. P., McGlinchey, R. E., & Salat, D. H. (2015). Close-range blast exposure is associated with altered functional connectivity in Veterans independent of concussion symptoms at time of exposure. Human Brain Mapping, 36(3), 911–922.

Rohling, M. L., Binder, L. M., Demakis, G. J., Larrabee, G. J., Ploetz, D. M., & Langhinrichsen-Rohling, J. (2011). A Meta-Analysis of Neuropsychological Outcome After Mild Traumatic Brain Injury: Re-analyses and Reconsiderations of Binder et al., Frencham et al., and Pertab et al. The Clinical Neuropsychologist, 25(4), 608–623.

Rosenfeld, J. V., & Ford, N. L. (2010). Bomb blast, mild traumatic brain injury and psychiatric morbidity: A review. Injury, 41(5), 437–443.

Rosvold, H. E., Mirsky, A. F., Sarason, I., Bransome Jr, E. D., & Beck, L. H. (1956). A continuous performance test of brain damage. Journal of Consulting Psychology, 20(5), 343.

Rugg, M. D., Cowan, C. P., Nagy, M. E., Milner, A. D., Jacobson, I., & Brooks, D. N. (1988). Event related potentials from closed head injury patients in an auditory "oddball" task: Evidence of dysfunction in stimulus categorisation. Journal of Neurology, Neurosurgery & Psychiatry, 51(5), 691–698. https://doi.org/10.1136/jnnp.51.5.691

Sauseng, P., Klimesch, W., Gruber, W. R., Hanslmayr, S., Freunberger, R., & Doppelmayr, M. (2007). Are event-related potential components generated by phase resetting of brain oscillations? A critical discussion. Neuroscience, 146(4), 1435–1444. https://doi.org/10.1016/j.neuroscience.2007.03.014

Segalowitz, S. J., Bernstein, D. M., & Lawson, S. (2001). P300 Event-Related Potential Decrements in Well-Functioning University Students with Mild Head Injury. Brain and Cognition, 45(3), 342–356. https://doi.org/10.1006/brcg.2000.1263

Sharp, D. J., Scott, G., & Leech, R. (2014). Network dysfunction after traumatic brain injury. Nature Reviews Neurology, 10(3), 156.

Shumskaya, E., Andriessen, T. M., Norris, D. G., & Vos, P. E. (2012). Abnormal whole-brain functional networks in homogeneous acute mild traumatic brain injury. Neurology, 79(2), 175–182.

Sivák, Š., Kurča, E., Hladka, M., Zeleňák, K., Turčanová-Koprušáková, M., & Michalik, J. (2008). Early and delayed auditory oddball ERPs and brain MRI in patients with MTBI. Brain Injury, 22(2), 193–197.

Slobounov, S. M., Gay, M., Zhang, K., Johnson, B., Pennell, D., Sebastianelli, W., Horovitz, S., & Hallett, M. (2011). Alteration of Brain Functional Network at Rest and in Response to YMCA Physical Stress Test in Concussed Athletes: RsFMRI study. NeuroImage, 55(4), 1716–1727. https://doi.org/10.1016/j.neuroimage.2011.01.024

Smith, E. E., & Allen, J. J. (2019). Theta-Band Functional Connectivity and Single-Trial Cognitive Control in Sports-Related Concussion: Demonstration of Proof-of-Concept for a Potential Biomarker of Concussion. Journal of the International Neuropsychological Society, 25(3), 314–323.

Smith, E. H., Banks, G. P., Mikell, C. B., Cash, S. S., Patel, S. R., Eskandar, E. N., & Sheth, S. A. (2015). Frequency-Dependent Representation of Reinforcement-Related Information in the Human Medial and Lateral Prefrontal Cortex. The Journal of Neuroscience, 35(48), 15827–15836. https://doi.org/10.1523/JNEUROSCI.1864-15.2015

Solbakk, A.-K., Reinvang, I., & Andersson, S. (2002). Assessment of P3a and P3b after Moderate to Severe Brain Injury , Assessment of P3a and P3b after Moderate to Severe Brain Injury. Clinical Electroencephalography, 33(3), 102–110. https://doi.org/10.1177/155005940203300306

Solbakk, A.-K., Reinvang, I., & Nielsen, C. S. (2000). ERP indices of resource allocation difficulties in mild head injury. Journal of Clinical and Experimental Neuropsychology, 22(6), 743–760.

Solbakk, A.-K., Reinvang, I., Nielsen, C., & Sundet, K. (1999). ERP indicators of disturbed attention in mild closed head injury: A frontal lobe syndrome? Psychophysiology, 36(6), 802–817.

Soltani, M., & Knight, R. T. (2000). Neural origins of the P300. Critical Reviews™ in Neurobiology, 14(3–4).

Spencer, K. M., Dien, J., & Donchin, E. (1999). A componential analysis of the ERP elicited by novel events using a dense electrode array. Psychophysiology, 36(3), 409–414.

Spencer, K. M., Dien, J., & Donchin, E. (2001). Spatiotemporal analysis of the late ERP responses to deviant stimuli. Psychophysiology, 38(2), 343–358.

Spencer, K. M., & Polich, J. (1999). Poststimulus EEG spectral analysis and P300: Attention, task, and probability. Psychophysiology, 36(02), 220–232.

Spikman, J. M., Naalt, J. V. D., Weerden, T. W. V., & Zomeren, A. H. V. (2004). Indices of slowness of information processing in head injury patients: Tests for selective attention related to ERP latencies. Journal of the International Neuropsychological Society, 10(6), 851–861. https://doi.org/10.1017/S1355617704106061

Sponheim, S. R., McGuire, K. A., Kang, S. S., Davenport, N. D., Aviyente, S., Bernat, E. M., & Lim, K. O. (2011). Evidence of disrupted functional connectivity in the brain after combat-related blast injury. Neuroimage, 54, S21–S29.

Stansbury, L. G., Lalliss, S. J., Branstetter, J. G., Bagg, M. R., & Holcomb, J. B. (2008). Amputations in US military personnel in the current conflicts in Afghanistan and Iraq. Journal of Orthopaedic Trauma, 22(1), 43–46.

Steele, V. R., Anderson, N. E., Claus, E. D., Bernat, E. M., Rao, V., Assaf, M., Pearlson, G. D., Calhoun, V. D., & Kiehl, K. A. (2016). Neuroimaging measures of error-processing: Extracting reliable signals from event-related potentials and functional magnetic resonance imaging. Neuroimage, 132, 247–260.

Stevens, M. C., Lovejoy, D., Kim, J., Oakes, H., Kureshi, I., & Witt, S. T. (2012). Multiple resting state network functional connectivity abnormalities in mild traumatic brain injury. Brain Imaging and Behavior, 6(2), 293–318.

Sutton, S., Braren, M., Zubin, J., & John, E. R. (1965). Evoked-potential correlates of stimulus uncertainty. Science, 150(3700), 1187–1188.

Tenke, C. E., & Kayser, J. (2012). Generator localization by current source density (CSD): Implications of volume conduction and field closure at intracranial and scalp resolutions. Clinical Neurophysiology, 123(12), 2328–2345.

TransformTukey function | R Documentation. (n.d.). Retrieved May 13, 2020, from https://www.rdocumentation.org/packages/rcompanion/versions/2.3.25/topics/transformTukey

Vakhtin, A. A., Calhoun, V. D., Jung, R. E., Prestopnik, J. L., Taylor, P. A., & Ford, C. C. (2013). Changes in intrinsic functional brain networks following blast-induced mild traumatic brain injury. Brain Injury, 27(11), 1304–1310.

Van de Vijver, I., Ridderinkhof, K. R., & Cohen, M. X. (2011). Frontal oscillatory dynamics predict feedback learning and action adjustment. Journal of Cognitive Neuroscience, 23(12), 4106–4121.

van der Naalt, J., Timmerman, M. E., de Koning, M. E., van der Horn, H. J., Scheenen, M. E., Jacobs, B., Hageman, G., Yilmaz, T., Roks, G., & Spikman, J. M. (2017). Early predictors of outcome after mild traumatic brain injury (UPFRONT): An observational cohort study. The Lancet Neurology, 16(7), 532–540. https://doi.org/10.1016/S1474-4422(17)30117-5

van Noordt, S., Wu, J., Venkataraman, A., Larson, M. J., South, M., & Crowley, M. J. (2017). Inter-trial coherence of medial frontal theta oscillations linked to differential feedback processing in youth and young adults with autism. Research in Autism Spectrum Disorders, 37, 1–10.

Vanderploeg, R. D., Curtiss, G., & Belanger, H. G. (2005). Long-term neuropsychological outcomes following mild traumatic brain injury. Journal of the International Neuropsychological Society, 11(3), 228–236.

Varela, F., Lachaux, J.-P., Rodriguez, E., & Martinerie, J. (2001). The brainweb: Phase synchronization and large-scale integration. Nature Reviews Neuroscience, 2(4).

Watts, A. T., Bachman, M. D., & Bernat, E. M. (2017). Expectancy Effects in Feedback Processing are Explained Primarily by Time-frequency Delta not Theta. Biological Psychology. http://www.sciencedirect.com/science/article/pii/S0301051117302107

Watts, A. T. M., & Bernat, E. M. (2018). Effects of reward context on feedback processing as indexed by time-frequency analysis. Psychophysiology, 0(0), e13195. https://doi.org/10.1111/psyp.13195

Watts, A. T., Tootell, A. V., Fix, S. T., Aviyente, S., & Bernat, E. M. (2018). Utilizing time-frequency amplitude and phase synchrony measure to assess feedback processing in a gambling task. International Journal of Psychophysiology.

Weathers, F. W., Litz, B. T., Herman, D. S., Huska, J. A., & Keane, T. M. (1993). The PTSD Checklist (PCL): Reliability, validity, and diagnostic utility. Annual Convention of the International Society for Traumatic Stress Studies, San Antonio, TX, 462.

Wechsler, D., Coalson, D. L., & Raiford, S. E. (2008). WAIS-IV: Wechsler adult intelligence scale. Pearson San Antonio, TX.

Wei, D., Qiu, J., Tu, S., Tian, F., Su, Y., & Luo, Y. (2010). Earthquake experience interference effects in a modified Stroop task: An ERP study. Neuroscience Letters, 474(3), 121–125. https://doi.org/10.1016/j.neulet.2010.03.005

Wessel, J. R., & Aron, A. R. (2013). Unexpected events induce motor slowing via a brain mechanism for action-stopping with global suppressive effects. Journal of Neuroscience, 33(47), 18481–18491.

Wienke, A. S., Basar-Eroglu, C., Schmiedt-Fehr, C., & Mathes, B. (2018). Novelty N2-P3a complex and theta oscillations reflect improving neural coordination within frontal brain networks during adolescence. Frontiers in Behavioral Neuroscience, 12, 218.

Witt, S. T., Lovejoy, D. W., Pearlson, G. D., & Stevens, M. C. (2010). Decreased prefrontal cortex activity in mild traumatic brain injury during performance of an auditory oddball task. Brain Imaging and Behavior, 4(3–4), 232–247.

Yago, E., Escera, C., Alho, K., Giard, M.-H., & Serra-Grabulosa, J. M. (2003). Spatiotemporal dynamics of the auditory novelty-P3 event-related brain potential. Cognitive Brain Research, 16(3), 383–390.

Yordanova, J., Devrim, M., Kolev, V., Ademoglu, A., & Demiralp, T. (2000). Multiple time-frequency components account for the complex functional reactivity of P300. Neuroreport, 11(5), 1097–1103.

Yuh, E. L., Cooper, S. R., Mukherjee, P., Yue, J. K., Lingsma, H. F., Gordon, W. A., Valadka, A. B., Okonkwo, D. O., Schnyer, D. M., & Vassar, M. J. (2014). Diffusion tensor imaging for outcome prediction in mild traumatic brain injury: A TRACK-TBI study. Journal of Neurotrauma, 31(17), 1457–1477.

Yurgil, K. A., Barkauskas, D. A., Vasterling, J. J., Nievergelt, C. M., Larson, G. E., Schork, N. J., Litz, B. T., Nash, W. P., & Baker, D. G. (2014). Association between traumatic brain injury and risk of posttraumatic stress disorder in active-duty Marines. JAMA Psychiatry, 71(2), 149–157.

Zhang, K., Johnson, B., Gay, M., Horovitz, S. G., Hallett, M., Sebastianelli, W., & Slobounov, S. (2012). Default mode network in concussed individuals in response to the YMCA physical stress test. Journal of Neurotrauma, 29(5), 756–765.

Zhang, Y., Kong, F., Han, L., ul Hasan, A. N., & Chen, H. (2014). Attention bias in earthquake-exposed survivors: An event-related potential study. International Journal of Psychophysiology, 94(3), 358–364.

Zhou, Y., Lui, Y. W., Zuo, X.-N., Milham, M. P., Reaume, J., Grossman, R. I., & Ge, Y. (2014). Characterization of thalamo-cortical association using amplitude and connectivity of

functional MRI in mild traumatic brain injury. Journal of Magnetic Resonance Imaging, 39(6), 1558–1568.

Zhou, Y., Milham, M. P., Lui, Y. W., Miles, L., Reaume, J., Sodickson, D. K., Grossman, R. I., & Ge, Y. (2012). Default-mode network disruption in mild traumatic brain injury. Radiology, 265(3), 882–892.

Zouridakis, G., Patidar, U., Situ, N., Rezaie, R., Castillo, E. M., Levin, H. S., & Papanicolaou, A. C. (2012). Functional connectivity changes in mild traumatic brain injury assessed using magnetoencephalography. Journal of Mechanics in Medicine and Biology, 12(02), 1240006.