Neurophysiological Alterations Following Concussion: Controlling for the Injury Factor

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NEUROPHYSIOLOGICAL ALTERATIONS FOLLOWING CONCUSSION:
CONTROLLING FOR THE INJURY FACTOR

by

Caitlin J. Masterson

A DISSERTATION

Presented to the Faculty of
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Major: Psychology

Under the Supervision of Professors Arthur C. Maerlender and Cary Savage

Lincoln, Nebraska

July, 2019
NEUROPHYSIOLOGICAL ALTERATIONS FOLLOWING CONCUSSION:
CONTROLLING FOR THE INJURY FACTOR
Caitlin J. Masterson, Ph.D.
University of Nebraska, 2019
Advisors: Arthur C. Maerlender and Cary Savage

The topic of mild traumatic brain injury (mTBI) has rapidly gained attention not only in academic science but also in popular media. Unlike severe traumatic brain injury, mTBI is difficult to diagnose. There are no objective diagnostic criteria, and symptoms can vary greatly across individuals. Further, although individuals with mTBI are frequently compared to non-injured individuals, it cannot be concluded with certainty that any differences found between groups can be attributed solely to the head injury and not a more general injury-factor. Identifying a sensitive and specific physiological signal across similar injury groups is critical to establishing a criterion that would facilitate the development of tools which could be rapidly employed. The purpose of the present study was to investigate neurophysiological functioning in individuals who recently sustained a mTBI or orthopedic injury, as well as non-injured individuals, using multiple electrophysiological analysis procedures.

Twenty-four participants ages 18-30 were recruited for this study. Individuals were in one of three groups: mTBI (3 males and 3 females; age $M$: 22.50), mild orthopedic injury (6 males and 2 females; age $M$:20.76), or non-injured (2 males and 8 females; age $M$: 21.50). Injured participants took part in the study no longer than ten days post-injury. All participants completed a resting state task, analyzed with quantitative EEG, and two cognitive event-related potential (ERP) tasks: auditory oddball and n-back.
Results indicated no significant group differences for resting state or n-back. However, the mTBI group displayed significantly larger P300 amplitudes during the auditory oddball. Although some individuals with mTBI may show reduced activation in brain areas supporting working memory, areas outside this network are recruited and included in order to meet task demands, which could account for the increase in amplitude. The current study lends support for the use of ERP, specifically with an auditory oddball task, in the identification of acute mTBI. Of primary significance is the inclusion of an orthopedic injury group and the finding that P300 amplitude is significantly increased only for those with mTBI. This provides an important basis for future research and strategies for the development of a rapid, objective measure of mTBI.
Dedication

I want to dedicate this dissertation to my parents, Jerry and Julie Masterson, and to my husband, Benjamin Thomas. Thank you for your unwavering love, support, and confidence in me. I never would have completed this graduate school journey without each of you.
Acknowledgements

First, to my mentor, Art Maerlender, for your advisement and encouragement over the last 5 years- thank you for never failing to push me out of my comfort zone and for helping develop the skills and knowledge you saw in me way before I did. You have made me a far better scholar than I was before moving to Nebraska. Thank you for always being willing to entertain my ideas, answer hundreds of questions, and to reassure me when I was certain I was doing everything wrong. I have no doubt your lessons will guide my work (and life) for years to come.

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To my UNL family: Colin, Josh, Molly, Rafay (even though you left), Bobby, and Grace- you all have made these last 5 years so much fun. Thank you for your continuous support as well as your willingness to share in misery, but most importantly, thank you for being my home away from home.

To my parents- there is no doubt in my mind that I would not be where I am today without you. Thank you for never putting on cap on my dreams, for letting me explore
who I wanted to become, and for making sure I knew I always have a soft place to land. Dad, thank you for being my #1 fan, my road trip buddy, and for never failing to answer the phone when I had a question about my health, my car, or when I just had to tell you about a great (or horrible) workout. Mom, thank you for being my sounding board, my life advisor, and for always reminding me just how funny we are together. You both have eased the burden of this long process with your constant support, whether it be in the form of a listening ear, a push, a hug, or a glass of wine - I am so grateful to have you as my parents.

Finally, to my husband Benjamin - it is difficult for me to fully express how much your unconditional love and support have meant to me, not just through this process, but throughout our entire relationship. Thank you for knowing exactly how to make me laugh, even when it’s completely inappropriate. For being my forever board game teammate, for not only understanding - but celebrating my competitiveness, for reminding me to never take work too seriously, to make time for the things that make me smile, and to always celebrate the top of each mountain - even if it may seem like a mole hill. I love you, and I am so excited for our post-graduate life together.
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# TABLE OF CONTENTS

LIST OF MULTIMEDIA OBJECTS ................................................................................. x

CHAPTER 1: INTRODUCTION ......................................................................................... 1
  1.1 General Introduction ......................................................................................... 1
  1.2 Electrophysiological Techniques ...................................................................... 3
      1.2.1 Quantitative Electrophysiology ............................................................... 3
      1.2.2 Event-Related Potentials ........................................................................... 5
  1.3 Purpose ............................................................................................................. 8
  1.4 Research Questions and Hypotheses ............................................................... 9

CHAPTER 2: METHOD ................................................................................................. 11
  2.1 Recruitment ..................................................................................................... 11
  2.2 Participants ..................................................................................................... 12
  2.3 Apparatus and Materials .................................................................................. 15
      2.3.1 Electrophysiological Measures ................................................................. 15
      2.3.2 Recording ................................................................................................ 16
  2.4 Procedure ........................................................................................................ 16
  2.5 Analysis ........................................................................................................... 19
      2.5.1 Quantitative EEG .................................................................................... 19
          2.5.1.1 Preprocessing .................................................................................... 19
          2.5.1.2 Statistical Analysis ........................................................................... 20
      2.5.2 ERP ......................................................................................................... 20
          2.5.2.1 Preprocessing .................................................................................... 20
2.5.2.2 Oddball Statistical Analysis .............................................. 21
2.5.2.3 N-back Statistical Analysis ............................................. 22
2.5.2.4 Response Accuracy Statistical Analysis ......................... 23

CHAPTER 3: RESULTS .................................................................................. 24
3.1 Question 1: Group Differences in Power During Resting State ...... 24
3.2 Question 2: Group Differences in P300 During ERP Tasks ........... 25
   3.2.1 Amplitude: Oddball ......................................................... 25
   3.2.2 Amplitude: N-back .......................................................... 27
   3.2.3 Latency: Oddball ............................................................. 30
   3.2.4 Latency: N-back ............................................................. 31
   3.2.5 Response Accuracy: Oddball ........................................... 33
   3.2.6 Response Accuracy: N-back ............................................. 35

CHAPTER 4: DISCUSSION ........................................................................... 37
4.1 General Discussion ........................................................................... 37
4.2 Limitations ....................................................................................... 41
4.3 Conclusions and Future Directions ............................................... 42

REFERENCES .......................................................................................... 43
LIST OF MULTIMEDIA OBJECTS

TABLES

Table 1.1 Sub-hypotheses for resting state power comparisons .........................11
Table 1.2 Sub-hypotheses for P300 comparisons ........................................11
Table 1.3 Participant demographics by group ..............................................14
Table 3.1 Post hoc group comparisons for oddball P300 amplitude ...............27
Table 3.2 $M$, $SD$, and effect sizes across groups for n-back P300 amplitude .......29
Table 3.3 $M$, $SD$, and effect sizes across groups for oddball P300 latency .......31
Table 3.4 $M$, $SD$, and effect sizes across groups for n-back P300 latency .......33
Table 3.5 $M$, $SD$, and effect sizes across groups for oddball response accuracy ...35
Table 3.6 $M$, $SD$, and effect sizes across groups for oddball response accuracy ...37

FIGURES

Figure 3.1 qEEG spectral maps for cognitive activity power unit ....................24
Figure 3.2 qEEG spectral maps for drowsy state power unit ..........................25
Figure 3.3 Spectral maps for P300 response to auditory oddball ....................26
Figure 3.4 Group performance for auditory oddball P300 amplitude ...............26
Figure 3.5 Spectral maps for P300 response to n-back ..................................28
Figure 3.6 Group performance for n-back P300 amplitude ...........................28
Figure 3.7 Group performance for P300 latency during oddball .....................30
Figure 3.8 Group performance for P300 latency during n-back .......................32
Figure 3.9 Response accuracy by group for the oddball task .........................34
Figure 3.10 Response accuracy by group for the n-back task .......................36
CHAPTER 1: INTRODUCTION

1.1 General Introduction

The topic of mild traumatic brain injury (mTBI) has rapidly gained attention not only in academic science but also in popular media. Making headlines, sport-related concussion (SRC) is a very common and recognizable form of mTBI. In fact, SRC accounts for approximately 9% of all injuries sustained for both men and women throughout high school and collegiate athletics (Gessel, Fields, Collins, Dick, & Comstock, 2007). Moreover, in 2015, the NFL reported the highest number of documented concussions in regular-season games, up 58% from the year before (Steifert, 2016).

Despite the notoriety of this injury, there is no universally accepted definition of mTBI. However, the World Health organization states that a person with a mild traumatic brain injury has had a traumatically induced physiological disruption of brain function, as manifested by one or more of the following: (1) loss of consciousness up to 30 minutes, (2) loss of memory for events immediately before or after the accident for as much as 24 hours, (3) alteration of mental state at the time of the accident (e.g., feeling dazed, confused, or disoriented), or (4) focal neurological deficit(s) that may or may not be transient. Additionally, the severity of the injury does not exceed the following: (1) loss of consciousness longer than 30 minutes, (2) posttraumatic amnesia exceeding 24 hours, or (3) Glasgow coma scale (GCS) score falling below 13 after 30 minutes (Carroll et al., 2004).
The assumption is that this mild injury is short-lived, typically in the region of minutes. However, long-term effects are common (Sharp & Jenkins, 2015). The resolution of obvious initial confusion is regularly followed by a multitude of symptoms that can include, but are not limited to, headache, fatigue, dizziness, irritability, memory impairment, sensitivity to light and noise, and sleep disturbance (e.g., Arciniegas, 2011). The majority of injured individuals overcome these symptoms in the first few months (e.g., Alexander, 1995), but a significant number of people report symptoms beyond six months (e.g., Norrie et al., 2010). These longer-term effects can lead to epilepsy and neurodegeneration, along with an increased risk for Alzheimer’s, Parkinson’s, and possibly chronic traumatic encephalopathy (CTE) (Baugh et al., 2012).

Unlike severe traumatic brain injury, mild traumatic brain injury is difficult to diagnose. Due not in small part to the heterogeneity of the injury and its symptoms, there are no objective diagnostic criteria. Classic imaging evaluations, such as CT scans, frequently show no tissue distortions, providing little information of value (Dupuis, Johnston, Lavoie, Lepore, & Lassonde, 2000). In fact, according to a review on the effectiveness of neuroimaging modalities for the detection of TBI, no one modality proved adequate for accurate diagnosis of all patients (Amyot et al., 2015). Because there are no current standard objective assessments for diagnosing mTBI, physicians and trainers rely heavily on patient self-reported symptoms. This may lead to trivialization of the consequences, and an athlete may be cleared to return to play before the brain has been given proper healing time. Returning to play or other situations that place the player at risk too soon can increase the individual’s vulnerability to second impact syndrome (SIS), which is very rare, though lethal. SIS occurs when the brain swells rapidly, and
catastrophically, after sustaining a second mTBI before the first has fully healed. This second impact can occur minutes, days, or even weeks after initial injury (Bey & Ostick, 2009). Although there are many tools that may be sensitive to mTBI, diagnostic accuracy continues to be a goal rather than a reality.

Identifying a sensitive and specific physiological signal (biomarker) is critical to establishing a criterion that would facilitate the development or calibration of tools that could be employed on the sideline of sporting events or in primary care offices. Previous research (e.g., Arciniegas, 2011; Haneef, Levin, Frost, & Mixrahi, 2013) examined the usefulness of electroencephalographic (EEG) data for making a diagnosis of mTBI, whereas other researchers argue the benefits of event-related potentials (ERP) and cognitive tasks (Gaetz & Berstein, 2001).

1.2 Electrophysiological Techniques

1.2.1 Quantitative Electrophysiology

EEG recordings generate a large amount of data that can be objectively analyzed by aggregating the data and performing quantitative analyses (qEEG) of various EEG components. This allows for identification of trends and subtle changes in an individual’s brain wave patterns (Haneef et al., 2013).

Among qEEG measures, frequency analyses and power changes are of particular interest in the study of mTBI (Arciniegas, 2011). The EEG is composed of various frequencies, including both high and lower frequencies. Traditionally, the EEG is divided into waves that are used to identify different stages of brain activation. The slowest waves, delta waves (1.5-4Hz), are low frequency, large amplitude signals that occur when
our brain is at rest during sleep. Theta waves (4.5-8Hz) can be seen when a person may feel drowsy. Alpha waves occur between 8.5-13 Hz and appear when a person is in what could be described as an “idle” state. When a person is mentally engaged, EEG output would show smaller amplitude beta waves (13.5-30Hz). Finally, at peak concentration, the smallest amplitude gamma waves (30.5Hz-64Hz) may be generated (Petrantonakis & Hadjileontiadis, 2011; Moeller, Tu, & Bazil, 2011).

Generally, the concept of power can be defined as the quantity or strength of frequency recordings (Harmony, 2013). One way of measuring this is by examining absolute power, or the strength of frequency recordings at certain scalp regions (Machado et al., 2007). Another measure is known as power spectrum density (PSD), which calculates the distribution of energy sampled into the frequencies composing that signal (Canuet et al., 2011). According to Stathopoulou and Lubar (2004), there are indications that people experiencing cognitive dysfunction may exhibit increased power in waves associated with drowsier states (i.e., delta, theta), whereas waves associated with cognitive activity (i.e., beta, gamma) may exhibit decreases in power.

Researchers have attempted to develop qEEG-based discriminant functions (e.g., Johnstone & Thatcher, 1991; Thatcher et al., 2001), or statistically derived analyses of data sets produced by qEEG. Their goal was to use these discriminants to help identify electrophysiological patterns that differentiate between individuals with mTBI and those without (Arciniegas, 2011). However, the feasibility of this concept has been debated in the literature (e.g., Nuwer, Hovda, Schrader, & Vespa, 2005; Gaetz & Bernstein, 2001). According to Nuwer and colleagues (2005), qEEG is plagued with clinical false positives and poor diagnostic credibility, leaving the resulting function controversial and
unconfirmed. Moreover, some discriminant functions are developed using individuals in an advanced stage of a disease or with a severe injury, making their applicability to mTBI weak at best. Consequently, it is possible that the applicability of the resulting discriminant may not be appropriate for individuals in the early stages of a disease or with a milder injury. Duffy, Hughes, Miranda, Bernad, and Cook (1994) suggest problems arise when (1) the discriminant is used as a substitute for clinical or electroencephalographic expertise, (2) it is inappropriately applied as a broad screening tool (3) the clinical question does not match what the discriminant was designed to answer, (4) the technologist allows artifact-ridden data to enter the discriminant, and (5) if the patient is not screened for unexpected cognitive deficits.

Conclusions drawn from qEEG do not provide distinguishing features of the mTBI diagnosis; further, the changes are not typically cause-specific. Other states can produce similar output or be co-occurring (e.g., depression). This could limit the clinical utility of qEEG (Arciniegas, 2011).

1.2.2 Event-Related Potentials

ERPs are another objective measure of brain function that have been discussed as a possible tool in the diagnosis of mTBI (Gaetz & Bernstein, 2001). Generally speaking, an ERP is scalp-recorded neural activity that is a direct response to a cognitive or sensory event (Luck, 2005). Individual ERPs are generated in response to specific stimulus events and are associated with various cognitive functions such as signal detection and decision-making (e.g., Donchin & Coles, 1988; Kutas & Federmeier, 2011). ERPs to specific events also can vary in the latency of their components, which could provide a measure
of the speed of cognition. Latency of various components of the ERP generally increase (i.e., slower reaction time) with illness or injury (Pratap-Chand, Sinniah, & Salem, 1988). Previous research used this measure to assess cognitive function following injury, or to track recovery over time (e.g., Segalowitz, Bernstein, & Lawson; von Bierbrauer & Weissenborn, 1998). Additionally, some suggest that ERPs may be more accurate for identifying cognitive dysfunction following brain injury. ERPs are more sensitive to injury and, unlike qEEG, the brain’s response to stimuli can be matched with specific cognitive functions, providing specific distinguishing features for mTBI diagnosis (Gaetz & Bernstein, 2001).

One of the most common ERP components studied in mTBI research is the P300, a positive ERP peak component that occurs generally between 250 and 500 milliseconds (ms) after stimulus onset (Luck, 2005). Representative of cognitive processes such as attention and working memory, P300 amplitude is typically reduced in individuals who experienced a neurologic disruption (Gosselin et al., 2012). The latency of P300, interpreted as the speed of stimulus classification resulting from event discrimination (Sur & Sinha, 2009), is also an important metric in mTBI research. Researchers have suggested that increased P300 latencies in concussed individuals are indicative of slower processing speed (Baillargeon, Lassonde, Leclerc, & Ellembrot, 2012).

Eliciting ERPs requires the incorporation of a cognitive task. Some of the most commonly used cognitive tasks in mTBI research include the auditory oddball (e.g., Segalowitz, 2001) and the n-back task (e.g., Ozen, Itier, Preston, & Fernandes, 2013). The auditory oddball task presents participants with occasional ‘target’ stimuli which have to be detected within a series of frequent ‘non-target’ stimuli (e.g., Linden et al.,
During the n-back task, sequential visual stimuli are presented, and participants are to remember each stimulus while new stimuli are presented. For each new item presented, the participant’s task is to decide if it is or is not the same as the stimulus presented “n” items before (Sweet, 2011).

Unfortunately, ERPs have some limitations in their clinical utility. First, the collection of ERPs is much more complex than passive data collection utilized by qEEG. ERPs are elicited in response to a specific event that must be presented in a standardized manner. Consequently, additional equipment is often required (e.g., computer, monitor, and an apparatus for stimulus presentation) for evaluating event integration. The addition of such equipment can place additional technical demands on the device operator. Moreover, although ERPs are more specific to certain cognitive functions, they can be somewhat limiting by their temporal characteristics. By definition, the ERP is elicited by a specific event. Ideally, it will result in a response only to that event. However, in the diagnosis of mTBI, which can manifest in a variety of ways and stem from multiple neurological dysfunctions, it is nearly impossible to identify a single paradigm that would be sufficient to capture even the majority of potential altered cognitive functions (Rapp et al., 2015).

Beyond the types of objective measures used, another topic worth noting is the populations typically used in mTBI research. Individuals with mTBI are frequently compared to non-injured individuals (e.g., Thompson, Sebastianelli, & Slobounov, 2005; Gosselin et al., 2012). However, as noted by Taylor and colleagues (2010), it cannot be concluded with certainty that any differences found between groups can be attributed solely to the head injury and not a more general injury-factor (such as pain and
discomfort). Evidence for neurophysiological function related specifically to brain trauma benefits from the inclusion of a comparison group with other non-head injuries.

Very few studies have included the use of an injured comparison group when examining mTBIs. Although they did not employ any electrophysiological measures, in 2016, Gorman and colleagues examined measures of processing speed and working memory across healthy children and children with TBI or an orthopedic injury. Results suggested children with TBI performed worse than both comparison groups for processing speed and visual-spatial working memory. Additionally, verbal working memory scores were again lower for the TBI group compared to the orthopedic group.

Looking specifically at EEG and an adult population, Dowman, Rissacher, and Shuckers (2008) examined EEG indices during pain-related activity. Although not necessarily an injury group, their results suggested the experience of general pain decreased theta and delta wave power. Taking it one step further, in 2015, Li et al. used both EEG and magnetoencephalography (MEG) to compare resting state power across individuals with mTBI and orthopedic injuries. Similarly, MEG results suggested that compared to the orthopedic injury group, individuals with mTBI exhibited significant over-activation in the delta, theta, and low alpha bands.

1.3 Purpose

Although there is a growing body of research emerging in the area of mTBI, there are still many important questions to answer and relationships to uncover. In the current study, the concussed group was compared not only to a non-injured comparison group, but also to a group of individuals who recently sustained a mild orthopedic injury (who
have not sustained a mTBI). The use of the group with only mild orthopedic injuries is a unique characteristic of this study.

Moreover, there is no universally accepted rapid, single objective measure of mTBI. Even commonly used, more subjective measures are not completely reliable across testers, as individual predictors are not always taken into account (Chin, Nelson, Barr, McCrory, & McCrea, 2016).

The purpose of this study was to directly compare different types of electrophysiological data collection and analyses across injury groups and a non-injured group, which may help to tease apart individual effects across multiple variables. It was anticipated that participants with mTBI would generate unique electrophysiological effects that differ from those without such injuries. To the best of our knowledge, no mTBI studies have controlled for a ‘general injury factor’ using both EEG and ERP. Results could lead to a greater understanding of the specific effects of mTBI on the brain and cognition. This would advance the development of an objective and reliable tool for more rapid identification of a mTBI injury.

1.4 Research Questions and Hypotheses

In the present study, two different research hypotheses were addressed, all with relevant sub-hypotheses (Tables 1.1 & 1.2). First, group differences in power during resting state were examined. To more cleanly assess power, frequency waves were collapsed into two units: *cognitive activity*, which consisted of gamma and beta waves, and *drowsy state*, which included theta, delta, and alpha waves (Stathopoulou & Lubar, 2004). Hypothesis 1 predicted significant group differences.
Hypothesis 1a: Relative to the non-injured comparison group, the mTBI group would exhibit a significant reduction in overall cognitive activity and a significant increase in drowsy state power (Stathopoulou and Lubar, 2004).

Hypothesis 1b: Relative to the non-injured group, the orthopedic injury group would exhibit significantly decreased overall cognitive activity and drowsy state power (Stathopoulou and Lubar, 2004).

Hypothesis 1c: Compared to the mTBI group, the orthopedic injury group would exhibit significantly lower drowsy state power, but no significant differences would be noted for cognitive activity (Dowman et al., 2008; Li et al., 2015).

Due to its common use in mTBI research, Hypothesis 2 examined P300 amplitude and latency. Significant group differences were predicted for both amplitude and latency.

Hypothesis 2a: Compared to the non-injured group and the orthopedic injury group, P300 amplitude would be significantly smaller for the mTBI group (Gosselin et al., 2012).

Hypothesis 2b: Similarly, compared to the non-injured and orthopedic injury groups, the mTBI group would exhibit increased P300 latencies (Baillargeon et al., 2012; Gorman et al., 2016).

Hypothesis 2c: Although the non-injured and orthopedic injury groups were predicted to be significantly different from the mTBI group, it was predicated that they will not be significantly different from each other (Gorman et al., 2016).
Table 1.1. Sub-hypotheses for resting state power comparisons

<table>
<thead>
<tr>
<th></th>
<th>Cognitive activity</th>
<th>Drowsy state</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-injured</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Orthopedic Injury</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>mTBI</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

*Note: 0 = x; - = y; + = z.

Table 1.2. Sub-hypotheses for P300 comparisons

<table>
<thead>
<tr>
<th></th>
<th>Amplitude</th>
<th>Latency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-injured</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Orthopedic Injury</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>mTBI</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

*Note: 0 = x; - = y; + = z.

CHAPTER 2: METHOD

2.1 Recruitment

Prior approval for this project was granted by the University of Nebraska-Lincoln Institutional Review Board. Injured participants were initially recruited from the University of Nebraska-Lincoln campus Health Center. A recruitment plan was made with the Health Center Director of Medical Research, as well as the physicians, and a timeline was set. Along with Health Center recruitment, flyers and word-of-mouth were used to inform possible participants of the study. Visits were made to the Health Center at least once a week to check in on recruitment and to meet with the staff for any updates. By the end of the spring semester, a total of three injured participants had taken part in the study.
Due to the lack of successful recruitment on campus, plans were approved to move the study to southwest Missouri because of the researcher’s connections to the local university as well as the medical communities. Approval to recruit student athletes for the injured groups was granted by Missouri State University’s Athletic Director. Flyers were hanged in the training room, trainers and coaches were informed, and weekly visits were made by the research staff to check in on recruitment progress. Along with Missouri State University, approval to recruit injured individuals was granted by Mercy Hospital in Springfield, MO and by Freeman Hospital in Joplin, MO. The researcher visited with physicians and staff at Mercy Orthopedic Hospital and provided flyers to be put up in exam and waiting rooms. At Freeman Hospital, an orthopedic surgeon and his residents were involved in identifying and recruiting injured participants. Additionally, medical students associated with Freeman Hospital put flyers up around the school and hospital campuses, and were involved in active recruiting. These medical students also were offered the opportunity to use some of the collected data for their own presentations. Despite approval from these three major institutions and intensive recruiting by the researcher, only 11 additional injured participants were recruited after seven months.

2.2 Participants

Twenty-four participants ages 18-30 were recruited for this study. Individuals were in one of three groups: non-injured, mild orthopedic injury, or mTBI. Participant demographics can be seen in Table 1.3. All participants were compensated for participation. Medical staff from the UNL Health Center, Missouri State University, Mercy Hospital in Springfield, MO, and Freeman Hospital in Joplin, MO screened
possible participants for the concussed group and/or the mild orthopedic injury group to
make sure they were appropriate candidates for participation. Study staff screened
individuals for the non-injured comparison group over the phone or through email to
ensure they were appropriate candidates for participation (i.e., met inclusion criteria, did
not meet exclusion criteria).

Criteria for inclusion in the concussed group was that each participant was
between the ages of 18-30 years and recently experienced a traumatically induced
physiological disruption of brain function. A health care professional may have
recognized this disruption through the manifestation of at least one of the following: any
loss of consciousness, any loss of memory for events immediately before or after the
accident, any alteration in mental state at the time of the accident (e.g., disorientation,
confusion, feeling dazed), and/or focal neurological deficit(s) that may or may not be
transient. Exclusion criteria for the concussed group included any loss of consciousness
for more than approximately 30 minutes, an initial Glasgow Coma Scale score less than
13, post-traumatic amnesia lasting longer than 24 hours, and diagnosis of ADD, ADHD,
or other developmental psychopathologies (e.g., Szuromi, Czobor, Komlosi, & Bitter,
2011). Additionally, there was no co-occurring orthopedic injury.

Criteria for inclusion in the mild orthopedic injury group was that the participant
was between the ages of 18-30 and recently experienced an upper or lower extremity
injury. At the University Health Center, per the medical research director: ankle injuries
were subject to the Ottawa Rules (Pires et al., 2014) to determine if an x-ray is needed.
Across other recruitment sources, injury severity classification was left to the discretion
of the clinician and based on x-ray results, bone tenderness, range of motion or
deformity, and mechanism of injury. Exclusion criteria for the mild orthopedic injury group included displaying any evidence of head trauma or symptoms of mTBI, and diagnosis of ADD, ADHD, or other developmental psychopathologies (e.g., Szuromi et al., 2011).

Individuals who indicated interest in taking part in the study gave their contact information to the medical staff. Medical staff and study staff communicated weekly to monitor potential participant interest. Study staff contacted potential participants to provide them with more information concerning the study, confirm whether they qualify for participation, and subsequently scheduled a lab session within seven days of injury.

Finally, individuals who had not sustained a mTBI or mild orthopedic injury were recruited. These participants completed the same testing session in order to provide a non-injured comparison group against which to compare the injury groups. These non-injured individuals were identified through use of flyers placed around the UNL campus and through word-of-mouth. Exclusion criteria for the non-injured comparison group included any history of head injury, any orthopedic injury within the last 90 days, and diagnosis of ADD, ADHD, or other developmental psychopathologies which require the use of psychotropic medication.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-Injured</th>
<th>Orthopedic Injury</th>
<th>mTBI</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>10</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Female (Male)</td>
<td>8(2)</td>
<td>2(6)</td>
<td>3(3)</td>
</tr>
<tr>
<td>Mean age in yrs (SD)</td>
<td>21.50 (2.88)</td>
<td>20.75 (1.91)</td>
<td>22.50 (4.64)</td>
</tr>
<tr>
<td>Handedness: R(L)</td>
<td>9(1)</td>
<td>7(1)</td>
<td>6</td>
</tr>
<tr>
<td>Education in yrs (SD)</td>
<td>14.80 (0.92)</td>
<td>14.75 (0.71)</td>
<td>15.33 (1.37)</td>
</tr>
</tbody>
</table>
2.3 Apparatus and Materials

2.3.1 Electrophysiological Measures.

All electrophysiological data collection was completed using the same portable equipment in a dark room in the CB3 ERP suite, the Missouri State University Health Center, or in Freeman Hospital. Stimuli were presented on a standard Dell LCD 15.5” (39.5 cm) monitor. The two ERP tasks required the participant's active involvement via a manual behavioral response (i.e., button press). All stimuli were presented using E-Prime 2.0 software.

For the auditory oddball task, a speaker was placed one meter behind and above the midline of the participant’s head. Volume was adjusted such that stimulus loudness levels were 80 dB SPL when measured at the participant’s ear. The participant listened to 100 randomized presentations of two tones, presented every 1400-1600ms. The tones were classified as “target” (30%) and “non-target” (70%) and counterbalanced across participants. Participants responded only to target tones by pressing a designated button on a handheld pad with their dominant thumb. Response time and accuracy recorded for all trials; however, only correct responses were submitted to statistical analysis (Ledwidge & Molfese, 2016).

During the n-back continuous performance task, the participant was presented with a continuous sequence of visual stimuli and asked to indicate whether a target stimulus matches the stimulus from "n" steps earlier in the sequence via a designated button press on a handheld pad. Participants were presented with 102 randomized presentations of letters (2 initial non-response) for 1000ms each, followed by a 500ms inter-stimulus interval. Participants responded to all stimuli, using their right thumb to
indicate a “match” (50%) or their left thumb to indicate a “non-match” (50%). Response time and accuracy was recorded for all trials, but only correct responses were submitted to statistical analysis.

2.3.2 Recording

Ongoing EEG was recorded using Netstation 4.4.2 software (Electro Geodesics Inc., EGI, Eugene, OR, USA). The sampling rate was 250 Hz. Electrode impedances were assessed before and after each measure and maintained below 60 kΩ. No filters were imposed during data collection.

2.4 Procedure

All study personnel received the same training regarding participant interaction, study procedures, data collection method, etc. Participants visited the data collection space to attend one testing session within one week of injury (if applicable). The principal investigator and/or a member of the study staff met the participant to begin the informed consent process, followed by collection of basic demographic information and then the EEG/ERP session. The lab visit (lasting no longer than 2 hours) ended with debriefing and compensation.

As soon as a participant entered the lab, the investigator or study staff member introduced her or himself and then described the procedures of the study in detail. Participants were encouraged to ask questions, and, if they chose to participate, they were asked to read and then sign an IRB approved informed consent form for this study. Next,
the participant filled out a basic demographic information form, entering information concerning his/her age, sex, education level, and race/ethnicity.

The participant’s head circumference was measured in order to determine the size of the high-density EEG net to be placed on their head for the EEG/ERP session. Two additional measurements of the participant's head were made: (1) the distance from the nasion to the inion, and (2) the distance from one tragus to the other tragus. These measurements allow for the identification of the vertex and guide correct EEG cap placement (Teplan, 2002). Prior to placement, the net was soaked in a warm, mild KCl solution for five minutes in order to decrease scalp impedance levels and increase connectivity once the electrode net is in place. The high-density Ag/AgCl net containing 256 electrodes was then placed on the participant's scalp. The EEG net was connected to a hospital grade isolation amplifier that isolates the participant from ground and the possibility of electric shock. Net adjustments were made to ensure quality data collection. All participants completed three EEG/ERP measures during one visit to the lab.

Participants were informed of their ability to take breaks as needed throughout the testing session. Additionally, all participants were informed that they may decline or end participation in any part of these sessions at any time. The EEG/ERP session lasted between 60 and 75 minutes. Although the participant was only actively involved for approximately 30 minutes of EEG testing, extra time was required to apply the electrode net to the participant's head and to make necessary adjustments throughout the testing session.

First, the participant completed the 4-minute resting state session. During this time, the participant was seated in a dark room and centered 1 meter in front of the
computer monitor. The participant’s gaze was fixed upon a white fixation cross in the center of the monitor. Following completion, the participant began the cognitive tasks. The two tasks, counterbalanced for order, included an auditory oddball and an n-back task. These tasks measured constructs including processing speed, working memory, cognitive flexibility, inhibition, and sustained attention (e.g., Isogly-Alkac, Kedzior, Karamursel, & Ermutlu, 2007; Jaeggi et al., 2003).

During the auditory oddball task, the participant was again asked to fix his/her gaze upon the fixation cross in the center of the monitor. Additionally, he/she listened to the randomized presentations of tones. Participants were instructed to respond only to target tones by pressing a designated button on a handheld pad with their dominant thumb.

The n-back continuous performance task presented participants with a continuous sequence of visual stimuli. They were instructed to indicate whether a target stimulus matches the stimulus from "n" steps earlier in the sequence via a designated button press on a handheld pad. Participants responded to all stimuli, using their right thumb to indicate a “match” or their left thumb to indicate a “non-match”.

Following completion of all three measures, study staff removed the electrode net and provided the participant with a towel to remove any excess water from his/her hair and face. Finally, as soon as the participant was ready, he or she was debriefed and compensated for his/her time. The entire session took no longer than two hours from initial entry into the laboratory to their departure.
2.5 Analysis

Electrophysiological measures using scalp recorded electrophysiological data and event-related potentials were obtained from each participant. The high-density electrode placements were used to calculate power across the frequency bands during resting state. In addition, peak ERP amplitude and latency measures were calculated for ERPs collected during each of the two tasks. Power, as well as peak ERP amplitude and latency measures, then were used to compare cognitive function and activity across the three groups.

2.5.1 Quantitative EEG

2.5.1.1 Preprocessing

First, the continuous EEG was digitally filtered by first removing the DC offset and then applying a 2\textsuperscript{nd} order 0.1 to 64-Hz Butterworth infinite impulse response bandpass filter (slope = 12 dB/octave). To correct for ocular artifacts, independent component analysis was applied to the data using EEGlab's runica routine. Components with characteristic time courses and scalp topographies associated with blinks and saccades were removed from the data. No more than two components were identified and removed per subject. To remove other sources of artifacts, the corrected data was then segmented into 1 second epochs. Epochs with voltages that exceeded a +/- 200 \mu V threshold were then rejected from the data. The retained data was then referenced to an average reference.

The artifact-free EEG segments were then used to calculate the scalp level power spectrum density (PSD) from 1-64 Hz (Canuet et al., 2011). The PSD was computed for five frequency bands: delta (1.5-4Hz), theta (4.5-8Hz), alpha (8.5-13Hz), beta (13.5-
30Hz) and gamma (30.5-64Hz) and collapsed into two power units: cognitive activity and drowsy state (Petrantonakis & Hadjileontiadis, 2011). To estimate the power level in these bandwidths, the data was first segmented into short epochs (120 epochs of 2 seconds per block, overlapping by 1.5 seconds (Stewart et al., 2010), tapered with a Hamming window, transformed via Fast-Fourier transform (FFT) to power spectra for each recording site (Allen & Cohen, 2010). This overlapping compensates for the minimal weight applied to the end of the epoch by the use of the Hamming window function, and allows for all data points to receive maximum weighting in some epoch (Stewart et al., 2010; Allen, Coan, & Nazarian, 2004).

2.5.1.2 Statistical Analysis

To assess differences between the three groups in these bandwidths, statistical spectral maps were computed for each group (mTBI, orthopedic injury, and non-injured) for each power unit. Differences in observed power between electrodes was then conducted with the False Discovery Rate (FDR) correction for multiple comparisons (Toppi et al., 2016).

2.5.2 ERP

2.5.2.1 Preprocessing

First, the continuous EEG was digitally filtered using a 0.1-Hz first-order high pass and 30-Hz Finite Impulse Response lowpass filter. The filtered data was then downsampled to 250 Hz and segmented to the onset of the target tones and visual stimuli
beginning 200 milliseconds pre-onset and continuous for 900 milliseconds post-onset. All segments were baseline corrected using the 200 ms pre-stimulus average.

Ocular artifacts in the epoched data were reduced by decomposing the data into topographic components using the runica ICA routine and removing components which correlated highly (> .80) with a blink template created via from averaging 200 blinks from open-eye resting state data recorded from 40 subjects (each subject contributing 5 blinks) on the EEG system used in this investigation.

After the artifact reduction process, bad channels were identified and interpolated using the ERP PCA toolkit. Bad channels were identified across the entire session via poor overall correlations (r <0.60) between neighboring channels and within each segment either as unusually high differences between an electrode’s average voltage and that of their neighbors (> 30 µv) or as extreme voltage differences within the electrode (> 80 µv min to max). A channel was also marked as bad for the entire session if more than 20% of its segments were classified as being bad. All identified bad channels were replaced using whole head spline interpolation. After bad channels were identified and interpolated, trials that had more than 8% of their channels interpolated were removed from the analysis set. The remaining trials were then referenced to an average reference.

2.5.2.2 Oddball Statistical Analysis

ERP components in the oddball task were quantified using temporal-spatial PCA in ERP PCA Toolkit. First, a temporal PCA was performed on the data using all time points from each participant’s averaged ERP as variables, considering participants, condition and recording sites as observations. This step reduced the temporal structure of
the ERP data to a set of temporal components. Promax rotation was used, and nine
temporal components (94.9% of total variance) were extracted based on parallel analysis
(Horn, 1965). The spatial distribution of these components was then decomposed using
spatial PCA. This PCA used all recording sites as variables, considering participants,
conditions and temporal factor scores as observations. This step reduced the electrode
structure (257-channels) to a set of virtual electrodes on which the original electrodes
loaded on. Infomax rotation was used, and five spatial components (87.0% of total
variance) were extracted based on parallel analysis.

Selection of the P300 component was conducted in a two-step process. First,
components that accounted for at least 2.5% of temporal-spatial variance were selected.
Following this, posterior components with peak timepoints in the 260 – 500 ms range
were identified.

Results were analyzed with SPSS Version 20, with reported results considered
statistically significant at the $p < .05$ level. A series of One-Way ANOVAs was used to
explore group differences in amplitude and latency of the P300. The significance of each
main effect and the associated effect size (eta-squared) was noted. Any significant main
effects were followed up with independent t-tests and effect size calculations using
Cohen’s $d$ and eta-squared.

2.5.2.3 N-back Statistical Analysis

ERP components in the n-back task were quantified using temporal-spatial PCA
in ERP PCA Toolkit. First, a temporal PCA was performed on the data using all time
points from each participant’s averaged ERP as variables, considering participants,
condition and recording sites as observations. This step reduced the temporal structure of the ERP data to a set of temporal components. Promax rotation was used, and eleven temporal components (94.9% of total variance) were extracted based on parallel analysis (Horn, 1965). The spatial distribution of these components was then decomposed using spatial PCA. This PCA used all recording sites as variables, considering participants, conditions and temporal factor scores as observations. This step reduced the electrode structure (257-channels) to a set of virtual electrodes on which the original electrodes loaded on. Infomax rotation was used, and three spatial components (79.6% of total variance) were extracted based on parallel analysis.

Selection of the P300 component was again conducted in a two-step process. First, components that accounted for at least 2.5% of temporal-spatial variance were identified. Following this, posterior components with peak timepoints in the 260 – 500 ms range were identified.

Results were analyzed with SPSS Version 20, with reported results considered statistically significant at the \( p < .05 \) level. A series of One-Way ANOVAs was used to explore group differences in amplitude and latency of the P300. The significance of each main effect and the associated effect size (eta-squared) was noted. Any significant main effects were followed up with independent t-tests and effect size calculations using Cohen’s \( d \) and eta-squared.

**2.5.2.4 Response Accuracy Statistical Analysis**

Means and standard deviations of correct responses for oddball and n-back were calculated using E-prime. Results were analyzed with SPSS Version 20, with reported
results considered statistically significant at the \( p < .05 \) level. One-Way ANOVAs were used to explore group differences in accuracy for each task. The significance of each main effect and the associated effect size (eta-squared) was noted. Any significant main effects were followed up with independent t-tests. Additionally, effect size calculations using Cohen’s \( d \) and eta-squared were carried out to examine the magnitude of group differences.

CHAPTER 3: RESULTS

3.1 Question 1: Group Differences in Power During Resting State

Statistical results indicated no significant differences between groups for either power unit: cognitive activity and drowsy state. Figures 3.1 and 3.2 present the spectral maps by group for each power unit, respectively.

![Figure 3.1. qEEG spectral map for cognitive activity power unit across groups during resting state.](image)
3.2 Question 2: Group Differences in P300 During ERP Tasks

3.2.1 Amplitude: Oddball

Results indicated a significant main effect and large effect size for response to the target tone ($F(2, 19) = 5.70, p < 0.05, \eta^2 = 0.38$). Spectral maps and P300 amplitude during the oddball target tone across groups can be seen in Figures 3.3 and 3.4, respectively.
Figure 3.3. Spectral maps showing P300 response to the oddball target tone. Red indicates greater activity.

Figure 3.4. Group performance for the oddball task (target tone) for the P300 amplitude.

Post hoc analyses are shown in Table 3.1. As hypothesized, there was a significant difference between the mTBI group and the non-injured group. Additionally,
the difference between the mTBI group and the orthopedic injury group was significant. Moreover, the effect sizes associated with these two comparisons were large. The difference between the non-injured and orthopedic injury groups was not significant and had a negligible effect size. The P300 amplitude was significantly higher for the mTBI group than for the non-injured and orthopedic injured groups.

Table 3.1. Post hoc group comparisons for oddball task (target tone) for P300 amplitude.

<table>
<thead>
<tr>
<th></th>
<th>mTBI</th>
<th>Non-Injured</th>
<th>mTBI</th>
<th>Orthopedic Injury</th>
<th>Orthopedic Injury</th>
<th>Non-Injured</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>7.68</td>
<td>2.22</td>
<td>2.26</td>
<td>2.87</td>
<td>2.22</td>
<td>2.87</td>
</tr>
<tr>
<td>SD</td>
<td>4.70</td>
<td>2.87</td>
<td>2.87</td>
<td>2.87</td>
<td>2.87</td>
<td>2.87</td>
</tr>
<tr>
<td>t</td>
<td>2.81</td>
<td>2.64</td>
<td>2.64</td>
<td>2.64</td>
<td>2.64</td>
<td>2.64</td>
</tr>
<tr>
<td>p</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>Cohen’s d</td>
<td>1.56</td>
<td>1.59</td>
<td>1.59</td>
<td>1.59</td>
<td>1.59</td>
<td>1.59</td>
</tr>
<tr>
<td>η²</td>
<td>0.38</td>
<td>0.39</td>
<td>0.39</td>
<td>0.39</td>
<td>0.39</td>
<td>0.39</td>
</tr>
</tbody>
</table>

*Note: Means and standard deviations in μV

3.2.2 Amplitude: N-back

P300 amplitudes of match stimuli were examined for correct responses to the n-back task. Spectral maps and P300 amplitude during n-back match across groups can be seen in Figures 3.5 and 3.6, respectively. A between-groups ANOVA was carried out to assess differences in peak amplitude for the stimulus across groups. The main effect was non-significant, and the effect size was negligible \( (F(2, 19) = 0.14, p = 0.87, \eta^2 = 0.01) \).
Figure 3.5. Spectral maps showing P300 response to the n-back match stimulus. Red indicates greater activity.

Figure 3.6. Group performance for the n-back task (match) for the P300 amplitude.
Follow up $t$-tests were not calculated because the main effect was not significant. However, because it is possible that statistical significance could have been constrained by the limited sample size, effect sizes were calculated using Cohen’s $d$ to explore potential group differences. The results appear in Table 3.2 and indicated that the difference between the orthopedic group and non-injured group was associated with a small effect size, but the effect sizes for the other comparisons were negligible.

Table 3.2. Means and standard deviations (in $\mu$V), and effect sizes across groups for n-back P300 amplitude.

<table>
<thead>
<tr>
<th></th>
<th>mTBI</th>
<th>Non-Injured</th>
<th>Orthopedic Injury</th>
<th>Non-Injured</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>2.52</td>
<td>2.92</td>
<td>2.12</td>
<td>2.92</td>
</tr>
<tr>
<td>SD</td>
<td>3.73</td>
<td>3.41</td>
<td>1.3</td>
<td>3.41</td>
</tr>
<tr>
<td>Cohen’s $d$</td>
<td>0.12</td>
<td>0.32</td>
<td>0.16</td>
<td>0.32</td>
</tr>
<tr>
<td>$\eta^2$</td>
<td>0.004</td>
<td>0.03</td>
<td>0.006</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Exploratory analysis of the change in amplitude from non-match to match was conducted to validate the findings. The overall performance for the match ($M = 2.56$, $SD = 2.89$) was significantly higher than the overall performance for the non-match with a large associated effect size ($M = 0.91$, $SD = 2.83$), $t(21) = 5.16, p < .001, d = 2.25$; therefore, validating the findings.
3.2.3 Latency: Oddball

Target tone latencies of P300 were examined for correct responses to the oddball task. Group responses can be seen in Figure 3.7. A between-groups ANOVA was carried out to assess differences in peak amplitude for the tone across groups. The main effect was not significant, and the effect size was negligible ($F(2, 19) = 0.12, p = 0.89$, $\eta^2 = 0.01$).

![Figure 3.7. Group performance for P300 latency during the oddball (target tone) task.](image)
Follow up t-tests were not calculated because of main effect was not significant. However, because it is possible that statistical significance could have been constrained by the limited sample size, effect sizes were calculated using Cohen’s $d$ and eta-squared to explore potential group differences in latency of P300 during the oddball task. These are shown in Table 3.3. Results indicated that the differences between the orthopedic group and the other two groups were associated with a small effect sizes, but the effect size associated with the difference between the non-injured and concussed group was negligible.

Table 3.3. Means and standard deviations (in ms), and effect sizes across groups for oddball P300 latency.

<table>
<thead>
<tr>
<th></th>
<th>mTBI</th>
<th>Non-Injured</th>
<th>mTBI</th>
<th>Orthopedic Injury</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean SD</td>
<td>Mean SD</td>
<td>Cohen’s $d$</td>
<td>$\eta^2$</td>
</tr>
<tr>
<td>mTBI</td>
<td>347 96</td>
<td>350 90</td>
<td>0.04</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Orthopedic Injury</td>
<td>347 96</td>
<td>367 60</td>
<td>0.25</td>
<td>0.02</td>
</tr>
<tr>
<td>Non-Injured</td>
<td>367 60</td>
<td>350 90</td>
<td>0.21</td>
<td>0.01</td>
</tr>
</tbody>
</table>

3.2.4 Latency: N-Back

Latencies for P300 were examined for match stimuli in the n-back task. Group responses can be seen in Figure 3.8. A between-groups ANOVA was carried out to assess differences in peak amplitude for the match stimulus across groups. The main effect was not significant, and the effect size was negligible ($F(2, 19) = 0.44, p = 0.65, \eta^2 = 0.04$).
Figure 3.8. Group performance for latency of the P300 during the n-back (match stimulus) task.

Follow up t-tests were not calculated because of main effect was not significant. However, because it is possible that statistical significance could have been constrained by the limited sample size, effect sizes were calculated using Cohen’s $d$ and eta-squared to explore potential group differences in latency of P300 during the n-back (match stimulus) task. These are shown in Table 3.4. Results indicated that the effect sizes associated with differences between the non-injured and the other two groups were approaching moderate. The latency of the orthopedic group was similar to that of the mTBI group, characterized by a negligible effect size.
Table 3.4. Means and standard deviations (in ms), and effect sizes across groups for n-back P300 latency.

<table>
<thead>
<tr>
<th>mTBI</th>
<th>Non-Injured</th>
<th>mTBI</th>
<th>Orthopedic Injury</th>
<th>Orthopedic Injury</th>
<th>Non-Injured</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td>Cohen’s d</td>
<td>η²</td>
</tr>
<tr>
<td>400</td>
<td>100</td>
<td>358</td>
<td>90</td>
<td>0.44</td>
<td>0.05</td>
</tr>
<tr>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td>Cohen’s d</td>
<td>η²</td>
</tr>
<tr>
<td>400</td>
<td>100</td>
<td>388</td>
<td>77</td>
<td>0.14</td>
<td>0.005</td>
</tr>
<tr>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td>Cohen’s d</td>
<td>η²</td>
</tr>
<tr>
<td>388</td>
<td>77</td>
<td>358</td>
<td>90</td>
<td>0.35</td>
<td>0.03</td>
</tr>
</tbody>
</table>

3.2.5 Response Accuracy: Oddball

Response accuracy was examined for the oddball task. Correct responses by group can be seen in Figure 3.9. A between-groups ANOVA was carried out to assess differences in response accuracy across groups. The main effect was not significant, and the effect size was negligible ($F(2, 19) < 0.001, p = 1.00, η² < 0.001$).
Follow up t-tests were not calculated because of main effect was not significant.

However, because it is possible that statistical significance could have been constrained by the limited sample size, effect sizes were calculated using Cohen’s $d$ and eta-squared to explore potential group differences in response accuracy for the oddball task. These are shown in Table 3.5. Results indicated that the effect sizes associated with differences between each group was negligible.
Table 3.5. Means, standard deviations, and effect sizes across groups for oddball accuracy.

<table>
<thead>
<tr>
<th></th>
<th>mTBI</th>
<th>Non-Injured</th>
<th>mTBI</th>
<th>Orthopedic Injury</th>
<th>Orthopedic Injury</th>
<th>Non-Injured</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>0.99</td>
<td>0.99</td>
<td>0.99</td>
<td>0.99</td>
<td>0.99</td>
<td>0.99</td>
</tr>
<tr>
<td>SD</td>
<td>0.09</td>
<td>0.07</td>
<td>0.09</td>
<td>0.09</td>
<td>0.09</td>
<td>0.07</td>
</tr>
<tr>
<td>Cohen’s $d$</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>$\eta^2$</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

3.2.6 Response Accuracy: N-back

Response accuracy was examined for the n-back task. Correct responses by group can be seen in Figure 3.10. A between-groups ANOVA was carried out to assess differences in response accuracy across groups. The main effect was not significant, and the effect size was small ($F(2, 19) = 0.17, p = 0.84, \eta^2 = 0.02$).
Follow up t-tests were not calculated because of main effect was not significant. However, because it is possible that statistical significance could have been constrained by the limited sample size, effect sizes were calculated using Cohen’s $d$ and eta-squared to explore potential group differences in response accuracy for the n-back task. These are shown in Table 3.5. Results indicated that the effect sizes associated with differences orthopedic injury and the other two groups were small. The response accuracy of the non-injured group was similar to that of the mTBI group, characterized by a negligible effect size.
Table 3.6. Means, standard deviations, and effect sizes across groups for n-back accuracy.

<table>
<thead>
<tr>
<th></th>
<th>mTBI</th>
<th>Non-Injured</th>
<th>Cohen’s d</th>
<th>η²</th>
</tr>
</thead>
<tbody>
<tr>
<td>mTBI Orthopedic</td>
<td>Mean 0.85</td>
<td>Mean 0.87</td>
<td>0.06</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Orthopedic Injury</td>
<td>SD 0.36</td>
<td>SD 0.33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Injured</td>
<td>Mean 0.87</td>
<td>Mean 0.94</td>
<td>0.34</td>
<td>0.03</td>
</tr>
<tr>
<td>mTBI</td>
<td>SD 0.36</td>
<td>SD 0.24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Injured</td>
<td>Mean 0.87</td>
<td>Mean 0.33</td>
<td>0.26</td>
<td>0.02</td>
</tr>
<tr>
<td>Orthopedic Injury</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mTBI Orthopedic</td>
<td></td>
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<td>Orthopedic Injury</td>
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<td>Non-Injured</td>
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CHAPTER 4: DISCUSSION

4.1 General Discussion

The unique contribution of the current study was that it allowed neurophysiological performance in individuals with mild concussion to be compared not only to a healthy group but also to a group with orthopedic injuries. Due to the fact that both injured groups were experiencing acute pain, the design allowed for distinction between any disparities in electrophysiological outcomes due to different injury mechanisms. Further, this study employed multiple methods of electrophysiological data collection in order to compare usefulness in teasing apart effects across groups. Although the small sample size in the mTBI group does not allow for robust inferences, many relevant findings emerged.

The small sample size of the current study likely affected the ability to detect group differences in power units during resting state using qEEG, thus limiting a
conclusive response to Research Hypothesis 1. Although qEEG is frequently used in mTBI research due to its convenience and the minimal demands it puts on patients, this type of electrophysiological analysis was unable to detect any differences in the current study. Even well-established differences between individuals with mTBI and non-injured individuals were not robust enough to be identified.

Hypothesis 2 predicted that there would be differences in P300 amplitude and latency across the groups during the ERP tasks. In the oddball task, the mean P300 amplitude of the mTBI group was significantly larger than both the non-injured and orthopedic injury groups. Moreover, the associated effect sizes were large and meaningful. As predicted, there was no difference between the non-injured and orthopedic injury groups.

It was originally hypothesized that the concussed group would display smaller P300 amplitudes in the oddball task, however the opposite effect emerged. This was not without precedent. Within mTBI literature, an ongoing debate exists concerning brain activity and the direction of change following the injury. Previous ERP research supports the notion that a reduction in neural activity (i.e., smaller amplitudes) might be expected, and studies using fMRI suggest similar reductions in brain activity when comparing concussed athletes to controls in working memory and attention tasks (e.g., Chen et al., 2004). However, Witt, Lovejoy, Pearlson, and Stevens (2010) found evidence for an increase in compensatory brain activity during the detection of novel stimuli. This suggests that although individuals experiencing the symptoms of mTBI may show reduced activation in typical brain areas supporting working memory, areas outside the working memory network are recruited and included in order to meet current task
demands (Ledwidge & Molfese, 2016), which could account for the relative increase in amplitude found in the current study.

As hypothesized, no significant differences in P300 amplitude existed between the non-injured and orthopedic injury groups. Consistent with previous studies, there were significant differences in oddball P300 amplitude between the mTBI and non-injured groups. The findings that there were no differences between the orthopedic group and the non-injured group suggests that the differences in neurophysiological performance are indeed the result of mild brain injury rather than simply the pain that comes from general injury. Little is known regarding cognitive functioning following an orthopedic injury. However, some studies that have examined cognitive outcomes following severe orthopedic injury (e.g., hip fracture) in the elderly found that of the people who qualified for study participation, fewer than half of their participants were diagnosed as having any cognitive impairments (Moncada, Andersen, Franckowiak, & Christmas, 2005; Guo, Sun, Wang, Li, & Liu, 2014). This suggests the presence of cognitive impairment following mild orthopedic injury is unlikely; therefore, appropriate objective measures should be able to accurately identify an mTBI over the existence of other similar pain-causing injuries.

There is a caveat to the notion that orthopedic injuries do not affect neurophysiological functioning. Although not statistically significant, the latency of the orthopedic group during the oddball task was longer than the latencies of the mTBI and non-injured groups. The effect sizes associated with these differences were small, in comparison to the effect size of the difference between the mTBI and non-injured, which was negligible. Similarly, the latency of the orthopedic group during the n-back task was
again longer than the non-injured group, with an associated effect size approaching a moderate level. Furthermore, this performance of the orthopedic group was comparable to that of the mTBI group. These trends provide some evidence of inefficient processing and further investigation into the neurophysiological effects of orthopedic injury is warranted.

In contrast to the differences identified during the oddball task, the n-back did not yield any significant group differences in amplitude. Although both tasks are frequently used in mTBI research, the oddball task is felt to produce more consistent results than the n-back or other working memory tasks (e.g. Potter, Jory, Bassett, Barrett, & Mychalkiw, 2002). More specifically, as noted by Jaeggi, Buschkuel, Perrig, and Meier (2010), the mixed results regarding reliability in their studies along with previous research make it difficult to draw any firm conclusions about the concurrent validity of the n-back task. Further, due to its low reliability, the n-back task may seem to not be a useful measure of individual differences. On the other hand, the auditory oddball task has been known to reliably elicit a response from P300 (Chen, Syue, Li, & Yeh, 2014) and to identity differences in performance between healthy controls and those with mTBI (Ledwidge & Molfese, 2016). Moreover, as previously stated, between group differences for compensatory brain activity (i.e., increased P300 amplitude) have been most evident during the detection of novel stimuli, such as an auditory oddball tone (Witt et al., 2010).

Response accuracy was examined in order to better understand group performance across tasks. No significant differences were found between groups for either the oddball or n-back tasks; however, this is not unexpected. According to Westfall and colleagues (2015), results suggesting no difference in behavioral performance (e.g.,
accuracy) is a common finding in mTBI research. These findings suggest any variations in brain responses due to head injury may only be identifiable by more sensitive measures such as EEG or ERP, and not standard accuracy or reaction time tasks.

The debate between the use of EEG and ERP in identifying mTBI is ongoing. Results of this study suggest ERP may be the more powerful tool for uncovering group differences. Whereas qEEG was likely affected by sample size and unable to detect any group differences, ERP successfully distinguished significant and large differences during the oddball task. Although there is added complexity with the use of ERP (e.g., more equipment required), successful discrimination between similar injury groups is a major advantage to using this electrophysiological method and should be considered when determining which type of data collection is best for rapid identification of mTBI.

4.2 Limitations

The major limitation of this study is the small sample size. Therefore, many results were underpowered and inconclusive. When interpreting results from a small sample, it is important to consider the risks. Specifically, small sample sizes commonly lead to a lack of power and therefore a greater risk of a Type II error, or concluding there is no effect when one does in fact exist. However, it is important to note the effect size highlight findings that support Hypothesis 2. Unlike significance, effect size is independent of sample size (Sullivan & Feinn, 2012). Additionally, although the three comparison groups were similar in age, handedness, and education level, they did differ in sex. Research regarding concussion outcomes between males and females is relatively immature and inconclusive (Merritt, Padgett, & Jak, 2019). Although it has been reported
that females have higher rates of concussion, it has been suggested that this could be due to help-seeking behaviors and symptom report differences between sexes (Mollayeva, El-Khechen-Richandi, & Colantonio, 2018). Moreover, the possibility of sex differences in cognitive task performance, specifically P300, is a consideration. Although results seem to be somewhat inconsistent (Kim et al., 2013), there is strong evidence that no significant sex differences exist for the auditory oddball task (e.g., Polich, 1986) or the n-back task (e.g., Archana, Johnson, & Kumar, 2013).

4.3 Conclusions and Future Directions

The current study involved consistent monitoring by the investigator as well as the involvement of multiple medical sites. Unforeseen challenges arose as recruitment of injured populations relied solely on the communication efforts of medical personnel: informing injured participants of the study as well as informing the research staff of individuals who expressed interest in the study. Any future studies attempting to use clinical or acutely injured populations need to secure more direct influence over those involved with recruitment. This influence could be in the form of working personally with the clinical population, the staff who has agreed to assist with recruitment, or building strong relationships with others who work personally with the population.

In summary, the current study lends support for the use of ERP, specifically with an auditory oddball task, in the characterization of acute mTBI. Of primary significance is the inclusion of an orthopedic injury group and the finding that P300 amplitude is significantly increased only for those with mTBI. This provides an important basis for future research and strategies for the development of a rapid, objective measure of mTBI.
References


