The Effect of Volitional Fatigue on Reaction Time and Neural Activity in Concussed Individuals: A Study of Cognitive Changes Post-mTBI

By

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July 2023

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ABSTRACT

Mild traumatic brain injury (mTBI) presents as an important public health concern in the United States, with an estimated 1.7 million people diagnosed annually (Diaz-Arrastia & Vos, 2014) and approximately 50% of all concussions that occur in the United States are unreported or misdiagnosed each year. The purpose of this project was to determine the extent that voluntary exhaustion exacerbates declined cognitive functioning known to exist in concussed individuals compared to non-concussed controls, additionally understanding the extent to which musculoskeletal fatigue can decrease cognition and further delay in reaction time in individuals with mild traumatic brain injuries. Twenty (N-20) participants were recruited to complete two trials of a virtual reality response time task before and after exercise to volitional fatigue. Fifteen(n=15) individuals were non-concussed with no history of concussion, and five(n=5) individuals had a history of concussion in the past year. After a 60s go/no-go task in Virtual Reality, each completed a fatiguing exercise protocol outside of virtual reality, and then repeated the VR task. Theta wave activity heatmaps revealed a significant decrease ($p < 0.01$) in activity across the left central/ motor complex region in the concussed group following exercise. The non-concussed group experienced no significant change ($p > 0.5$) in theta activity following exercise across all regions. Alpha wave activity heatmaps revealed a significant increase ($p < 0.01$) in activity across both the left and right frontal regions in the concussed group following exercise. No significant change ($p > 0.1$) in alpha activity following exercise across all regions was observed in the non-concussed group. A two-way repeated measures ANOVA was completed for all measures collected (Mean Score, Mean Score Accuracy[ScA], Linger Time[LT], Motor Reaction Time[MRT], and Visual Reaction Time[VRT]) across group (C=Concussed/H=Non-Concussed) and condition (Pre/Post-Exercise). Although averages among groups for Score ($F(1,18) = 1.43$, $p > 0.05$), ScA ($F(1,18) = 0.633$, $p > 0.05$), and MRT ($F(1,11) = 4.59$, $p > 0.05$) appeared to possibly be related, none of them yielded significant results. VRT ($F(1,18) = 2.36$, $p >$

0.05) and LT ($F(1,18) = 0.033$, $p > 0.05$) averages for both groups across both tasks did not yield significant effects. Despite this, a small within-subjects MRT * Group effect was found ($\eta^2 = 0.294$, $p = 0.055$) indicating potentially practical significance.

The findings of this project point to the understanding of a drastic increase in cognitive workload following fatigue in concussed individuals, indicating that those suffering from concussion experience increased utilization of cognitive resources to accurately perform the same visual and motor reaction tasks that they completed prior to exercise, while non-concussed participants experience little-to-no change following fatigue. The results demonstrate that following exercise to volitional fatigue, concussed individuals have significantly increased cognitive activity over the regions of the brain predominately involved in decision-making and reasoning skills.

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A Thesis

Presented to the Faculty of the Department of Kinesiology

East Carolina University

In Partial Fulfillment of the Requirements for the Degree

Master of Science in Kinesiology

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July 2023

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LIST OF SYMBOLS OR ABBREVIATIONS

1. MTBI – Mild Traumatic Brain Injury
2. RTP – Return to Participation/Play
3. EEG – Electroencephalography
4. MSI – Musculoskeletal Injury
5. MSk – Musculoskeletal
6. GCS – Glasgow Coma Scale
7. VR – Virtual Reality
8. BCTT – Buffalo Concussion Treadmill Test
9. HR – Heart Rate
10. BP – Blood Pressure
11. VAS – Visual Analog Scale
12. RPE – Rate of Perceived Exertion
13. PAR-Q+ – Physical Activity Readiness Questionnaire+
14. VRT – Visual Reaction Time
15. MRT – Motor Reaction Time

CHAPTER 1: INTRODUCTION

Mild traumatic brain injury (mTBI), also widely known as concussion, presents itself as an important public health concern in the United States, with an estimated 1.7 million people diagnosed annually. At least 75 percent of all TBIs in the United States are classified as mild traumatic brain injuries (mTBIs) in the form of concussions or brain injuries resulting from direct impacts to the head, blast injuries, or whiplash (Diaz-Arrastia & Vos, 2014) and often occur as a result of sports-related contact injury. Typical mTBIs are classified as a 13-15 on the Glasgow Coma Scale (GCS) (Teasdale & Jennett, 1974) and usually do not show physical signs or symptoms. These injuries have been shown to cause prolonged impairments to cognitive functioning even after clearance for return-to-participation (RTP), including delayed reaction time and decreased visuo-motor accuracy (Sterr et al., 2006, Levin & Diaz-Arrastia, 2015).

With approximately 50% of all concussions that occur in the United States going unreported or misdiagnosed each year, more efforts to investigate objective diagnostic techniques to identify mTBI injuries have been implemented. Some newer techniques include pathological computed tomography(CT), brain metabolite measurements, eye tracking, and even microRNA assays from human saliva, (Pietro et al., 2021, Kontos et al, 2014) Although this previous research has been conducted to understand the current effectiveness of concussion evaluation methods, results have yielded varying evidence for each technique, with no single, gold-standard technique for diagnosis existing, and widely accepted tests having questionable reliability (Starling et al., 2016, McKeithan et al., 2019) Despite these efforts, patients suffering from mTBI can experience cognitive impairments which can develop immediately or with presentation delayed up to 6-24 hours later (Lynall et al., 2022), causing an even more dramatic barrier to the identification of mTBI. Without a proper diagnosis and treatment intervention, cognitive deficiencies resulting from mTBI such as delayed reaction time and inhibited accuracy can drastically impact the ability to perform regular tasks of daily living that utilizes these skills, such as driving and obstacle navigation.

In athletes, misdiagnosing, not reporting, or completely missing the diagnosis of a mTBI can lead to an improper return-to-play protocol completion or even a failure to prescibe RTP protocol initiation. Even following the return-to-play protocol completion, concussed athletes can experience extended impairments of neurocognition (de Freitas Cardoso et al., 2019). These findings indicate that the effects of cognitive deficits could severely impact players' ability to accurately perform the skillset required for their sport. Lower extremity musculoskeletal injury (MSI) is associated with neuromuscular and neurocognitive deficits (Herman et al., 2017). The increased injury risk following mTBI suggests that current mTBI diagnostic techniques do not fully capture persistent neuromuscular and/or neurocognitive deficits associated with mTBI. Increased demands associated with fatiguing physical activity can result in altered visuomotor processing, more decision-making and altered motor control. Three potential mechanisms for this process have been observed: temporal desynchronization of brain activity, reduced neural communication resulting in an increase in decision-making time, and inhibition of visual and motor control processes (Wright et al., 2017).

In general, it is widely understood that musculoskeletal fatigue can induce biomechanical alterations that can increase the likelihood of injury including muscular compensation and improper balance between muscle use for critical movements (McLean & Samorezov, 2009). Particularly, mTBIs often present with severe fatigue alongside neurocognitive deficits typically causing a mass inability to perform motor tasks accurately. With previous studies showing that dynamic postural control and cortical pathway disruption can persist beyond a return-to-play protocol, and that these impairments can increase the risk of lower limb injury, it is imperative to understand the mechanisms by which fatiguing physical activity can exacerbate the declined cognitive functioning following mTBI (Bourne et al., 2019).

Purpose

The purpose of this project was to determine the extent that voluntary exhaustion exacerbates declined cognitive functioning in concussed individuals compared to non-concussed controls. A secondary purpose was to additionally understand the extent to which musculoskeletal fatigue can decrease cognition and further delay in reaction time in individuals with mild traumatic brain injuries.

Hypothesis

It was hypothesized that concussed individuals would present with lower visual accuracy and faster motor and visual reaction times, indicating some level of increased impulsivity prior to exercising when compared to their non-concussed counterparts, and that these levels will become worse following exercise in both groups. Additionally, it was hypothesized that EEG spectral power analyses for both alpha and theta event related spectral power will reveal a desynchronization, characterized by inverse activity among alpha and theta wavelengths over task-involved regions, which may become more significant following exercise.

Delimitations

1. Concussed participants have been diagnosed by a licensed medical provider.

2. Concussed participants are males and females aged 18 or older and have been previously cleared for RTP by their diagnosing provider.

3. Concussed participants experienced their injury within 13 months prior to participation in the study.

4. Control participants were males and females aged 18 or older and without a history of concussion.

Limitations

1. The analyses are limited to the accuracy of the equipment used: EEG, Virtual Reality Go/No-Go Tasking, and concussion reporting.

2. The thesis results will not be able to provide information related to the variables associated with MSI risk because the study follows a retrospective design comparing concussed individuals to non-concussed control.

CHAPTER 2: REVIEW OF THE LITERATURE

This literature review will examine previous research conducted in the following fields of interest: 1) the prevalence, incidence, and current diagnostic status of concussions, 2) cognitive measurements in concussion assessment, and 3) cognitive changes and subsequent risks as a result of fatigue.

mTBI Prevalence and Incidence

An estimated 1.7 million people are diagnosed with mTBIs annually (Diaz-Arrastia & Vos, 2014), often occurring as a result of sports-related contact injury. This equates to about $76.5 billion spent in healthcare costs in the US on TBIs each year (Seifert, 2007). While the prevalence of concussions continues to rise, the ability to objectively measure and diagnose mTBIs is still lacking (Prince & Bruhns, 2017). With little-to-no reliable means of diagnosing a concussion, approximately 50% of all concussions that occur in the United States going unreported or misdiagnosed each year (Goldberg et al., 2015), with actual values suspected to be much higher due to blatant non-reporting of professional and collegiate athletes, where the stigma of injury presence exists (Langlois et al., 2006).

mTBI Symptoms and Diagnostic Variability

Concussions, specifically mild traumatic brain injuries, cause prolonged impairments such as fatigue, headache, visual changes, and declines in cognitive functioning even after clearance for return-to-participation, including delayed reaction time, and postural imbalances (Levin et al., 2015). Despite recent increases in research surrounding the mechanisms of cognitive deficits resulting from concussions, understanding how these changes truly impact the ability of mTBI victims to accurately identify and respond to environmental changes and the presentation of stimuli is scarce. Although previous studies have supported the notion that frontal and temporal white matter damage result from mTBI, with both relating to cognitive dysfunction postinjury (Niogi &

Mukherjee, 2010), these abnormalities have historically been termed "complicated" (Williams et al., 1990) without the production of a mechanical explanation for these deficits. This potential characteristic neural damage caused by mTBIs may explain the long-term impairments experienced by some patients post-injury (Shenton et al., 2012), but has yet to be thoroughly investigated. To better understand the effects of concussion on cognitive functioning, many studies have observed the neuropsychological outcomes of mTBIs (Karr et al., 2014), noting that neuroimaging results for individuals with mTBI, including MRI, did not correlate with long-term impairments in cognitive performance (Lee et al., 2008), but that significant mood and cognitive changes persisted over the life-time in young college students who had received an mTBI in the past (Vynorius, 2016) This discrepancy among previous studies validates the concern surrounding the ability to provide an accurate and timely diagnosis following concussion to allow for the most efficient care and treatment response time. More recent studies have indicated that oculomotor tracking could potentially be used to identify and diagnose mTBI (Warlick et al., 2022), while specific oculomotor measurements of simple and discriminate reaction times to environmental stimuli experience delays even in the long-term as a result of mTBI (Danna-Dos-Santos et al., 2018). These recent findings give hope to the future of addressing the public concern of mTBI diagnostics and has shown to be a reliable form of identifying injury, however due to the small sample sizes in these past studies, this methodology should continue to be examined further.

Buffalo Concussion Treadmill Test

The Buffalo Concussion Treadmill Test (BCTT) is one standardized and validated protocol used to assess the degree of exercise tolerance in individuals with active concussions. Following the recommendations provided by Leddy et al., 2013 along with the American Heart Association's Guidelines for contraindications to testing (Gibbons et al., 2002), this exercise test protocol can be conducted to safely ensure volitional fatigue in potentially concussed individuals (Leddy et al., 2007, Clausen et al., 2016, Cordingley et al., 2016, Leddy et al., 2018).). The administration of this test points to the ability to monitor autonomic dysfunction experienced by concussed patients through HR and BP monitoring (Leddy et al., 2011).

Go/No-Go Tasks

Go/No-Go tasks are another experimental model allowing for measuring and observing reaction time and response accuracy, especially to assess cognitive functionality (Gomez et al., 2007). The task requires a participant to push a button or respond when they see a "go" target and withhold a response when they see a "no-go" target. This method of reaction time measurement can be produced in immersive VR, allowing individuals to experience a cognitive sense of presence like that experienced in a real environment, without the immediate risk of injury or danger. Impulsivity and cognitive functioning through decision-making and reasoning skills can be used to appropriately measure deviations from normal cognitive functioning such as those experienced as both a result of mTBI and musculoskeletal fatigue (Helmers et al., 1995, Rochat et al., 2009, McDonald et al., 1993). This type of task is beneficial in recording visual reaction time (VRT) the time between the presentation of the target and the initiation of eye movement towards the target as well as motor reaction time (MRT) the time between the presentation of the target and a trigger pull or response, which can be used to identify deviations from normal cognitive functioning.

Electroencephalography

Electroencephalography (EEG) measurements allow for the visualization of brain activity through spectral analysis to be monitored. In previous studies, EEG has been used to note significant increases in cognitive workload during simple and discrimination reaction tasks in concussed individuals indicating that individuals suffering from concussion often work a lot harder, cognitively, than their non-concussed counterparts to perform mental tasks (Sandri Heidner et al., 2022,2023). These studies have observed that complex retrieval processes are reflected by alpha wave desynchronization from the encoding of new information, reflected by theta oscillations. While the use of EEG in the assessment of post-concussive alterations is relatively novel, this approach has consistently been efficient at deciphering residual neurocognitive deficits post-concussion (Munia et al., 2017).

Neural signatures produced in non-concussed individuals consist of spectral power of both theta and alpha bands that is higher immediately post-fatigue, and it has been consistently supported that increases in alpha and theta power are observed as a result of the exhaustion of cognitive resources (Cheng & Hsu, 2011, Wascher et al., 2014). Notably, according to a meta-analytical review, by Conley et al. (2019), most studies that utilized alpha (~9-12 Hz) and theta (~4–8 Hz) wave analysis in concussed individuals when compared to non-concussed controls reported a decrease in alpha and theta power across all regions when compared to controls. Additionally, a recent study found that both alpha and theta spectral power on the motor cortex and central sulcus of concussed participants was overall significantly reduced without the implementation of fatigue protocols in the group, indicating that neural signatures consisting of spectral power in both the alpha and theta frequencies may indicate the current status of cognitive efforts within specific brain regions (Sandri Heidner et al., 2023). Based on previous literature, mTBI generally leads to both acute and chronic decreases of alpha and theta power all over the brain, but in some cases, theta power seemed to return to normal activity through upregulation over the long-term following injury. While an understanding of what these changes may mean specifically is limited, it has been clearly established that the recording of electrical activity generated by the brain through scalp electrodes via EEG can be used to detected neural deviances from normal functioning.

Virtual Reality

Virtual reality environments facilitate stimulus control, and stereoscopic vision allows participants to perceive motion-in-depth, similar to how the environment would be received outside of VR. Immersive virtual reality allows for the consistent use of standardized and reproducible protocols (Sandri-Heidner et al., 2023). Previous studies have additionally shown that motor control strategies can consistently be challenged in a life-like virtual reality environment, without the immediate risks associated with concussed individuals performing tasks in the real-world environment (Sandri-Heidner et al., 2020).

Post-Concussion Risk of Musculoskeletal Injury

With concussion history being associated with altered motor control and compensating gait patterns in clinically asymptomatic patients (Guskiewicz et al., 2001), previous findings indicate that concussed athletes have increased odds of sustaining a lower extremity musculoskeletal injury after completing a full return to play protocol than their nonconcussed teammates (Brooks et al., 2016)). Emerging evidence suggests that these deficits can continue to persist well into late-stage injury recovery and can cause significant insufficiencies in athletes even after completing an RTP protocol (McCrory et al., 2013). Poor neuromuscular control has been demonstrated to be a risk factor for musculoskeletal injury in general (Herman et al., 2017), and decreases in cognitive domains such as reaction time, processing speed, and visual and verbal memory, can drastically increase the hazard risk for individuals experiencing cognition changes resulting from mTBI (Swanik et al., 2007). While these findings contribute to the general knowledge of concussion and musculoskeletal injury, the current understanding regarding the nature of the relationship between different aspects of neurocognitive performance and musculoskeletal injury risk is limited (Herman et al., 2017).

Potential Causes of Increased Risk

Fatigue

Physical exertion can negatively impact balance-based metrics due to muscular fatigue (Yaggie & Armstrong, 2004). Whole body fatigue is achieved by exhausting multi-level muscle groups, including the cardiovascular and neuromuscular systems (Vuillerme & Hintzy, 2007). Exertion experienced during physical activity, like sports, can be mimicked using maximal treadmill or cycling exercise tests to volitional fatigue. Volitional fatigue is defined as the participants' expressed inability to continue exercising, despite strong encouragement to continue by the testing staff, or as measured by a Visual Analog Scale (VAS) or Rating of Perceived Exertion (RPE), to examine the effects of fatigue on several components of the body including oculomotor activity and cognition. Previous projects have indicated that EEG analysis focusing on spectral power in the alpha and theta wave regions show decreases in power directly associated with active cortical processing (Sandri-Heidner, 2022), and that this workload seems to be exacerbated by concussion injury (Thompson et al., 2005). Under these conditions, it is understandable that exercising concussed individuals, especially by way of returning athletes to play without full cognitive recovery, may worsen the cognitive deficits already present in individuals experiencing a concussion. However, an understanding of how these neurocognitive deficits may increase the risk of musculoskeletal injury after trauma is not clear and has not been significantly studied, indicating a need for further analysis of the effects of musculoskeletal fatigue on neural activity.

Delayed Reaction Time

Previous meta-analytical reviews note the broad framework of persistent sensorimotor impairments that follow an mTBI occurrence for many months or even years past the time of return to sport participation (McPherson et al., 2019). One specific, and quite important, aspect of neurocognition assessment is reaction time, which has continuously shown to be significantly delayed as a result of brain injury (Danna-Dos-Santos et al., 2018, Hulkower et al., 2013). Investigations using electroencephalography (EEG) have found the use of EEG monitoring to be an appropriate assessment of cognitive performance (Bell & Cuevas, 2012). Additionally, EEG has also been used in conjunction with various cognition tests. Changes to alpha and theta wave oscillations in power during simple and discrimination reaction tasks, congruent with delayed reaction times in concussed individuals, indicate that those suffering from concussion often require more cognitive effort than their non-concussed counterparts to perform mental tasks (Klimesch, 1999). This monitoring of EEG during reaction tasks has been successful in anticipating human mistakes in the discrimination of response targets based on the distribution of alpha-theta synchronizes (Besserve, 2008). These EEG correlates, specifically the reduction of alpha wave activity and subsequent increase in theta activity seems to be related to widespread cortical activation, indicative of complex task performance or increased workload at rest (Schapkin, 2020).

Impulsivity

Impulsivity can be connotatively described as the tendency to act with little or no forethought. Impulsive actions are typically poorly conceived, unduly risky, and inappropriate to the situation. Executive functions and socio-emotional changes have consistently been recorded as symptoms and side effects of concussion, especially increased impulsivity following mTBI (Rochat et al., 2009). It is theorized that increased impulsivity may be positively associated with injury occurrence (Bazargan-Hejazi et al., 2007) due to the creation of premature and risky responses to potentially dangerous stimuli. Go/no-go tasks are discriminate reaction-based tasks, in which participants are required to respond to a "target object" but must withhold a response to any object which is not the target, designed to measure cognitive impulsivity (Helmers et al., 1995, Mychasiuk, 2015). Additionally, linger time, the time that a person fixates their gaze on a target before initiating a response can also be a reliable measure of assessing how quickly an individual takes to process the information presented in front of them (Armstrong, 2018).

With a lack of studies specific towards fatigue and impulse-related risk following concussions, it is important to identify how a hastened return to fatiguing physical activity can exacerbate the symptoms already presented by concussions. The previous research that is available on the topic does make a considerable note that concussed brains often work similarly to non-concussed fatigued brains in several domains. The issue with this understanding is that in-depth research investigating the specific mechanisms that cause these previously presented deficits.

In conjunction, the use of an appropriate fatiguing protocol, the recording of go/no-go task responses to assess reaction time, and EEG to measure cognitive workload can reasonably be expected to effectively produce a clearer understanding of the cognitive mechanisms which cause significantly decreased accuracy and subsequent risk of injury, especially in athletes that are returning to sports without proper recovery time following an mTBI.

CHAPTER 3: GOALS AND METHODS

OBJECTIVE:

The purpose of this project is to first identify if exertion to voluntary exhaustion exacerbates declined cognitive functioning in concussed individuals compared to non-concussed controls and to additionally understand the extent to which musculoskeletal fatigue can decrease cognition and further delay in reaction time in individuals with mild traumatic brain injuries.

METHODS:

Participant Recruitment

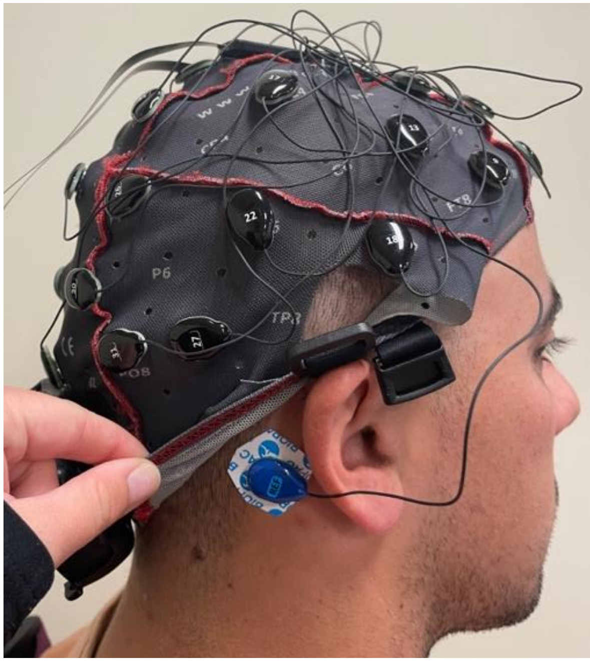
Participants were recruited using fliers and email threads sent out to potential candidate groups for the study, including adult sports teams, military personnel, college students and faculty/staff. Five concussed individuals and fifteen non-concussed individuals were recruited to participate in the study. Inclusion criteria for participants in the concussed group required individuals to be over the age of 18 with a recent mild traumatic brain injury diagnosed by a licensed medical provider within the past 13 months, that had been and has been cleared for RTP, with no previously known cardiovascular, renal, or metabolic dysfunction. Concussion history and injury circumstances were self-reported by the participant using a concussion history screening form (Cronbach α= 0.87). Physical Activity readiness was determined following the 2022 Physical Activity Readiness Questionnaire (PAR-Q+) to ensure the appropriateness of participation (Goodman et al., 2011). Inclusion criteria for participants for the non-concussed group required individuals to be over the age of 18 with no history of mild traumatic brain injury, and no previously known cardiovascular, renal, or metabolic dysfunction. Exclusion criteria for both groups included an age below 18 years, any history of cardiovascular, renal, or metabolic dysfunction, and any history of concussion or other head injuries within the past twenty-four hours.

Testing Protocol-Preparation

The nature of the study was first explained to the individual, and all individuals were provided with written consent to participate and given a paper copy of the informed consent at request. Following informed consent, using the 2022 PAR-Q+, each participant's health history was voluntarily provided to assess their ability to participate in the study depending on presence or history of signs/symptoms indicative of cardiovascular, renal, or metabolic dysfunction. Participants in the experimental group were asked to complete a prescreening questionnaire which included the date of head injury, details on the cause of injury, symptoms and associated onset and cessation, and presence of diagnosis. Following eligibility assessment, participants were prepared for EEG data collection by being fitted with a 32-channel g.Nautilus electroencephalography cap (g.Tec medical engineering GmbH Sierningstrasse 14 A-4521 Schiedlberg Austria/Europe).

For cap placement, participants were measured from their nasion to their inion, and a small mark was placed (1/10th of the distance using the nasion as the reference) on the participant's forehead with a non-toxic permanent Sharpie marker. The front edge of the cap was aligned with the mark, ensuring that the cap was placed appropriately. The mastoid regions behind the ear were prepped for the placement of two reference electrodes (Kendall Electrodes, Covidien llc, Mansfield, MA USA).

A small gauze pad with a mild abrasive skin prepping lotion (Mavidon Lemon Prep 6625 White Dr. Rivera Beach, Fl. 33407) was used to abrade the area behind the ear, clearing the area of dead skin cells and contaminants, allowing the reference electrodes to be in strong contact with the skin.




Figures 1 and 2: The skin is prepped using a mild abrasive, and reference electrodes are placed directly behind the ear on the bilateral mastoid processes.

Additionally, a Polar H10 heart rate sensor (Polar Electro Oy, Professorintie 5, FI-90440 Kempele, Finland) was snugly fitted to the participant's chest and connected via Bluetooth to the Polar Beat (©Satya Narayan 2012) mobile application monitoring software on a Motorola Moto Z^2 Play. The Polar HR monitor was verified to be actively collecting HR and exercise data prior to data collection.

Testing Protocol-VR RT Task

After EEG and HR data impedance was verified and confirmed to be within appropriate measures, participants were be instructed to stand on a force plate in the center of the room and was fitted with an HTC Vive Pro Eye virtual reality (VR) headset integrated with Tobii Pro infrared eye tracking technology (Tobii Technology, Danderyd Municipality, Sweden) to complete a VR visual and motor reaction time (RT) go/no go task. The VR environment was first calibrated using a 5-point gaze calibration model, requiring the participant to fixate their gaze onto 5 individual targets, which appeared in different regions of the VR field until the target disappeared. The calibration was then checked by the study team under a 0-10 coded proximity score produced by gaze accuracy in relation to the target, with 0 being not at all in the vicinity of the target and 10 being in the central 0.5° of it. Once calibrations were completed, and the participant indicated full understanding of the VR task requirements, the test was started.

Figure 3: Participants were fitted with both an EEG cap as well as VR headset to complete a VR go/no-go task.

A dynamic environment, in which participants are moving straight ahead in a procedurally generated tunnel, was developed and rendered into virtual reality using Unity Software (Unity Technologies, San Francisco, CA). Every 5 seconds a ball-shaped target appeared in a random spot 15 meters away from the participant creating the setup for the go/no go task. The targets were striped black and white, with either a left or right tilt. Participants were instructed to pull the trigger on the HTC VIVE handheld controller only when the target has a right tilt. Each target remained visible for 1.5 seconds and has a coded proximity measurement in the format of a 0-10 score. Gaze behavior was recorded using the eye-tracking system for all movements at a sampling rate of 120Hz, and the gaze site at reaction time produced a scored result following the coded proximity measurement system. Visual reaction time was determined as the time between the presentation of the target and the initiation of eye movement towards the target. Motor reaction time was determined as the time between the presentation of the target and the detection of a trigger pull.

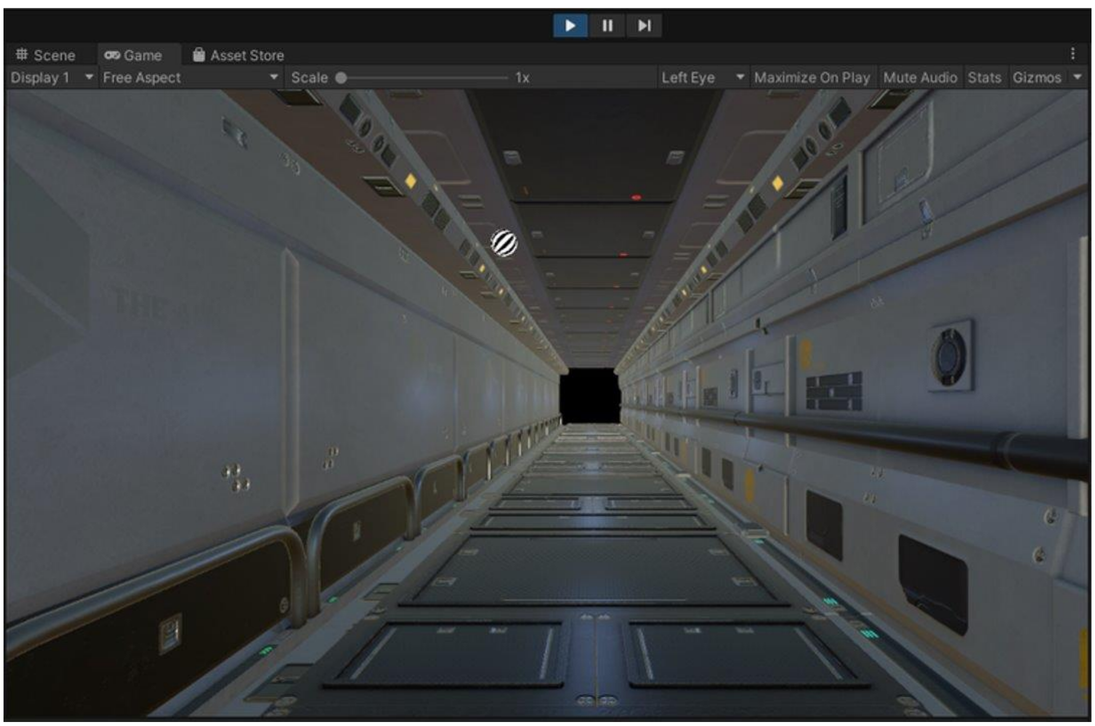


Figure 4: Presentation of a "No-Go" target, displaying a left-tilt pattern, in the procedurally generated tunnel.

Testing Protocol-BCTT

Following the VR RT task, the EEG cap was removed, leaving the reference electrodes in place, and participants were walked to a separate room containing a treadmill and cooling devices to maintain appropriate room temperature. Before beginning the Buffalo Concussion Treadmill Test (BCTT) protocol, participants were evaluated for any contraindications as referenced by the American Heart Association prior to exercise testing.

The use of a 0-10 concussion symptom-based Visual Analog Scale (VAS) and a 6-10 Borg Rating of Perceived Exertion (RPE) scale(Borg, 1982) was explained and demonstrated to the participants and resting scores were obtained. Participants were advised that they will be asked to rate symptom severity and exertion at each minute during exercise. After being seated for 2 minutes, a resting HR was collected. The participant then began the BCTT protocol by standing on the sides of the treadmill while the treadmill was set to an initial speed of 3.2mph for participants up to 5’10”, and 3.6mph for those 5’10” and above. The starting incline was set to 0 degrees. After beginning the test on the treadmill, the stage was changed each minute, increasing the incline by 1%. At the beginning of each stage, HR, RPE, and VAS was obtained and recorded using the Buffalo Concussion Treadmill Test Assessment Form. Once the participant had reached voluntary exhaustion, indicated by an RPE of > 17 without significant symptom exacerbation, or symptom exacerbation indicated by an increase of 3 or more points on the VAS scale from resting VAS score, the test was terminated.

At this time, participants did not complete the cool-down period described in the typical administration of the BCTT but instead, were allowed to walk back to the VR room. The time period was monitored to ensure participants were beginning the second task within 5 minutes following termination of the exercise test, and that RPE levels did not fall below an 11 on the Borg

RPE scale, to maintain volitional fatigue when the task was performed. After towel-drying the hair and scalp to remove moisture, the EEG cap was reconnected to the reference electrodes, refitted to the head, and the participant performed the virtual reality reaction time task procedure a second time following voluntary fatigue.

METHODS- Data Reduction

EEG Data

EEG data was collected at 250-500 Hz using a 32-channel cap with impedance kept below 10 kΩ. Continuous EEG data was exported from the g.Recorder(g.Tec Neurotechnology USA Inc., Albany, New York) acquisition software, translated into an appropriate file type.

Pre-Processing was completed through MatLab 2022(MathWorks, Natwick, Massachusetts), using functions from the EEGLab DarbeliAI toolbox, removing broken channels, 23 and 28, which exist over the cerebellum, and down sampling all of the files to 250Hz. A high (1 Hz) and low (55 Hz) pass filter was applied, and then linear detrending was completed. A component analysis was completed, and any components that were not related to brain activity were manually removed. Following, the dataset was re-referenced to the average and underwent a Laplacian Transformation which removes source conductance. These data were extracted and exported for manual analysis in SPSS (IBM Corp Version 28.0. Armonk, NY) across group and brain region. Spectral power heatmaps were produced depicting brain activity changes indicated by p-level defined significance across each brain region, for each group and each condition.

VR Response and Eye-Tracking Data

Visual and motor reaction time was measured and recorded in milliseconds. Visual accuracy was coded as a proximity measurement in the format of a 0-10 score, with 0 being not at all in the vicinity of the target and 10 being in the central 0.5° of it. The proximity coding for accuracy resembles the scoring technique of a dartboard; A gaze fixated on the outermost ring of the target would illicit a score of one, and the score would increase as the gaze fixates closer to the center of the target. Response time and eye-tracking data were recorded as raw data through Unity with coding for each condition and participant group. The data were extracted from the files and reduced using Python Programming Software (V3.11.4, Fredericksburg, Virginia) for mean statistical analysis. The data were exported to SPSS for analysis across groups.

METHODS- Data Analysis

EEG Data

To analyze cortical activation, a separate Mixed Model (2 group x 2 trial x 4 brain region) ANOVA was conducted on the influence of concussed status and brain region on absolute power in both the alpha and theta frequencies. This ANOVA allowed for the calculation of the mean natural log of event-related spectral power differences across condition and group for both alpha and theta wavelengths.

VR Response and Eye-Tracking Data

To analyze VRT and MRT, a separate Mixed Model (2 group x 2 trial) ANOVA was conducted across mean response times, in milliseconds (ms), calculated within Python across condition and group for MRT and VRT. To analyze visual accuracy, the mean response accuracy codes produced by Unity was translated into a percentage for each group and condition using Python. A separate Mixed Model (2 group x 2 trial) was conducted across mean response accuracy, in percent form, and a two-way repeated measures ANOVA was conducted to determine significance of between groups factors.

Overall Analysis

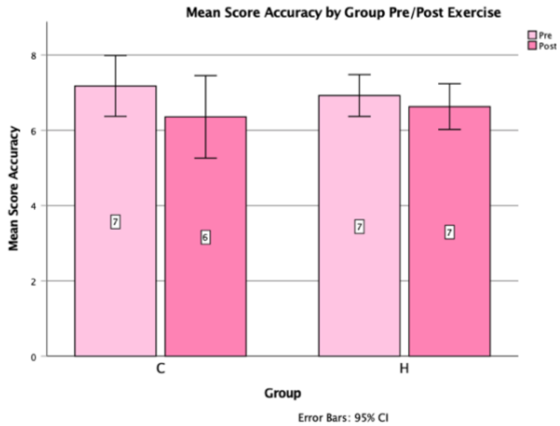
For all ANOVA related testing, preliminary analysis was performed to check for violations of statistical assumptions. A simple effects test was used for any found significant interactions, following a significance level, set α priori, at $\alpha=0.05$. Raw data was used to calculate effect size for all measures to assess presence of practical significance.

CHAPTER 4: RESULTS

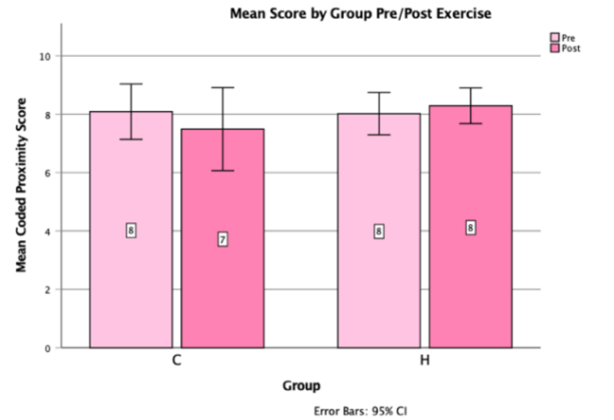
VR Response Time and Eye-Tracking Pre- and Post-Fatigue

A total of twenty (N=20) participants were enrolled in and completed this study. The non-concussed non-concussed group consisted of fifteen (n=15) participants, and the concussed group consisted of five participants (n=5), all of which completed the protocol successfully.

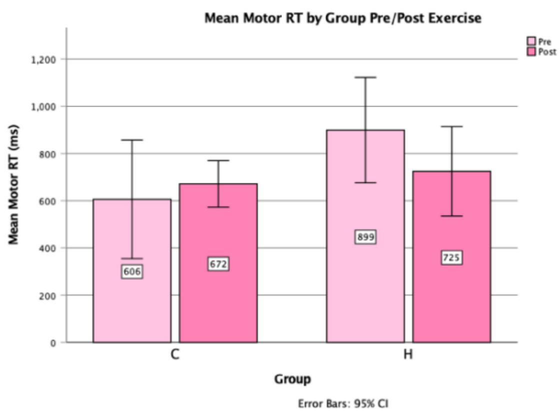
A two-way repeated measures ANOVA was completed for oculomotor measures collected (Mean Score, Mean Score Accuracy, Linger Time, Motor Reaction Time, and Visual Reaction Time) across group (C=Concussed, H= Non-Concussed) and condition (Pre/Post-Exercise). Averages among groups for Score ($F(1,18) = 1.43$, $p = 0.247$), Score Accuracy ($F(1,18) = 0.633$, $p = 0.437$), and Motor Reaction Time ($F(1,11) = 4.59$, $p = 0.055$) yielded no statistically significant results. Visual Reaction Time ($F(1,18) = 2.36$, $p = 0.142$) and Linger Time ($F(1,18) = 0.033$, $p = 0.857$) averages for both groups across both tasks did not yield significant main effects. Despite these measures not revealing statistical significance, a small-to-medium within-subjects MRT * Group effect was found ($\eta^2 = 0.294$, $p = 0.055$) using partial eta-squared (η^2). Partial Eta Squared values indicate the size of effect the independent variable(s) (fatigue status) had on the dependent variable (MRT), indicating potentially practical significance.



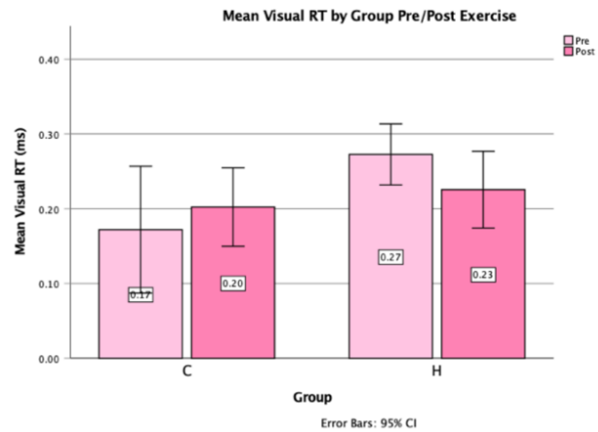
5.1.



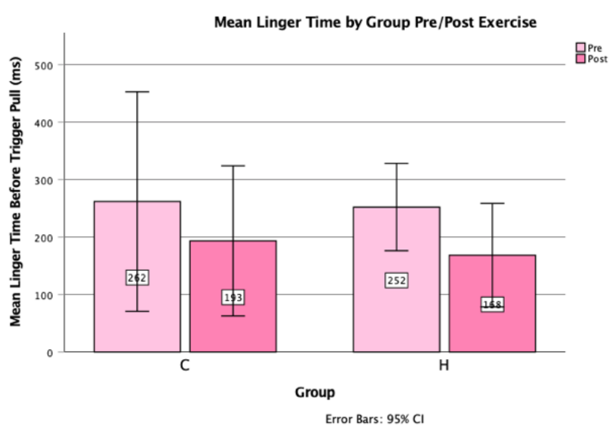
5.2.



5.3.



5.4.



5.5.

FIGURES 5.1-5.5: *Mean and standard deviations with 95% CI Error Bars of Virtual Reality oculomotor measures comparing non-concussed and concussed participants both pre- and post-exercise intervention.*

Note: *5.1.Mean Score Accuracy*Group (p=0.437, η^2=.034) 5.2. Mean Score*Group (p=0.247, η^2=0.74) 5.3.Mean MRT*Group (p= 0.055, η^2=0.294) 5.4. Mean VRT*Group (p=0.142, η^2=0.116) 5.5. Mean Linger Time*Group (p=0.857, η^2=0.002)*

Electroencephalography

A total of twenty (N=20) participants were enrolled in and completed this study. The non-concussed group consisted of fifteen (n=15) participants, and the concussed group consisted of five participants (n=5), all of which completed the protocol successfully. A separate Mixed Model (2 group x 2 trial x 4 brain region) ANOVA was conducted on the influence of concussed status (C=Concussed, H= Non-Concussed), trial/condition (Pre/Post-Exercise) and brain region (Frontal, Parietal, Central/Motor, Occipital) on absolute power in both the alpha and theta frequencies. Spectral power heatmaps were produced depicting brain activity changes indicated by p-level defined significance across each region.

Alpha wave activity heatmaps revealed a significant increase ($p < 0.01$) in activity across both the left and right frontal regions in the concussed group following exercise. The non-concussed group saw no significant change ($p > 0.1$) in alpha activity following exercise across all regions.

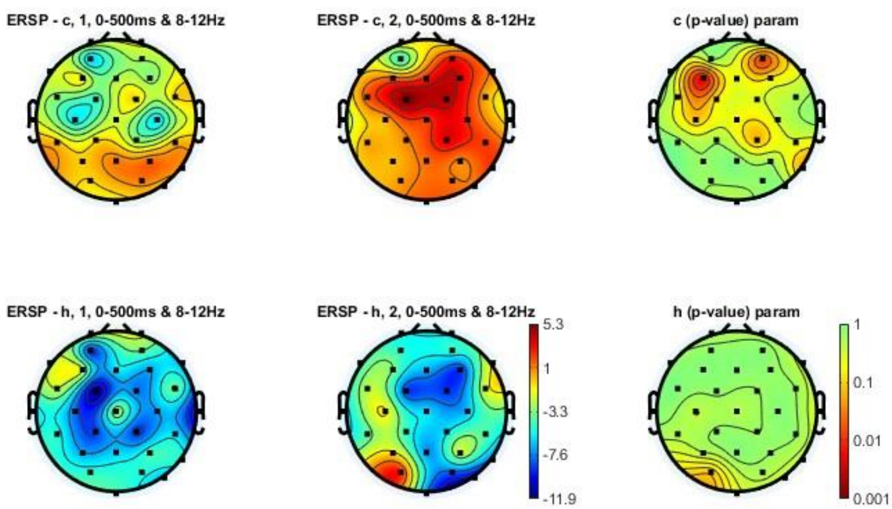


Figure 6: Averaged ERSP in the alpha wavelength (8-12Hz) across group(concussed and non-concussed as indicated by c=concussed and h=non-concussed) and condition (pre/post-exercise) as indicated by pre=1 and post=2. Overall changes in activity are shown in column 3, expressed in terms of significance.

Theta wave activity heatmaps revealed a significant decrease ($p < 0.01$) in activity across the left central/ motor complex region in the concussed group following exercise. The non-concussed group experienced no significant change ($p > 0.5$) in theta activity following exercise across all regions.

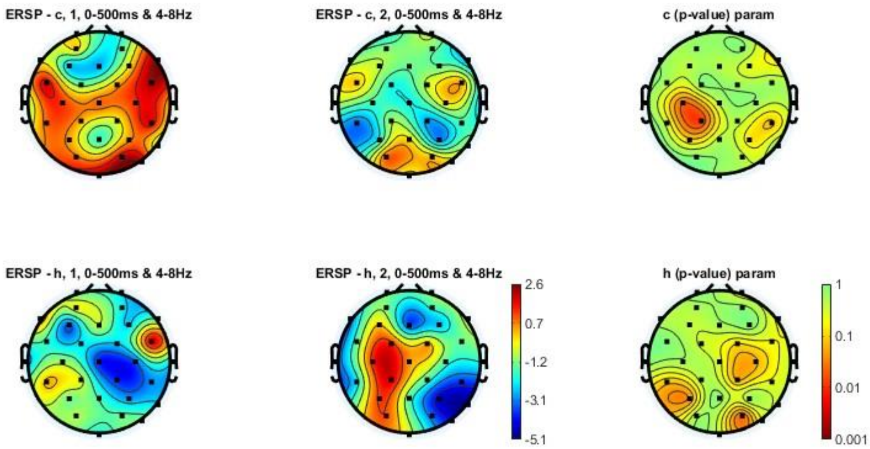


Figure 7: Averaged ERSP in the theta wavelength (4-8Hz) across group (concussed and non-concussed) as indicated by c=concussed and h=non-concussed and condition (pre/post-exercise) as indicated by pre=1 and post=2. Overall changes in activity are shown in column 3, expressed in terms of significance.

Interestingly, prior to exercise, concussed individuals experienced an increase in theta wave activity across all regions during the VR task when compared to their non-concussed counterparts. Additionally, following exercise, concussed participants experienced a dramatic increase in alpha activity across all regions, when compared to their non-concussed counterparts at the same stage in the protocol.

CHAPTER 5: DISCUSSION

This project was designed to investigate and better understand how the relationship between concussion, oculomotor skills, and modulation of alpha and theta power spectra on seven major regions of the brain are exacerbated following moderate physical exertion. Our initial hypothesis was that all participants who were subject to the fatigue protocol would have decreased stimulus response times and decreased score accuracy following fatigue, and that concussed participants would show a worsened performance on all tasks following exercise when compared to their non-concussed counterparts. It was additionally hypothesized that all participants would show notable decreases in alpha and subsequent increases in theta spectral power across regions involved in decision-making and thoughtful reasoning skills following physical exertion, but that non-concussed participants would maintain or only slightly decrease spectral power in these areas when compared to the injured participants.

The first comparison was observed between both the non-concussed and concussed groups before and after fatiguing exercise, on visual accuracy and motor/visual reaction time components. Although all within-group interactions were found to be non-significant, a small practical interaction was found between physical activity and motor reaction time in both non-concussed and concussed groups. It is well-understood that concussions negatively impact vision and reaction time measurements that utilize vision in processing (Gunasekaran et al., 2019, Lempke, 2021). Due to the small sample size of concussed individuals (n=5), the presence of even a small practical effect indicates that a larger sample size of concussed individuals and a more proportionate sample size between both groups may depict a more relevant and accurate idea of how much physical exertion can exacerbate the cognitive declines as it relates to response time and accuracy in concussed individuals.

Although the results were not statistically significant, both concussed and non-concussed participants had the same average coded proximity score and score accuracy prior to exercise, which seems to point towards an understanding of no difference in baseline visual accuracy in a non-fatigued state. While non-concussed participants' average score and score accuracy remained the same post-exercise, the concussed group's average score and score accuracy both decreased by one indicating some decrease in cognitive performance following fatigue. Due to the small sample size in the concussed group, it is expected that differences may not be significant, however, even with small changes seen in the post-exercise condition of the concussion group, it points in the direction of a deeper understanding that fatigue may exacerbate overall decreases in visual and motor accuracy in concussed individuals. These ideas are important to understand, especially in the context of returning athletes to play following a concussion. Despite the long-term period that had passed in these participants, our results still showed changes that indicate a declined cognitive functioning in the concussed group. The presence of decreased visual and motor accuracy following fatigue may be related to an increase in impulsive actions. This notion directs towards the idea that athletes and individuals who have suffered from a concussion in the past, especially in more recent situations, may be more at risk for injury in sport associated with increased impulsivity, decreased visual and motor accuracy, and elongated reaction and decision-making times.

Mean VRT and MRT times in both groups were non-significant, but the trends in the data show that non-concussed individuals had faster response times, with no change in accuracy, while the concussed group had slower response times, with a decrease in accuracy. The decrease in response time and paired no-change in accuracy in the non-concussed group seems to lead to the idea that non-concussed individuals can process and decode visual stimuli faster, with the same amount of accuracy, potentially as a result of increased arousal and focus resulting from physical exercise, when compared to pre-exercise. Additionally, the concussed groups seemed to increase their reaction time, indicating an increase in time taken to decode the stimuli presented. Although these reaction times increased, the score and score accuracy decreased in the concussed group following exercise. These two findings paired together seem to indicate that the increased workload experienced in the concussed individuals contributes to an exacerbated declined cognitive functioning characterized by longer processing times and decreased accuracy. Linger time, as characterized by the time the participant fixated their gaze on the target prior to initiating a trigger pull was measured, but both groups experienced a relatively similar decrease in linger time prior responding to the targets, which is consistent with typical responses to fatigue, and general impulsivity, indicating that concussion status may not influence gaze time prior to stimuli response.

Recent literature has noted that the presence of neural signatures consisting of reduced spectral power in both the alpha and theta waves are indicative of increased cognitive efforts within these brain regions without the implementation of fatiguing protocols (Sandri Heidner et al., 2023). Our findings, however, provide a new window into this concern. With the addition of a fatiguing protocol, we found that there was a significant increase in alpha wave activity over the frontal region in the concussed group, with a relatively similarly significant change in theta activity across both the non-concussed and concussed groups.

While theta waves are typically produced during states of relaxation (Klimesch et al., 1999), we expect to see an increase in primarily alpha wave activity during wakeful rest, which indicates a higher level of cognitive workload. The literature reviewed has shown that the reduction of alpha wave activity and subsequent increase in theta activity seems to be related to widespread cortical activation, indicative of complex task performance or increased workload at rest (Von Stein & Sarnthein, 2000, Sandri Heidner, 2023) and therefore would be expected in groups experiencing heightened states of cognitive work. The results of this study, however, demonstrate that following exercise to volitional fatigue, concussed individuals have significantly increased alpha activity over the regions of the brain predominately involved in decision-making and reasoning skills. This finding interestingly points to the understanding of a drastic increase in cognitive workload following fatigue in concussed individuals indicating that those suffering from concussion are working a lot harder, cognitively, to accurately perform the same visual and motor reaction tasks that they completed prior to exercise. When comparing these results to those of the non-concussed group, we can see that this group did not experience significant changes in alpha activity following exercise, indicating that fatigue had little-to-no effect on the cognitive workload in non-concussed individuals.

Prior to exercise, however, concussed individuals were already showing higher activity in both the theta and alpha wavelengths, compared to the non-concussed individuals. This finding is expected, as it points towards a general increase in cognitive workload at rest in individuals suffering from potential neural injuries as a result of mTBI (Teel et al., 2014, Munia, 2017). Increases in both alpha and theta power in all trials within the concussed group were observed as a result of the exhaustion of cognitive resources, aligning with the findings of recent studies (Cheng & Hsu, 2011; Wascher et al., 2014). These findings were expected based on other previous studies investigating the evidence of brain functional deficits following mTBI (Munia, 2017). As expected, non-concussed participants had relatively similar presentations of alpha and theta rhythm power both before and after their bout of moderate intensity activity. It was expected that both wavelengths would have would have experienced an increase, resulting from musculoskeletal fatigue, indicating a general compensation mechanism of increased cognitive workload to offset the reactive effects of fatigue, however, this diversion from what was expected may be confounded by several variables that were not accounted for including age, sex, and equalizing the time out from injury.

Overall, the non-concussed group remained relatively stable with only minor or no changes to the measured values following the exercise protocol to volitional fatigue. Differences were seen in the concussed group that reflected an increase in cognitive workload at baseline, pre-exercise measures when compared to the non-concussed group. Those individuals experienced a significant increase in alpha activity within the frontal region as well as the motor cortex that indicates a dramatic increase in workload following fatigue on a brain that is already working harder at baseline. These findings did support the initial hypothesis, that concussed individuals present with lower visual accuracy and decreased motor and visual reaction times, This result does indicate that there may be some increased impulsivity in the concussion groups, but it does not seem to be as related to response time as previously shown, however due to our small sample size this is something that should absolutely be investigated more to identify the existence of correlates within larger sample sizes. Additionally, it was hypothesized that EEG spectral power analyses for both alpha and theta event related spectral power would reveal a desynchronization, characterized by inverse activity among alpha and theta wavelengths over task-involved regions, which would become more significant following exercise. These results were seen through a dramatic increase in alpha activity and a significant increase in theta activity concussed group following exercise. These findings support those of recent studies that identify the existence of a neural signature specific to concussed individuals and the presence of significant cognitive changes following concussion (Sandri Heidner, 2023).

The combination of these factors is important in determining the mechanistic causes of the statistical increase in lower limb musculoskeletal injury risk that is seen in post-concussion athletes (Ramirez et al., 2022, McPherson et al., 2019). With a general lack of diagnostic ability, these signs and symptoms are unable to be caught early in the intervention period, which could potentially contribute to even worsened cognitive effects over time. Some recent publications show that individuals can pass RTP protocol examinations, while still showing an experienced cognitive deficit that can be detected in EEG neural signatures over affected brain regions (Teel et al., 2014, Sandri Heidner, 2023). In general, it is understandable that these results may point toward a better understanding of how the presence of neural signatures and the desynchronization of alpha and theta wave activity among brain region can be used to measure and assess brain injury and recovery progression in the future.

Limitations

Studies investigating the reliability of oculomotor and cognitive measures to assess injury status have shown to be repeatable and reliable in individuals 18-45 years of age (Kiderman, 2020). In the instance of this study though, an age range of 18–45 years old may not be conservative enough, and there may also be substantial differences between males and females regarding the outcomes of cognition post-mTBI. Initial surveys did record factors such as age, sex, time out from injury, mechanism of injury, and other anthropometric measures, however, due to the novelty of the nature of this study, these factors were excluded from analysis to produce a general understanding of the effect of concussion status on neural and oculomotor factors that may contribute to increased injury risk, especially in the athletic population. The factors that were excluded in this study could provide a clearer understanding of this effect and may provide additional insight on the environmental and biological dependent variances in concussed individuals. Additionally, sample size was small, with a concussed group of only five, and a non-concussed group of fifteen, and may have contributed to the findings of this project.

Future Directions

Future research should likely be aimed at differentiating between the potential causes and correlates of the variances in spectral power when assessing concussed participants, and possibly investigating the differences within specific age ranges and between sexes. The cause and degree of concussion should also be differentiated and investigated on an individual level to determine the neural mechanism of injury and its direct results to understand how certain injury types may impact different components of cognition and stimuli response. The combination of these factors is important in determining the mechanistic causes of the statistical increase in lower limb musculoskeletal injury risk that is seen in post-concussion athletes and should be examined further with larger sample sizes, and efforts to control for statistical deviances, to truly understand the impact that fatigue has on concussed individuals, and to develop a clear model of the pathway that results in increased injury risk following mTBI.

CHAPTER 6: CONCLUSION

Our initial hypothesis was that all participants who were subject to the fatigue protocol would have decreased stimulus response times and decreased score accuracy following fatigue, and that concussed participants would show a worsened performance on all tasks following exercise when compared to their non-concussed counterparts. It was additionally hypothesized that all participants would show notable decreases in alpha and subsequent increases in theta spectral power across regions involved in decision-making and thoughtful reasoning skills following physical exertion. Differences that were seen in the concussed group reflected an increase in cognitive workload at baseline, pre-exercise, measures when compared to the non-concussed group. Those individuals experienced a significant increase in alpha activity within the frontal region as well as the motor cortex that indicates a dramatic increase in workload following fatigue on a brain that is already working harder to make rational decisions at baseline. The neural activity findings deter from what was initially expected but provides a better explanation for how the human brain may function following concussive injury.

The findings of this project produce a snapshot of the mechanistic deficits that occur as a result of mTBI and allow for the current knowledge of concussions to be developed further. Our results demonstrate that even up to a year post-injury, neural deviances are still very much present in brains that have experienced an mTBI. The neural deviances seen as a result of injury creates a clearer image of how cognitive deficits remain present in the long-term following injury and provides a new perception of how the human brain compensates to match baseline levels when injured and fatigued. This new ideology opens doors to an even broader understanding of how returning athletes to sports without a true measure of concussion status may drastically increase the risk for subsequent injury and emphasizes the importance of developing objective measures for diagnosing and assessing mTBI status to provide the most appropriate and effective plan of care.

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APPENDIX A. Institutional Review Board Approval

EAST CAROLINA UNIVERSITY
University & Medical Center Institutional Review Board
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600 Μοψε Βουλεϖαρδ •Γρεενϖιλλε, ΝΧ 27834
Οφφιχε **252-744-2914** •Φαξ **252-744-2284** •
rede.ecu.edu/umcirb/

Notification of Initial Approval: Expedited

From: Biomedical IRB
To: Karen Warlick
CC: Nicholas Murray
Date: 11/4/2022
Re: UMCIRB 22-001726
Fatigue and Reaction Time in Concussed Individuals

I am pleased to inform you that your Expedited Application was approved. Approval of the study and any consent form(s) occurred on 11/3/2022. The research study is eligible for review under expedited category # 4,6,7. The Chairperson (or designee) deemed this study no more than minimal risk.

As the Principal Investigator you are explicitly responsible for the conduct of all aspects of this study and must adhere to all reporting requirements for the study. Your responsibilities include but are not limited to:

1. Ensuring changes to the approved research (including the UMCIRB approved consent document) are initiated only after UMCIRB review and approval except when necessary to eliminate an apparent immediate hazard to the participant. All changes (e.g. a change in procedure, number of participants, personnel, study locations, new recruitment materials, study instruments, etc.) must be prospectively reviewed and approved by the UMCIRB before they are implemented;

2. Where informed consent has not been waived by the UMCIRB, ensuring that only valid versions of the UMCIRB approved, date-stamped informed consent document(s) are used for obtaining informed consent (consent documents with the IRB approval date stamp are found under the Documents tab in the ePIRATE study workspace);

3. Promptly reporting to the UMCIRB all unanticipated problems involving risks to participants and others;

4. Submission of a final report application to the UMICRB prior to the expected end date provided in the IRB application in order to document human research activity has ended and to provide a timepoint in which to base document retention; and

5. Submission of an amendment to extend the expected end date if the study is not expected to be completed by that date. The amendment should be submitted 30 days prior to the UMCIRB approved expected end date or as soon as the Investigator is aware that the study will not be completed by that date.